THE INHERITANCE OF SUSCEPTIBILITY TO THE GROSS LEUKEMIA VIRUS IN MICE

FRANK LILLY[1]

Division of Experimental Chemotherapy, Sloan-Kettering Institute for Cancer Research, Sloan-Kettering Division, Cornell Graduate School of Medical Sciences; and Department of Genetics, Albert Einstein College of Medicine, New York

Received October 27, 1965

ACUTE lymphatic leukemia, originating in the thymus and frequently involving the spleen, lymph nodes and liver, occurs spontaneously in a large percentage of mice of two inbred strains of independent origin: the AK (and its substrain, AKR) and the C58. GROSS (1951, 1961) has isolated a virus from strain AK leukemic tissues which, when inoculated into mice of the inbred C3Hf/Bi or C57BR strains during the first postnatal days, will induce a high incidence of a similar disease in these normally low-leukemic strains.

All four of these inbred mouse strains (AK, C58, C3H and C57BR) possess the complex *H-2*^{k} allele in their genetic makeup. The *H-2* (Histocompatibility-2) locus controls the major system of antigens responsible for homograft rejection in mice (GORER and MIKULSKA 1959; SNELL 1959; AMOS 1959) and also functions as a blood group determinant. These antigens are found predominantly in tissues with a high content of reticuloendothelial cells (BASCH and STETSON 1962), and during embryonic development their appearance is correlated with the genesis of the lymphatic system (MÖLLER 1963; SCHLESINGER 1964). Because of the presence of the *H-2*^{k} allele in all of these susceptible strains, it seemed possible that susceptibility to leukemia induction by the Gross virus might be governed by a gene closely linked to or even identical with the *H-2* locus or some part of it.

The results of a pilot experiment showed a close association, in segregating generations of crosses involving a susceptible strain carrying the *H-2*^{k} allele and a resistant strain carrying the *H-2*^{b} allele, between the homozygous *H-2*^{k}/*H-2*^{k} phenotype and susceptibility to the virus, and this prompted us to explore the phenomenon in greater detail.

A preliminary report, concerning the association between H-2 type and virus susceptibility in these larger experiments, has already appeared (LILLY, BOYSE and OLD 1964). Further analysis of these results shows that the C3Hf/Bi genome includes at least two unlinked, recessive genes, either one alone capable of conferring susceptibility to the Gross virus. One of these genes either is an allele at the *H-2* locus or is closely linked to it, while another segregates independently.

[1] Present address: Department of Genetics, Albert Einstein College of Medicine, Bronx, New York 10461.

MATERIALS AND METHODS

Mice: All mice used in these experiments were derived from the colonies of DOCTORS E. A. BOYSE and L. J. OLD. These strains are maintained from a single line of descent by strict brother-sister matings; frequent checks for possible heterogeneity with respect to histocompatibility are made by random skin-grafting within the various strains. The strains used were: C3Hf/Bi (H-2^k), C57BL/6 (H-2^b), 129 (H-2^b), I (H-2^l), and AKR (H-2^k).

H-2 Typing: The method used for detecting H-2 antigens was essentially the hemagglutination technique of GORER and MIKULSKA (1954). Individuals of F_2 hybrid generations were typed for the presence or absence of both parental H-2 types; those of backcross generations, which must possess the antigens of the backcross parental strain, were typed only for the presence or absence of antigens of the other parental strain involved in the cross.

Isoantisera for H-2 typing were prepared by inoculating normal or tumor cells from one parental strain into normal recipients of the other parental strain involved in a given cross to be studied. After three to five inoculations at intervals of about two weeks, the antiserum was obtained by tail-bleeding the recipients 12 to 14 days after the last inoculation.

Virus: Four leukemic C3Hf/Bi mice, having received Gross Passage A virus (GROSS 1957) neonatally, were obtained in 1962 from DOCTOR LUDWIK GROSS. The leukemic organs (thymus, spleen, lymph nodes and liver) of these animals were disrupted in a glass homogenizer and suspended in cold saline to a final concentration of 20%. After two centrifugations to remove most of the remaining cells and cell fragments, the supernatant was passed through 02 Selas filter candles whose integrity had been checked by their retention of *E. coli*. This filtrate was stored at —60°C in small vials and was injected into newborn mice of a number of strains.

