Oculocutaneous Hypopigmentation of Angus Cattle

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Congenital defects are abnomalities of structure or function present at birth. They may affect only a single anatomical structure such as the eye, an entire system, parts of several systems or involve several body systems, or combine functional and structural defects (syndrome). Many different congenital defects, either of genetic, environmental, or unknown cause, or due to environmental-genetic interaction have been identified in cattle and other food producing animals and many more undoubtedly exist. Defects range from blemish to severe anomalies and may be manifested by embryonic mortality, fetal death, mummification, abortion, dysmaturity, premature birth, fullterm stillbirth, or nonviable or viable neonate. With increasing use of modern technology such as artificial insemination and embryo transfer in domestic animals, defects no longer are rare; all are important.[15]

The majority of studies of pigmentation defects have taken place in the mouse. Since it is easy to handle, has low maintenance cost, and can produce a large number of generations in a short period of time, it is particularly suited for this research. Studies involving cattle necessarily take more time and money. This paper presents clinical, clinipathologic, gross, microscopic and electron microscopic studies of oculocutaneous hypopigmentation in Angus cattle.

Materials and Methods

Oculocutaneous hypopigmentation of black Angus cattle was first brought to our attention in 1980 in connection with longterm studies of congenital defects, the methods of which have been described earlier.[11 15] It occurred in registered Angus herds in various parts of the United States. This condition is a heretofore undescribed genetic abnormality of color involving iris color, skin, and hair.

Affected Angus cattle and controls were obtained from various states and herds by the Congenital Defects Laboratory, Department of Pathology. They were housed throughout this study at the Animal Resource Facility, College of Veterinary Medicine, Kansas State University, Manhattan, Kansas. Specimens from 34 cattle were used in this study: 25 affected, 2 albinos, and 7 normals as presented in table 1.

Various clinical clinicopathologic, gross and microscopic procedures were performed. Blood was collected in sterile E.D.T.A. tubes from the jugular vein of six affected cattle for 25 consecutive days. Red blood cell and white blood cell counts were made on a Coulter Counter (senior model). Total protein and fibrinogen were measured on a Refractometer. Blood smears were stained with Wright's stain and complete blood counts done at the Kansas State University hematology laboratory.

Blood also was collected, via the jugular vein, in clot tubes from five affected cattle and five normal cattle of the same age. This blood was checked for coagulation times. Serum from one affected and one normal animal was submitted to Consolidated Biomedical Laboratory[a] for determination of phenylanine levels.

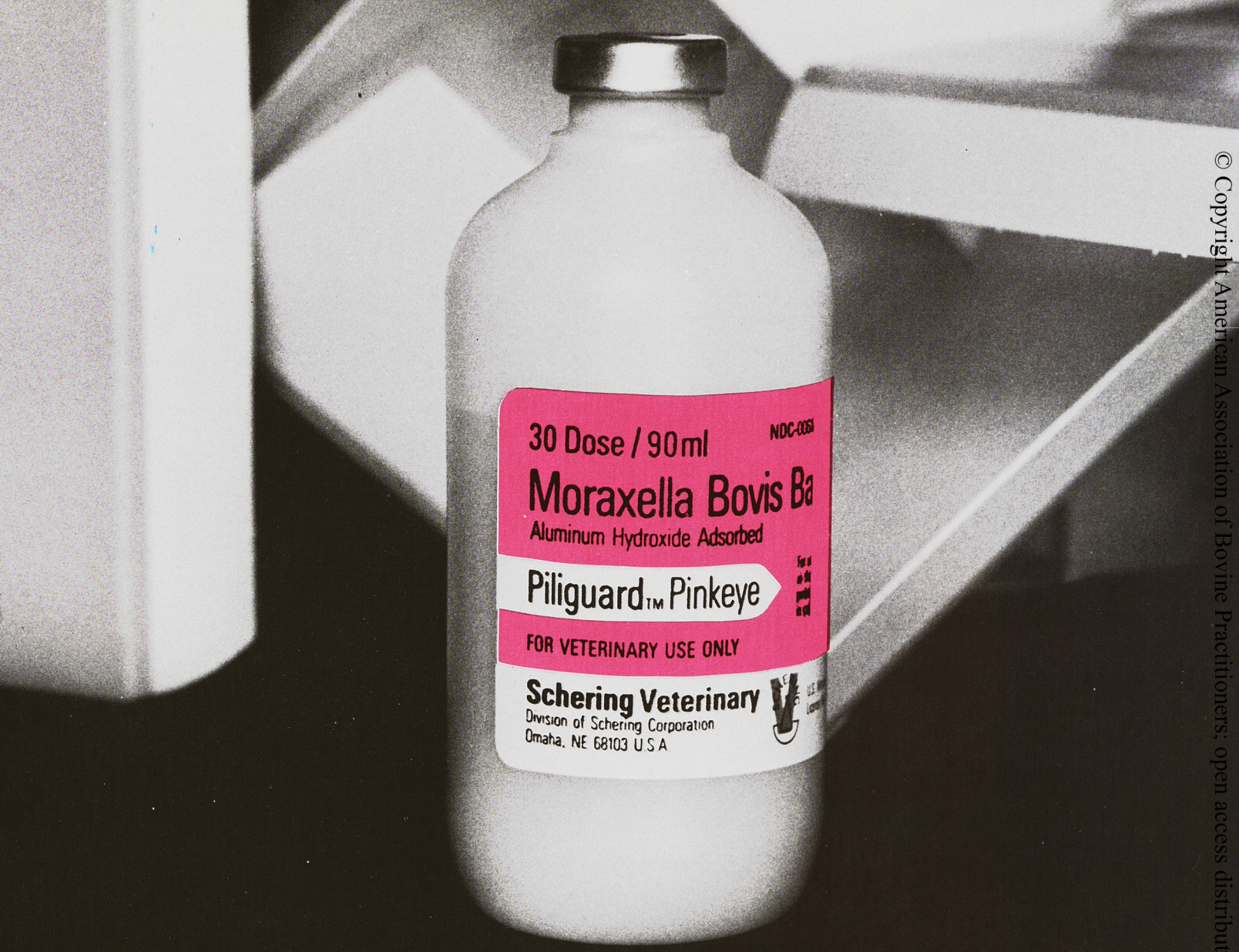
Blood smears from six affected cattle were stained with Giemsa and also Sudan Black and examined for the presence of abnormal leukocytic granules.[23]

