THE FAMILIAL OCCURRENCE OF THE CHEDIAK-HIGASHI SYNDROME IN MINK AND CATTLE[1]

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CHEDIAK (1952) observed anomalous granulations in peripheral blood and bone marrow leukocytes of a four-year-old girl. Several investigators have since reported similar granules in leukocytes of both male and female patients from different parts of the world.

While there have been some differences reported in the various cases, the composite picture of the syndrome as described by several investigators is consistent (HIGASHI 1954; SATO 1954; SATO 1955; DONOHUE and BAIN 1957; EFRATI and JONAS 1958; SARAIVA, AZEVEDO, CORREA, CORVALHO and PROSPERO 1959; PAGE, BERENDES, WARNER and GOOD 1962). People with the condition are partial albinos since the hair and eyes have less pigmentation. They have photophobia, nystagmus and an increased red reflex of the eyes. They are unusually susceptible to pyogenic infections. All cases reported exhibited anomalous leukocytic granulations in the peripheral blood and bone marrow. Few patients have survived longer than seven years of age. The syndrome appears to be inherited by means of an autosomal recessive gene.

LEADER, PADGETT and GORHAM (1963) and PADGETT, LEADER and GORHAM (1963) have reported the occurrence of a panleukocytic anomaly of Aleutian type mink morphologically identical to that occurring in the Chediak-Higashi syndrome (CH-S) of man.

We have recently found that the CH-S also occurs in partial albino (PA) Hereford cattle. In this paper, data will be presented concerning the familial occurrence of the CH-S in mink and cattle. The presence of hypopigmentation, photophobia, abnormal leukocytes, recessive hereditary patterns and marked susceptibility to infections offers strong evidence that the abnormality is the same in all three species.

MATERIALS AND METHODS

The mink were from our stock herd or mink of known genetic background from ranches in Eastern and Western Washington. All animals were examined for the leukocytic anomaly by

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peripheral blood smears stained with Giemsa (Wolbach's modification) (*Manual of Histologic and Special Staining Techniques*, 1957, page 111). The symbol *aa* will be used to designate the homozygous recessive Aleutian genotype (SHACKELFORD 1950). Fifty families of mink with a parental genotype *aa* × *aa*, 12 with parental genotype *Aa* × *aa*, and ten with parental genotype *AA* × *aa* were examined. Of the heterozygous to homozygous recessive matings, in seven of the families the female, and in five the male, was the homozygous recessive animal. Blood smears from 28 different color phases (phenotypes) of mink were also examined for the anomaly.

The cattle were a part of Washington State University's (WSU) Department of Animal Science Experimental Herd. The original stock for the group of cattle used was obtained in 1958 from a purebred Hereford herd located near Waitsburg, Washington. Material from six of 16 PA cattle was available for microscopic examination.

RESULTS

The occurrence of abnormal leukocytes in mink resulting from three types of matings is shown in Table 1. From the mating *Aa* × *aa*, approximately one half (22/50) of the offspring showed the anomaly, and these 22 offspring were all identifiable as mink homozygous for the allele *a* for Aleutian coat color. Approximately one half of the offspring with the anomaly were male and one half female no matter which parent was the recessive in the mating, indicating that the trait is not sex linked. The homozygous dominant to homozygous recessive matings yielded no offspring with the anomaly and the homozygous recessive to homozygous recessive matings yielded all offspring with the anomaly. These are the expected results of a simple recessive trait.

Table 2 lists 28 color phenotypes of mink which were available for examination, the occurrence of the leukocytic anomaly in the mink, and the probable recessive genotype of each phase. All of the mutant color phases carrying the *aa* genotype possessed the leukocytic anomaly. Mink not having the *aa* genotype did not have the anomaly.

The familial relationship of the cattle is shown in Figure 1. Sixteen PA animals were born in the herd and all but three have died. The three survivors include two adults, a female four years of age and a male three years of age; the third is a female two months old. None of the PA cattle has lived longer than four years of age. Both adults are white but have hypopigmentation of the iris and a ghost pattern (i.e. fawn color) where the normal red Hereford pigmentation occurs. At birth the calf was completely white with no apparent ghost pattern, but had a grey iris similar to the other PA cattle. All of the PA cattle observed in this herd have had photophobia and nystagmus. Abnormal leukocytes, the same as those

TABLE 1

The occurrence of leukocytic anomaly in mink families of known matings

Parental genotype	Number of families	Number of kits	Mink with abnormal leukocytes		Mink without abnormal leukocytes	
			Male	Female	Male	Female
Aa × *aa*	12	50	9	13	12	16
aa × *aa*	50	240	130	110	..	..
AA × *aa*	10	42	..	..	19	23