Another large pool of 10% filtrate was similarly prepared from the leukemic C3Hf/Bi animals of this first passage, and this pool was the source of all Gross virus used in these experiments. The standard inoculum in all cases was 0.05 ml of filtrate, injected intraperitoneally into 3 to 5 day-old mice.

Leukemia incidence: The animals were examined frequently for signs of enlarged spleen, thymus or lymph nodes, and the final diagnosis of leukemia was made at autopsy of the animals, sacrificed in an advanced stage of the disease or occasionally after death from the disease. In a small number of cases it was considered necessary to confirm the diagnosis of leukemia by histological examination of the organs or by checking the ability of the suspect tissues to grow progressively in normal, histocompatible recipients. Fewer than 5% of the animals inoculated with Gross virus died after weaning from causes other than leukemia within the observation period (>250 days). Latent periods were calculated in days from the date of virus inoculation until the earliest detection of leukemia.

ANALYSIS OF RESULTS

Parental strains and F_1 hybrids: Fifty mice of the C3H strain (*H-2^k/H-2^k*), whose incidence of spontaneous leukemia is very low, were uniformly susceptible to leukemogenesis by the Gross Passage A virus. The latent period for leukemia induction was sharply defined: 68.7 ± 1.4 (SE) days, and was significantly shorter in females than in males (64.4 ± 1.7 *vs.* 73.0 ± 1.8 days). Statistical differences in mean leukemia latent periods of mice inoculated at ages 3, 4 or 5 days were not significant, but they indicated a trend toward longer latent periods with increasing age at injection.

By comparison, C57BL (*H-2^b/H-2^b*) mice, which also have a negligible incidence of spontaneous leukemia, were highly resistant to Gross virus leukemogenesis. Only one of 123 mice of this strain developed the disease before the last of the C3H mice had done so. When the observation period was extended to ten

months after virus inoculation, the leukemia incidence rose to 26% (mean latent period: 191 days).

When cells of some of these C57BL leukemias were tested for their ability to absorb antibodies directed against Gross virus-induced antigens (SLETTENMARK and KLEIN 1962; OLD, BOYSE and STOCKERT 1965), they were indeed found to possess these antigens.

Thus the incidences of leukemia in the C3H and C57BL strains illustrated in Figure 1 were radically different as functions of time. If attention is restricted to the early period, up to 100 to 150 days following virus inoculation, two unambiguous classes of response are defined: susceptibility and resistance to short-term Gross virus leukemogenesis.

The leukemia incidence in the F_1 generation ($H\text{-}2^k/H2^b$) in Figure 1 represents the combined results with both reciprocal hybrids; the incidences in the two groups after ten months attained 5/47 (10.6%; mean latent period, 225 days) for the (C3H♀ × C57BL♂) F_1 and 6/79 (7.6%; mean latent period, 285 days) for the reciprocal cross. Thus resistance to the Gross virus is completely dominant in this cross at the virus dose employed. The basis for the relatively lower inci-