Urine was collected and divided into two aliquots. One was adjusted to a ph of 8 with sodium hydroxide. The other was left normal. The two samples were left to stand at room temperature for 96 hours. They were examined periodically for discoloration.

Hair was removed from five affected cattle, on an area of the right shoulder two inches in diameter with a commercial depilatory. Thirty days later, regrowth hair was plucked and cleared.[21] The cleared hair was mounted on slides with Ames coverslipping resin. A second aliquot of hair was submitted to dopa and tyrosine tests.[8]

Biopsies were taken by standard surgical procedure from the left shoulder of six affected cattle and samples of the

[a] *Consolidated Biomedical Laboratory, Wichita, Kansas 67201.*



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*Developed in conjunction with Dr. C. Brinton, University of Pittsburgh and Bactex, Inc. V-PGP-17

TABLE 1: Cattle Used in the Study.

Case #	Breed	State of Origin	Sex	Pigment Diagnosis
1	Angus	South Dakota	F	OCH[a]
2	Angus	South Dakota	M	OCH
3	Angus	Illinois	M	OCH
4	Angus	Illinois	M	OCH
5	Angus	New York	F	OCH
6	Angus	South Dakota	M	OCH
7	Angus	South Dakota	M	OCH
8	Angus	Missouri	M	OCH
9	Angus	Illinois	M	OCH
10	Angus	South Dakota	F	OCH
11	Angus	South Dakota	F	OCH
12	Angus	South Dakota	M	OCH
13	Angus	Kansas	F	OCH
14	Angus	Kansas	F	OCH
15	Angus	Missouri	F	OCH
16	Angus	Nebraska	F	OCH
17	Angus	South Dakota	F	OCH
18	Angus	Missouri	F	OCH
19	Angus	Nebraska	F	OCH
20	Angus	North Dakota	F	OCH
21	Angus	North Dakota	M	OCH
22	Angus	Kansas	M	OCH
23	Angus	Kansas	F	OCH
24	Angus[b]	South Dakota	F	OCH
25	Angus[b]	South Dakota	F	OCH
26	Holstein	Nebraska	F	Albino
27	Holstein	Nebraska	F	Albino
28	Angus	South Dakota	F	Normal
29	Angus	Kansas	M	Normal
30	Angus	Kansas	M	Normal
31	Charolais	Kansas	M	Normal
32	Brown Swiss	Kansas	F	Normal
33	Angus X Simmental	Kansas	M	Normal
34	Angus	Kansas	F	Normal

[a] OCH = Oculocutaneous hypopigmentation.
[b] Biopsy only.

others were taken at necropsy. The skin biopsies were divided into two parts, stapled to wooden tongue depressors and placed in 10% buffered formalin or physiological saline, respectively. Specimens in saline were refrigerated for use in the dopa test, as described.[22]

Skin was removed from animal number 22 at necropsy and immediately cut in thin slices approximately 1 mm thick. Two different procedures, fixed and fresh, were used in this dopa test.

In the fixed test, the tissue was fixed 1 hour in 2% glutaraldehyde, then washed three minutes with distilled water. It was then incubated in dopa solution for one hour at 37°.[25] The solution then was changed and incubation was continued for 10 hours. After removal from the incubator, tissue was washed five minutes with distilled water then fixed in glutaraldehyde. The control procedure was the same, except control tissues were incubated in buffer without dopa.

