SUSCEPTIBILITY TO SPONTANEOUS PNEUMONITIS IN AN INBRED STRAIN OF BEIGE AND SATIN MICE¹

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ABSTRACT

Among mice of strain SB/Le, homozygous for the mutant genes beige (*bg*), satin (*sa*), and white-bellied agouti (*A^w*), 70% developed progressive pneumonitis by 6 months of age. Among backcross offspring from an outcross to C57BL/6J-*A^w-J*, 49% of homozygous beige and 11% of nonbeige genotypes developed pneumonitis by 6 months of age. The evidence indicates that a specific action of the beige gene increases susceptibility to progressive pneumonitis. Lymphadenopathy, including reticulum cell neoplasms and atypical lymphoproliferative lesions, was observed in high incidence in *sa* + *sa bg* males, suggesting a closer association with satin than with beige. Beige mice show giant lysosomal granules in the leukocytes and pigment dilution closely analogous to the Chediak-Higashi syndrome in man and similar disorders in mink and cattle. Strain SB/Le provides a convenient model in a laboratory animal for study of the increased susceptibility to infection analogous to that of the Chediak-Higashi syndrome.

BEIGE (*bg*), a recessive coat color mutation in mice probably radiation induced, was first reported at Oak Ridge by KELLY in 1957. Slate (*bg^{sl}*), recognized as an allele of beige in 1965 (CHASE 1965), was first observed at Brown University in 1955 (CHASE 1959) and described by PIERRO and CHASE (1963). In 1960 a spontaneous mutation to beige (*bg^j*) occurred at The Jackson Laboratory in strain C57BL/6J (LANE 1962). Phenotypically all beige mice have a lighter coat, ears, tail, and eyes than nonbeige mice. Microscopically, PIERRO and CHASE (1963) and PIERRO (1963) found that the pigment granules in the cortex and medulla of the hair and in the choroid and retina of the eye are reduced in number but larger than normal. LUTZNER, LOWRIE and JORDAN (1967) found giant granules in the neutrophils, eosinophils, and lymphocytes of peripheral blood in beige mice. These characteristics are strikingly similar to those of the Chediak-Higashi syndrome in man, the Aleutian trait in mink, and the partially albino Hereford cow. Increased susceptibility to bacterial and some viral infections is characteristic of the syndrome in man, mink, and cattle (PADGETT *et al.* 1968).

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A highly atypical lympho-proliferative disorder is common in man and mink. It is considered malignant by several groups of investigators (WINDHORST *et al.* 1968), and nonmalignant by others (PADGETT *et al.* 1967). LUTZNER *et al.* (1967) noted that several beige mice developed lung and eye infections. BENNETT, BLUME and WOLFF (1969) found no increased incidence of infection or "lymphomalike" infiltrates in young beige mice of strain C57BL/6J-*bg'*.

In 1961 The Jackson Laboratory acquired homozygous beige mice on a heterogeneous background from Dr. L. B. RUSSELL of Oak Ridge National Laboratory. These mice were also homozygous for the mutant genes satin (*sa*) and white belled agouti (A^w) and were of the genotype *sa bg/sa bg A^w/A^w*. Satin, a recessive mutation, also possibly radiation induced, was first reported at Oak Ridge by MAJOR (1954). The texture is altered to produce a silky coat with a high sheen. Medullary air spaces are absent and melanin granules are spread throughout the medullary area of each hair shaft. Satin is linked to beige in Linkage Group XIV with about 9% recombination (ST. AMAND and CUPP 1958).

Descendants of the two imported sibling pairs were bred brother by sister, and in 1971 were given the inbred strain designation SB/Le. From 1963 at generation F_7 it was noted that many mice in the stock developed a progressive pneumonitis by about 6 months of age. By 1967 the stock had been inbred for 20 generations and 70% of the animals observed at 6 months were showing pneumonitis. The affected stock offered an opportunity to determine whether the presence of the beige gene in homozygous condition influenced the occurrence of spontaneous pneumonitis. The results of the genetic test are reported in this paper.

