later stages of infection(6).

The marked increase in serum gamma globulins following untreated Brucella infection has previously been demonstrated experimentally in guinea pigs(6,7) and in man(8,9). Our absorption studies indicate that this gamma globulin is not absorbed by *Br. abortus* cells. This may be indicative of a nonspecific outpouring of proteins in response to infection. There is a possibility, however, that the acute phase gamma globulins contain some nonabsorbable antibody.

Summary. Six rabbits were infected intravenously with a single massive dose of *Br. melitensis*. Three were treated by subcutaneous administration of streptomycin and tetracycline for 2 weeks and 3 were left untreated. The untreated rabbits developed a markedly increased gamma globulin content in their serum, which was not appreciably changed by absorption with killed whole *Br. abortus* cells. In addition, the blocking phenomenon was demonstrated in low titers in serum of these rabbits by 29th day of infection. Antibiotic therapy was effective in preventing the rise of gamma globulins and of blocking antibody through the 59th day.

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Received March 13, 1959. P.S.E.B.M., 1959, v101.

A Single-Gene Antagonism Between Mother and Fetus in the Mouse.* (24966)

W. F. HOLLANDER AND JOHN W. GOWEN
Dept. of Genetics, Iowa State College, Ames

Genetic antagonism between mother and fetus has not hitherto been demonstrated in the mouse(2,3). The purpose of the present paper is to demonstrate such a condition. This however differs from the classic types of incompatibility with Rh-antigens in man and erythrocytic antigens in livestock(1), since erythroblastosis fetalis and hemolytic icterus of the newborn has not appeared. A new sort of antagonism is therefore involved. Evidence for fetal antagonism appeared during genetic analysis of a new mutant type named "hair-loss" (Fig. 1). This is a simple recessive Mendelian character which originated as spontaneous mutation in this laboratory. It is characterized by progressive degeneration of hair follicles over entire body, loss of hair becoming obvious after age of about 5 weeks (Fig. 2). There is some resemblance to previously known mutant type, "hairless," gene *hr* in linkage Group III, but the new type, "hair-loss," proves to be in linkage Group VI, and has therefore been given a distinctive gene symbol, *hl*.

Methods. Homozygous hair-loss type has been maintained as a moderately inbred stock. For the present study, outcrosses have also been made with various other genetic types. Linkage-test matings for the VI group involved the marker genes *bt* ("belted"), *Ca* ("Caracul"), and *N* ("Naked"). Reciprocal matings served as controls. Standard mating has been one male with one female, usually not separated for littering. The young were weaned in a different box at about 4 weeks of age. In many cases, litters were recorded

* Journal Paper No. J-3559 of Iowa Agric. and Home Economics Exp. Station, Ames. This work received assistance from Contract No. AT(11-1) 107 from U. S. Atomic Energy Comm.

