APMIS

SUPPLEMENTUM NO. 122, VOL. 115, 2007

Inherited Disorders in Danish Cattle

by
Jørgen S. Agerholm

Department of Veterinary Pathobiology
Faculty of Life Sciences
University of Copenhagen
Bülowsvej 17
DK-1870 Frederiksberg C
Denmark

Blackwell Munksgaard 2007

This dissertation is based on the following 10 original articles, which are referred to in the text by their roman numerals (I–X):

I: Agerholm JS, Houe H, Jørgensen CB, Basse A. Bovine leukocyte adhesion deficiency in Danish Holstein-Friesian cattle. II. Pathoanatomical description of affected calves. Acta Vet Scand 1993;34:237–43.

II: Agerholm JS, Lund AM, Bloch B, Reibel J, Basse A, Arnbjerg J. Osteogenesis imperfecta in Holstein-Friesian calves. J Vet Med A 1994;41:128–38.

III: Agerholm JS, Hafner A, Olsen S, Dahme E. Spinal dysmyelination in crossbred Brown Swiss calves. J Vet Med A 1994;41:180–8.

IV: Agerholm JS, Andersen O. Inheritance of spinal dysmyelination in calves. J Vet Med A 1995;42:9–12.

V: Agerholm JS, Bendixen C, Andersen O, Arnbjerg J. Complex vertebral malformation in Holstein calves. J Vet Diagn Invest 2001;13:283–89.

VI: Agerholm JS, Arnbjerg J, Andersen O. Familial chondrodysplasia in Holstein calves. J Vet Diagn Invest 2004;16:293–8.

VII: Agerholm JS, Bendixen C, Arnbjerg J, Andersen O. Morphological variation of "complex vertebral malformation" in Holstein calves. J Vet Diagn Invest 2004;16:548–53.

VIII: Agerholm JS, Andersen O, Almskou MB, Bendixen C, Arnbjerg J, Aamand GP, Nielsen US, Panitz F, Petersen AH. Evaluation of the inheritance of complex vertebral malformation syndrome by breeding studies. Acta Vet Scand 2004;45:133–7.

IX: Leifsson PL, Agerholm JS. Familial occurrence of bovine dilated cardiomyopathy in Denmark. J Vet Med A 2004;51:332–5.

X: Rude H, Agerholm JS, Maddox-Hyttel P, Christensen K, Flagstad P. Renal lipofuscinosis in Danish slaughter cattle. J Comp Pathol 2005;132:303–12.

APMIS Suppl. 122: Vol. 115, 2007
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ISSN 0903-4641

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Preface

My research on bovine inherited disorders began in January 1989 when I started my PhD studies at the Royal Veterinary and Agricultural University in Copenhagen, Denmark (now Faculty of Life Sciences (LIFE), University of Copenhagen). These studies focused on the occurrence of inherited diseases and congenital malformations in Danish cattle, and formed the basis of my postgraduate education within the field of veterinary special pathology and research methodology. After this period, the cattle breeding associations continued to finance my further research during my employment at the Danish Veterinary Institute (now National Veterinary Institute, Technical University of Denmark) (1992–2000) and from 2000 at the Royal Veterinary and Agricultural University. Although I have studied other areas of veterinary pathology, genetic disorders in cattle became my primary research area, and throughout the years I have devoted my time to this subject. Now – 18 years after my introduction to inherited disorders and after publication of a PhD thesis and 24 international publications on that subject – I have written my dissertation. I have selected 10 articles as the basis. These articles focus on my main contribution to the subject: the morphology of inherited disorders, their inheritance, and the identification of affected breeding lines. The aim is to summarise the results of my research and to provide an updated review of inherited disorders in Danish cattle, focusing on the above areas. Other researchers have published comprehensive international reviews of inherited disorders in cattle, and it is not my intention to compete with their substantial contributions. My work is rather meant to be complementary to these reviews, and they should be consulted for aspects not included here. It is my hope that this dissertation will provide valuable information for veterinary surgeons, scientists, and breeding associations, and inspire others to enter this important and interesting field.

The diversity of my research has brought me into contact with many people, to whom I should like to express my gratitude. Many deserve to be mentioned, but I must confine myself to the few. First of all, I thank *Axel Basse*, who originally introduced me to veterinary pathology and infected me with his unlimited enthusiasm. I should also like to express my sincere thanks to my co-workers throughout the years: *Knud Christensen* for inspiring discussions and invaluable help with statistics, *Jens Arnbjerg* for interpreting the radiographs, and *Ole Andersen* for his continuing collaboration and support.

