# Congenital Defects of Current Concern and Interest in Cattle: A Review

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Since ancient times, defective animals have provoked man's curiosity and fears. Today we cannot neglect to carefully monitor and study these defects in cattle. Many defective calves are stillborn or may die shortly after birth. Some defects are linked with fetal death and abortion. However, they comprise a portion of losses accepted by most cattlemen as normal and unavoidable, but nonetheless, of considerable economic importance. Congenital defects are defined as abnormalities of structure or function present at birth. The distinction between normal variants and abnormalities is not always obvious. Many different types of congenital defects have been identified in various breeds of cattle and more exist and will be identified as knowledge expands. Cattle breeders and practicing veterinarians are the prime source of identifying and controlling these troublesome defects. Diseases and defects if found to be genetic may spread insidiously through breeds and become difficult to control. Therefore, it is desirable to recognize genetic problems early to prevent their spread. There is a changing attitude in the veterinary profession and cattle breed associations about congenital and inherited diseases (91,101). Most cattle breed associations and artificial breeding service units have programs to monitor and control undesirable genetic traits and defects. Moreover, some cattle breed associations have adopted disclosure procedures for bulls and cows discovered to be heterozygotes of an undesirable genetic trait, factor or defect.

Cattle breeders need the advice of veterinarians to recognize such defects in their cattle and the effects it may have upon their breeding programs. This paper reviews nature, cause and effect of congenital defects in cattle. Particular emphasis is placed in some new control procedures. In addition, some defects of recent interest and concern are discussed.

## Definition

Congenital defects are abnormalities of structure and function present at birth. Congenital frequently held to be synonymous with genetic is no longer acceptable, because many but not all are caused by genetic factors. Teratogen is defined as and agent causing abnormal development. Teratology is a division of embryology and pathology dealing with abnormal development and congenital defects.

## Nature and Effect

Congenitally defective calves pose a diagnostic challenge to the practicing veterinarian. They also act as sentinels of man's environment. Many malformed calves are stillborn or die soon after birth. Some defects are linked with embryonic and fetal deaths, abortions and resorptions. Many defective calves are not reported and thereby escape the various monitoring systems.

A defective neonate is an adapted survivor from a disruptive event at one or more stages in the complexly integrated sequences of embryonic or fetal development. If the disruptive event is not immediately lethal, it is followed by the remaining normal development sequences which must accomodate the event and its sequellae in succession. Often this is not possible and the affected embryo or fetus dies before completing development and is resorbed or aborted, often undetected.

Susceptibility to injurious agents varies with the stage of development and decreases with age. Before day 14 (period of preattachment), the zygote or embyro is resistant to teratogens but susceptible to genetic mutations and chromosomal aberrations. During the embryonic period (day 14-42), the embryo is highly susceptible to teratogens but this decreases with embryonic age as the critical periods for the various organs are passed. The fetus (day 42 plus) becomes increasingly resistant to teratogenic agents with age with exception of the later differentiating structures such as cerebellum, palate and urogenital system.

Defects may affect only a single structure or a single function, involve several body systems, or combine functional and structural defects (syndrome). All body structures and functions may be affected. Defects may be obvious grossly, but some are not recognized except after careful clinico-pathologic and postmortem examination. The definition of syndromes in veterinary medical genetics appears to be important because it allows for more accurate diagnosis of some of these troublesome conditions.

The frequency with which various parts of the body are affected, vary according to breed, geographic location, season, sex, age of parent, and level of nutrition.

Development defects may be lethal, semi-lethal, compatible with life and have little effect, may impair viability or have an esthetic effect. Although economic losses due to congenital defects are less than those from infectious, chemical and nutritional agents, they may be economically important to individual cattle breeders. With the increasing use of artificial insemination and embryo transfer, defects are no longer rare and all are important. Collectively in cattle, congenital defects cause economic losses by increasing perinatal calf mortality, decreasing the dam's productivity, and by decreasing the value of viable defective calves. In addition, one of the more serious losses involves decrease of value of relatives of

defective calves. Productivity may be reduced by longer calving intervals. Additional economic losses occur when congenital defects are only a partial manifestation of a syndrome that also include embryonic and fetal mortality. Therefore, new or more expensive management practices may be required. Herd improvement is lessened through losses of replacements and consequent reduction in culling potential. Congenital defects may be an added source of confusion in diagnosing other clinical entities or abortion. Finally, control measures may require extensive and expensive adjustments of breeding programs.

## Frequency

**The frequency of congenital defects in animals is unknown. Because congenital defects are caused by hereditary and environmental factors, or their interactions, the frequency of individual defects, or defects of each body system, and the total number of defects will vary among breeds, geographical locations and seasons. In addition, interest of observer may bias data collection.**

The incidence of congenital malformation among all calves seems to range from 1/500 to 3/100 births, with 40 to 50% born dead and only a small fraction of the defects not being externally visible (12, 14, 38, 39, 60, 92, 94-96). Losses of newborn dairy calves from stillbirths in DHIA herds in the United States amounted to 6% (12). In 4,980 births in Ohio herds surveyed in 1957 to 1960, 36 calves in every 1,000 had a congenital defect (39). Bilateral dissection of 108 calves, and unilateral dissection of 31 calves, identified 103 different defects (99).

A study of 1,000 German calves included 532 stillbirths, 84% had signs of neonatal asphyxia; 6.9% were congenitally malformed, and the remaining 9.1% had evidence of infection. Of the malformed 468 calves that died within 3 months, 2.8% had congenital malformations that caused death within 3 days and 5.1% had nonlethal malformations and died from some other cause (38). In range herds of Angus and Herefords involving 6,406 calvings over a 10 year period, stillbirths amounted to 4.4%; 28% of the stillbirths were abnormal or 1% of all calves (38).

Studies in Hesse, Germany for nine years totaled 2,293 defective calves (German Black Pied, German Red Pied, Semmental, Yellow cattle, Red cattle and crossbreeds). Frequency was estimated to be 0.25 percent. Relative frequency of the various body systems affected was: central nervous system (21.6%), musculative (13.7%), anomalous twins (10.0%), congenital systemic disturbances such as hydrops (9.5%), defects of large body cavities such as schistosomum reflexum (9.3%), facial skeleton (8.8%), bones of leg including joints (6.9%), digestive (4.3%), urogenital (4.3%), bone and cartilage (2.8%), heart and vessels (2.7%), skin (2.0%), and others (1.7%) (94-96).

A total of 137,717 patients in veterinary college clinics in the United States and Canada contained 6,455 animals with congenital defects (92).

## Causes

Many congenital defects have no clearly established cause, others are caused by environmental factors, others have genetic causes. Environmental and genetic interaction may account for a considerable proportion of the defects encountered.

Teratogenic factors in cattle include: toxic plants, Akabane virus, bluetongue virus, bovine virus diarrhea virus, drugs, trece elements, and irradiation (6-7, 15, 26, 35-37, 41, 50-54, 67, 70, 78-80, 88, 90, 98).

The occurrence of crippled-calf disease and cleft palate in Utah and on Kodiak Island is due to ingestion of lupines (*L. sericeus, L. caudatus, L. nootakatensis*) between days 40 to 60 of pregnancy (52, 67, 97). Anagyrine has been identified as the toxic alkaloid causing the problem and lupines vary in anagyrine content during plant growth cycle (52). Other plants are suspected of causing defects (52).