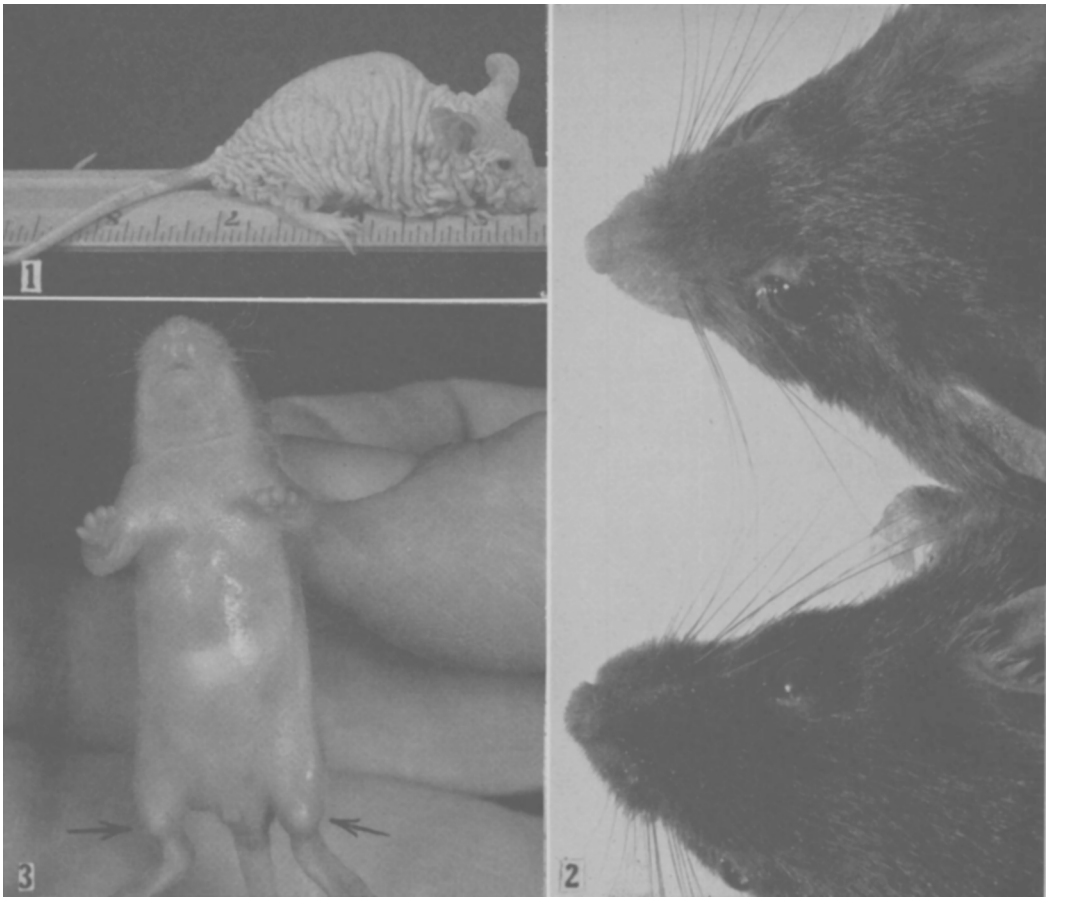

FIG. 1. A mature (7-mo-old) "hair-loss" mouse.
FIG. 2. Five-wk-old mice. Upper: initial stage of "hair-loss." Lower: normal.
FIG. 3. Nine-day-old mouse with spontaneously broken legs (arrows). The mother was "hair-loss."

within 24 hours after birth, and observed daily, but this was not a regular procedure. Classification of marker genes was completed some time between 5 days of age and weaning. Final classification for hair-loss condition was recorded at age of 5 to 8 weeks. Other details of care were routine: weekly changing of boxes by competent personnel, feed† and water *ad lib.* and air-conditioned quarters.

Results. Matings of hair-loss mice to heterozygous normals provided most revealing information. The expected ratio of hair-loss and normal progeny from such matings is 1:1. Where the sire was hair-loss and the dam normal, the results are in very good agreement with this expectation (Table I). However, in the reciprocal mating, where the sire was he-

† Both Purina Lab Chow and Wayne Lab Blox have been used.

TABLE I. Reciprocal Matings of Hair-Loss × Heterozygous Normal.

Sire	Dam	Data period	Progeny classified: Hair-loss	Progeny classified: Normal
Hair-loss	Normal	1.	252	246
"	"	2.	719	700
"	"	3.	168	163
"	"	Total	1139	1109
		Expectation*	1124	1124
Normal	Hair-loss	1.	74	18
"	"	2.	751	440
"	"	3.	267	89
"	"	Total	1092	547
		Expectation*	818.5	818.5

* Genetic ratio 1:1; null hypothesis for mortality effect.

TABLE II. Mortality and Survival of Belted (bt) and Caracul (Ca) Progeny in Linkage Tests with Hair-Loss (hl).

Chromosome linkage phase of sire*		Progeny classified: Dying before classification of hair-loss			Surviving to classification of hair-loss	
		Ca	+†		Ca	+
Ca	+	70	59		290	646
+	hl			y	356	
Ca	hl	7	28		135	63
+	+			y		72
		bt	+		bt	+
hl	+	48	23		178	385
+	bt			y	207	
hl	bt	21	26		204	138
+	+			y		66

* All sires were mated to homozygous multiple recessive females.

† The + symbol represents the normal allelic type.

y = apparent mortality.

terozygous normal and the dam hair-loss, the ratio diverged markedly in favor of hair-loss progeny. This result was obtained in 3 successive periods, chronologically, the ratio averaging 2:1.

The discrepancy was readily traced to differential mortality. In the first place, there was no difference in litter size at birth; 72 litters from heterozygous normal females had a median of 9½ young, while 145 litters from hair-loss females gave the same value. Mortality of young, however, was around 3 times as high for hair-loss dams as for normals, particularly before 2 weeks of age. Since these young could not be classified for hair-loss, the marker genes *Ca* and *bt* were utilized as indicators. Their distributions in coupling *vs.* repulsion phases consistently showed higher mortality in the group expected to be non-hair-loss (Table II). Intercurrent disease such as infantile diarrhea was absent during this period.

Much of the mortality occurred even before genes *Ca* and *bt* could be classified. Breakdown of available data indicates that the very early mortality (first 2 days) is related to reproductive work (litter size and lactation) by the dam. This is true for normal dams as well as hair-loss dams, but in the case of the latter is greatly magnified. Litter size shows little relation to mortality where the dam was nursing a previous litter during pregnancy, but in the absence of lactation there does appear to be some correlation of mortality and litter size (Table III). Multiparous females which had not been nursing had a low amount of early mortality.