It would not have been possible to conduct these studies without the help of the breeders and veterinarians who submitted animals for examination, or without the help of the cattle advisers and technicians who provided pedigrees, breeding data, and other valuable information. Many thanks are due to my colleagues and the technical staff at the former Danish Veterinary Institute, and at LIFE, for their tremendous assistance. I also wish to thank the scientists and laboratory staff at the former Danish Institute of Agricultural Sciences for their cooperation and for providing results on parentage control and genotyping. Danish Cattle and the breeding associations are acknowledged for their collaboration and for their financial support. Sincere gratitude is extended to the management of Danish Cattle, the breeding associations, the former Danish Veterinary Institute, and the Department of Veterinary Pathobiology, LIFE, especially *Henrik Nygaard*, *Thorkild Lykke*, *Knud Børge Pedersen*, *Helge V. Krogh*, *Thomas Krogh Nielsen*, *Henrik Elvang Jensen* and *Christian Friis*, for making the studies possible.

Last – but certainly not least – I should like to express my heartfelt thanks to my wife *Suzanne* and to my sons *Rasmus* and *Morten* for having listened patiently to exhausting stories of dead calves throughout the years.

Jørgen S. Agerholm
Copenhagen, June 2007

Abbreviations

The use of abbreviations for inherited syndromes has been limited to Chapter 5, where abbreviations are used when appropriate in the sections referring to specific disorders. The abbreviations are defined at the beginning of each section. Elsewhere, designations have been written in full to achieve a greater degree of reader friendliness.

Country abbreviations are used attached to herd book numbers to indicate the nationality of the animal. The following abbreviations are used:

CAN:	Canada
D:	Germany
DK:	Denmark
F:	France
NLD:	The Netherlands
I:	Italy
S:	Sweden
US/USA:	United States of America

Symbols

- □ Homozygous normal male
- ○ Homozygous normal female
- ◇ Homozygous normal individual of unknown sex
- ◧ Heterozygous male
- ◐ Heterozygous female
- ◆ Heterozygous individual of unknown sex
- ■ Homozygous affected male
- ● Homozygous affected female
- ◆ Homozygous affected individual of unknown sex
- ···· Animals of similar sex and genotype as the previous animals
- * Within a symbol refers to an animal of unregistered descent

Danish designations

Several inherited disorders found in Danish cattle have been given designations in Danish. These names often refer to the clinical manifestation of the disorder. Such descriptive designations have been used to facilitate communication between veterinarians, breeding associations and breeders. To make this dissertation more useful for readers without a veterinary education and to avoid confusion between Danish and English terms, a list of Danish designations is given.

Bovine progressive degenerative myeloencephalopathy: weaversyndromet
Chondrodysplasia: bulldogkalv
Congenital paralysis: medfødt arvelig lamhed
Ichthyosis foetalis: fiskeskælsyge
Progressive posterior paralysis: staldkrampe
Renal lipofuscinosis: oksens sorte nyrer
Spinal dysmyelination: medfødt lammelse
Spinal muscular atrophy: liggekalvesyndromet
Syndactylism: muldyrfod

Names of institutions

Names used for institutions in this thesis are referring to their names before January 1st 2007 when the Royal Veterinary and Agricultural University merged with the University of Copenhagen and the Danish University of Pharmaceutical Sciences and became the Faculty of Life Sciences, University of Copenhagen. Simultaneously the Danish Institute of Agricultural Sciences merged with the University of Aarhus and became the Faculty of Agricultural Sciences, University of Aarhus and the Danish Institute for Food and Veterinary Research merged with the Technical University of Denmark and a number of other institutions.

1. Introduction

Inherited disorders are of interest in all animal species. However, the intensive use of individual sires in cattle breeding and the structure of bovine breeding programmes make this species especially vulnerable to the effects of undesirable traits. The use of insemination and development of methods for dilution and conservation of semen has established the necessary basis for extensive exploitation of sires with a superior genetic constitution. Such elite sires may produce huge numbers of progeny. Generally, sires used for artificial breeding produce progeny in numbers of hundreds to several thousands depending on the size of the breed and the superiority of the bull. But individual sires may be exploited even more, with insemination numbers above 1 million. It is obvious that such extensive use of individual sires may lead to dissemination of undesirable genes within a breed.

Sires for breeding purposes are often produced by mating of males and females with a superior genetic background. In this way, families of closely related elite sires are created and undesirable recessive genes may be transmitted through the generations. Although close inbreeding is not performed, the extensive use of genetically related sires may lead to a build up of disease alleles in the population and the subsequent occurrence of diseased animals in relatively large numbers. An unrecognised spread of the allele for bovine leukocyte adhesion deficiency occurred in this way for several decades, which subsequently led to an estimated prevalence of 0.46% affected calves in the US Holstein population (156).