Prenatal viral infections act as teratogens in cattle. Cerebellar hypoplasia is caused by prenatal infection with bovine virus diarrhea virus (BVD) (15, 26, 50, 51); hydranencephaly may be linked to prenatal infection by bluetongue virus (79-81, 88-89); and prenatal Akabane virus infection has caused hydranencephaly and arthrogryposis (35-37, 41, 53-54, 90, 98).

Teratogenic agents are difficult to identify but follow seasonal patterns and know stressful conditions. They may be linked to maternal disease rather than following a familial pattern. Maternal disease patterns vary but calves from heifers are more frequently affected; fetal Ig is frequently detectable; abortion incidence is increased; and morbidity may be observed in the herd or other associated animals on the farm.

Genetic defects are pathophysiologic results of mutant genes or chromosomal aberrations occurring in any environment. Except for chromosomal aberrations, genetic defects are recognized only when they occur in characteristic intergenerational patterns and intragenerational familial frequencies. One of the most common chromosomal defects in domestic animals is centric fusion of arcocentric chromosomes to form Robertsonian translocations encountered in high frequency in cattle with genetic defects. Chromosomal defects and aberrations in chromosomal number are becoming increasingly important for studying the etiology of congenital defects in cattle (103).

The primary effect of diagnosis is prevention, particularly of those defects that involve impairment of structure or function and hence usefulness of the calf or the loss of calves. Even undesirable inherited traits that do not impair usefulness should be listed on the pedigree or in any advertisement of breeding stock.

Although causes of many congenital diseases in cattle are not known, many follow simple Mendelian inheritance, mostly simple autosomal recessive inheritance (60, 66, 69, 71-78, 91, 101-104). Other monofactorial inheritance patterns are described as overdominant, dominant, or incompletely dominant whereas only a few reports describe sex-linkage. Congenital defects may also be inherited as a polygenic (27, 102). There is need to find in some cattle breeds the families which have least or none of undesirable traits due to multiple gene inheritance such as seen in spastic paresis, defects of the reproductive system and umbilical hernia.

Diagnosis of genetically caused congenital defects is based on the rule that genetic diseases run in families, thus congenital defects occur in typical intergenerational and intragenerational patterns requiring enumerating normal and abnormal offspring and identifying their familial relationships. Various statistical methods are used to analyze such data. Breeding trials are necessary to confirm inheritance patterns (66).

The recessive inheritance pattern involves only two kinds of animals — normal or defective. Only a few normal animals carrier, heterozygote can transmit the disease. Although two defective parents produce only defective calves, most defective animals do not reproduce; hence, most defectives are born to normal parents. Each normal parent (heterozygote) that pro-

duce a defective animal transmits one of the two abnormal genes necessary to produce the defective offspring. But most normal animals cannot transmit the disease. When the non-disease-carriers are mated with other noncarriers, or even with carrier normals, they produce only normal offspring.

When normal animals that produce a defective offspring are mated repeatedly, 25% of their progeny should be defective and 75% normal. Two of every three normal calves from such parents carry a hidden recessive gene that they may transmit to their progeny just as their parents transmitted the abnormal gene to them. Thus, recessive defects are "carried" generation after generation by normal animals (carriers) and result in insidious spread of the undesirable gene through the population. Carrier animals (or hetrozygotes) for a disease condition, transmitted as autosomal recessive are identified indirectly only after they have defective offspring.

Eliminating defective progeny usually keeps recessive defects at low frequencies. But breeds in which only a few animals produced most breeding animals or in which many animals are closely related to some single outstanding animal are vulnerable and serious outbreaks of genetic defects may result. That happens when the foundation animal carries a recessive gene unknown to its owners. The defect is then exposed when descendants of such animals are mated. Inbreeding, therefore, is one way to expose the presence of abnormal recessive genes.

Other simple inheritance patterns include dominance, incomplete dominance ,and overdominance. Dominance is just the reverse of recessive inheritance pattern. With dominant inheritance the normals breed true, but the abnormals may produce both normals and abnormals. The defect does not skip generations as in recessive inheritance. Dominant defects are easily controlled by eliminating all defective animals.

Incomplete dominance creates three kinds of animals — normal, slightly abnormal, and severely abnormal. The normal and the severely abnormal animals breed true. The slightly abnormal animals, when mated together, produce ¼ normal progeny, ½ slightly abnormal progeny, and ¼ severely abnormal progeny. The disease is easily controlled by eliminating all abnormal progeny.

Overdominance is like incomplete dominance, in that three kinds of animals are produced, normal, superior, and abnormal; normal and abnormal animals breed true. The superior animals, when mated with other superiors produce ¼ normal, ½ superior, and ¼ defective offspring. The superior animals usually are selected as replacements in preference to normal animals but at the cost of losing 25% of their offspring from like mates because they are defective. Overdominant traits are difficult to control because all superior animals also carry the undesirable gene and owners are reluctant to choose inferior breeding animals.

A few reports describe characteristics linked with sex. Another class of genetic diseases is caused by chromosomal aberrations. However, structural and numerical aberrations of chromosomal material have not yet reached the diagnostic significance encountered in man.

To summarize, genetically-caused diseases run in families — in typical intergenerational patterns and intragenerational family frequencies. Various statistical methods are used to analyze such data. Test matings are necessary to confirm the inheritance pattern.

Identifying the cause may be difficult and failure to do so results in diagnostic and control problems. Veterinarians are required to advise on control that may include adjusting breeding programs if the defect is hereditary, or altering hard management practices if it is environmentally-induced.

Studying congenital defects - nature's experiments - may contribute much to our understanding of normal and pathological development as man's planned experiments. The wide variety of congenital defects is amazing as they may affect all body structures and functions.

## Kansas Genetic Disease Program

The Kansas genetic disease program consist of the following: gathering and recording information, analyzing and interpreting information, and communicating and using results. Epidemiology of genetic defects has to be considered in three etiological contexts: unknown, suspected, and known causes. All three categories are handled in our system.

I. *Gathering and Recording*

Initial case reports are received in many forms from veterinarians, breed organizations, AI organizations, extension personnel, and herd owners and are recorded in chronological order. Histories including breed, age of parents, parentage of affected and unaffected control calves, geographic region, season, type of pasture, soil type, exposure to, or suspected exposure to teratogenic plants, feeding and management practices, breeding records, maternal medical and vaccination records, disease status of herd, periods of stress, drugs administered, congenital defects observed previously, and history of any similar congential defects in neighboring herds.

All defective calves are subject to standardized necropsy, and the defects are classified by body system primarily involved. Serum samples are taken to check for bovine virus diarrhea, and other viral antibodies. Samples of brain and other tissues are taken for possible virus isolation. Fluorescent antibody techniques are also employed. Histologic examination is done and selected cases are submitted for electron microscopic studies.

Breeding records may be analyzed for evidence of inbreeding and for characteristic intergenerational transmission patterns and intragenerational frequencies. Etiologic diagnosis is made after the results of all the above tests have been carefully considered. Results are filed in a central abnormality file.

II. *Analysis and Interpretation*

Preliminary analysis and interpretation are made during the gathering and collecting phase proceeding through the following steps:

1. Check to see whether a similar abnormality has been reported among a bull's offspring.
2. Check the case against similar cases recorded in central abnormality file.
3. Check the literature file for reports of similar defects in cattle.
4. Check literature in other species (man and animals).
5. Check all herd health data, necropsies and other tests as outlined above.

III. *Communication and Using Results*

Communicating and using results consist of the following points: Many genetic defects have not been clearly identified to date and await description and clarification. A single undesirable recessive trait can rapidly become a real problem in a breed of cattle. Maintenance of a recording system by breed organizations, AI centers and other institutions is the most efficient and least expensive way to monitor undesirable traits.