MATERIALS AND METHODS

Inbred strain SB/Le male mice (genotype *sa bg/sa bg A^w/A^w*) at generation F_{20} or more, from the colony known to have progressive pneumonitis, were mated to C57BL/6J- A^w-J/A^w-j females from a colony known to be free of gross evidence of pulmonary disease. The F_1 offspring, both male and female, were backcrossed to SB/Le. This cross produced four genotypes: homozygous satin beige, (*sa bg/sa bg*); heterozygous satin beige ($+/+/sa bg$); homozygous satin, heterozygous beige (*sa +/sa bg*); and heterozygous satin, homozygous beige ($+/bg/sa bg$). The last two classes represent the recombinant classes and were expected to occur only 9% of the time. Mice were raised until at least 30 of each sex of each of the two recombinant classes were obtained. The numbers of the two other classes saved were determined by the available storage space during this time. All mice were housed with their parents until weaned at 21 to 28 days of age. At weaning all littermates of the same sex were placed together in holding pens. In order to conserve space, mice from different parents were often housed together, but more than six mice were never stored in one pen. Animals were held until 6 months of age $\pm$ 1 week and then autopsied. Exceptions were 8% of backcross mice, predominantly males, that died before 6 months of age (Table 1). Three satin males developed lymphadenopathy at 4 and 5 months of age.

At autopsy the mice were weighed, gross changes in organs were noted, and the lungs were examined with a dissecting microscope. Pleural changes, adhesions, and extent of consolidation were recorded for each lobe. Spleens were measured and enlargement of lymph nodes was noted. In each genotype showing abnormal lungs, lobes from at least five affected mice were saved for histologic study. Examples of enlarged lymph nodes, spleens, and other organs were also saved. Abnormal lungs of 45 strain SB/Le mice were cultured by the method of HAYFLICK (1965) for mycoplasmas. Ten lungs were also cultured aerobically and anaerobically on blood agar and in thioglycollate broth. Nasopharyngeal washings from 7 mice were cultured.

In addition to 440 backcross mice, 30 F_1 and 44 strain SB/Le parents were autopsied and the

lungs observed for disease. Similarly, 67 C57BL/6J-*sa bg/sa bg* and 43 C57BL/6J-*+/+/sa bg* breeders from backcross generations 5 to 7, and 400 SB/Le were examined at autopsy.

RESULTS

Pneumonitis: There was high incidence of pneumonitis in all of the homozygous beige (*bg*) genotypes (Table 1). In the nonbeige mice a comparable incidence was observed in backcross males of genotype *sa +/sa bg*. There was no indication of illness until the pneumonitis was well advanced. Weight loss was then noted, particularly in males. Neither chattering nor clinical signs of middle or inner ear infection were observed. At autopsy the spleen was usually enlarged in the presence of advanced pulmonary consolidation.

Grossly, the pulmonary inflammation in all genotypes showed either adhesions alone or consolidation with or without adhesions. The earliest evidence of pleuritis consisted of moist spots at the hilum or peripherally, followed by filmy adhesions, and finally by fibrous plaques and adhesions. The earliest evidence of consolidation consisted of whitish spots peripherally or at the hilum. Peripheral raised "pearls" were frequently noted. Consolidation could involve parts of lobes or several entire lobes.

Histologic samples of lobes with adhesions alone revealed underlying pneumonitis which sometimes appeared to be undergoing resolution. The "pearls" were peripheral nodules of consolidation in which the alveoli were filled with mixtures of degenerating polymorphonuclear leukocytes and macrophages. The larger areas of consolidation usually included dilated bronchioles and bronchi surrounded by lymphoid tissue (Figure 2). The lumens often contained mixtures of polymorphonuclear leukocytes and macrophages. The alveoli in the consolidated areas were filled with macrophages, and scattered areas often contained

TABLE 1

Incidence of pneumonitis in mice reaching 6 months of age: Strain SB/Le, F₁ hybrids with C57BL/6J, and backcross to SB/Le

Genetic background	Genotype	Sex	Number observed from weaning	Number dead before 6 mo.	- Number autopsied	Pneumonitis	
						Number	Percent
SB/Le	<i>sa bg/sa bg</i>	♀	—	—	53	38	72
		♂	—	—	35	23	66
C57BL/6J × SB/Le*	<i>+/+/sa bg</i>	♀	—	—	20	0	—
		♂	—	—	10	0	—
SB/Le × (B6 × SB)F ₁	<i>sa bg/sa bg</i>	♀	52	0	52	17	33
		♂	60	6	54	30	56
	<i>+ bg/sa bg</i>	♀	61	4	57	29	51
		♂	35	2	33	20	61
	<i>sa +/sa bg</i>	♀	32	0	32	2	6
		♂	30	7	23	12	52
	<i>+/+/sa bg</i>	♀	107	1	106	4	4
		♂	101	18	83	9	11

* Age range 5 to 17 months.