Inherited disorders in cattle are mostly caused by autosomal recessively inherited genes. It is characteristic that the action of autosomal recessive genes only becomes expressed as a diseased phenotype if present in both loci. Therefore, autosomal recessively inherited disorders are of greater concern in cattle breeding than are disorders with dominant inheritance or recessive X-linked inheritance. As dominant or recessive X-linked genes are expressed in the phenotype of males, sires carrying such genes are mostly omitted from breeding. However, if the defective allele produces a desirable phenotype in heterozygous individuals, such animals may be used for breeding. A classic example of this is the Dexter breed, in which heterozygous individuals constitute a desirable compact phenotype, while homozygous dominant individuals are aborted due to severe chondrodysplasia (304). In sires, dominant inherited defects may also be present only in a certain proportion of spermatozoa due to gonadal mosaicism. Such sires are phenotypically normal but produce defective progeny in segregation patterns not consistent with simple Mendelian inheritance. Bovine cases of osteogenesis imperfecta are probably the result of this phenomenon (64, II).

Before the development of freezing procedures for semen, cattle breeding was performed by natural breeding or by the use of fresh semen. The geographical distances, infrastructure and means of transportation thus limited the use of individual sires. Consequently, the occurrence of inherited disorders was mostly a local or regional phenomenon. Despite these limitations, international spread of undesirable traits with breeding sires did occur. An early example of this is the skeletal malformation acroteriasis. The gene for this defect was spread in Swedish cattle through the Holstein sire *Gallus M. 77* (born 1890), which was imported to Sweden and founded an important breeding line (309). With the development of methods for semen conservation, inherited disorders changed from mainly having a local effect to having an international effect. This wider perspective means that inherited disorders in cattle have attained international importance.

The methods used in cattle breeding and their implications for the spread of unfavourable genes make surveillance of inherited disorders an important part of bovine health programmes. Such programmes have existed for many years and have widened our knowledge of inherited bovine diseases considerably (10, 180). They are generally based on passive surveillance, which depends on recognition of suspected cases in the herds. Consequently, the identification of inherited disorders is often

positively associated with an increasing gene frequency in the population. Passive surveillance is therefore less able to identify low prevalence disorders. The aim of the surveillance system is to identify some of the consequences of the breeding strategy, but prevention of inbreeding relies on the efficiency of the breeding systems. If an active surveillance program was used this could include examination of progeny obtained through breeding between closely related individuals, which at least should include the highest-ranking breeding sires. Such testing of valuable sires is controversial and is generally not used by breeding associations due to the economic implications of identifying recessively inherited disease genes. It is important to remember that most individuals are assumed to be carriers of recessively inherited disorders (204, 216) and to realize that most recessively inherited diseases occur as a result of inbreeding rather than by the mere presence of disease genes in the population.

In addition to the problems related to identifying disorders of low prevalence, passive surveillance is compromised by the ability to recognise certain disorders in herds. Disorders that are obvious to the breeder or veterinarian are more likely to be recognised than diseases that require detailed examination to be diagnosed. Generally, skeletal malformations, severe neurological disorders, and diseases of the skin are readily recognised, while defects of the internal organs are less obvious and are sometimes only identified accidentally. This is exemplified by the bovine leukocyte adhesion deficiency syndrome, which was not identified by surveillance systems although it occurred in several countries. This lethal syndrome of immunodeficiency was in fact diagnosed by coincidence in a study on mastitis (156), although previous observations had indicated the presence of a familial immunological disorder in Holsteins (275). In addition, passive surveillance is compromised by the age of the animal as an association between clinical signs and a genetic aetiology is more likely to occur in calves than in adult cattle. Also defects causing embryonic or foetal mortality are difficult to recognise although they are probably rather prevalent (298). Nevertheless, genetic disease programmes have documented their value for breeding associations despite the limitations of passive surveillance. This is mainly due to the established cooperation between breeding associations and researchers, which has formed a solid basis for reducing the prevalence of specific inherited defects.

The prevalence of a recessively inherited disorder is mostly reduced by culling or limiting the use of sires that are heterozygous for the defect. Heterozygous individuals can be identified by different methods. Examination of affected progeny by clinical examination or necropsy is a classic method, which in Denmark has been used to identify carriers of, for example, spinal muscular atrophy (8) and spinal dysmyelination (III). Although this method requires several years of progeny examination, it is effective and can identify a wide range of disorders. However, it has a major disadvantage in that the genotype of a sire cannot be determined until progeny are born and reach the age of disease development. The time span can be reduced if the disorder is expressed in the foetus, as, for example, in syndactylism and the arachnomelia syndrome (124, 167). Meanwhile, testing of sires by examination of foetuses is only applicable on a small scale. Therefore, eradication of inherited disorders by progeny examination is for the most part slow. Another method is identification of animals expressing a heterozygous genotype. Some inherited enzyme deficiencies may allow discrimination between genotypes by analysis for enzyme activity in blood. However, due to variation of enzyme activities in animals, differentiation between carriers and normal individuals may not always be possible (143). A third method is genotyping of animals by genomic analysis. Recent developments within molecular biology and genetics have made possible efficient and rapid identification of heterozygous animals by this approach. Different methods have been used in Danish cattle, including genetic markers (226) or testing for a causal base mutation in a gene (149, 279, 280). The Danish breeding associations have efficiently reduced the prevalence of bovine leukocyte adhesion deficiency, complex vertebral malformation, and spinal dysmyelination based on results obtained by these methods, thus demonstrating their superiority to progeny examination.