If evidence on a bull is presented that he carries an undesirable recessive gene, most organizations proceed to label the bull as heterozygote and remove him entirely from service. If he is not removed, advertisement material should carry infor-

mation concerning the congenital defect. Sometimes it is desirable to test a bull for a recessive gene before he is used. If the bull is of standard phenotype, he may be bred to unknown populations. Occurrence of defects would justify removal from AI service or at least labeling the bull. The suspected bull may be bred to known heterozygotes for a trait, to his own daughters, or to abnormal homozygous individuals that survive to reproductive age. These tests are time-consuming and expensive but they are much less expensive than trying to control a defect after it has spread insiduously through a cattle breed.

For study and testing of bulls or females for genetic skeletal defects such as polydactyly or syndactyly, combination of superovulation, embryo transfer, and preterminal cesarean section; saves considerable time and reduces expenses (10, 25, 44-45, 73).

The practicing veterinarian has a central role in the control and prevention of genetic diseases in cattle. He should strongly discourage use of genetic carriers in breeding programs. He should also strongly discourage use of breeding animals which have been treated for genetic disorders. He should furthermore encourage notification of such genetic problems to breed associations and AI centers. He should also readily respond to requests for advice from cattle breeders. Much more information is needed on incidence and nature of various congenital defects. Only the practicing veterinarian is in a position to help collect these data. The first step in the control of genetic diseases is diagnosis of the defect and the determination of its mode of inheritance.

## Some Congenital Defects of Current Interest and Concern

The following section reviews a sample of defects of current interest and concern and contrasts these to known defects of known environmental origin. This list is not complete but gives some inside in some of the genetic diseases in beef and dairy cattle. Most breed organizations have listings of their concern available to breeders and veterinarians.

## Genetic Diseases of the Skin

Most congenital diseases of the skin described in cattle have a genetic cause. Many more exist in various breeds of cattle and will be identified as knowledge expands. Nature, cause, and frequency of bovine skin defects were recently studied (72). Coat color inheritance has recently been reviewed (87).

1. *Albinism*

Albino calves were observed in two Charolais herds. The type of albinism was complete and pattern of occurrence was compatible with a simple autosomal recessive gene (43). The calves had pale skin and lacked pigment. The iris was pink and pupils were slit-like and there was an albinotic reflex. The calves were blind in bright daylight due to photophobia. Histologic examination verified the complete absence of pigmentation in skin and eyes (43). Albinism is rare but occurs in all breeds of cattle.

A new albinotic color deficiency was recently identified at KSU. The defect appears to be inherited as a simple autosomal recessive trait. Heterochromia irides in Angus cattle is characterized by brown hair over the entire body surface insetad of black, as is typical for Angus. The muzzle, hooves, scrotum in males, also are brown. The skin surface is brownish to grey. This is particularly obvious at the glabrous skin, such as around eye lids, ear openings, muzzle, anal and reproductive openings. The most distinguishing factor involves iris color, dark black iris of Angus cattle is replaced by a light usually two-colored iris (Figure 1). This gives a double-ringed appearance to the iris when viewed closely: an outer, faintly brown ring and an inner, light blue ring circling the pupil. The pupils always appear constricted in daylight. From a distance, the eyes appear white. The ocular fundus is albinotic. Another incomplete albino trait in Hereford cattle is an autosomal dominant (86). It is associated with ocular defects such as coloboma (86).

2. *Fragility of skin* (Ehlers- Danlos Syndrome)

Fragility of skin occurred in Simmental and Charolais calves from two different herds. It was characterized by extreme fragility of the skin and laxity of joints. Collagenous tissues of the body exhibited fragmentation and disorganization of collagen fibers. Fibroblasts grown from diseased calves contained relatively higher levels of procollagen than fibroblasts of normal calves. Accumulation of procollagen may be due to an insufficiency of procollagen peptidase (72). This defect is seen in various breeds of cattle.

3. *Epitheliogenesis imperfecta*

Shorthorn and Angus calves affected with epitheliogenesis imperfecta had extensive epithelial defects of skin, tongue, buccal mucosa, and hooves (Figure 2). Affected calves died of septicemia. Histologic examination disclosed abrupt transition from normal epidermis to lesions of epitheliogenesis imperfecta. The epidermis adjacent to the defects was hyperplastic with an increase in the germinal layer. Within the defect there was complete lack of epidermis and its adnexal structures and lymphocytes and polymorphonuclear leukocytes infiltrated the defective area. Genealogic data collected were suggestive of simple autosomal recessive inheritance. Epitheliogenesis is a rare defect in beef and dairy calves (72).

4. *Ichthyosis congenita*

The skin of two neonatal Chianina was hairless and covered with irregular large horn plates separated by deep fissures. Horn plates ranging from 1 cm to 8 cm in diameter, measuring 0.5 cm in thickness, were yellow-grey and had a level and smooth surface. The fissures separating the horn plates measured 2 to 8 millimeters in depth. The bottom of the fissures were covered with short stubby hairs upon histologic examination. Excessive hyperkeratosis was seen. Father x daughter matings indicated this defect to be due to homozygosity of a simple autosomal recessive gene. Figure 3 shows a Chianina calf affected with ichthyosis.

5. *Hypotrichosis*

Hypotrichosis was studied in horned and polled Hereford cattle (42). The cases ranged from slightly to severely affected. Secondary changes of the skin were common. The skin was thin and pliable with only few hairs observed per unit area on the lateral and ventral neck, face, ears, thorax, flank, rump, and forehead. The hair coat over the eyelids, around prepuce, umbilicus, and switch of tail was thin, wavy, and silky (Figure 4). Microscopic examination revealed an epidermis 2 to 3 cell layers thick, with dermal papillae poorly differentiated. Frequently, the hair shafts were fragmented and did not conform to the internal contours of the hair follicles.

Hair follicles typically were shallow and evenly cylindrical. In thick sections stained with toluidine blue, Huxley's cells of the hair follicles contained spheroidal microdroplets of semitranslucent, pleomorphic material, abundant in the region of differentiation and transformation of papillary cells into inner and outer hair sheaths (Figure 5). These microdroplets appeared to be electron dense trichohyalin granules. The trichohyalin granules of hair follicle cells from hypotrichotic calves lacked the micro- and macrofilaments usually associated with trichohyalin granules of normal animals. Hypotrichosis

in Herefords is inherited as a simple autosomal recessive trait according to field data and results of breeding trials.

## Genetic Diseases of the Central Nervous System

Congenital defects of the central nervous system are common and of economic significance. Frequency of congenital defects in cattle varies according to breed. Within breeds, such factors as function or structure affected, level of nutrition, environment, age of parents, and management modify both frequency and type of defects. Congenital defects of the central nervous system, skeletal system, and muscular system are most frequently encountered.

Overall frequencies of congenital defects as well as those of structure or function affected are difficult to obtain as many defects are identified only by necropsy examination. Many defects go unnoticed and others are not reported for economic reasons, others occur so rarely as to defy accurate accounting, and frequent reporting of other defects may reflect high interest of the observer rather than high incidence of the defect. Although economic losses due to congenital defects are less than losses due to diseases caused by nutritional or infectious agents, defects may cause considerable economic losses to individual cattle owners. Congenital defects due to genetic causes are particularly important because losses may be repeated generation after generation. The incidence of congenital defects among all calves seems to range from 1/500 to 3/100, with 40-50% born dead.