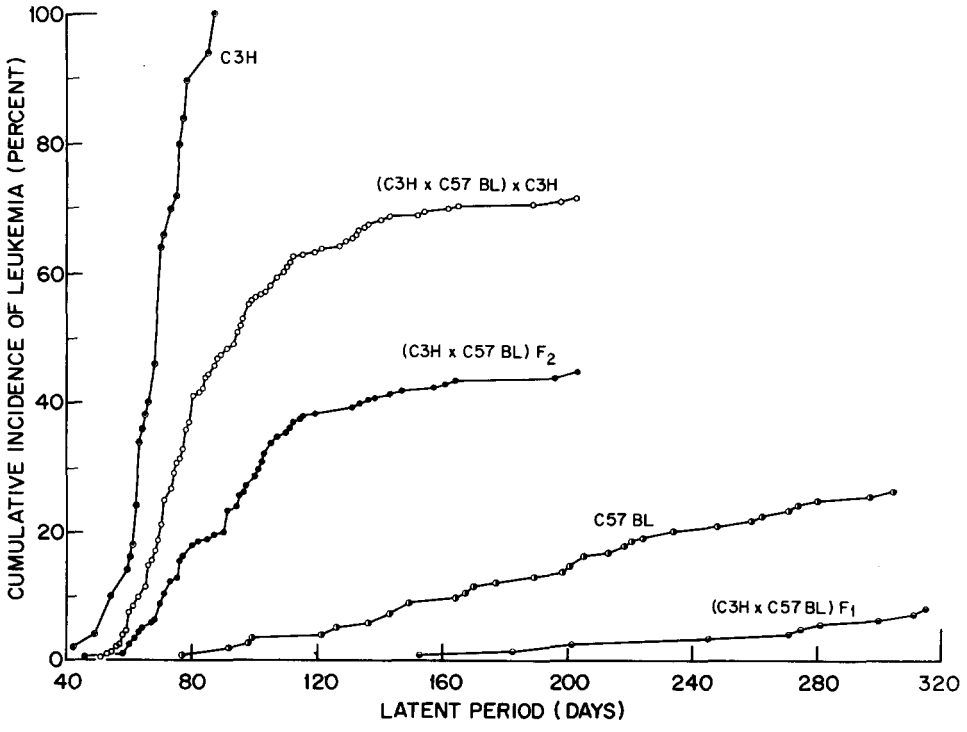

FIGURE 1.—Cumulative incidences of leukemia in C3Hf/Bi and C57BL/6 mice and in their F_1, F_2 and backcross hybrids, inoculated with Passage A Gross virus. The data for males and for females are combined.

dence in the F_1 mice by comparison with the C57BL mice has not been investigated.

Strain 129 mice ($H\text{-}2^b/H\text{-}2^b$) were also highly resistant to Gross virus leukemogenesis. No leukemias occurred during 12 months after virus challenge in the 17 mice of this strain, and only two of ten (C3H × 129) F_1 hybrids became leukemic, after latent periods of 145 and 244 days, respectively.

Backcross and F_2 generations: 1. *Leukemia incidence in whole populations.* When backcross generations, obtained by crossing the resistant (C3H × C57BL) F_1 hybrids to the susceptible C3H strain, were challenged with Gross virus, the incidence of leukemia after ten months attained 161/224 (72%) in the population as a whole. When the F_2 hybrids of this strain combination were similarly challenged, the final incidence was 92/205 (45%). These incidences are compared with those in the parental and F_1 populations in Figure 1.

Assuming that the phenotype of each mouse with respect to leukemia susceptibility was not affected by environmental conditions, then these figures can be used in an attempt to determine the probable number of genes influencing susceptibility in this cross. If Gross virus susceptibility were determined by a single gene with the alleles *Rgv* for resistance and *rgv* for susceptibility, then the proportion of susceptible (*rgv rgv*) animals in the backcross (*Rgv rgv* × *rgv rgv*) should be ½ and that in the F_2 generation, ¼. The observed proportions of susceptible animals were, in fact, significantly greater than this.

If, on the other hand, *two* independent pairs of alleles (*Rgv-1*, *rgv-1* and *Rgv-2*, *rgv-2*) determine susceptibility, then two alternatives exist: (a) the presence of a dominant allele for resistance at *either* locus (*Rgv-1* or *Rgv-2*) suffices to render the animal resistant; in this case, the proportion of susceptible animals (those homozygous for the recessive alleles at both loci) in the population will be *smaller* than in the case of single-gene determination; or (b) the simultaneous presence of the dominant allele for resistance at *both* loci (*Rgv-1* and *Rgv-2*) is necessary to determine virus resistance; in this case, the proportion of susceptible animals (those homozygous for the recessive alleles at either or both loci) in the population will be *larger* than in the case of single-gene determination.

Since the actual proportions observed were larger than in the case of single-gene determination, it appears that Gross virus susceptibility in crosses of C3H and C57BL is determined by two or more genes, and that the phenotype *virus resistance* results from the simultaneous presence of a dominant allele for resistance at these loci.