In the fresh tissue dopa test tissues, both test and control, were handled as in the fixed, except they were not placed in the 2% glutaraldehyde for one hour.

All cattle, except two which were biopsied and one perfused, were euthanatized with T-61[b] intravenously via the jugular vein or humanely killed at a state licensed slaughter house.

Removal of ocular tissue was done as rapidly and accurately as possible, without causing trauma to the delicate tissues. Tissues were removed and placed in formalin within 15 minutes after euthanasia or slaughter, and no more than 30 minutes elapsed between time of death and fixation.

Perfusion technique: Animal number 18 was treated with sodium heparin[c] (1,000 units/ml) intravenously, then deeply anesthetized with a combination of xylazine[d] (100 mg/ml) and thamylal sodium[e] (2% w/v). The chest cavity was opened at the sternum and the heart was isolated from the pericardial sac. A trocar attached to tubing was placed in both the right and left ventricles. The vascular system then was flushed with normal saline. The saline entered the left ventricle by gravitation while the tube from the right ventricle was left open to drain. When the return fluid from the right ventricle was fairly clear, Karnovsky's fixative,[7] composed of 2% gluteraldehyde and 2.5% paraformaldehyde in a phosphate buffer, was perfused into the carcass via the tube in the left ventricle. This was continued until the muscle masses were hard. The animal was necropsied and specimens were immersed in Karnovsky's fixative.[7] Tissues from the iris, ciliary body, retina, and skin were immediately diced finely, fixed in 1% osmium tetraoxide, rinsed in phosphate buffer, dehydrated in graded ethanols and placed in propylene oxide, a transitional solvent. Infiltration and embedding were done in LX-112[f] resin, polymerized at 65°C for 18 hours. Thick sections were cut[g] at 0.5 to 1.0 microns and stained with toluidine blue for light microscopic orientation. Thin sections were cut at 70 nanometers, stained with manyl acetate and lead citrate on

[b] *T-61 Euthanasia Solution, American Hoechst Corp., Animal Health Division, Somerville, NJ.*

[c] *Heparin sodium injection, Rugby Laboratories, Inc., Long Island, NY.*

[d] *Rompun, Haver Lockhart, Bayvet Division Cutter Lab., Inc., Shawnee, KS.*

[e] *Biotal, Bio-Ceutic Laboratories, Inc., St. Joseph, MO.*

[f] *Ladd LX-112 Resin, Ladd Research Industries, Inc., Burlingtown, VT.*

[g] *Sorvall Porter-Blum MT-2 Ultra-microtome, Ivan Sorvall, Inc., Newton, CT.*

180-mesh coppergrids, then examined by TEM[h]

Eyes were removed from affected animals at necropsy and .2 cc of fluid was removed from the posterior chamber, with a syringe and twenty gauge needle, and replaced with .2 cc of 10% buffered formalin. The complete eye was emersed in 10% buffered formalin for seven days. After removal from the formalin, the eyes were washed with running cold tap water for 24 hours, then placed in 60% ethanol until the cornea was clear. The eyes were cut paramidline to leave a center section approximately ¼-inch thick. These center pieces were placed in crickets for further processing.

Brain and other tissues and organs were removed at necropsy, examined grossly, and placed in 10% buffered formalin for further processing. The central nervous system tissues and all other tissue samples were processed routinely and were sectioned at 9 microns or 6 microns, then stained routinely with hematoxylin and eosin (H&E) and Fontana as described.[16]

Results

The group of affected cattle examined in this study fall in the broad category of albinotic, but a more descriptive terminology is oculocutaneous hypopigmentation.

The color of the body haircoat was light chocolate with the upper body lighter in color than the lower portion of the body. The neck, head, and switch of the tail were darker in color. The poll hair and fringe hair of the ears was lighter than the basic body color (Fig. 1). The females seemed to get progressively lighter with age; the bulls seemed to darken. The darker color of the bulls first appeared at about puberty and was thought to be due to increased testosterone levels . The texture of the haircoat was normal.

The glabrous skin of the eyelids, muzzles, lips, and teats were a light slate grey. This color did not vary with age.

The affected cattle had hooves that were almost as black as normal Angus.

The irises were pale sky blue centrally, giving a cartwheel effect with a half moon above and below the constricted pupil. Peripherally to the blue area, the iris changed color to tan. There was a lack of corpora nigras. When the sun was shining brightly, the blue area was very evident. The pupil was constricted to a horizontal slit approximately 1 mm across (Fig. 2).

Ophthalmic examinations were conducted in a dark room because adequate dilatation of the pupil could not be achieved in the sunlight with 1% atropine. The tapetum of the choroid was a pale yellow-green and the vessels were quite prominent.