Nature, cause and frequency of congenital malformations of the central nervous system (CNS) were studied on 117 congenital defects and were recorded in the 97 calves. These defects consisted of 66 cases of internal hydrocephalus, 14 spina bifida, 10 Arnold-Chiari malformation, 10 cerebellar defect, 5 meningoencephalocele, 4 anencephaly, 3 microencephaly, 2 agenesis of corpus callosum, 2 hydranencephaly, and 1 arhinencephaly. Common concurrent anomalies were internal hydrocephalus with multiple ocular defects and myopathy; internal hydrocephalus and arthrogryposis; Arnold-Chiari malformation with spina bifida and arthrogryposis; anencephaly with meningoencephalocele. Other malformations had only a few assoociated anomalies (23). In a second group of 160 calves studied for causes of neonatal death, 35 calves were affected with CNS defects. Internal hydrocephalus was the most common defect in that group.

No satisfactory classification system has been established for CNS defects because multiple organ systems are frequently involved at the same time and causes may be unknown or diverse. CNS defects are classified here into five groups by combining the anatomical and functional approaches: (i) cerebral defects and malformations involving only or mainly the cerebrum; (ii) defects of the cerebellum and brain stem, congenital diseases involving only or mainly the cerebellum and brain stem; (iii) spinal cord defects: (iv) spastic and paralytic diseases; and (v) storage diseases (17).

## Cerebral Defects

*Agenesis of Corpus Callosum*

Isolated cases of this defect have been seen in various breeds of cattle (21). We have encountered the defect mainly in horned Hereford calves (Figure 6).

There are three types of the abnormality: (i) complete absence of the corpus callosum, (ii) partial corpus callosum present anteriorly, (iii) partial corpus callosum present posteriorly. The variations may represent variable gene expressivity, possibly owing to modifying genetic factors (17, 21).

*Anencephaly*

Anencephaly is a malformation involving nonclosure of the anterior portion of the neural tube and failure of the cranium to develop. Anencephaly is a misnomer in neonatal animals for absence of the brain because a normal pons, medulla, and cerebellum or dysplastic vestiges are usually present (17, 20).

*Hydranencephaly*

Hydranencephaly is defined as a complete or almost complete absence of the cerebral hemispheres in a cranium of normal conformation, with the space filled with cerebrospinal fluid surrounded by a thin membranous cerebral tissue (17). A congenital abnormality characterized by hydranencephaly or arthrogryposis, or both, occurs sporadically or as epidemics in calves. Arthrogryposis and hydranencephaly (A-H syndrome) of calves is caused by prenatal infection with Akabane virus (35-37, 53, 54).

Arthrogryposis, defined as permanent abnormal joint contracture, present at birth, includes more than one etiologic or pathologic entity and is worldwide in distribution in all major breeds of cattle. Arthrogryposis of hereditary nature consists of tetramelic arthrogryposis and cleft palate. The contractures of the legs are symmetrical. Prenatal viral infection with Akabane virus can cause arthrogryposis, usually associated with hydranencephaly (35-37, 53, 54).

*Internal Hydrocephalus*

Hyrocephalus, the commonest CNS defect in cattle, is characterized by accumulation of excessive fluid in the cranial cavity within the ventricular system (internal hydrocephalus). Congenital internal hydrocephalus in cattle appears to be inherited in many breeds as a simple autosomal recessive trait.

The basic pathogenesis of hydrocephalus is considered to be a disturbance of the cerebrospinal fluid pathway, but in some cases the pathogenesis is obscure. Stenosis or obstruction of the aqueduct may be caused by an aberrant developmental defect, inflammation, neoplasia, parasitic cysts or abnormal cranial bone development. Hydrocephalus has been observed to be associated with achondroplasia and other forms of dwarfism and also with the amputated syndrome.

Congenital hydrocephalus in Hereford and Shorthorn calves was accompanied by a stenotic aqueduct, cerebellar hypoplasia, myopathy, and multiple ocular anomalies: retinal detachment and dysplasia, cataract, microphthalmia, and persistent pupillary membranes (31).

Hydrocephalus is common in beef cattle and calves affected with internal hydrocephalus are born dead or die within a few days. Results of breeding trials at Kansas State University with Hereford and Shorthorn cattle are compatible with a simple autosomal recessive inheritance. The homozygous affected calves were dead at birth and had internal hydrocephalus, myopathy, and bilateral microphthalmia (Figure 7). Congenital hydrocephalus in Hereford and Shorthorn calves was accompanied by stenotic aqueduct, cerebellar hypoplasia, myopathy, and multiple ocular anomalies: retinal detachment and dysplasia, cataract, microphthalmia, and persistent pupillary membranes. In contrast BVD induced hydrocephalus had different lesions (6-7).

Hydrocephalic horned Hereford calves had reduced body size and weight; narrow, refined facial features, cranial doming; caudodorsal-rostroventral angulation of palpebral fissures, microphthalmia, and protruding edematous tongues Micropolygyrus of the cerebral convexities appears to result from the dorsal evaluation of gyri located within the longitudinal fissure to the cerebral surface Shallow sulci form secondarily. Attenuation of the convolutions on the dorsal

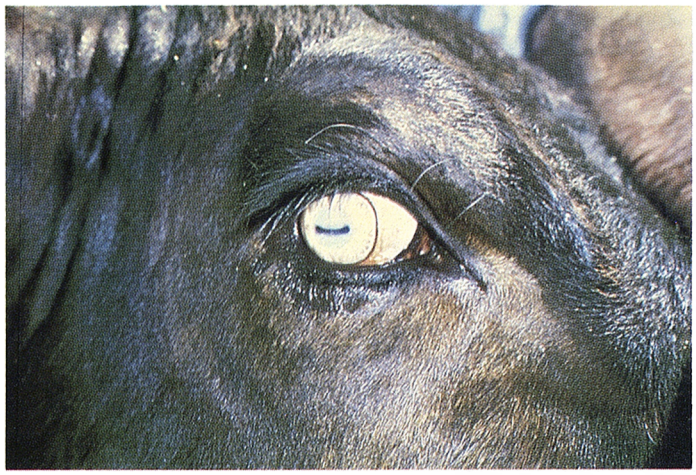

Fig. 1 Heterochromia irides in Angus cattle. Notice reduction of pigment in iris and slit-like pupil indicating photophobia.

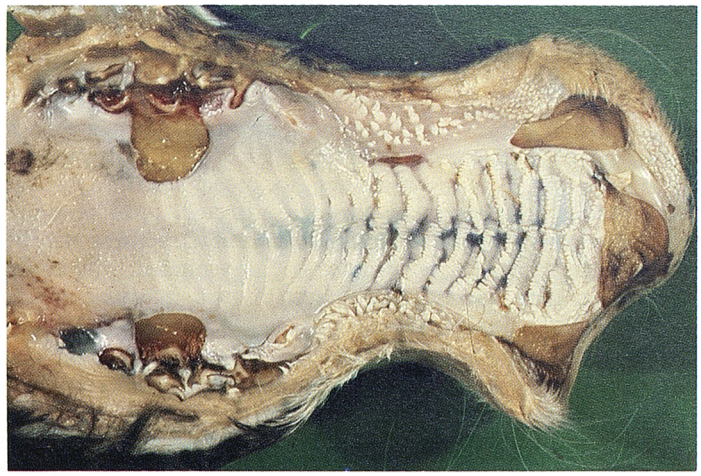

Fig. 2 Epitheliogenesis imperfecta in Angus calf. Notice epithelial defects on hard palate and lips.