Due to the severe impact of inherited disorders on breeding programmes and the economic consequences for breeders and breeding

associations, intervention must be based on high quality research. Critical evaluation of research results by external reviewers, i.e. by publication in well-reputed international scientific journals, provides the reliability demanded by the breeding associations. Providing this information must have the highest priority in bovine genetic programmes and is the most important reason for collaboration between scientists and breeding associations. Three fundamental aspects of inherited disorders must be described: 1) the morphology, 2) the inheritance, and 3) the breeding lines affected. The research on which this dissertation is based (I–X) has focused on these three aspects.

Determination of the mode of inheritance is an important goal when studying possible inherited disorders. The mode of inheritance is often indicated by the occurrence in a familial pattern, the sex of affected calves, and the parental phenotypes. Occurrence of defective progeny of both sexes following breeding between genetically related and phenotypically normal animals indicates an autosomal recessive mode of inheritance. However, such an occurrence of a disorder could be due to other causes, i.e. teratogens, and it must be emphasised that such observations are only indicative and must be confirmed. It must also be emphasised that breeding between genetically related animals is so common in cattle that even several cases of a disorder can occur by coincidence in a breeding line. Such an example is provided by research into the complex vertebral malformation syndrome of Holstein calves. The initial studies showed that 17 malformed calves were genetically related to two widely used sires (A: *Carlin-M Ivanhoe Bell* (US1667366); B: *Pawnee Farm Arlinda Chief* (US1427381)) (V). Later, molecular genotyping determined that only *Carlin-M Ivanhoe Bell* was a carrier of complex vertebral malformation (280). This example clearly demonstrates that interpretation of inbreeding requires great caution.

Analysis of segregation patterns is a classic method for evaluation of inheritance. The ratio between affected and unaffected animals can be determined by experimental breeding trials. An example would be experimental breeding between a sire and his daughters. However, it is often possible to select animals from the general population, thus avoiding experimental mating. A prerequisite for this is registered pedigrees and matings in addition to a relatively high number of carriers in the female population. The inheritance of several disorders in Danish cattle has been studied in this way by analysing the segregation following breeding between a heterozygous sire and daughters of another heterozygous bull (224, IV, VIII). Such studies are less expensive than breeding trials, and, as the necessary number of pregnant females is often available in the population, a result can be obtained within a short period of time. However, it is essential that the progeny is available for examination. Increased intrauterine mortality among affected progeny, as seen in, for example, the complex vertebral malformation syndrome (VIII), is devastating for a study, as aborted foetuses mostly remain unexamined. Analysis of segregation patterns for non-congenital disorder may also be problematic. Calves may die due to dystocia or neonatal infections before lesions have developed, or animals may have to be maintained for a long period for lesions to develop. Spinal muscular atrophy (8), renal lipofuscinosis (X) and hereditary dilated cardiomyopathy (IX) are examples of such disorders. Introduction of molecular genotyping in breeding studies may reduce some of these problems, as segregation ratios among genotypes can be determined in the neonatal animals.

The effective interventions made possible by molecular genotyping can rapidly reduce the number of diseased calves in a population. If heterozygous sires are totally removed from a breeding population, defective calves will only be born for an additional 9 months, corresponding to the length of the gestation period in cattle. This effectiveness is a compromising factor for further research into the defect, as additional cases must be produced experimentally. Experimental production is expensive due to the long gestation period of cattle and as cows usually only give birth to a single calf. Breeding between homozygous affected animals is effective as all progeny are diseased. However, this is only possible for non-lethal defects or if treatment of affected animals is possible, as for hereditary zinc deficiency (193). Superovulation and embryo transfer may reduce the number of homozygous affected parents needed, as has been applied to syndactylism (124) and in-

herited congenital myoclonus (128). Breeding between heterozygous animals is another way to produce affected progeny. If parents with confirmed heterozygous genotype of an autosomal recessive gene are used, a segregation ratio between phenotypically normal and affected calves of 3:1 is expected. Consequently, a rather high number of pregnant animals are needed to produce a sufficient number of defective progeny for further studies. Sophisticated laboratory techniques, such as cloning and genotyping of embryos, may prove useful as homozygous affected embryos can be selected, thus reducing the number of cows needed. Due to the economic implications, research into many inherited disorders has relied on the availability of defective animals from the general population and has been performed only over a short period of time. Consequently, many aspects have not been adequately examined. This is not satisfactory from a scientific point of view, but from a breeding point of view the implications are limited, as the lack of affected animals is reflecting a problem that has been solved.