TABLE 2

Various color phenotypes of mink with and without abnormal leukocytes

Mink without abnormal leukocytes		Mink with abnormal leukocytes	
Phenotype (Color phase)	Recessive (Color genotype)	Phenotype (Color phase)	Recessive (Color genotype)
Palomino	*hp hp*	Aleutian	*a a*
Heinen buff	*p p, ba ba*	Saphire (royal)	*p p, a a*
Double pearl	*p p, bp bp, A a*	Triple pearl	*p p, bp bp, a a*
Black eye hedlund white	*h h*	Red eye hedlund white	*h h, a a*
Moyle buff	*bm bm*	Lavender	*bm bm, a a*
Fawn	*b b, bm bm*	Violet	*p p, bm bm, a a*
Finnish topaz	*b b, bs bs*	Blue iris	p^s p^s, *a a* or p^s *p, a a*
Pastel ambergold	*ba ba*		
Opaline	*p p, b b, bm bm*	Hope	*p p, ba ba, a a*
Natural dark	No recessives	Winterblue	*p p, b b, a a*
Kuskaquim	Unknown, probably no recessives		
Silver sable	*F f*		
Albino white	*c c*		
Pastel red eye	*b b, bg bg*		
Pastel green eye	*bg bg*		
Pastel brown eye	*b b*		
Pastel imperial	*bi bi*		
Pastel socklet	*bs bs*		

As nearly as could be determined, the recessive genes for color carried by the animals examined are listed. The genotypic designations used are those suggested by SHACKELFORD (1950).

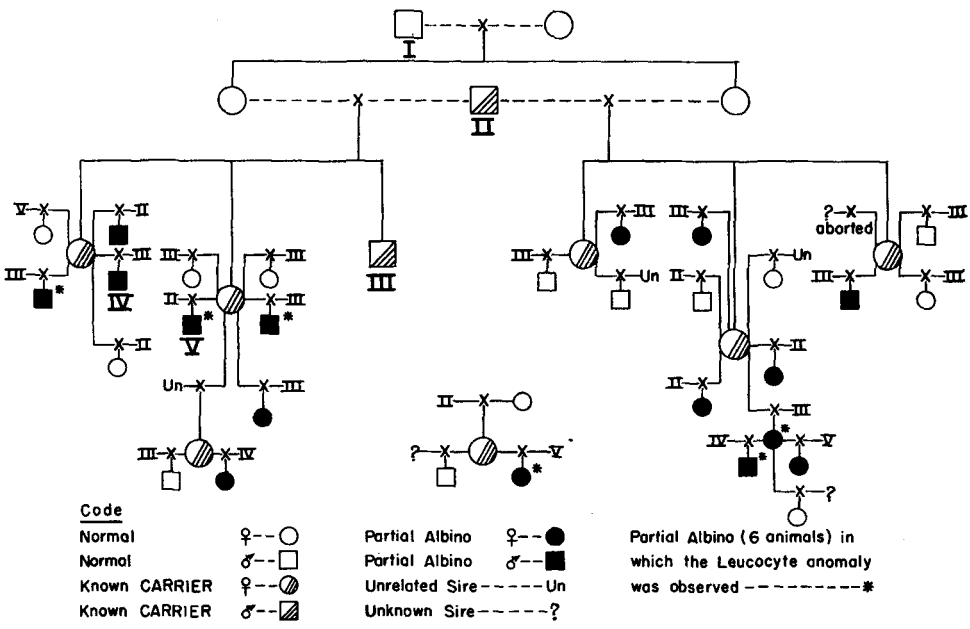
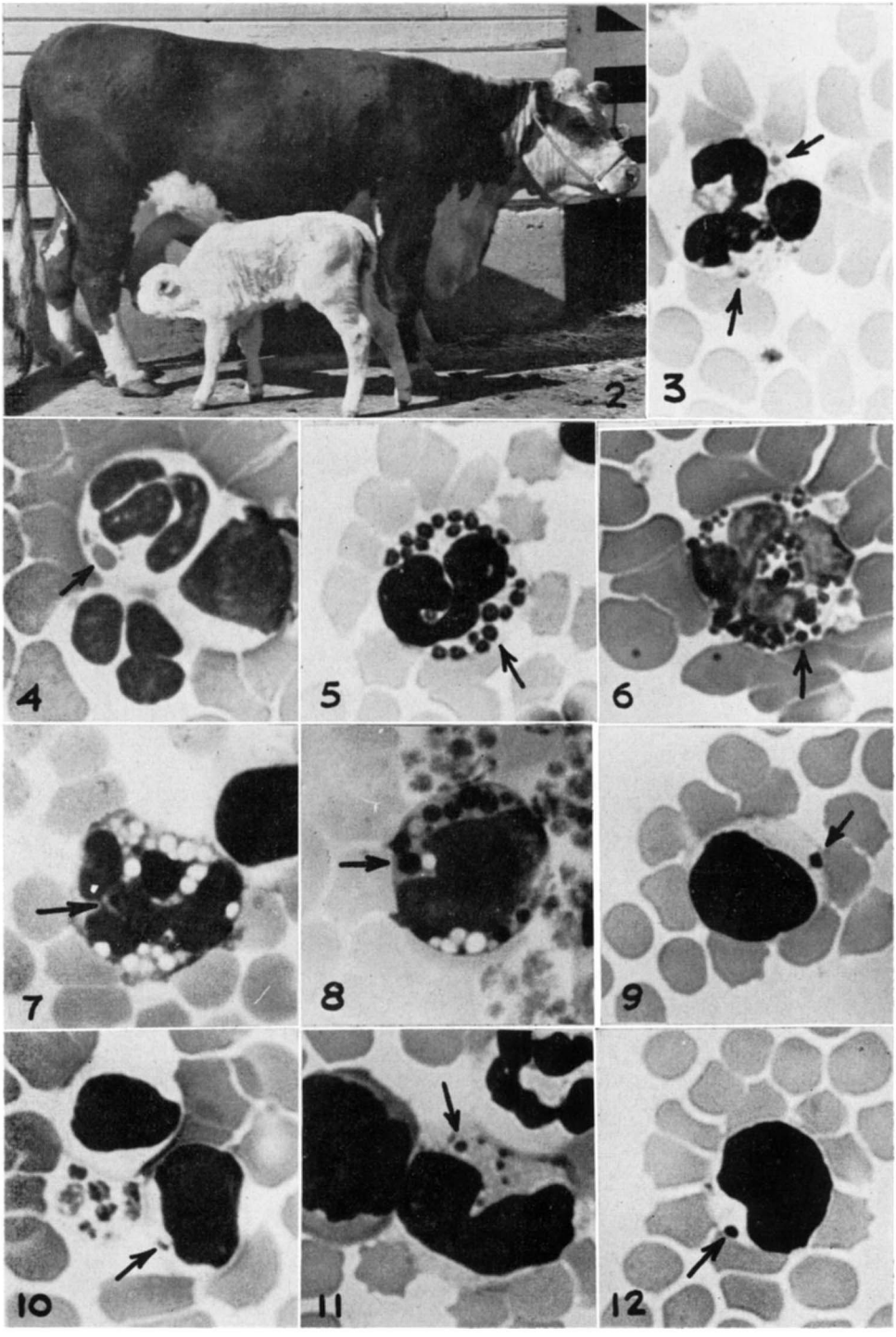