Fig. 3 Ichthyosis congenita in Chianina calf. Notice horn-like plaques covering body surface.

Fig. 4 Hypotrichosis in a Hereford calf.

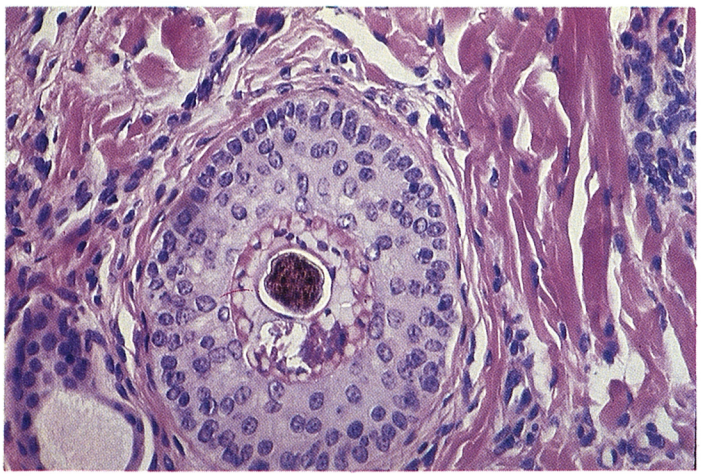

Fig. 5 Cross section of a hairbulb of a Hereford calf affected with hypotrichosis. Notice trichohyaline granules in Huxley's layer of the hair.

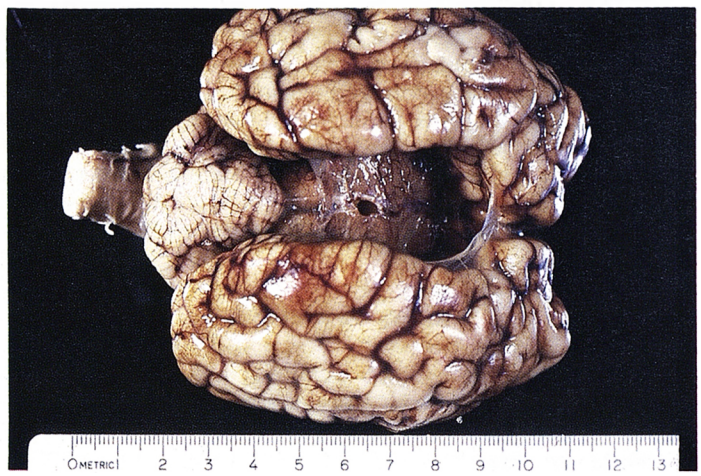


Fig. 6 Agenesis corpus callosum in a Hereford calf. This calf had similar clinical signs to internal hydrocephalus.

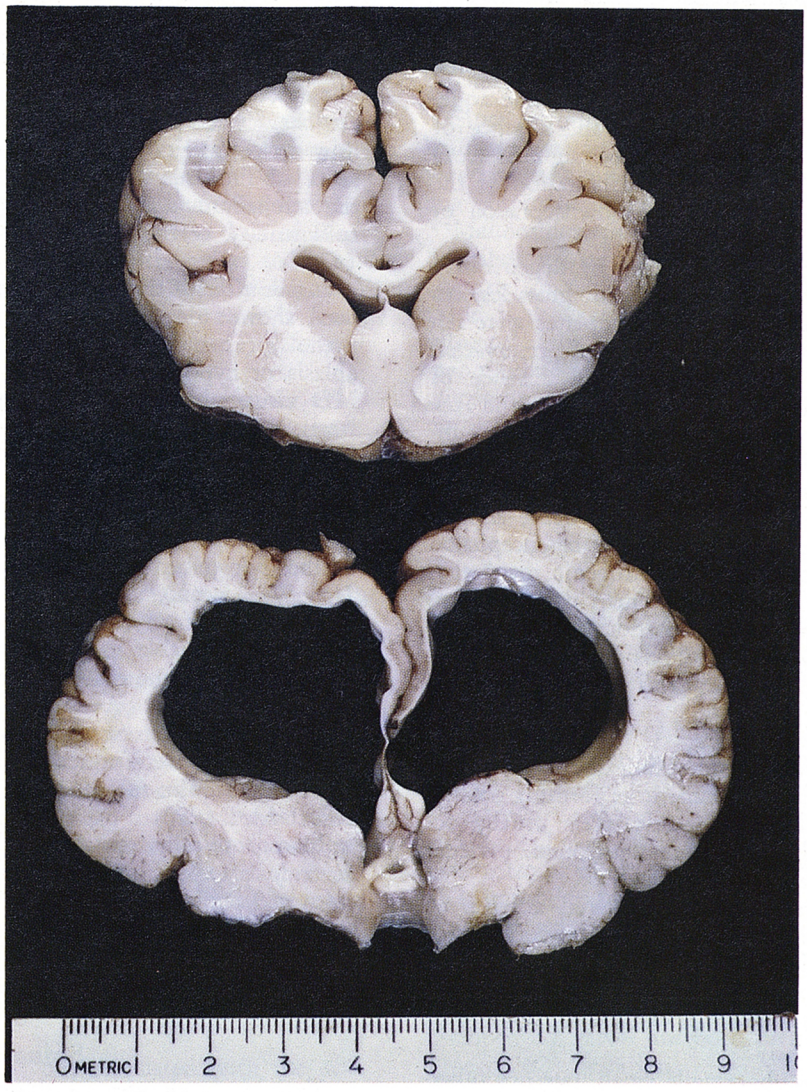


Fig. 7 Cross section of a hydrocephalic brain (bottom) compared to cross section of brain from a normal calf.

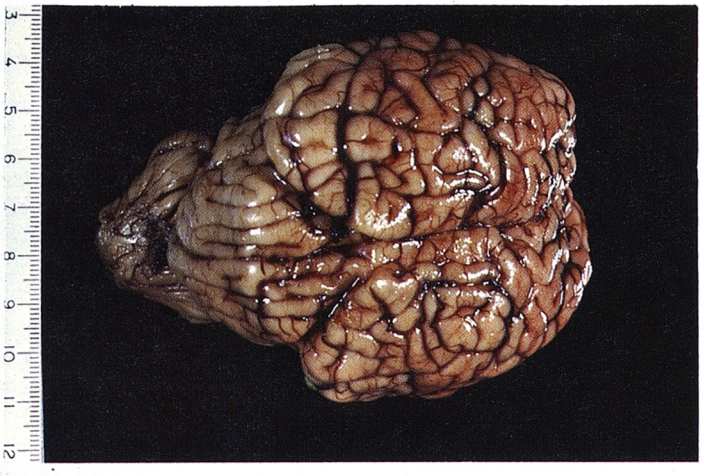

Fig. 8 Brain from an Angus calf affected with Arnold-Chiari defect.

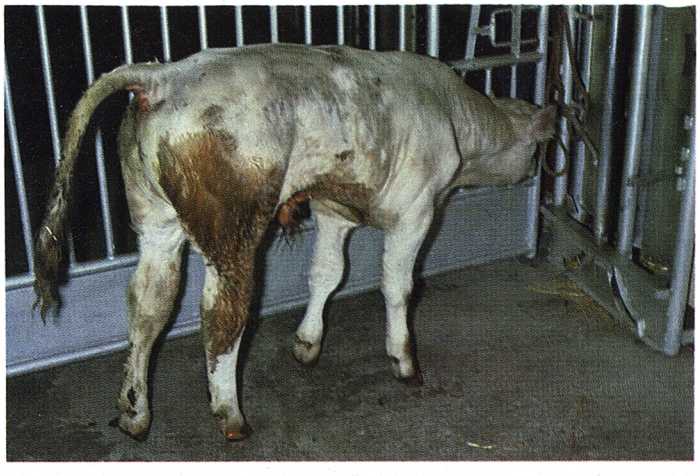

Fig. 9 Charalois calf affected with spastic paresis. Notice stance of hind legs.

cerebral surface and cystic dilation of the optic chiasma were presumably the effects of pressure of severe internal hydrocephalus (5).