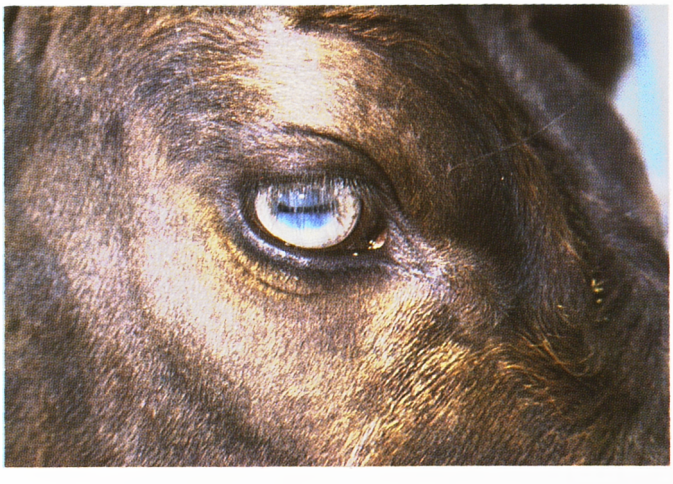
The haircoat of calves 26 and 151 were black as normal black Angus calves. Their eyes were characteristic of the affected cattle, except the irises had flecks of dark brown. Calf 3 did not shed in the summer of 1981, and her hair was light copper colored.

The temperament of the affected cattle, as a general rule, was calmer than normal Angus cattle. This was particularly evident in the six head that were bled for twenty-five consecutive days. Even on the last days, there were no problems in handling these cattle. Two cattle had undesirable dispositions. An adult bull was aggressive when a person entered the pen and a male calf would try to climb out of the pen.

The cattle were active and grazed normally at dusk, throughout the night, and into early morning and on overcast days. The cattle sought shade when the sun was bright, even on cool days. On bright days, they would leave the shade to eat their grain, but after eating they would return to the darkness of the barn.

Figure 1: Angus heifer affected with oculocutaneous hypopigmentation. Notice white eyes, slate grey muzzle, light hooves, and the typical chocolate color.

Figure 2: Eye of an Angus heifer affected with oculocutaneous hypopigmentation. Notice constricted pupil and light blue iris coloration.



[h] *Hitachi Model H-300 Electron Microscope, Nissei Sanyo American, Ltd., Mountain View, CA.*

Blood coagulation times were normal in both affected and non-affected cattle.

Blood smears stained with Sudan Black and Giemsa failed to exhibit any enlarged lysosomes. Blood counts on six cattle, for twenty-five consecutive days, disclosed no abnormalities.

Phenylalanine levels in the serum of one affected and one normal animal were approximately the same, .5 MG/DL, and .7 MG/DL, respectively.

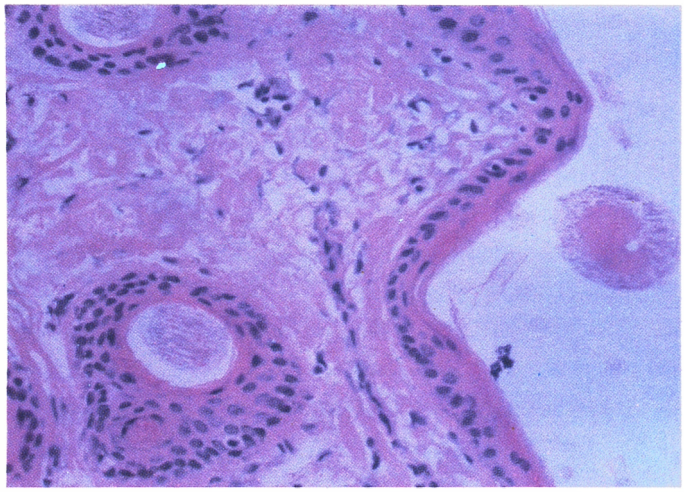
Urine failed to develop any pigment when left to stand at room temperature for 96 hours.

The cleared hair of affected cattle had a very fine brown pigment on an amber background in the cortex, while unaffected cleared hair was a solid black.

The dopa reaction was positive on both skin sections and anagen hair bulbs. This was evidenced by an increase in pigment in the melanosomes of the skin and in the hair bulbs.

The dermis examined with a light microscope and H & E stain had a few melanophages containing light amber melanosomes (Fig. 3). There was also a slight dermatitis with an infiltration of PMN's.

Figure 3: Skin of affected bull 35. Notice lack of pigmentation of basal layer.