If multiple genes control virus resistance, then the proportion of resistant animals in the backcross generation should be $(\frac{1}{2})^n$ and that in the F_2 generation $(\frac{3}{4})^n$, where n is the number of genes involved. The observed proportions of resistant animals in the two populations (i.e., 28% in the backcross and 55% in the F_2) agree closely with the expected values for $n = 2$ ($P > .21$ in the backcross, $P > .75$ in the F_2) and are statistically incompatible with the hypotheses $n = 1$ or $n = 3$ ($P < .0004$ in each case). This implies that the C3H substrain possesses two unlinked, recessive genes, either one alone capable of determining Gross virus susceptibility.

Similar results were obtained in crosses involving strain C3H and the Gross virus-resistant strains 129 and I. Here the final incidences of leukemia were 19/30 (63%) in the (C3H × 129) × C3H and 42/56 (75%) in the (C3H × I) × C3H backcrosses; this also corresponds to a proportion approximating $(\frac{1}{2})^n$ ($n = 2$) of resistant animals in these populations.

2. *Leukemia incidence in relation to H-2 type.* The final incidences of leukemia in these backcross and F_2 generations of C3H × C57BL crosses, subdivided according to H-2 type, are represented in Figure 2. The incidence among $H\text{-}2^k/H\text{-}2^k$ homozygotes was > 90% in both backcross and F_2 mice, whereas the animals homozygous or heterozygous for the $H\text{-}2^b$ allele showed a much lower incidence: 56% in the backcrosses and 26% in the F_2 generation developed leukemia.

This very high susceptibility of the $H\text{-}2^k/H\text{-}2^k$ segregants clearly indicates the presence in the C3H genome of a recessive gene for Gross virus susceptibility in close proximity to the map location of *H-2* in linkage group IX. The fact that approximately 10% of $H\text{-}2^k/H\text{-}2^k$ segregants did *not* develop leukemia within the ten month observation period may indicate either that (1) the Gross virus susceptibility gene is located roughly 10 map units away from *H-2*, allowing recombination to occur to the extent of 10%, or (2) some portion of the *H-2* locus itself determines this susceptibility, but with a penetrance of only 90%.

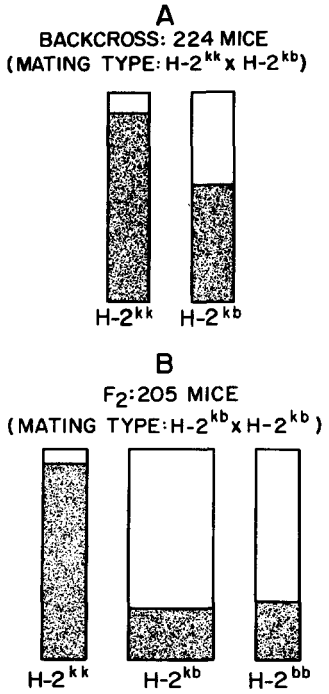

FIGURE 2.—Final incidences of Gross virus-induced leukemia in backcross (A) and in F_2 (B) generations, segregating for *H-2* alleles, from crosses of C3Hf/Bi ($H\text{-}2^k$) and C57BL/6 ($H\text{-}2^b$). The shaded area of each bar represents the fraction of mice which developed leukemia.

The observed level of susceptibility in the $H\text{-}2^k/H\text{-}2^b$ and $H\text{-}2^b/H\text{-}2^b$ segregants, on the other hand, corresponds closely to that expected in each case on the basis of assuming one further independently segregating gene with this same function.

Gene symbols have been provisionally assigned to these two genes: *Rgv-1* and *rgv-1* as the alleles for virus resistance and susceptibility, respectively, at the locus linked to *H-2*, and *Rgv-2* and *rgv-2*, respectively, for those at the locus independent of *H-2*.

The mean latent periods for the induction of leukemia were essentially identical in the $H\text{-}2^k/H\text{-}2^k$ segregants of both the backcross and the F_2 animals. By comparison, the mean latent period in the parental C3H strain was about 20 days shorter. This may be an indication that, although all (or almost all) of the $H\text{-}2^k/H\text{-}2^k$ segregants of both populations are homozygous for *rgv-1*, only a portion of them (50% in the backcross, 25% in the F_2 generation) are also homozygous for the susceptible allele *rgv-2*. The animals not homozygous for *rgv-2* might then be expected to show a slightly prolonged latent period for leukemia induction.