Mesencephalic kinking at the anterior portion of the aqueduct, lateral splaying of the dorsal thalamus, and absence of the interthalamic adhesion are features. The sigmoid configuration of the brain and the splaying configuration of the thalamus resemble the cephalic flexure and diencephalon of 40-day-old bovine embryos, respectively (5).

Most major skeletal muscles were affected by degenerative lesions. The quadriceps has the most consistent gross lesions. Although terminal nerve fibers and motor endplates were not examined, grouped distribution of atrophic fibers, preservation of neuromuscular spindles and cross striations, absence of lipid replacement, little or no inflammatory response, and lack of regeneration were compatible with neurogenic atrophy. Innervation of skeletal muscle takes place during early fetal life, however, it plays no part in muscle morphogenesis. Later in gestation, muscle becomes dependent on its nerve supply. Primary maldevelopment and hypoplasia of the mesencephalon is thought to be the cause of apparent neurogenic myopathy. Muscular development and movement in man develops progressively from cephalic to caudal portions, providing a plausible explanation for the severe lesions in the quadriceps (5). Other types of internal hydrocephalus do occur (8-9, 17, 31-32, 34-35).

*Meningocele and Meningoencephalocele*

Meningoencephalocele refers to protrusion of meninges and brain tissue through a cranial cleft sometimes forming a large liquid-filled sac(17, 29). Meningoencephalocele usually occurs in the frontal region, but some are midfrontal, parietal, or occipital (17).

Tibial hemimelia is characterized by bilaterial absence of tibias and associated defects such as meningoencephalocele and reproductive system abnormalities. This syndrome results from homozygosity of a simple autosomal recessive gene and occurs in Galloway and Simmental cattle (68, 69).

*Microencephaly or Microcephaly*

This anomaly refers to an abnormally small, but not otherwise glossy deformed brain or head. It is a rare defect, but it has been described in Hereford calves as reviewed (17). The normal-sized cranial cavity was only partly filled by the brain, all parts of which were greatly reduced. The most striking abnormality was in the cerebrum, which was characterized by a decrease in the number of gyri and absence of the corpus callosum and fornix (17).

## Defects of the Cerebellum and Brain Stem

*Arnold-Chiari Malformation*

The Arnold-Chiari malformation consists of a herniation of tongue-like processes of cerebellar tissue through the foramen magnum into the anterior cervical spinal canal with caudal displacement and elongation of the medulla oblongata, pons and the 4th ventricle (Figure 8). It is often accompanied by spina bifida, hydrocephalus and meningomyelocele.

Pathogenesis of the defect is obscure (17, 18).

*Cerebellar aplasia, or hypoplasia and degeneration*

As reviewed, cerebellar hypoplasia was first described as a genetic defect in Herford calves, many possibly hereditary cases have been documented in Hereford, Ayrshire, Shorthorn, Angus, and unknown breeds (17). The clinical signs, usually present at birth, are characterized by recumbency with extended limbs, intermittent opisthotonus, and ataxia. The mode of inheritance appears to be simple autosomal recessive.

Macroscopically the cerebellum is absent or small and tough, the surface often appears smooth, and on cross-section the folia of the cortex are small and narrow. The cerebral hemispheres and brain stem appear normal. Microscopic changes are characterized by narrow and irregular folia, abnormally thin molecular and granular layers, and almost complete absence of Purkinje cells. In the most severely affected cases, the cerebellum is not visible grossly (cerebellar aplasia), but rudimentary cerebellar tissue may be found microscopically (17).

In addition to the genetic aetiology, numerous viruses have been shown to produce congenital defects in animals. The pathological changes in the allegedly genetic form of cerebellar aplasia or hypoplasia seem to differ from those of the BVD-MD virus-induced cerebellar defect. The ocular lesions and large irregular cavities in the folial white matter and the inflammatory processes observed in cases of BVD-MD viral origin have not been described in those of the genetic form, while cerebella aplasia has not been seen in the viral cerebellar hypoplasia and degeneration (17). Cerebellar cortical atrophy has been described in a Charolais calf (19).

*Hereditary neuraxial edema and congenital brain edema*

Polled Hereford calves affected with hereditary neuraxial edema were unable to raise their heads, lay quietly without struggling and showed incoordination and coarse muscular tonic contractions. A sudden touch or loud noise elicited vigorous extension of the legs and neck. Withdrawal and patella reflexes were present. All were able to suck their dams when aided. The subject has been reviewed recently and new cases added (22).

Macroscopically, most of the brains appeared normal. More severely affected brains appeared swollen. A microscopic spongy vacuolar appearance of the central nervous tissue was widespread along the long axis of myelinated fibres in the white and grey matter. Myelination appeared slightly deficient but glial or microglial reactions were not present. The lesion was interpreted as being caused by edema.

## Spinal Cord

Various developmental spinal cord defects of calves have been described under the terms spina bifida and spinal dysraphism (status dysraphicus) (16-17, 24, 61). Spina bifida implies a defect of the vertebrae with or without spinal cord anomalies. Spinal dysraphism is a myelodysplasia or a malformation of the spinal cord especially of the central canal, with or without involvement of vertebrae (16, 17).

Spina bifida is defective closure of the dorsal vertebral arches, which has been described infrequently in cattle and occurs most frequently in the lumbar region, but may be at any point along the vertebral column. It has been described in several breeds of cattle (16, 17). Other associated defects are hydrocephalus, Arnold Chiari defect, arthrogryposis, neuromyodysplasia, kyphoscoliosis, lordosis, cleft plate, and taillessness.

## Spastic and Paralytic Diseases

This group of diseases includes those with clinical evidence implicating CNS involvement and genetic studies indicate a hereditary basis. The diseases in this group may virtually be functional disorders (17).

*Spastic paresis*

Spastic paresis is characterized by spastic contracture of the muscles and extension of the stifle and tarsal joints of the affected hindlimb(s), and thus has been referred to as "contraction of the Achilles tendon," "straight hock," and "Elsoheel". Spasticity characteristically affects the gastrocnemius

and superficial flexor muscles and tendons, but in some cases the biceps femoris, semitendinosus, semimembranosus, quadriceps, and abductor muscles may be involved. Usually the clinical signs indicate a unilateral condition, with the right hind limb being more frequently involved; bilateral involvement seems less common. This progressive disease varies in severity and time of onset and occurs in calves from three to six months of age or as late as two years or later. Sometimes the abnormality of gait is found in the first few days of life, but it usually is not seen until calves are six weeks to eight months old when it becomes more obvious. Severely affected calves may exhibit a pendulous, contracted limb entirely free from the ground (Figure 9). It is found in many different breeds of cattle.

Although spastic paresis is assumed to be genetic, the evidence is inconclusive. Initially it was thought to be inherited as a simple recessive, however, genetic influence(s) as well as environmental factors play an important part. Some investigators advise that animals with straight hocks and with greater hock joint angles should not be bred because both hock conditions predispose to spastic paresis. Most recently the role of trace elements such as lithium was discussed (4).