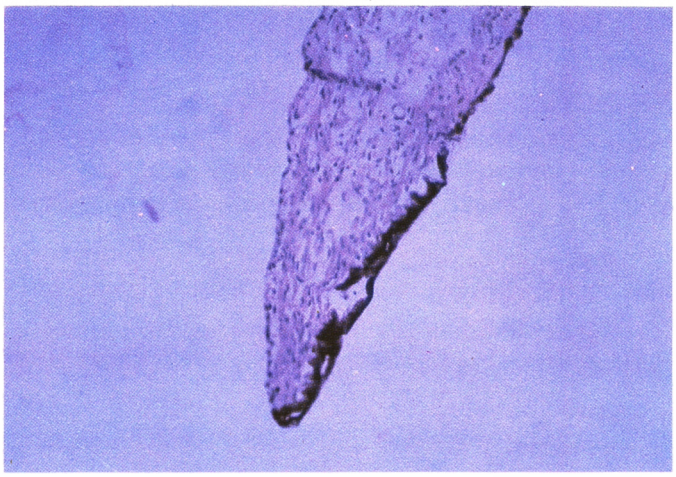


The epidermis examined with H & E stain had distinctly fewer visible melanosomes than normal skin. Those that were visible were of normal shape and size, but were light amber color.

The Fontana stain of the skin revealed many more melanosomes than did the H & E. The Fontana-stained, affected sections could not be readily detected from Fontana-stained, normal sections. The number, shape, and size of melanosomes in both the normal and the affected were approximately the same.

The eye, examined with a light microscope and H & E stain, had a lack of pigment in the pigmented layer of the retina, ciliary body, and iris. The visible melanosomes were amber. The anterior half of the iris was almost completely devoid of pigment. Those melanosomes present were amber in color (Fig. 4).

Figure 4: Tip of iris, affected heifer 3. Note, lack of pigmentation of stroma and epithelial layer.

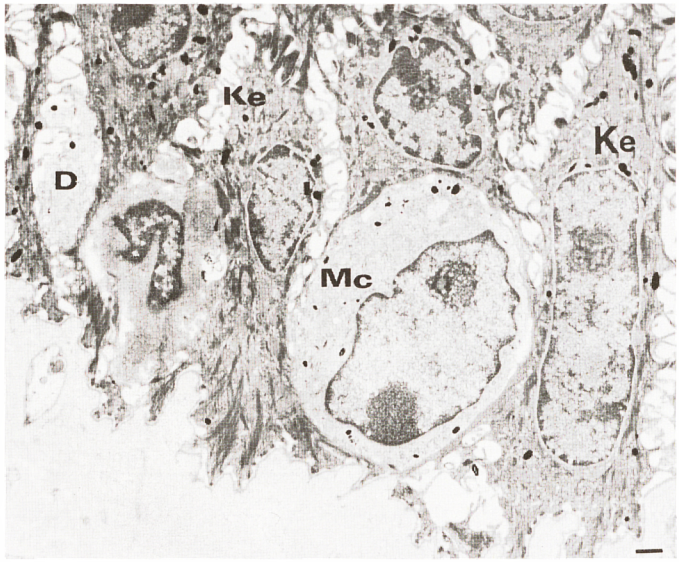


The Fontana stain of the eye revealed many more melanosomes than the H & E stain, except for the anterior leaf of the iris. The anterior leaf of the iris had somewhat fewer melanosomes than normal eyes.

Brains of all affected animals examined at necropsy, except calf number 26, had a moderate hydrocephalus. Heifer number 3 had a chronic bronchopneumonia. There were no other gross abnormalities.

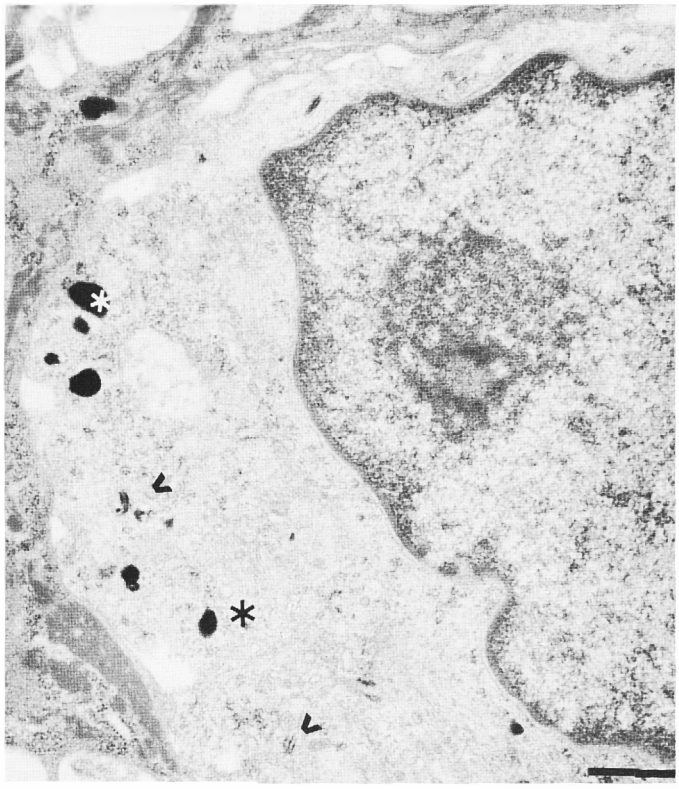
There were some immature Stage II melanosomes in the skin, along with numerous Stage IV. Stage II melanosomes were close to the nucleus of the melanocytes, while melanosomes out in the dendrites were primarily Stage IV (Fig. 5).