FIGURE 1.—Pedigree of partial Albino Hereford cattle (Washington State University Herd).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observed in the *aa* mink, were found in all six of the cattle from which material was available. Figure 1 gives the pedigree of the PA Hereford herd at WSU and identifies the six animals in which the anomaly was observed. Figures 2–12 illustrate the leukocytic anomaly in both mink and cattle.

DISCUSSION

Associated with the abnormal leukocytes there has been consistently a partial albinotic characteristic in mink, cattle, and people. This partial albino state is difficult to define in mink where many light coat colors are present. There are mink with light coat colors which do not possess the leukocytic anomaly. However, these animals do not have the *aa* genotype. The pelt of the Aleutian mink (*aa*) has a definite bluish gunmetal sheen when compared to the natural dark mink and all other color phases carrying the recessive Aleutian genotype are lighter in color than Aleutians. Two groups of these mink (Pearls and Hedlund White) in the heterozygous state (*Aa*) have dark eyes while in the homozygous recessive state (*aa*) the eyes are red. Mink with *aa* genotype show signs of photophobia in bright sunlight.

All available data indicate that the syndrome in mink is invariably associated with the Aleutian genotype *aa* thereby indicating a rather diverse pleiotropic effect (coat color, eye color, leukocytic anomaly) of the gene *a*. The alternative to this explanation is that these various characteristics are controlled by a coordinate cluster of closely or absolutely linked genes, each gene affecting but one characteristic in the syndrome.

The Aleutian mutation occurred on the Paul Autio Ranch in Oregon in 1941 (WARIS, personal communication). The parent animals can be traced to wild mink trapped in Oregon in 1928 and 1929 and bred to ranch-raised wild-type, Alaskan male. The first mutant animals showing the gunmetal coat color were inbred to produce more mink of this color phase. Mink of this phenotype, which was designated as Aleutian, were weaker than their parents and few survived longer than one year (WARIS, personal communication). They were later outbred,