The two-gene hypothesis is further strengthened by the observation that the incidence among $H\text{-}2^k/H\text{-}2^b$ segregants in the backcross population was biphasic. In the earlier phase (up to 90 days), those $H\text{-}2^k/H\text{-}2^b$ animals developing leukemia (presumably by virtue of homozygosity for *rgv-2*) did so only slightly later than their $H\text{-}2^k/H\text{-}2^k$ littermates, half of which must be homozygous for both susceptibility factors. In the second phase (after 100 days), the incidence was similar to that in the parental C57BL strain, which is homozygous for both alleles for resistance.

Table 1 summarizes the relationship between H-2 type and Gross virus leukemia incidence in these crosses. In addition, similar results are shown, using the same experimental design, with strains 129 ($H\text{-}2^b/H\text{-}2^b$) and I ($H\text{-}2^l/H\text{-}2^l$) as the resistant parental strains in crosses with C3H. Of 30 mice of the cross (C3H × 129) × C3H, all of 14 $H\text{-}2^k/H\text{-}2^k$ segregants became leukemic, and 5/16

TABLE 1

H-2 type and Gross virus leukemia incidence

	C3Hf/Bi × C57BL/6				C3Hf/Bi × 129		C3Hf/Bi × I	
	C3H backcross		F_2		C3H backcross		C3H backcross	
H-2 type	Inc.*	L.P.†	Inc.	L.P.	Inc.	L.P.	Inc.	L.P.
kk	95/105 (90%)	86	54/58 (93%)	94	14/14 (100%)	95	26/29 (90%)	92
kb (or kl)	67/119 (56%)	90	28/110 (25%)	105	5/16 (31%)	69	16/27 (59%)	80
bb	.....	..	10/37 (27%)	81	.....	..	.....	..
Total	162/224 (73%)	87	92/205 (45%)	96	19/30 (63%)	88	42/56 (75%)	88

* Leukemia incidence: *number leukemic/number observed.*
† Mean latent period (days).

(31%) of the *H-2*^{k}/ *H-2*^{b} animals did so. Similarly, in the (C3H × I) × C3H cross, 90% of *H-2*^{k}/*H-2*^{k} segregants developed leukemia, as compared with 59% in the *H-2*^{k}/*H-2*^{l} group.

Spontaneous leukemogenesis in the AKR strain, from which the Gross Passage A virus was originally isolated, was also investigated to determine the influence of H-2 type on susceptibility to this neoplasm. Since the (AKR × C57BL)F_1 hybrid, *H-2*^{k}/*H-2*^{b}, has only a very low incidence of spontaneous leukemia, the susceptible backcross, AKR × (AKR × C57BL), was observed for leukemia incidence, and the results are illustrated in Figure 3. Here the *H-2*^{k}/*H-2*^{b} segregants showed a slowly but steadily rising incidence curve, approximating linearity; this was also true of their *H-2*^{k}/*H-2*^{k} littermates, but only after a marked initial incidence of leukemias, not paralleled in the *H-2*^{k}/*H-2*^{b} group, occurring at about the same time (days 250 to 320) as the peak incidence in the parent AKR strain.

Statistical analysis of these results reveals that the difference in the *final* leukemia incidences of the two segregant groups (41.1% for the *H-2*^{k}/*H-2*^{k} group and 29.9% for the *H-2*^{k}/*H-2*^{b}) was not significant ($.20 > P > .10$). However, at 320 days, at the end of the peak incidence period in the *H-2*^{k}/*H-2*^{k} group, the incidences of 29% (*H-2*^{k}/*H-2*^{k}) and 8% (*H-2*^{k}/*H-2*^{b}) were significantly different ($P < .001$). It thus appears that *H-2*^{k} is either identical with or linked to a determinant of susceptibility to spontaneous leukemogenesis in AKR mice.