Figure 5: Skin of affected heifer 18. Melanocyte (Mc). Keratinocyte (Ke). Dendrite (D). Bar = 1 μm.



The Malanocytes of the iris had many melanosomes. These melanosomes were variable in size and maturity. There were melanosomes with dark centers and lighter periphery. Laminae of the matrix could be seen in the periphery of some of these. There were Stage IV melanosomes that had two dark areas that were joined into compound melanosomes. Melanosomes were seen starting to melanize, but the melanin was not in the normal pattern. In these, melanin was laid down in short strips that at times were at right angles to each other. In others, the melanin was laid down in an irregular circular pattern within the melanosome. The melanin was flocculent in character (Fig. 6).

Figure 6: Lower right. Skin of affected heifer 18. Note stage IV melanosomes (star) and stage III melanosomes (open arrowhead). Bar = .5 μm.



The melanosomes of the ciliary body were very numerous within the cytoplasm of the melanocytes. The melanosomes varied greatly in size and density. There was variation in density within the melanosomes with the center being the most dense and one or two less dense halos surrounding the center. The melanin present was flocculent and foamy. In some of these, laminae could be seen in the outer layers. There were also melanosomes with no melanin and laminae disorganized, not lying in regular parallel lines but arranged at various angles. In some, the laminae were thick, disrupted, and had no distinct pattern (Figs. 7-9).

Figure 7: Iris from affected heifer 18. Note nucleus (Nu), stage II melanosomes (arrowheads) and many stage IV melanosomes with stage II halos in area (star). Bar = 1 μm.

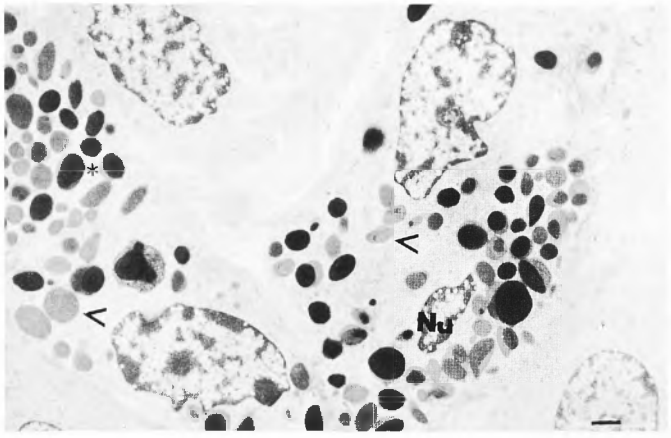
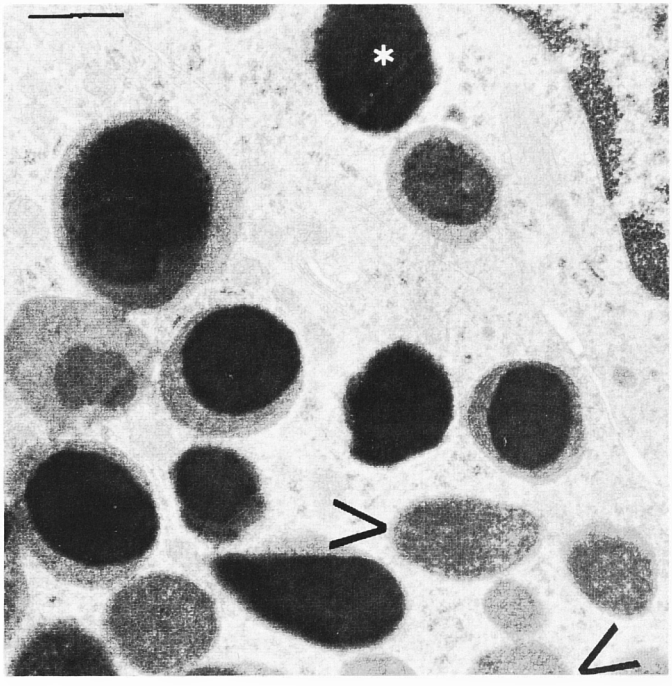


Figure 8: Upper left. Ciliary body from affected heifer 18. Note flocculent melanin in stage IV melanosome (star), stage II melanosomes and many incompletely melanized melanosomes. Bar = .5 μm.