Although the prevalence of a recessively inherited disorder is significantly reduced and may approach zero, the abnormal gene may persist in the population and remain unrecognised for a long period of time. It is thus possible that already characterised defective genes in the course of time can re-enter the population of breeding sires and, unless the sires are tested systematically, an initially concealed increase in gene frequency may develop. The persistence of recessive genes in the female population for decades and the re-occurrence of defective calves following the use of breeding sires that turned out to be carriers has been observed in Denmark. Calves affected by hereditary zinc deficiency (10) or chondrodysplasia (7) (Fig. 1) have appeared in this way. Therefore, persistent surveillance and testing of breeding sires is necessary.

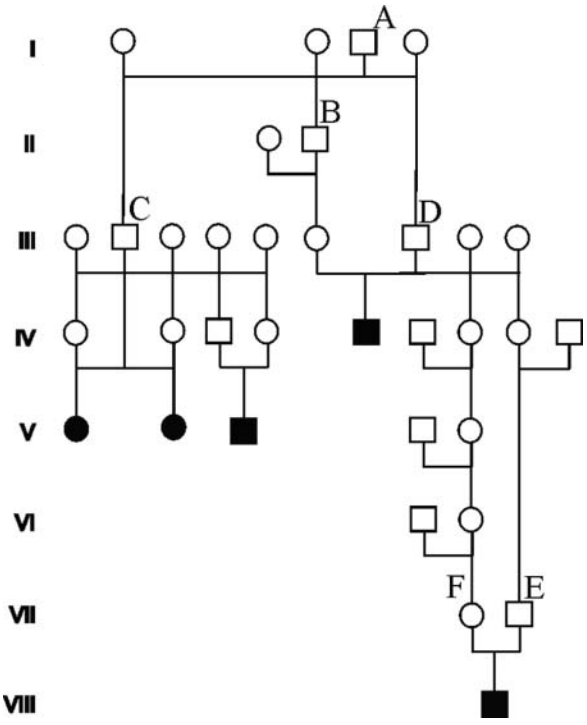


Fig. 1. Genealogical diagram showing the genetic relationship between five cases of chondrodysplasia in the Danish Red Dairy breed. Four cases in generation IV and V were reported in 1974, while the case in generation VIII was found 15 years later. Sire A: *Thy Skov*; B: *NOF Kel*; C: *NØ Gerber*; D: *NOF Lød*; E: *HV Flid*; F: 060480-00463.

2. Danish cattle breeds

The Danish cattle population has been decreasing during the study period (1989–2005), from a total of 2.2 million animals (1990) to around 1.6 million (2004). The number of calvings in dairy heifers/cows decreased from 769,000 to 569,000, while the number of calvings in suckler heifers/cows increased from 86,000 to 102,000. Most numerous are Danish Holsteins (375,000 cows in 2003/2004), followed by the Jersey breed (62,000 cows), Danish Red Dairy breed (44,000 cows), crossbreeds (35,000 cows), and Danish Red Holstein (5,000 cows). A wide range of beef breeds is represented in Denmark, but generally the numbers are low. The most prevalent beef breeds are the Limousine and Hereford breeds (around 8,300 and 4,800 purebred cows, respectively (2004 figures)) (61).

Most genetic diseases in Danish cattle have been found in Holsteins and the Danish Red Dairy breed, thus partly reflecting the breed composition of the national cattle population. Besides reflecting the number of animals, these observations may also be due to other conditions, such as differences in breeding strategies, inbreeding levels, and value of calves. However, the findings may also be due to two factors that greatly influence the ability to recognise inherited disorders. The awareness of the breeder is probably the most important single factor. If breeders are informed about inherited disorders, cases are likely to be found. This situation developed among breeders of the Danish Red Dairy breed when information on bovine progressive degenerative myeloencephalopathy was given. This led to a high level of producer awareness, which subsequently resulted in the recognition of two other inherited neurological diseases: spinal muscular atrophy (121) and spinal dysmyelination (III). So there is a self-perpetuating effect of identifying an inherited disorder within a specific breed, as this leads to an increased awareness. The herd size is the other important factor. This is especially the case when natural breeding is used as the sire is often used in a single herd only. As many disorders have an autosomal recessive mode of inheritance and as the mean herd size of beef cattle herds in Denmark is only 11 purebred/hybrid animals (61), affected animals generally occur in low numbers unless there is severe inbreeding. This combination of small herd size and low number of affected calves makes recognition of inherited disorders in suckler cattle in Denmark difficult, as most herds will only encounter one or very few cases. So unless the farmer submits the first case and this turns out to have a documented inherited defect, cases will remain unrecognised. Consequently, the identification of inherited disorders primarily within the Holstein breed and the Danish Red Dairy breed does not necessarily indicate that inherited defects are more common in these breeds than in other breeds in Denmark.