FIGURE 1.—Age incidence of pneumonitis in strain SB/Le mice.

masses of degenerating polymorphonuclear leukocytes. Areas of necrosis and organization were common but frank abscesses were not observed.

The progressive increase in incidence of pneumonitis with age in strain SB/Le is shown in Figure 1. There was no significant sex difference. Sixty-one of 88 (69%) of these strain SB/Le mice autopsied at 6 months of age had gross evidence of consolidation or adhesions (Table 1). None of the 30 F_1 breeders autopsied at from 5 to 17 months of age showed any gross evidence of pulmonary disease. Of the 196 homozygous beige backcross mice ($sa\ bg/sa\ bg, +\ bg/sa\ bg$) autopsied, 96 (49%) had pneumonitis. The incidence in males was significantly higher than in females. Of the 244 heterozygous beige backcross mice ($sa\ +/sa\ bg, +\ +/sa\ bg$) autopsied, only 27 (11%) had pneumonitis and 21 of these were males.

There was a significantly higher death rate among male backcross animals before 6 months of age, averaging 15%. The extent to which fighting, pneumonitis, or other causes were involved in the death rate of the different genotypes was not determined.

The incidence of pneumonitis in the recombinant class of heterozygous beige,

TABLE 2

Incidence and extent of pneumonitis in SB × (B6 × SB)F₁ backcross mice at 6 months of age

Phenotype and genotype	Sex	Number of mice	0	Extent of pneumonitis*				Percent pneumonitis
BEIGE								
<i>sa bg/sa bg</i>	♀	52	35	4	5	4	4	33
	♂	54	24	2	9	9	10	56
+ <i>bg/sa bg</i>	♀	57	28	2	4	9	14	51
	♂	33	13	1	10	5	4	61
NON-BEIGE								
<i>sa +/sa bg</i>	♀	32	30	1	1	0	0	6
	♂	23	11	5	2	2	3	52
+ + <i>/sa bg</i>	♀	106	102	2	2	0	0	4
	♂	83	74	1	5	2	1	11

* 0 = No gross pulmonary changes. + = Pleuritis or adhesions without consolidation. ++ = Consolidation of less than ½ lobe or equivalent. +++ = Consolidation of ½ to 1 lobe or equivalent. ++++ = Consolidation of more than 1 lobe or equivalent.

homozygous satin, backcross males (*sa +/sa bg*) was not significantly different from that of the homozygous beige backcross males. However, the average extent of pulmonary involvement was less (Table 2) and microscopically the areas of grossly observed "consolidation" usually showed interstitial pneumonitis and atelectasis rather than the bronchopneumonia characteristic of the homozygous beige genotypes.

Cultures for mycoplasma in the lungs of the 45 strain SB/Le mice with pneumonitis were negative. Additional bacteriological studies on the lungs of 10 mice demonstrated a beta hemolytic *Streptococcus* of the pyogenic group in 3, *Staphylococcus epidermidis* in 2, and *Escherichia coli* in 1. *Pasteurella pneumotropica* was found in the nasopharyngeal washings of 2 of 7 strain SB/Le mice, and *Streptococcus fecalis* in one of these.

Three litters of SB/Le mice were Caesarean derived, fostered on strains free of gross evidence of pneumonitis, and maintained in the same conventional animal room as affected mice. Ten of 11 developed pneumonitis by 8 months of age.

Five of 67 C57BL/6J-*sa bg/sa bg* and none of 43 C57BL/6J-+ + */sa bg* mice autopsied showed gross evidence of pneumonitis.

Lymphadenopathy: Moderate to marked enlargement of multiple lymph nodes and spleen, suggestive of lymphoma, was observed at autopsy in 23 mice (Table 3). Histological sections of enlarged nodes were available in eight cases. All showed extensive to complete replacement of nodal architecture by varying mixtures of histiocytes, lymphocytes, and reticulum cells together with scattered plasma cells and polymorphonuclear leukocytes. In three cases the diagnosis of reticulum cell neoplasm, type B, was made on the basis of complete replacement and enlargement of the nodes by a characteristic mixed cell population containing many immature cells showing high mitotic activity (Figures 3-4). Another case of reticulum cell neoplasm was diagnosed in a section of spleen. The distribution of the four cases of reticulum cell neoplasm among the backcross geno-