The relatively high incidence of spontaneous leukemia in the *H-2*^{k}/*H-2*^{b} segregants may be due to an additional independent gene for susceptibility, as appears to be the case in the Gross virus-inoculated crosses. Alternatively, it could repre-

H-2 phenotype	Mice observed	Leukemic deaths: Number	Leukemic deaths: % of total	Leukemic deaths: Latent period (days)	Non-leukemic deaths: Number	Non-leukemic deaths: Age at death (days)
kk	85	35	41.2	337 ± 97	50	485 ± 102
kb	77	23	29.9	397 ± 94	54	490 ± 98
kk+kb	162	58	35.8	360 ± 100	104	488 ± 100

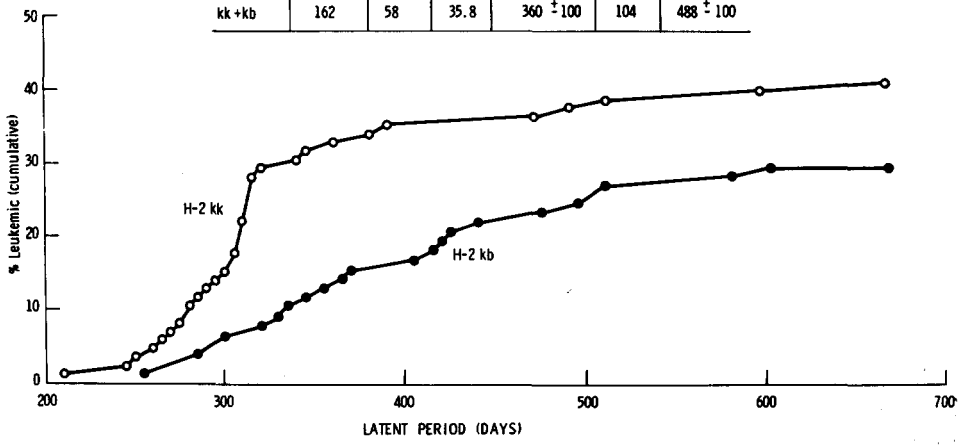

FIGURE 3.—Cumulative incidences of spontaneous leukemia in the AKR × (AKR × C57BL/6) backcross generation, according to H-2 type.

sent a low level of leukemogenesis similar to that seen in the C57BL mice inoculated with Gross virus.

(3). *Influence of other factors upon leukemogenesis.* The segregating generations of C3H × C57BL crosses were prepared by matings representing all reciprocal crosses pertinent to the study of possible sex-linked or maternal influences upon Gross virus leukemogenesis.

If a recessive gene for virus susceptibility were located on the X and/or Y chromosomes of the C3H strain, there should result a sex difference in the leukemia incidences of these populations. Examination of the incidences in these various reciprocal crosses reveals no such differences, and one may conclude that there is no sex-linked gene exerting an influence upon Gross virus susceptibility.

If the genotype of the mother were an important factor in the leukemia susceptibility of the offspring (see LAW 1954), then the leukemia incidence in the backcross generation should be higher when the mother is of the pure C3H strain than when she is of the hybrid genotype. This also was not found to be the case.

Among the other segregating genes studied with respect to their effects upon leukemogenesis in these crosses, none exerted a significant influence. The genes so examined were: agouti and *H-6* in the C3H × (C57BL or 129) crosses, piebald in crosses of C3H × I and albino in the AKR backcross.

DISCUSSION

Susceptibility to leukemogenesis by the Gross virus seems to be determined by two independent genes in the crosses examined, and one of these genes is associated with *H-2* in linkage group IX.

Significant findings have been noted recently concerning genetic factors in the susceptibility of mice to other virus-induced diseases. The viruses studied include: yellow fever and several strains of encephalitis viruses (SABIN 1952a, b), ectromelia (SCHELL 1960), mouse hepatitis (BANG and WARWICK 1960), West Nile (GOODMAN and KOPROWSKI 1962), Friend (ODAKA and YAMAMOTO 1962), polyoma (CHANG and HILDEMANN 1964) and influenza A (LINDEMANN 1964). In each case, the evidence indicates that strain differences in susceptibility are due to one gene or, at most, a small number of genes. Only one of these genes has been located on the linkage map; this is one of those responsible for the runting effects of the polyoma virus in the AKR strain and is linked to albino in linkage group I.

Several questions remain to be answered concerning the genetic determination of susceptibility to the Gross virus, such as the location of the *H-2*-linked susceptibility factor *rgv-1* within or adjacent to the *H-2* locus. Furthermore, the mechanisms of the genetic control of susceptibility remain to be studied.