The genetic composition and names of cattle breeds in Denmark have changed over time. When reviewing the literature on inherited disorders in cattle in Denmark, uncertainty may arise as to which breeds are actually affected because of the varying use of breed designations, i.e. Holstein, Holstein-Friesian, Danish Holstein-Friesian, Black Pied Danish Cattle of Friesian descent, Black and White Danish Dairy breed, Black and White Danish Milk breed, and Sortbroget Dansk Malkerace. To avoid confusion, a single designation is used for each breed, i.e. Danish Holstein breed. This simplification is not correct from a breeding point of view, as the constitution of the animals may have varied over time due to fluctuation in the genetic composition of the breed. However, such simplification is acceptable within the scope of this dissertation. The Danish nationality of the breed is generally included in the name. This has been done for convenience to facilitate reference to the occurrence of disorders in Denmark. Nevertheless, inherited disorders in cattle clearly often have an international perspective. In this respect, national cattle populations do not constitute separate breeds and the designation Danish in this dissertation simply refers to the physical presence of the animal in Denmark, even thought it may have a predominantly foreign genetic background. A similar approach has been carried out for cattle breeds in other countries, especially for Holsteins. A recent study has in fact demonstrated that the global population of Holstein cattle can be considered as one single population unit (315).

3. Labelling of sires for inherited disorders

Sires that are used for insemination in Denmark are labelled for certain hereditary disorders based on their descent or test results. Four labels are used. A sire can be labelled as non-carrier, confirmed carrier, likely carrier, or possible carrier of a specific disorder. The labelling policy is based on the following general criteria:

- A sire can be labelled "non-carrier" if this can be proved, i.e. by genotyping of the animal itself or by progeny examination in certain breeding combinations, of which farther-daughter matings are often used.
- A sire is labelled as "confirmed carrier" if this has been documented, i.e. by genotyping or by the occurrence of at least two affected progeny. It is a demand that the diagnosis in progeny has been confirmed by an approved method and that parentage has been confirmed.
- The label "likely carrier" is used if only one affected progeny has been found. Diagnosis and parentage must be confirmed as for "confirmed carrier" and the label has mostly been used when a genotyping test was unavailable.
- The label "possible carrier" applies to animals that are genetically related to a confirmed carrier within the last three generations. This label is mostly used when genotyping methods are unavailable.

Females can be labelled in a similar way, but labelling is mostly based entirely on descent. Labelling of sires in Denmark is performed by the breeding associations, and is controlled and regulated by the Danish Veterinary and Food Administration. Information on the disease status of sires is publicly available.

By the end of 2005, labelling for the following disorders was used in Denmark: bovine leukocyte adhesion deficiency, complex vertebral malformation, chondrodysplasia in Holsteins, syndactylism, congenital paralysis, bovine progressive degenerative myeloencephalopathy, spinal muscular atrophy, spinal dysmyelination, hereditary zinc deficiency, and rectovaginal constriction. Labelling has been based on genotyping of sires by molecular methods (complex vertebral malformation and bovine leukocyte adhesion deficiency), progeny examination (spinal muscular atrophy, hereditary zinc deficiency, and rectovaginal constriction), or both (syndactylism, chondrodysplasia in Holsteins, bovine progressive degenerative myeloencephalopathy, and spinal dysmyelination). Labelling of some sires has been adapted from foreign breeding associations and the exact basis is not known. Similarly, no detailed basis for labels given to sires prior to 1989 is accessible. Labelling of sires for spinal muscular atrophy and spinal dysmyelination is based on extensive progeny examination, which included necropsy of almost 500 calves (Table 1). Genotyping has been performed at the former Department of Animal Genetics, the Royal Veterinary and Agricultural University, Denmark, at the former Danish Institute of Agricultural Sciences, and at foreign laboratories.

A list of sires diagnosed as carriers of hereditary diseases until 31 December 2005 is given in Appendix 1. Sires labelled as "likely carriers" have been included in the "confirmed carrier group". Labelling of sires as "likely carriers" mostly refers to spinal muscular atrophy and spinal dysmyelination. However, as all "likely carriers" of these defects are genetically linked to "confirmed carriers", they can beyond any doubt be regarded as true carriers.