TABLE 3

Incidence of lymphadenopathy by 6 months of age

Genetic background	Genotype	Sex	Number of mice	Gross lymphadenopathy		Number examined histologically	Reticulum cell neoplasm	Histological diagnosis	
				Number	Percent			Atypical lymphoproliferative lesions	Hyperplasia
SB/Le	<i>sa bg/sa bg</i>	♀	53	0					
		♂	35	0					
(B6 × SB)F ₁	+ +/ <i>sa bg</i>	♀	20	0					
		♂	10	0(3)*	(30)*	1		(1)*	
SB × (B6 × SB)F ₁	<i>sa bg/sa bg</i>	♀	52	0					
		♂	54	2	4	2		2	
	+ <i>bg/sa bg</i>	♀	57	0					
		♂	33	0					
	<i>sa +/sa bg</i>	♀	32	0					
		♂	23	10	43	5	1(1)†	1†	2†
	+ +/ <i>sa bg</i>	♀	106	2	2	1	1		
		♂	83	6	7	3	1	2	

* F₁ mice with lymphadenopathy were 7, 10, and 17 months old at autopsy.

† Only spleen saved.

types was: 2 male *sa +/sa bg*, 1 male + +/*sa bg*, and 1 female + +/*sa bg*. Lymph nodes of the other five mice showed a similar pattern of extensive to complete replacement of architecture by varying mixtures of histiocytes, more mature lymphocytes, reticulum cells and fibroblasts, together with scattered plasma cells and polymorphonuclear leukocytes (Figure 5). In this group there were fewer immature cells and fewer mitotic figures. They were considered highly atypical, different from the common inflammatory lymphadenopathies, and have been tabulated as atypical lymphoproliferative lesions. Sections of enlarged spleens showed hyperplasia of white and red pulp with increased erythropoiesis and granulocytopoiesis in two cases, and highly atypical reticuloendothelial hyperplasia in another. There was a significantly higher incidence of pulmonary consolidation among the 23 mice with lymphadenopathy than expected, 13 *vs.* 5.

FIGURES 2-5.—Sections stained with hematoxylin and eosin.

FIGURE 2.—Pulmonary consolidation, peribronchial and periarterial lymphoid hyperplasia, and subpleural inflammation in strain SB-*sa bg/sa bg*, 6 months of age. (45 ×).FIGURE 3.—Replacement of lymph node architecture by mixture of reticulum cells, histiocytes, and immature lymphocytes in pattern of reticulum cell neoplasm, Type B. Genotype + +/*sa bg*, male, 6 months of age. (140 ×).

FIGURE 4.—Higher magnification. Note predominance of immature cells and frequency of mitotic figures. (580 ×).

FIGURE 5.—Atypical hyperplasia of lymph node with mixture of histiocytes, mature lymphocytes, and fibroblasts in *sa +/sa bg*, male, 6 months of age. (350 ×).

FIGURE 6.—Normal granules of neutrophile of +/+ genotype, stained with Sudan Black B. Blood smear, (1750 ×).

FIGURE 7.—Giant granules of neutrophile of strain SB-*sa bg/sa bg* stained with Sudan Black B. Blood smear, (1750 ×).

Giant peroxidase-positive and Sudan Black-positive granules were demonstrated in most of the polymorphonuclear leukocytes of strain SB/Le-*sa bg/sa bg* (Figures 6-7).

DISCUSSION

The progressive pneumonitis observed here involves two processes that occur both separately and in combination, pleuritis and consolidation. The consolidation closely resembles the chronic respiratory disease of mice and rats (CRD) described by NELSON. NELSON (1967) has postulated both a mycoplasma and a virus as etiologic agents for CRD. BRENNAN, FRITZ and FLYNN (1969) have postulated *Mycoplasma pulmonis*, other as yet uncultivated mycoplasmas, and *Pasteurella pneumotropica* as etiologic agents for the common pneumonias of mice, casting doubt on the existence of NELSON's virus. Pleuritis and pleural adhesions have been described in mice in association with acute bacterial infections (DINGLE 1941) but not with CRD.

Our limited bacteriological examinations uncovered several bacteria that could cause the pleuritis. The failure to demonstrate any mycoplasmas with HAY-FLICK's method suggests that the readily cultured types were not present. The findings are consistent with the concept that increased susceptibility to infection by a number of bacteria and possible viruses is involved as in the case of the Chediak-Higashi and related syndromes. Systematic transmission studies, combined with bacterial and viral identification, will be required to determine the etiologic factors involved.