In this connection, two other known genes of the ninth linkage group, both closely associated with *H-2*, merit attention. One of these is the genetic determinant of the TL (Thymus Leukemia) antigen (BOYSE, OLD and STOCKERT 1963). TL is a surface antigen found in the thymic tissue alone of certain mouse

strains, including most of the strains having a high incidence of spontaneous leukemia (but not AKR); in addition, the antigen often characterizes leukemias arising in strains not possessing it normally in their thymuses. However, since there is no demonstrated difference in the TL alleles of the various strains studied in this work, all of which have TL-negative thymuses, the possible relationship of the *Rgv-1* locus with the gene governing TL cannot yet be elucidated.

The second gene of interest in this connection is *Ss* (SHREFFLER and OWEN 1963). The two alleles of this locus, Ss^h and Ss^l, determine the concentration of a specific serum globulin in mice, which is detected by the Ouchterlony immunodiffusion technique. The variant is apparently controlled by some portion of the *H-2* locus itself (SHREFFLER 1964), and among the inbred mouse strains examined, only those possessing the $H\text{-}2^k$ allele also possessed the Ss^l allele (low serum concentration). Since the $H\text{-}2^k$ allele was shown in the present studies to be closely associated with *rgv-1*, it is therefore apparent that the possible identity of the *Ss* and *Rgv-1* loci should be studied.

Speculations concerning the mechanisms by which genes may control susceptibility to the Gross leukemia virus could involve most of the specific events known or supposed to occur between the initial contact of mouse with virus and the ultimate appearance of leukemia. As a first example, the products of Gross virus susceptibility genes may be present on the cell surface (as the H-2 substances are known to be), where they function as receptor sites for Gross virus; according to this hypothesis, the $H\text{-}2^k$ substance might combine specifically with the virus and effect its penetration into the cell, while the $H\text{-}2^b$ substance (as well as hypothetical molecular hybrids between it and the $H\text{-}2^k$ substance in $H\text{-}2^k/H\text{-}2^b$ heterozygotes) would be incapable of functioning in this manner, resulting in noninfection at the cellular level. However, susceptibility has usually proved dominant in cases where cellular receptors for virus are involved (RUBIN 1965).

Another possible mechanism is that of virus susceptibility genes determining a host antigen or antigens similar to the principal virus antigen(s), so that hosts possessing them fail to recognize the virus as foreign material and to produce antibodies against it.

Further examples of hypothetical virus resistance mechanisms include the following: the genes for virus resistance may be concerned with the earlier development of immunological competence with respect to viral antigens; virus resistance genes may control the synthesis of anti-viral antibodies; and virus resistance genes may involve the production of interferon molecules.

It is to be hoped that the finding of genes governing Gross virus susceptibility, one closely associated with a major histocompatibility factor, may provide a tool for the investigation of cellular mechanisms in viral leukemogenesis.

The author wishes to acknowledge his gratitude to DOCTORS L. J. OLD and E. A. BOYSE, in whose laboratories most of this work was done. These studies were supported by grants from the American Cancer Society and by contract PH 43-65-612 from the National Cancer Institute, U. S. Public Health Service.

SUMMARY

Susceptibility to the Gross leukemia virus in mice has been studied in crosses of virus-resistant and virus-susceptible inbred strains. Two independent loci appear to determine virus susceptibility; one of these (*Rgv-1*) is closely linked to *H-2* in the ninth linkage group, while the other (*Rgv-2*) segregates independently.

LITERATURE CITED

AMOS, D. B., 1959 Some iso-antigenic systems of the mouse. Can. Cancer Conf. **3**: 241–258.

BANG, F. B., and A. WARWICK, 1960 Mouse macrophages as host cells for the mouse hepatitis virus and the genetic basis of their susceptibility. Proc. Natl. Acad. Sci. U. S. **46**: 1065–1075.

BASCH, R. B., and C. A. STETSON, 1962 The relationship between hemagglutinogens and histocompatibility antigens in the mouse. Ann. N. Y. Acad. Sci. **97**: 83–94.