A number of additional inherited disorders have been recognised in Denmark. Familial patterns of occurrence have been recognised and cases have been genetically linked to each other. Pedigree analyses have identified a number of sires that most likely are carriers. These are also shown in Appendix 1 to provide the basis for the estimations made in Chapter 4, and to ensure that future cases can be genealogically compared to them. Nevertheless, it must be emphasised that parentage analysis has not been systematically performed.

Programmes to control inherited disorders mostly rely on the ability to identify heterozygous sires. It is therefore of interest to analyse the extent to which heterozygous sires have been identified. For disorders inherited in an auto-

TABLE 1. *Annual number of confirmed cases of spinal muscular atrophy and spinal dysmyelination in 477 Danish Red Dairy calves submitted due to suspicion of an inherited neurological disorder*

Year	Spinal muscular atrophy	Spinal dysmyelination	Other disorders[#]
1989	28	2	18
1990	27	5	25
1991	33	4	25
1992	19	15	15
1993	4	21	2
1994	12	60*	33
1995	8	14	27
1996	5	13	13
1997	7	4	7
1998	1	1	11
1999	0	1	7
2000	0	1	3
2001	0	0	1
2002	1	0	2
2003	1	0	1
2004–2005	0	0	0
Total	146	141	190

[#]Disorders associated with recumbency in the Danish Red Dairy breed.
*Including 21 cases examined as part of a breeding study.

somal recessive manner, this can be clarified by analysis of disease status in sons of confirmed carriers, as heterozygous and homozygous normal sires must segregate 1:1, if it is assumed that their dams are homozygous normal and that there is no selection for or against specific genotypes. If it is hypothesized that all carriers have been detected (sires labelled "confirmed/likely carrier"), then the remaining sires must be homozygous normal (sires labelled "free/possible carrier"). Testing of observed numbers of sires affiliated to these two categories against the 1:1 hypothesis by the chi-square test shows that significantly fewer heterozygous sires than expected have been identified (Table 2). The figures for bovine leukocyte adhesion deficiency and the complex vertebral malformation syndrome were analysed further to evaluate a possible bias in the observed numbers. Labelling for these diseases differed from the other disorders as it was based on genotyping and as a large group of sires with unknown genotype was found. An initial analysis including only genotyped sires showed a persistent highly significant lack of carriers, thus excluding a major bias from the sires with unknown genotype as the cause (data not shown). A comparison between genotype and year of birth showed that the two genotypes segregated 1:1 until 1991 for bovine leukocyte adhesion deficiency and until 2000 for complex vertebral malformation syndrome (Fig. 2), thus demonstrating that heterozygous males did not enter the breeding program for young sires after genotyping had become available, and thereby created a bias.

It is important to note that identification of carriers by progeny examination depends on the gene frequency in the female population. Consequently, the efficiency with which carriers are detected is lower during the initial spread of a disease gene and at the end of an elimination campaign, thus compromising the data obtained through these periods.

The results show that identification of sires based on passive surveillance is an inefficient way of identifying carriers and that other methods should be used. The inability to effectively identify all carriers in the initial breeding scheme causes a delay in reducing the prevalence of diseased calves. However, heterozygous sires that pass undetected through the initial breeding scheme will probably be identified later on if used extensively.

TABLE 2. *Observed and expected genotype of sires that are sons of confirmed heterozygous sire and are used for insemination in Denmark*

	Observed numbers		Expected numbers[2]		Chi-square value
	Homozygous normal/unknown genotype	Heterozygous genotype	Homozygous normal/unknown genotype	Heterozygous genotype	
Complex vertebral malformation	1054 (454/600)	286	670	670	440.17***
Syndactylism	23 (8/15)	4	13.5	13.5	13.37***
BPDME[1]	68 (2/66)	7	37.5	37.5	49.61***
Spinal muscular atrophy	181 (4/177)	50	115.5	115.5	74.29***
Spinal dysmyelination	85 (4/81)	30	57.5	57.5	26.30***
Hereditary zinc deficiency	67 (0/67)	6	36.5	36.5	50.97***
Bovine leukocyte adhesion deficiency	616 (270/346)	141	378.5	378.5	298.05***
Rectovaginal constriction	77 (3/74)	16	46.5	46.5	40.01***

[1] Bovine progressive degenerative myeloencephalopathy.
[2] Assuming that the contribution from the dam is similar for both groups and no selection for or against heterozygous sires.
***P<0.001, df=1.