*Spastic syndrome*

The spastic syndrome, also referred to as the remittent or periodic spastic syndrome, crampy neuromuscular spasticity, posterior paralysis, progressive posterior paralysis, or stretches, is a chronic, progressive disease characterized by intermittent spastic contraction of the back, neck, and front legs. Between attacks, muscle function is normal, however complete recovery never occurs. Many animals affected with the spastic syndrome have straight rear limbs and weak hocks, the conformation observed in animals affected with spastic paresis. Such conformation appears to favor arthritis, foot disease, and lameness. The spastic syndrome has been observed in some cattle with spondylosis (17).

## Metabolic Diseases

*Storage Disease*

A lysosomal storage disease is one associated with the accumulation and storage of some substance within lysosomes due to enzyme deficiency preventing a specific catabolic reaction. Criteria for a disease to be classified as an inborn error of lysosomal catabolism are: (i) the disease should be a storage disease; (ii) it should be inherited; (iii) the storage substance, not necessarily homogeneous, should be stored at least initially within lysosomes; (iv) there should be partial or absolute deficiency of one of the lysosomal enzymes, which would normally hydrolyse the storage material as reviewed recently (47-49).

Such a disease is mannosidosis, originally reported as pseudolipidosis, associated with a deficiency of mannosidase and occurs in Angus cattle as a simple recessive (46-49, 71). A deficiency of mannosidase results in storage of an oligsaccharide containing glucosamine and mannose (47).

Clinically, the disease is characterized by ataxia, incoordination, head tremor, aggression, and failure to thrive. Calves may be affected at birth, but usually clinical symptoms do not appear until they are several weeks or months old (49, 71).

Most affected cattle die within the first 12 months of life. However, $\alpha$-mannosidosis is also a cause of neonatal mortality in Angus calves. The primary lesions is vacuolation of neurons with vacuoles formed from saccular dilations of the Golgi apparatus. Secondary lesions include spheroidal swellings of axions due to local accumulations of electron-dense bodies, mitochondria, and a local proliferation of neurofilaments. PAS-positive, lipofuscin-like globules occur frequently within astrocytes, microglia, and pericytes of blood vessels. Vacuoles also occur in macrophages of the lymph nodes (11, 46).

Since affected calves have an absolute deficiency of $\alpha$-mannosidase, and heterozygotes have a partial deficiency of this enzyme, mannosidosis can be controlled by identifying and eliminating heterozygotes (47-49, 71).

Mannosidosis in Angus and Murrey Grey cattle, originally described in Australia and New Zeland, has recently been recognized in the United States (71). Mannosidosis in Angus cattle is associated with a deficiency of mannosidase and is inherited as a simple autosmal recessive. The deficiency of mannosidase results in storage of an oligosaccharide containing glucosamine and mannose in neurons and other cells. Mannosidase activity is used to test cattle for normal activity (homozygous) and reduced activity in heterozygous individuals (46-49, 71).

## Skeletal Defects

Congenital defects of the skeletal system are common and of economic significance. The entire skeletal system may be affected as in osteopetrosis or single defects may be affecting facial, axial or appendicular skeleton.

*Osteopetrosis*

Osteopetrosis, a generalized skeletal defect is seen in purebred and grade red and black Angus calves, Hereford calves and has been seen in one Simmental calf (33, 40, 58). Affected calves are stillborn, have long bones which are solid, fragile and lack bone marrow cavities (Figure 10). Externally, osteopetrotic calves may be recognized by a short lower jaw and impaction of molar teeth. Congenital osteopetrosis is characterized by excessive formation of primitive endochondral bone, but complete lack of bone resorption. It is due to homozygosity of a simple autosomal recessive gene. Osteopetrosis may be mistaken for an abortion problem because osteopetrotic calves are born prematurely at 251 to 272 days (mean 262) gestation.

Syndactyly or mulefoot is defined as fusion or nondivision of functional digits. It is due to homozygosity of a simple autosomal recessive gene with incomplete penetrance and varying degrees of expressivity and pleiotrophic effect (1-3,-44, 55, 57, 63, 75, 85). It is the commonest inherited skeletal defect of Holstein cattle in the United States. It is also seen in Angus, Chianina, Simmental and Crossbred cattle. Syndactyly affects in Holstein cattle most frequently the right front foot, followed by the left front and then hind feet (Figure 11). Syndactylous cattle are susceptible to stress in particular higher ambient environmental temperature.

A program developed to test syndactyly in Holstein and Angus cattle uses superovulation of homozygous affected, syndactylous cows; insemination with semen of bulls to be tested, embryo transplant, and preterminal cesarian section (10, 44). Females may be tested by using semen from affected bulls, embryo transfers, and by early fetal recovery (74).

*Polydactyly*

Polydactyly is defined as an increased number of digits. It is a common defect in domestic animals including cattle. In cattle, although all four feet may be affected, there is a predilection for the front feet. Polydactyly affecting front feet in Simmental cattle has been studied using superovulation, embryo transfer, and recovery of fetuses at 70 days of gestation. Polydactyly seems to be inherited as a polygenic (25,-45).

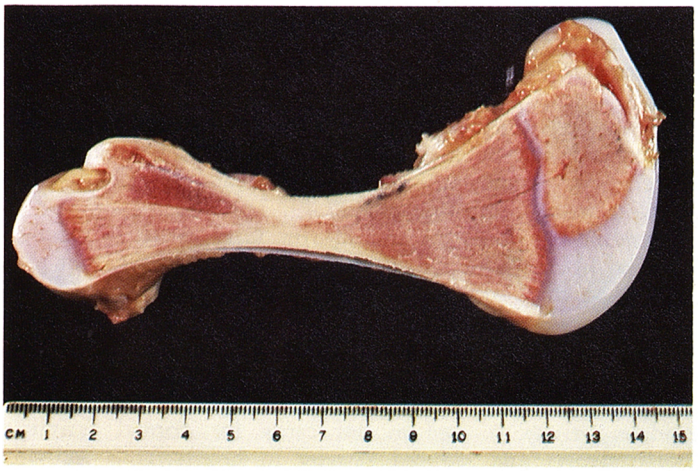

Fig. 10 Longitudinal bisection of a femur of an Angus calf affected with osteopetrosis. Notice solid bone and lack of bone marrow cavity.

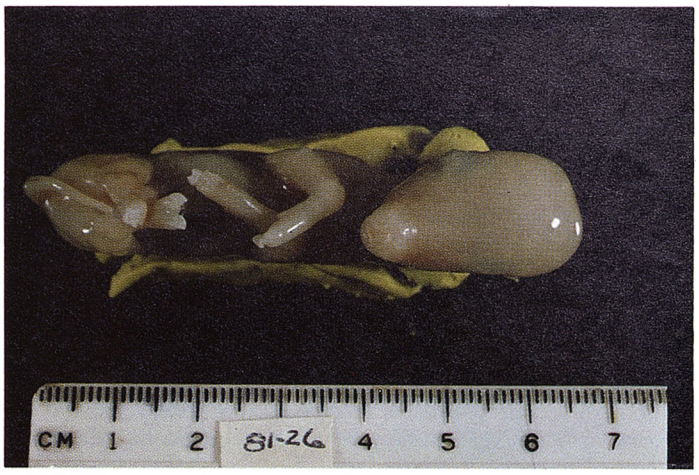

Fig. 11 Sixty day Holstein fetus affected with syndactyly. Notice syndactyly of right and left front feet and right hind foot. Left hind foot is normal.