The homozygous beige mice (*sa bg/sa bg*, + *bg/sa bg*) had a significantly higher incidence of pneumonitis than the nonbeige mice. The difference is strikingly clear in the case of the backcross beige females with 42% pneumonitis as compared with 5% in the nonbeige females. The difference in males is significant if both nonbeige groups (*sa +/sa bg*, + + */sa bg*) are added together.

In these experiments on spontaneous pneumonitis both genetically determined susceptibility and environmental exposure to infectious agents can be critical. All mice were exposed to at least one *sa bg/sa bg* parent. The high incidence of pneumonitis in the *sa +/sa bg* males raises the question of a susceptibility locus, other than beige, associated with the approximately 10cM segment of Linkage Group XIV marked by beige and satin. However, the pneumonitis was significantly less advanced grossly and histologically than in the homozygous beige males. Either an additional closely linked susceptibility locus or increased environmental exposure to infectious agents could explain the high incidence of pneumonitis in this small group of males. The simplest hypothesis for both males and females indicates that beige is a major susceptibility factor, analogous to that of the Chediak-Higashi syndrome.

Genetic background is of major importance in the occurrence of spontaneous pneumonitis in homozygous beige genotypes. In the course of crossing satin and beige into the C57BL/6J background, the incidence of pneumonitis diminished to less than 8% by the 5th to 7th generation. C57BL/6J-*bg⁺/bg⁺* mice have not shown spontaneous pneumonitis. In our experience homozygous beige (*bg*) mice

have a high incidence of pneumonitis only where the strain SB/Le background predominates. To determine whether the other beige mutant alleles in the mouse, which also produce giant lysosomal granules in the leukocytes and pigment changes analogous to those of the Chediak-Higashi syndrome, also increase susceptibility to infection will require quantitative exposure to known bacterial and viral agents.

In the Chediak-Higashi syndrome in man and in Aleutian disease of mink there are associated atypical lymphoproliferative lesions that have been diagnosed as malignant lymphomas (WINDHORST *et al.* 1968). In our study, enlargement of multiple lymph nodes as well as spleen, grossly suggesting lymphoma, was observed in 3 of 10 F₁ hybrids from 7 to 17 months of age and in 20 of 440 backcross mice, 6 months of age or less. Ten of these occurred among 23 *sa* +/*sa* *bg* males.

While in this primarily gross pathological study, sections of lymph nodes or spleen were saved in only 12 of 23 cases, all of the lymph nodes sectioned showed complete to extensive replacement of normal architecture by an atypical cellular infiltrate of histiocytes, lymphocytes, and reticulum cells. Reticulum cell neoplasm, type B of DUNN (1954) was diagnosed in two of the three cases with tissue available from the *sa* +/*sa* *bg* males and highly atypical reticuloendothelial hyperplasia in the spleen of the third case. While reticulum cell neoplasms are common tumors of old age in many inbred strains of mice (MURPHY 1966) their occurrence by 6 months of age is extremely rare. The C57BL/6J strain, with a 40% incidence of reticulum cell neoplasms late in life (MURPHY unpublished data), could have contributed the genetic background and a possible viral agent for such neoplasms. With the limited histological material available it is not possible to determine whether the atypical lymphoproliferative lesions represent an early stage of neoplasia or an unusual chronic inflammatory reaction. The same diagnostic problem is involved in the Chediak-Higashi syndrome in man.

The high incidence of lymphadenopathy in satin males (*sa* +/*sa* *bg*) suggests a closer association to satin than to beige. A definitive morphologic and genetic analysis of the lymphomas and the lymphoproliferative lesions will require complete autopsies and transplant studies on the different genotypes at ages well beyond 6 months.

A number of close associations of specific genes and lymphocytic neoplasms are known for the mouse, including yellow (*A^y*) which in the heterozygous state also increases susceptibility to reticulum cell neoplasms (DERINGER 1970). In this study both parent strains were homozygous for white-bellied agouti (*A^w*). There is as yet no evidence that *A^w* increases body weight or tumorigenesis as does its allele *A^y*.

The striking similarity of these atypical lymphoproliferative lesions to the "lymphoma-like" infiltrates of the Chediak-Higashi syndrome in man makes them a pertinent model for further study whether or not they are found to be associated with beige, satin, or an infectious agent.

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