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FIGURE 2.—A phenotypically normal dam which is a carrier for the Chediak-Higashi syndrom and her partial albino heifer calf. Note the faint ghost pattern of normal Hereford pigmentation of the calf. FIGURES 3 and 4.—Abnormal neutrophils from the partial albino calf (3) shown in Figure 2 and an Aleutian (*aa*) mink (4). There are several enlarged granules in the cytoplasm of the cells (arrows). The peroxidase stain is positive as in normal neutrophil granules. FIGURES 5 and 6.—Abnormal eosinophils from the partial albino calf (5) and an Aleutian (*aa*) mink (6) with enlarged cytoplasmic granules. In animals with the syndrome, 100 percent of the eosinophils are abnormal. FIGURES 7 and 8.—Abnormal basophils from the partial albino calf (7) and an Aleutian (*aa*) mink (8). Note the vacuolated cytoplasm and enlarged granules (arrows). FIGURES 9 and 10.—Abnormal lymphocytes with an enlarged cytoplasmic granule (arrows) from the partial albino calf (9) and an Aleutian (*aa*) mink (10). These granules have the same staining characteristics as the azurophil granules occasionally seen in normal lymphocytes. FIGURES 11 and 12.—Abnormal monocytes with enlarged granules in the cytoplasm from the partial albino calf (11) and an Aleutian (*aa*) mink (12). As in the lymphocyte, these granules are thought to be enlarged azurophil granules.

then backcrossed and stronger animals were produced than in the original mutation.

Mink with the *aa* genotype have been shown to be considerably more responsive to the Aleutian disease agent (HENSON, GORHAM, LEADER and WAGNER 1962; HENSON, GORHAM and LEADER 1963). HARTSOUGH (personal communication) first observed the gross lesions of Aleutian disease in 1946. These lesions occurred in mink with the *aa* genotype derived from stock from the Paul Autio Ranch. The question arises as to whether the Aleutian mutaiton and the Aleutian disease agent originated at the same time. It seems extremely unlikely that two matching mutations would occur simultaneously. It is more probable that the disease was present and undiagnosed in dark mink *AA* prior to 1941. When sufficient Aleutians (*aa*) were bred, they became infected and the greater susceptibility of this genotype led to the diagnosis of a "new" disease. HELGEBOSTAD states that mink with the Aleutian genotype (*aa*) are weaker than standard mink. They whelp fewer kits and the kits are less hardy (HELGEBOSTAD 1963). This genotype is more susceptible to abscesses (American Fur Breeder, 1961, p. 111). Aleutian-type mink are capable of producing antibodies against distemper virus and botulism toxoid. This suggests that their susceptibility to disease may rest in factors other than inability to produce protective antibody.

In 1958, HAFEZ, O'MARY and ENSMINGER (1958) reported on albino-dwarfism in the WSU experimental herd. They suggested that the dwarf and partial albino characteristics were probably independent. This observation is probably valid since only two of 16 PA cattle in the WSU herd have been dwarfs and three of 21 of the phenotypically normal animals in this herd have been dwarfs. DETLEFSON (1920) reported on albinos from reputed purebred Holsteins although they were unregistered. COLE, VAN LONE and JOHANSSON (1934) reinvestigated the herd reported by DETLEFSON and studied an albinotic dilution of coat and eye color in another herd of Holstein cattle. They suggested that the abnormality was due to a simple recessive gene. PETERSON, GILMORE, FITCH and WINTER (1944) reported on albinism in Holstein cattle, and reinvestigated the herds reported by DETLEFSON and COLE. They confirmed COLE's opinion that the diluted coat color was due to a simple Mendelian recessive. In none of these cases was there any mention of abnormal leukocytes. However, since the PA characteristic was present, the leukocytic anomaly may also have been present. It appears from Figure 1 that the animal introducing the PA trait was sire No. II, Prince Larry 39, a purebred registered Hereford bull. It is not known whether the mutation originated in this animal or whether it was passed to him. The trait in cattle appears to be a simple Mendelian recessive as it is in man and mink.

Knowledge concerning the frequency of occurrence of this gene in the population of man and cattle is lacking. However, it is likely that since this is an undesirable characteristic in cattle, animals with CH-S are probably slaughtered.

Since the pelts of the Aleutian-type mink were more valuable than many of the other color phases, ranchers selectively bred these animals, and this gene is now widely disseminated in the mink population.

Inasmuch as CH-S has already occurred in such widely diverse mammals as

man, mink, and cattle, it is likely that it occurs in other species. The so-called lethal factor in grey Karakul sheep reported by NEL and LOUW (1953) is a likely possibility.

It appears from the available information that essentially the same gene or controlling mechanism is involved in all three species and that it performs the same functions in all three species. This suggests that the gene or controlling mechanism is of common phylogenetic origin.

SUMMARY

A syndrome closely similar to the Chediak-Higashi syndrome of man is described in mink and cattle. This syndrome, characterized by abnormal leukocytes, hypopigmentation, and increased susceptibility to disease, appears to be conditioned by an autosomal, recessive gene in each of three species. The gene for this anomaly is widely distributed in the mink population. No information is available for man and cattle on the number of carriers in the population. It appears that essentially the same gene controlling the similar phenotypes may be involved in all three species.

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