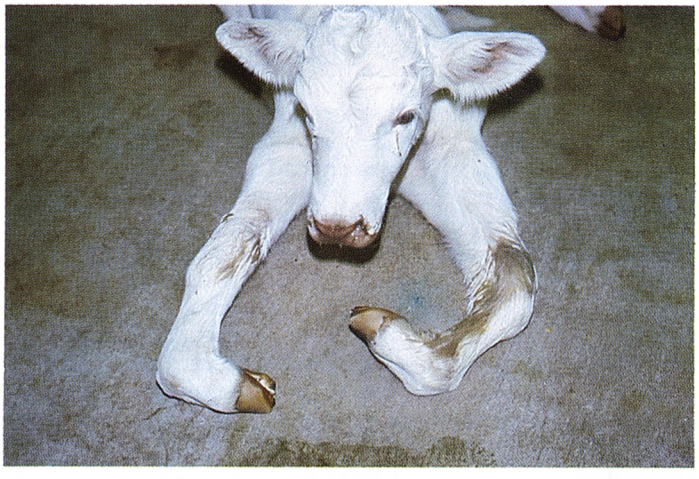

Fig. 12 Arthrogryposis in a Charolais calf. The calf was also affected with cleft palate.

Fig. 13 Weaver condition in Brown Swiss cattle.

Fig. 14 Photodynamic dermatitis in a Limousin bull affected with protoporphyria.

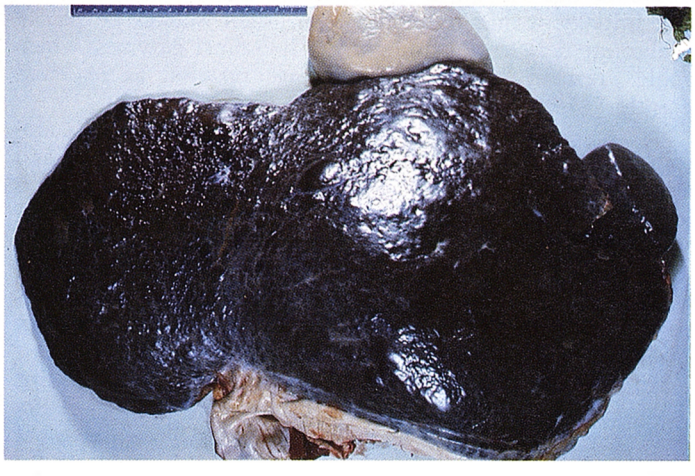

Fig. 15 Cirrhosis of liver from bull in figure 14.

Fig. 16 Recto-vaginal constriction (RVC) in a Jersey heifer. Notice that examiner is not able to perform normal rectal examination.

*Tibial Hemimelia*

A syndrome, encountered in Galloway cattle consists of bilateral tibial hemimelia, ventral abdominal hernia, cranioschisis, and meningocele, and defects of the reproductive system (68-69).

## Defects of the Muscular System

*Arthrogryposis in Calves*

Congenital defects characterized by contracture of legs (arthrogryposis) occur frequently in calves and may be inherited as a simple autosomal recessive trait (28). Nonhereditary examples of arthrogryposis have been studied (35-36, 52, 67, 101).

Arthrogryposis, defined as permanent abnormal joint fixation, present in the arthrogrypotic syndrome includes more than one etiologic or pathologic entity and is worldwide in distribution in all major breeds of cattle (30, 35-37, 56, 59,-62, 70, 83). Arthrogryposis of hereditary nature consists of tetramelic arthrogryposis and cleft palate (28). The contractures of the legs are symmetrical. Prenatal viral infection with Akabane virus can cause arthrogryposis, usually associated with hydranencephaly (35-37).

A recent study summarized the importance of the arthrogryposis syndrome in cattle (83). Arthrogryposis, studied during a 3-year period totaled 76 malformed arthrogrypotic calves. Investigations for environmental factors were negative. However, analysis of pedigrees and matching which produced arthrogrypotic calves confirmed that the arthrogryposis syndrome (contracture of legs and cleft palate) in Canadian Charolais calves is due to an autosomal recessive gene with complete penetrance (83). These findings are similar to those in the United states (30, 62).

*Weaver*

The weaver condition is a familial neuro-muscular disorder in Brown Swiss Cattle. Clinical signs (a weaving gait) appear when calves are 6 to 8 months old and progress the next 12 to 18 months to recumbency (Figure 12). Muscular lesions affect mainly the large muscle masses of the hind legs (64).

The weaver condition is common in Brown Swiss cattle and is most likely inherited as an autosomal recessive trait.

## Other Defects

*Protoporphyria*

Protoporphyria is a photosensitizing disease in Limousin cattle caused by homozygosity of a simple autosomal recessive gene. Heterozygote animals may be detected by breeding trials, determination of ferrocheletase activity in a variety of tissues or fibroblast cultures, and quantitation of free-protoporphyrin in circulating red blood cells (93).

Limousin cattle affected with protoporphyria may have photodynamic dermatitis (Figure 14). Cattle affected with protoporphyria may have ataxia and seizures. Furthermore, protoporphyric cirrhosis of the liver may occur in Limousin cattle affected with protoporphyria (Figure 15). Thus, there is a great similarity to human protoporphyric patients where a wide variation among patients has been noted in this genetic disease (100).

Protoporphyria has been reported as an autosomal dominant disease in man (13). Measurements of heme synthase activity in sonicates of cultured skin fibroblasts and whole liver homogenates from protophorphyria, heterozygous and normal cattle indicate that the disease is caused by homozygosity of a simple autosomal recessive gene (13).

## Recto-vaginal constriction in Jersey Cattle

Recto-vaginal constriction affects anus and vulvo-vestibular area of Jersey cows. It is a simple autosomal recessive condition. The defect is characterized by inelastic constrictions at the junction of the anus and rectum and the vestibule and vulva (Figure 16). The bull has stenosis of the anus. Cows are unable to calve naturally and calves are usually taken by C-section or episiotomy. Rectal examinations are difficult to perform on these animals (65, 75).

In addition, Jersey cows affected with rectovaginal constriction are prone to develop udder edema at calving time frequently followed by severe mastitis.

## Congenital atresia of the gut

Recent work in Germany indicated that atresia coli may be caused by rectal palpation (84, 86). Results obtained thus far indicated that palpation of the amnionic sac around day 40 of gestation could cause atresia coli in calves (84, 86).

## Conclusions

Animal breeders and veterinarians are involved every day in the improvement of animal health and production. The goal is to produce a quality pet or working animal or to improve dairy and meat production. Accurate diagnosis of diseases and defects, partly or wholly caused by genetic factors, is necessary before control measures can be established. Such diagnosis involves understanding of hereditary patterns of disease. Many different congenital defects, either of genetic, environmental, or unknown cause or due to environmental-genetic interaction have been identified in cattle. It is important to recognize congenital defects which are of economic significance to the cattle breeding industry. Not only is diagnosis important but methods to control genetically induced defects in cattle should be available. Most cattle breed associations and artificial breeding organizations have programs for controlling undesirable traits and genetic defects.

The Kansas genetic disease program consists of the following: gathering information, recording information, analyzing and interpreting information and communicating and using the results. Recent genetic diseases of concern are hypotrichosis, arthrogryposis with cleft palate, weaver condition, recto-vaginal constriction, internal hydrocephalus, mannosidosis, osteopetrosis, tibial hemimelia, polydactyly, and syndactyly. They are the diseases used here to illustrate their diagnosis and control in cattle populations.

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