grain. These effects would, of course, be greatly reduced compared with those in the macrocrystals, because of dilution by the random parts of the network. However, if they could be detected, they would give some measure of the number of atoms in regular array with respect to those in random array. It might be informative to examine data in the transition region with this in mind.

With the liquid preserving the structure of the crystal to this extent, it is natural to think of melting as introducing an ever-increasing number of defects into the lattice, decreasing the grain size to some small but critical value where long-range order ceases and the structure fails.

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13. C. E. Wicks and F. E. Block [*U.S. Bur. Mines Bull.* **605** (1963)] give 1.84 kcal at the melting point, 2001°K.
14. I am indebted to Dr. Dan McLachlan, Jr., and Dr. Henry H. Blau for helpful discussions.

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Susceptibility to Two Strains of Friend Leukemia Virus in Mice

Abstract. *A mutant strain of the Friend leukemia virus is described. The parental virus strain, passaged through ICR/Ha mice, shows no or very little activity by the spleen-focus assay in BALB/c mice (by comparison with highly susceptible DBA/2 and ICR/Ha mice) and produces typical Friend disease in these mice only exceptionally; susceptibility to this strain of virus is recessive in the (C57BL/6 × DBA/2) F_1. By contrast, the mutant virus strain is as active in BALB/c mice as in DBA/2 or ICR/Ha mice; susceptibility to the mutant virus strain is dominant in the (C57BL/6 × DBA/2) F_1.*

The problem of the host strain specificity of the Friend leukemia virus in mice has been investigated a number of times since Friend's report (*1*) of a very narrow range of strain susceptibility. BALB/c mice appear to be highly susceptible to the virus in some studies (*2*), while in others they appear quite resistant, the difference being attributed sometimes to the mouse substrain used and sometimes to the virus strain used. Although "BALB-adapted" virus has been reported (*3*), the nature of the adaptation has not yet been elucidated.

We now report the comparison of two strains of Friend virus (FV), one obtained from the other by passage through mouse hosts relatively resistant to the parental virus strain.

Except for commercially obtained, random-bred ICR/Ha Swiss albino mice, all mice were from our own inbred colonies. The mice were usually 6 to 12 weeks old when inoculated with virus. The inbred strains used were: DBA/2, BALB/c, C3Hf/Bi, A, and C57BL/6; in addition, certain F_1 hybrids between them were also used.

Virus preparations were obtained as follows. The greatly enlarged spleens from mice injected with virus 2 to 3 weeks previously were homogenized in nine times their weight of cold phosphate-buffered saline. The homogenates were centrifuged relatively slowly, the supernatant was recentrifuged for 4 minutes at about 7000*g* and this second supernatant, either as such or after filtration through Selas 02 filter candles, was used as the basic virus inoculum.

Our "parental" strain of FV, established in 1965 from Friend's line passed continuously through DBA/2 mice (191 passages), has been passed exclusively through ICR mice; we refer to it as Friend-S (F-S) virus. This F-S virus was injected at passage two into six BALB males, of which two developed splenomegaly after a prolonged period of latency (4 to 6 weeks, as compared with 2 weeks in the ICR passage animals). The spleen of one of these was used to establish a separate line of virus which has been passed exclusively through BALB mice; this virus strain is designated Friend-B (F-B) virus.

Two criteria of virus susceptibility have been used in these studies: (i) the activity, determined by the spleen-focus assay (4), of a virus preparation in an unknown mouse strain by comparison with its activity in the strain of origin, and (ii) the ability of mice of a given strain to sustain virus growth upon serial passage.

Preparations of the parental F-S virus strain routinely show the same high activities when assayed in either ICR or DBA/2 mice, and either mouse strain readily supports the serial passage of F-S virus. On the other hand, no activity is generally observed when adult BALB or C57BL mice are used. However, BALB mice are not totally resistant to the virus, for the typical disease syndrome may be induced in them by the injection into adults of exceptionally large doses of F-S virus or by inoculating them up to 10 days postnatally with more usual virus doses. F-S virus has never produced either overt Friend disease or spleen foci in any mice of the C57BL strain in our laboratories.

From these facts it emerges that three classes of strain susceptibility to F-S virus can be defined. Class I mice (DBA/2, ICR/Ha; also C3Hf/Bi) are highly susceptible as adults to the virus. Class II mice (BALB/c; also A) are relatively resistant to the virus as adults, but as babies they are susceptible. Class III mice (C57BL/6) are highly resistant under all circumstances investigated.

Preparations of the variant F-B virus show approximately the same activity whether ICR, DBA/2, or BALB mice are used for their assay. No activity is seen in C57BL mice. The disease syndrome produced in susceptible animals by F-B virus appears grossly similar to that of F-S virus, although periods of latency may be slightly shorter with the former and, in general, extracts containing F-B virus demonstrate somewhat higher virus titers than do similarly prepared extracts containing F-S virus. Baby mice of susceptible strains, inoculated with preparations of F-B virus, show a much higher rate of infant mortality than when F-S virus is inoculated.

Despite the fact that a given F-B virus preparation shows identical

spleen-focus titers in BALB and in ICR mice, the ICR animals do not easily support the serial passage of this virus strain. In four attempts to establish lines of F-B virus maintained in ICR hosts, two lines were lost after two and four passages, respectively, in ICR mice, and the other two continued to show slow, irregular growth for several passages in ICR mice. Each of these two lines that grew slowly and irregularly retains its high infectivity for BALB mice, however, indicating that their properties have not reverted to those of F-S virus.