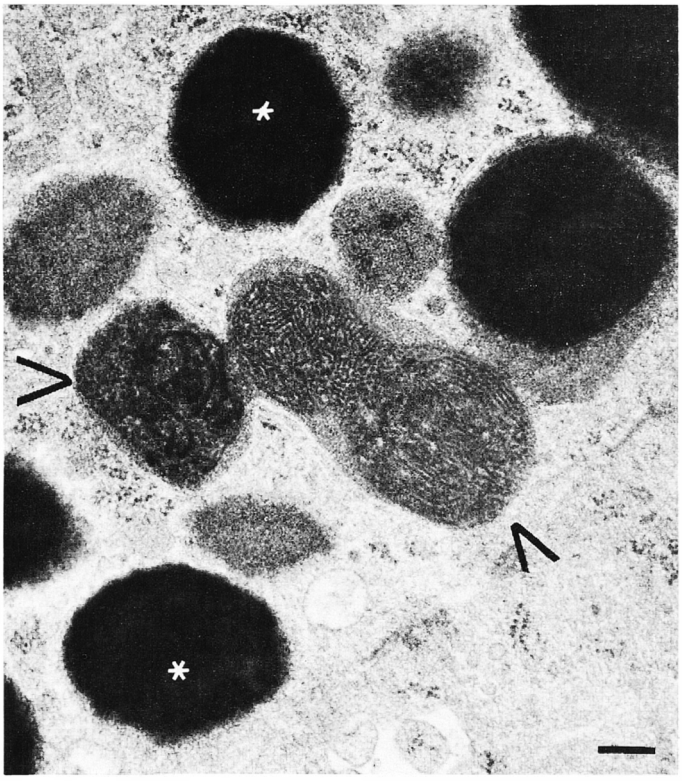
Part of the breeding trials were reported earlier but are summarized here. Four affected dams bred to an affected Angus bull have produced affected calves. The Congenital Defects Laboratory at K.S.U. in conjunction with the Central Sandhills Area Extension Service, Mullen, Nebraska, has bred 51 Herefords to an affected bull (#35). All 52 calves (one set of twins) were of normal coloration expected of Angus x Hereford crosses.

Two Simmental cows, bred to an affected bull, had grey

and white calves as in like crosses with normal Angus.

The cross of an affected bull with two albino Holstein cows produced offspring that were black with white markings, as did the cross of an affected bull with two normal Holstein cows.

Figure 9: Ciliary body from affected heifer 18. Note flocculent stage IV melanosomes (star) and stage II with disorganized matrices (arrowhead). Bar = .25 μm.



Discussion

Albinism may be classified as partial, incomplete, and complete as reviewed recently.[9 15] In partial albinism, the iris is blue and white centrally and brown peripherally, and the coat color is usually characteristic of the breed or more dilute.[5 10 12 13 18] Incomplete albinos have colobomas of the nontapetal fundus and tapetal fibrosum hypoplasia.[19] Incomplete albinism is inherited as an autosomal dominant.[13] A form of partial albinism is encountered in the Chediak-Higashi syndrome reported recessively inherited.[20] It includes besides its albinotic features abnormally large, membrane-bound organelles in various cell types and increased susceptibility to infection.[20] Complete albinism, a simple autosomal recessive, are characterized by pure white coats, white to pink irises but a normal tapetum lucidum.[6 14] Pigment defects in man, domestic and laboratory animals are frequently associated with defects involving central nervous system, ears and eyes.[2 15 26] A dominant gene in merle dogs may involve ocular defects such as colobomas and microphthalmia.[2]

Oculocutaneous hypopigmentation Angus cattle were examined to see if there were any related defects, as seen in other species. The Chediak-Higashi syndrome discounted after repeated examinations of the blood revealed no enlarged lysosomes. These cattle also did not show repeated sickness, as seen in cattle afflicted with Chediak-Higashi.[20]

Clotting time of blood was the same as other cattle housed in the same pens and, therefore, a Hermansky Pudlack-like syndrome was ruled out.[4] A syndrome like cyclic neutropenia of grey collie dogs was ruled out after 25 consecutive C.B.C.'s showed no evidence of abnormal deviations.[1]

Dopa test on hair bulbs and skin was positive. This is a test for the presence of tyrosinase and, therefore, the production of melanin by the melanocyte. Melanosomes that were in the early stages turned black. Those that were in the last stage and those in the keratinocytes had already completed their melanization and did not have tyrosine with which to form more melanin. The true albino has no tyrosinase and, therefore, is negative to the dopa test. Because copper is needed for the action of tyrosinase and the dopa test was positive, it was concluded that this was not a copper deficiency.

A phenoketanuric-like syndrome was considered, but urine checks for phenylketones and check of blood phenylalinine level revealed nothing unusual.

The clinical signs, constricted pupils and reluctance to be in the light, can be attributed to the lack of pigment in the eye. The purpose of the pigment of the iris is to restrict the amount of light entering the ocular structure. The dark pigment of the iris and the pigmented layer of the retina absorb part of the light, which has entered through the iris and pupil.

The moderate hydrocephalus seen in all but one of the examined cattle may or may not be part of this syndrome. Clinically, there were no signs that would lead to the belief that this was a problem in these cattle.

