ANIMAL MODEL OF HUMAN DISEASE

Hirschsprung's Disease, Aganglionic or Hypoganglionic Megacolon

Animal Model: Aganglionic Megacolon in Piebald and Spotted Mutant Mouse Strains

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Biologic Features

Bielschowsky and Schofield reported a 10% incidence of aganglionic megacolon in mutant piebald strains of mice.[1,2] The association of anomalous coat pigmentation with a deficiency of ganglion cells in the myenteric plexus is not surprising, since skin melanoblasts and the enteric plexuses are migratory derivatives of the embryonic neural crest.[3,4] In 1966, Lane[5] described two mutant mouse strains she had developed at the Jackson laboratories; each was characterized by striking changes in coat pigmentation and the tendency to develop fatal aganglionic megacolon. She named one strain piebald-lethal and the other lethal-spotting. In both, the syndrome appeared to be determined by a single autosomal recessive gene.

In the piebald-lethal (S^L) strain, the homozygotes (S^LS^L) are black-eyed and white-coated except for patches of black pigment; they invariably develop megacolon. These homozygotes tend to develop megacolon early in life, often dying of diarrhea and enterocolitis before breeding age is attained. The establishment of colonies of this stock for study is accordingly difficult.

The lethal spotting strain (L^s) physically resembles the piebald lethal strain except that the ears and tail are less pigmented. By cross-breeding the agouti-colored L^s heterozygote, one-fourth of the offspring are spotted homozygotes developing megacolon. These homozygotes tend to survive longer than the S^LS^L strain and are usually able to breed for several months before dying of the effects of megacolon. Cross-

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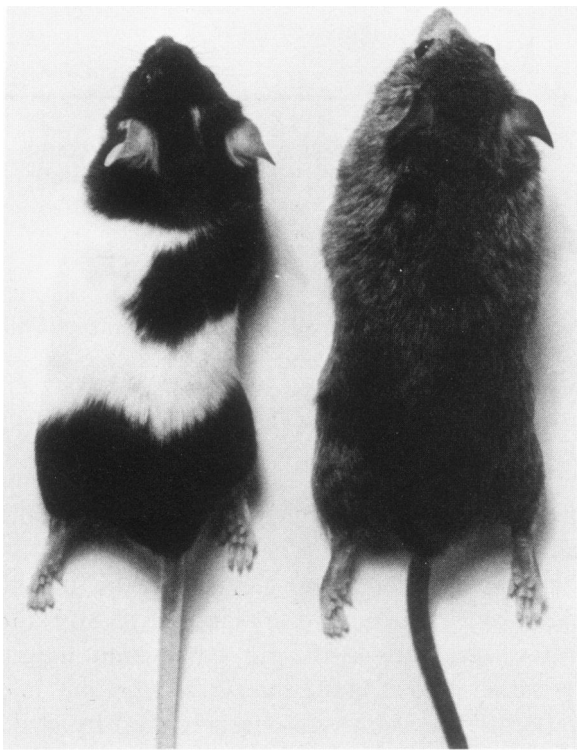

Fig 1—Lethal spotted mutant homozygote (L^sL^s) on left compared with agouti-colored heterozygote. Note the growth retardation in the affected mouse.

breeding of homozygotes can produce litters in which all members develop aganglionic megacolon.[5,6] Abdominal distension and gross megacolon becomes obvious in most animals by 2 to 3 weeks of age.

In both strains, the pathologic anatomy is similar.[5,7,8] In its fully developed form, the colon is grossly distended with fecal material, save for a short, distal segment devoid of feces extending approximately 1.5 cm proximal to the anus. Just above this segment the colon is maximally distended with condensed fecal pellets; this impaction tends to be gelatinous. This appearance contrasts strikingly with the serially spaced fecal pellets typically of the normal mouse colon. Histologically, the aganglionic zone is variable in length, extending 1 to 2.5 cm proximal to the anus with a transition zone of about 2 cm interposed between aganglionic and normally ganglionic colon. Histologic, histochemical or ultrastructural studies have been carried out on both strains, and despite minor differences, similar results have been reported[7,8] concerning the abnormality in cholinergic and adrenergic innervation in the aganglionic segments and transitional zones.

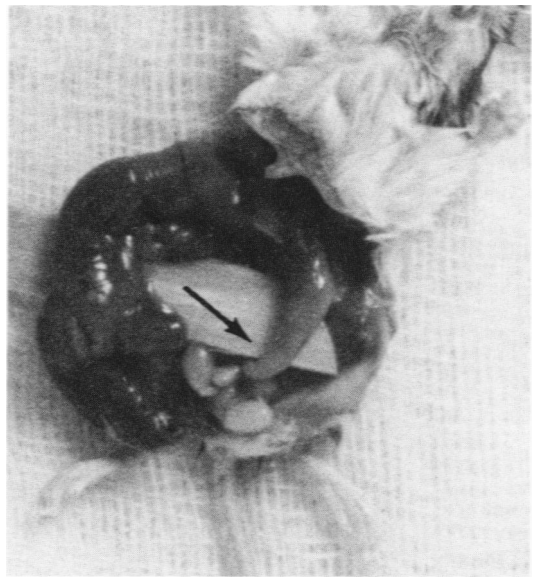

Fig 2 — L^5L^5 mouse showing massive megacolon and distal narrowed segment (*arrow*).

Comparison with Human Disease

Hirschsprung's disease occurs in siblings in 3.6% of cases, as compared to .02% of the general population.[4] It may furthermore accompany a number of heredofamilial diseases and syndromes, pathogenetically derived from neural crest maldevelopment—the neurocristopathies.[4] Massive megacolon in both man and mouse can occur with hypoganglionosis as well as complete aganglionosis.[9] In these aspects, the murine disease parallels the human condition. Nonetheless, significant differences in fine structural and histochemical features between human and murine megacolon probably exist. Specifically, increased number and size of intramural cholinergic fibers has repeatedly been observed in the aganglionic segment of Hirschsprung's disease,[7,9] the converse of findings in the mouse. Also, the increase in intermuscular adrenergic fibers described by others in the human could not be shown in the aganglionic zone of the mouse. Thus the murine model may not be sufficiently comparable to the human conditions to help resolve the many conflicting and controversial observations and concepts concerning the pathophysiology of Hirschsprung's disease. It is, however, extremely adaptable to morphologic studies, as well as to *in vitro* pharmacologic investigations of isolated colon segments.[10] It has also been used to delineate abnormalities in electrical activity of aganglionic colon *in vivo*.[11]

Availability

Mice from the mutant strains which manifest murine megacolon are available at Jackson Laboratories, Bar Harbor, Me.

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