Similarly, attempts to repeat the isolation from the F-S virus line of variants similar to F-B virus have met with irregular success. In two of eight attempts, virus from BALB mice showing typical FV splenomegaly after infection with F-S virus (either as babies or, using high-titer preparations, as adults) failed to survive a single passage in BALB mice. Of the six lines established in the successful attempts, five produced splenomegaly slowly or in a small percentage of recipients in the first BALB-to-BALB passage, but subsequent passage through BALB mice was considerably easier. After five to six such BALB passages, preparations of these virus substrains were assayed in both ICR and BALB hosts, and in all six cases similar titers were obtained in the two mouse strains, indicating that the original F-S virus strain had in each case been altered to a new line with properties similar to those of F-B virus.

An indication of immunological relationship between the two virus strains was provided by an experiment showing that prior treatment of BALB mice with F-S virus conferred protection against subsequent inoculation with F-B virus. Three groups of 25 BALB mice each received intraperitoneal inoculations of a highly active F-S virus preparation diluted 1 : 1, 1 : 10, or 1 : 100.

Twelve of the 25 mice receiving the highest virus dose developed splenomegaly and were retired from the experiment. The remaining 13 mice of this group and all 25 mice of the other groups received on day 13 an intravenous injection of a dilution of a F-B virus preparation that had high activity in normal BALB mice, and all but 6 out of 63 mice were completely protected against the focus-forming activity of the F-B virus preparation.

In a small experiment of similar design, ten ICR mice were completely protected against F-S virus by prior treatment with a 1 : 1000 dilution of a F-B virus preparation.

Table 1. Susceptibility of three classes of mouse strains and of their F_1 hybrids to two strains of Friend leukemia virus, F-S and F-B virus. + Indicates highly susceptible both by the criterion of the spleen-focus assay and by that of ability to sustain the serial passage of the virus; ± indicates resistant as adults to all but very large virus doses, but routinely susceptible as babies; − indicates resistant under all conditions investigated.

Class of mice	Susceptibility to	
	F-S virus	F-B virus
I (DBA/2, ICR/Ha, C3Hf/Bi)	+	+
II (BALB/c, A)	±	+
III (C57BL/6)	−	−
(I × II) F_1	±	+
(I × III) F_1	±	+
(II × III) F_1	−	+

Susceptibility to these two variants of FV was studied in crosses of susceptible and resistant mouse strains. In general, susceptibility to F-B virus is inherited as a dominant character, while susceptibility to F-S virus is inherited as a recessive character. In particular, the results with the F_1 hybrids of the strains C57BL and DBA/2 have provided a sharp distinction between the two virus strains. Preparations of either F-S or F-B virus show maximum activity when assayed in DBA/2 mice. Neither virus strain shows any activity in C57BL mice. Preparations of F-B virus show nearly identical activities in (C57BL × DBA/2) F_1 hybrids and in parental strain DBA/2 mice. By contrast, F-S virus preparations with high activity in the DBA/2 strain show little or no activity in these same F_1 hybrids. Thus, susceptibility to F-B virus is dominant and that to F-S virus is recessive in the same cross.

The susceptibility studies with the two virus strains (Table 1) indicate that the response of F_1 hybrids of a cross of classes I and III is similar to that of class II mouse strains. This is notable, particularly in view of the fact that the inbred class II mice are presumably homozygous at all autosomal loci, while the (I × III) F_1 hybrids are necessarily heterozygous at any autosomal determinants of FV susceptibility at which the parental strains differ.

These findings emphasize the question of whether a single locus with three or more alleles controls susceptibility to both variants of FV in all mouse strains, or if two or more independent genes function to determine the response to FV. Four studies (*3*, *5*), each with different combinations of susceptible and resistant mouse strains and different techniques to determine susceptibility or resistance in individual mice, offer data compatible with a single-gene hypothesis. In view of our findings, this hypothesis may now be summarized as follows. The three classes of mouse strains, I, II, and III, have the alleles S_I, S_{II}, and S_{III}, respectively, and, being homozygous, their resultant phenotypes are: S_IS_I, susceptible to F-B and to F-S virus; $S_{II}S_{II}$, susceptible to F-B virus, resistant to F-S virus; and $S_{III}S_{III}$, resistant to F-B and to F-S virus. Furthermore, the hybrid S_IS_{III} genotype determines the same phenotype as that of the homozygous $S_{II}S_{II}$ genotype, and the S_{II} allele is dominant over both the S_I and the S_{III} alleles.

However, a two-gene hypothesis could also be invoked to explain the findings. Thus, if one gene, with alleles *A* for resistance and *a* for susceptibility, determines the response to F-S virus, and if another gene, with alleles *B* for susceptibility and *b* for resistance, determines the response to F-B virus, then the genotypes of the various classes of mouse strains and of their F_1 hybrids would be: I, *aa*, *BB*; II, *AA*, *BB*; III, *AA*, *bb*; (I × II) F_1, *Aa*, *BB*; (I × III) F_1, *Aa*, *Bb*; and (II × III) F_1, *AA*, *Bb*.

Our data are consistent with both of these hypotheses, and further studies with the two virus strains in segregating generations of appropriate crosses will be necessary to distinguish between them and to facilitate the study of the mechanisms of genetic resistance to FV.

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