The color of the skin and eyes is mainly due to the melanin produced by the melanocytes. This melanin can be either eumelanin, black and brown, or pheomelanin, which includes reds and yellow. In this project, the main concern was the highly insoluable eumelanins. Due to its insolubility, little is known about the true structure of eumelanin, however, there are many aspects that have been ascertained experimentally over years of study.

Melanin of the skin is formed by the melanocytes, which migrate in the embryo from the neural crest. These cells are dendritic and locate on the basement membrane of the epidermis. Here, they interdigitate with keratinocytes and produce melanosomes which are phagocytized by the keratinocytes. Each melanocyte produces melanosomes, which migrate out into the dendrites supplying melanosomes to many keratinocytes. Once in the keratinocyte, they are carried to the surface, being degraded on the

way to be eventually sloughed off at the surface. In order for melanin to have much influence on color, some of it must enter the keratinocytes.[28] The same basic concept is true with hair. The melanocytes of the hair bulb deposit melanin in the growing hair and it is disposed of as the hair grows and is shed.

The melanocytes of the eye are derived from the optic cup. They are non-dendritic and do not continuously produce melanin. They produce their complement of melanosomes, then apparently cease production.[3] The melanocytes of the eye become the retinal pigmented epithelium and the pigmented layers of the ciliary body and iris.

Melanogenesis primarily takes place within the melanosome of the melanocyte. Eumelanins are formed when tyrosinase from the ribosomes comes into contact with tyrosine in the melanosome. Copper is needed for the action of tyrosinase. Further non-enzymatic reactions take place to yield eumelanin. The eumelanin is then polymerized and attached to a protein to make the final melanoprotein. The melanosome is produced by the golgi and consists of a membrane-bound protein matrix upon which the eumelanin is laid. Various stages have been assigned to the maturity of the melansome. Stage I is a spherical membrane-delineated vesicle which has no melanin and the internal structure is visible with the electron microscope. Stage II is an oval organelle with numerous filaments. Stage III is an oval organelle with an internal structure similar to stage II that has become partly obscured by melanin. Stage IV, the last stage, is completely melanized and the melanin completely blocks the viewing of internal structure.[27]

From the previous discussion, it can be seen that a multitude of defects could occur to vary the color of the animal. These defects could range from structural defects in the melanocyte to defects in the biochemical reactions within the melanosomes. The most common biochemical defect is the lack of production of tyrosinase. This, in turn, causes a lack of production of melanin and results in an albino. The lack of melanocytes in the epidermis also results in a white animal. The most common structural defect in the melanocyte appears to be the enlarged melanosomes of the Chediak Higashi syndrome.

The results of breeding trials suggest that oculocutaneous hypopigmentation is simple autosomal recessive in inheritance. The affected animals are normal breeders even though they are less active in the daylight hours.

One bull used in a Nebraska test indicated that the defect did not impair reproductive efficiency. However, care should be taken to use the affected bull as a terminal cross or with cows of different blood lines.[24]

It would seem prudent to refrain from using affected (photophobic) females as brood cows. The photophobia restricts grazing to night-time hours which may result in less milk production and lighter weaning weights in their calves.

Examination of the cattle clinically, with the light microscope and the electron microscope, determined that the lack of pigmentation of the skin and hair had no effect on the health or well-being of the affected cattle. It may, however, be looked upon with disfavor by producers who prefer a solid black color.

The fine structure of the melanosomes of the affected cattle showed many irregularities in the matrix and the melanin. These may or may not be actual defects, since the fine structure of the normal melanosomes was usually obscured by melanin.

The fine structure of the melanosome is under genetic control and the differences seen in the affected eyes of cattle were comparable to those seen in the eye of the brown mouse.[17]

It is speculated that the light tan color of the eye was due to the abnormal melanosome matrix. Possibly, few abnormalities were seen in the matrix of melanosomes in the skin because the change of color was not as extreme as that in the eyes.

It is further speculated that there has been a genetic mutation, causing the Golgi apparatus to malfunction and lay down abnormal matrix. Whether this abnormal matrix is just abnormal in arrangement or is abnormal in protein content is unknown. There is the possibility that the abnormal structure gives the lighter color or that the protein of the matrix lacks correct binding sites for the melanin.

Therefore, it is concluded that the affected cattle have a normal biochemical melanin pathway and the color change is due to the abnormal melanosomal matrix.

Summary

A genetic color mutation in black Angus cattle was evaluated by clinical, clinicopathological, gross, microscopic and electron microscopic examinations. The defect is inherited as simple autosomal recessive.

The condition resulted in the cattle being hypopigmented and photophobic. Coat color was chocolate brown and the irises were pale blue around the pupil with tan periphery.

The iris and ciliary body had malformed melanosomal matrices, immature melanosomes and flocculent melanin. It was postulated that the hypopigmentation was due to the abnormal matrices.

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