After age of 2 weeks mortality largely ceased. Examination of the young in high-mortality classes revealed that growth disturbance was the rule. They were generally smaller than their litter mates, and often runty. Commonly between fifth and tenth days of age one or more legs became broken, with swelling and inflammation at the site, generally near middle of tibia and fibula or ulna and radius (Fig. 3). Mice surviving such injury recovered quickly and in no case were of the hair-loss type.

TABLE III. Ratios of Dead/Surviving Young, for the First Two Days after Birth, from Matings of Hair-loss Mice.

Parents: Type of sire	Parents: Type of dam	Nursing while pregnant	Litter-size classes (inclusive): 1–5	6–8	9–11	12–16	Total	Mortality, %
Hair-loss	Normal (hetero.)	No	0/16	0/ 92	6/185	1/ 86	7/379	2
"	" "	Yes	0/ 5	5/ 38	18/101	4/ 74	27/218	11
"	Normal (homo.)	No					2/217	1
"	" "	Yes					20/ 56	26
"	Hair-loss	No					0/ 86	0
"	"	Yes					4/ 13	24
Normal (hetero.)	Hair-loss	No	0/21	27/174	47/257	50/175	124/627	17
" "	"	Yes	18/16	33/ 91	85/119	111/164	247/390	39
Normal (homo.)	"	No					9/116	7
" "	"	Yes					22/ 33	40

When hair-loss females were mated with homozygous normal males, practically all surviving young suffered the same sort of growth handicap.

Since all evidence pointed to an antagonism of hair-loss mothers toward their non-hair-loss young, the next question was whether the milk was the seat of the disturbance. To test this possibility, newborn young from hair-loss mothers were immediately transferred to normal females for fostering. Here again cases of inferior growth, broken legs, and mortality occurred. Reciprocal fostering was not tried.

Detailed pathological study of young dying in the first few days has not been undertaken. Preliminary observations revealed no significant anomaly; the blood picture seems normal. Death apparently is the consequence of respiratory difficulty, the lungs often being poorly inflated.

Discussion. Minor maternal effects on fetal development in the mouse have previously been demonstrated(2) by reciprocal crosses. Such effects were apparently not associated with known genes, and were not of such antagonistic sort as in the present case. A more striking difference between reciprocal crosses was early noted by Reed(5) for the gene "Fused" (tail vertebrae). However, antagonism was not the mechanism there(3).

In the case of hair-loss, the antagonism shows a close analogy to that involving blood-type genes, in that the mother is of the homozygous recessive type and the affected fetus is heterozygous for the dominant allele. It will be of interest to determine whether the "hairless" (*hr*) type behaves like "hair-loss" in this respect; hairless females have been considered "poor mothers," and not extensively bred(3). Also a comparison with the effects of several "histocompatibility" genes (3) seems needed. Since our mice have been considerably mongrelized for these linkage studies, they probably have a rather random assortment of such genes. However, for this linkage group (*VI*) no histocompatibility locus has been identified.

The mechanism of the antagonism remains to be elucidated. Since there is no evident icterus or red-cell aberration, serological antagonism, if any, probably involves other tissues. No "build-up" of antagonism in multiparous mothers was noted, provided they were not nursing a previous litter during pregnancy. The relation of maternal "over-work" to increased early mortality is most interesting and can account for much variation in data. Possibly the better nutritional status of the young from "rested" dams makes them more able to withstand the antagonism.

Possibly this new sort of antagonism is more related to such incompatibilities as those observed in grafting of plants. Another strong example is a dominant gene, in chromosome III of Drosophila, which causes death of all daughters of a female carrying it, but not the daughters of a male carrying it(4). Conceivably some such principles operate in mongolism and failure of species hybridization.

Summary. A new type of maternal-fetal incompatibility, not involving erythroblastosis, is demonstrated by reciprocal matings in mice. The conditioning factor is a recessive mutant gene named "hair-loss." Normal-hair progeny of hair-loss mothers are ordinarily born alive but suffer excessive mortality during first 2 weeks, even when fostered by normal mothers. The syndrome consists of inadequate lung inflation, inferior growth, and fragile bones. Mortality is very high when a previous litter was being raised by the mother during pregnancy, but seems otherwise not related to parity.

The authors are indebted to Dr. W. J. Miller, Serology Laboratory, Univ. of California at Davis, for information on incompatibility situations in livestock.

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Received March 16, 1959. P.S.E.B.M., 1959, v101.