BOYSE, E. A., L. J. OLD, and S. LUELL, 1963 Antigenic properties of experimental leukemias. II. Immunological studies *in vivo* with C57BL/6 radiation-induced leukemias. J. Natl. Cancer Inst. **31**: 987–995.

CHANG, S. S., and W. H. HILDEMANN, 1964 Inheritance of susceptibility to polyoma virus in mice. J. Natl. Cancer Inst. **33**: 303–313.

GOODMAN, G. T., and H. KOPROWSKI, 1962 Macrophages as a cellular expression of inherited natural resistance. Proc. Natl. Acad. Sci. U. S. **48**: 160–165.

GORER, P. A., and Z. B. MIKULSKA, 1954 The antibody response to tumor inoculation. Improved methods of antibody detection. Cancer Res. **14**: 651–655. —— 1959 Some further data on the H-2 system of antigens. Proc. Roy. Soc. London B **151**: 57–69.

GROSS, L., 1951 "Spontaneous" leukemia developing in C3H mice following inoculation, in infancy, with AK-leukemic extracts, or AK-embryos. Proc. Soc. Exp. Biol. Med. **76**: 27–32. —— 1957 Development and serial cell-free passage of a highly potent strain of mouse leukemia virus. Proc. Soc. Exp. Biol. Med. **94**: 767–771. —— 1961 *Oncogenic Viruses*. New York, Pergamon Press.

LAW, L. W., 1954 Maternal influence in experimental leukemia of mice. Ann. N. Y. Acad. Sci. **57**: 575–583.

LINDEMANN, J., 1964 Inheritance of resistance to influenza virus in mice. Proc. Soc. Exp. Biol. Med. **116**: 506–509.

LILLY, F., E. A. BOYSE, and L. J. OLD, 1964 Genetic basis of susceptibility to viral leukaemogenesis. Lancet **ii**: 1207–1209.

MÖLLER, G., 1963 Phenotypic expression of isoantigens of the H-2 system in embryonic and newborn mice. J. Immunol. **90**: 271–279.

ODAKA, T., and T. YAMAMOTO, 1962 Inheritance of susceptibility to Friend mouse leukemia virus. Japan. J. Exp. Med. **32**: 405–413.

OLD, L. J., E. A. BOYSE, and E. STOCKERT, 1963 Antigenic properties of experimental leukemias. I. Serological studies *in vitro* with spontaneous and radiation-induced leukemias. J. Natl. Cancer Inst. **31**: 977–986. —— 1965 The G (Gross) leukemia antigen. Cancer Res. **25**: 813–819.

RUBIN, H., 1965 Genetic control of cellular susceptibility to pseudotypes of Rous sarcoma virus. Virology **26**: 270–276.

SABIN, A. B., 1952a Genetic, hormonal and age factors in natural resistance to certain viruses. Ann. N. Y. Acad. Sci. **54**: 936–944. —— 1952b Nature of inherited resistance to viruses affecting the nervous system. Proc. Natl. Acad. Sci. U. S. **38**: 540–546.

SCHELL, K., 1960 Studies on the innate resistance of mice to infection with mousepox. II. Route of inoculation and resistance; and some observations on the inheritance of resistance. Australian J. Exptl. Biol. Med. Sci. **38**: 289–299.

SCHLESINGER, M., 1964 Serologic studies of embryonic and trophoblastic tissues of the mouse. J. Immunol. **93**: 255–263.

SHREFFLER, D. C., 1964 A serologically detected variant in mouse serum: Further evidence for genetic control by the Histocompatibility-2 locus. Genetics **49**: 973–978.

SHREFFLER, D. C., and R. D. OWEN, 1963 A serologically detected variant in mouse serum: Inheritance and association with the Histocompatibility-2 locus. Genetics **48**: 9–25.

SLETTENMARK, B., and E. KLEIN, 1962 Cytotoxic and neutralization tests with serum and lymph node cells of isologous mice with induced resistance against Gross lymphomas. Cancer Res. **22**: 947–954.

SNELL, G. D., 1959 Transplantable tumors. pp. 293–345 *The Physiopathology of Cancer*. Edited by F. HOMBURGER. Hoeber, New York.