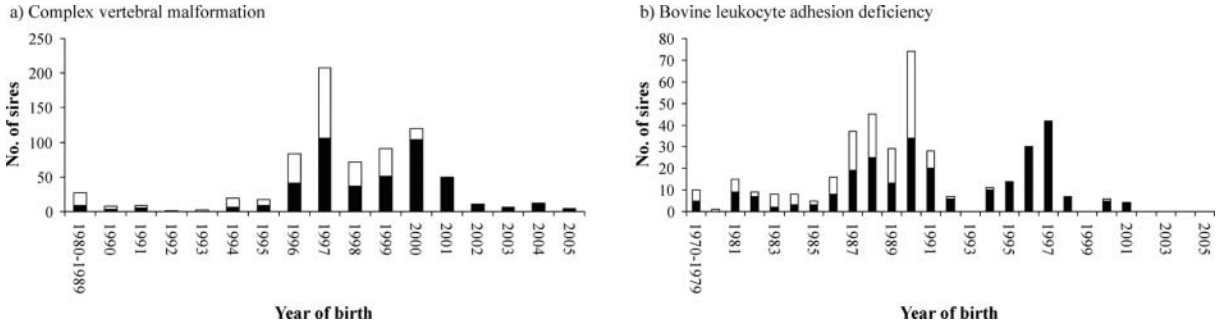


Fig. 2. Annual ratio between homozygous normal sires and sires that are heterozygous for a) complex vertebral malformation syndrome, and b) bovine leukocyte adhesion deficiency. ■ Homozygous normal sires; □ Heterozygous sires.

4. Estimation of disease extent 1971 to 2005

It is of interest for breeding associations and scientists to know the approximate number of calves affected by genetic diseases. These estimations can be used by breeding associations to make decisions regarding intervention in breeding programmes, can show the magnitude of a disease problem, and can be used to evaluate the efficiency of the surveillance programme. It is important to stress that estimates are simply numbers calculated based on a hypothesis and a range of precautions, which may increase or decrease the estimate. It is outside the scope of this dissertation to provide a detailed statistical analysis of the number of affected calves, and even if this were done, the influence of a wide range of assumptions could always be disputed. However, with relation to the cattle health programme it is of interest to know the magnitude of the problem, and therefore a simple and transparent approach is used. Consequently, one should not focus on the exact numbers but rather on changes over time and disease levels counted in hundreds or thousands of animals. A number of precautions are discussed, but their exact influence on the estimate is not given.

Affected and unaffected animals occur in consistent patterns if carriers of disorders with simple Mendelian autosomal recessive inheritance with complete penetrance are mated. These segregation ratios can be used to calculate an expected number of diseased progeny if the genotype of certain individuals in their pedigree is known, i.e. if two heterozygous individuals are mated then 25% of the progeny will be affected and 75% unaffected. As most of the inherited disorders in Danish cattle are inherited autosomal recessively, they therefore follow predictable patterns.

Danish breeding sires are labelled for several inherited disorders (see Chapter 3) and as breeding data and pedigrees of cattle in Denmark are extensively registered in the Danish Cattle Database, data on progeny can be extracted for certain combinations of sires. Data, which included the number of calves born (stillborn or viable) from 1 January 1971 to 31 December 2005, were extracted and analysed for segregation ratios for each of the labelled disorders and for congenital erythropoietic porphyria, hereditary dilated cardiomyopathy, and chondrodysplasia in the Danish Red Dairy breed. The sires that formed the basis for data selection are shown in Appendix 1. The following breeding combinations were used (see Fig. 3):

- $Sire_{II}$ mated to daughters of $Sire_{III}$, giving a segregation ratio between unaffected and affected progeny of 7:1.
- $Sire_{II}$ mated to females related to $Sire_{IV}$, giving a segregation ratio between unaffected and affected progeny of 15:1.
- $Sire_{II}$ mated to females related to $Sire_{V}$, giving a segregation ratio between unaffected and affected progeny of 31:1.

The segregation ratios are reached under the assumption that the gene frequency was zero in dams of the oldest generation (generation III, IV and V, respectively). The number of affected progeny from each of these combinations was added and analysed annually and in total.

Analysis of segregation ratios in full-term or near full-term calves is only an applicable method if the chance of an affected calf equals the chance of an unaffected calf surviving the gestation period. This is not the case for complex vertebral malformation (225, VIII). Therefore, the number of embryos (N_{total}) that resulted in the observed number of calves (N_{obs}) had to be calculated. By applying the results obtained by *Nielsen et al.* (225), who determined that only 23% of affected foetuses survived to gestation day 260, the total number of embryos could be calculated as:

$$N_{obs} = (PR_{Normal} \times N_{total}) + ((PR_{Defect} \times N_{total}) \times 23\%),$$

where PR_{Normal} and PR_{Defect} are the prevalence of normal and defective progeny in the sire combination (Fig. 3).

The number of defective embryos can subsequently be calculated as:

$$\text{Number of defective embryos} = PR_{Defect} \times N_{total}.$$

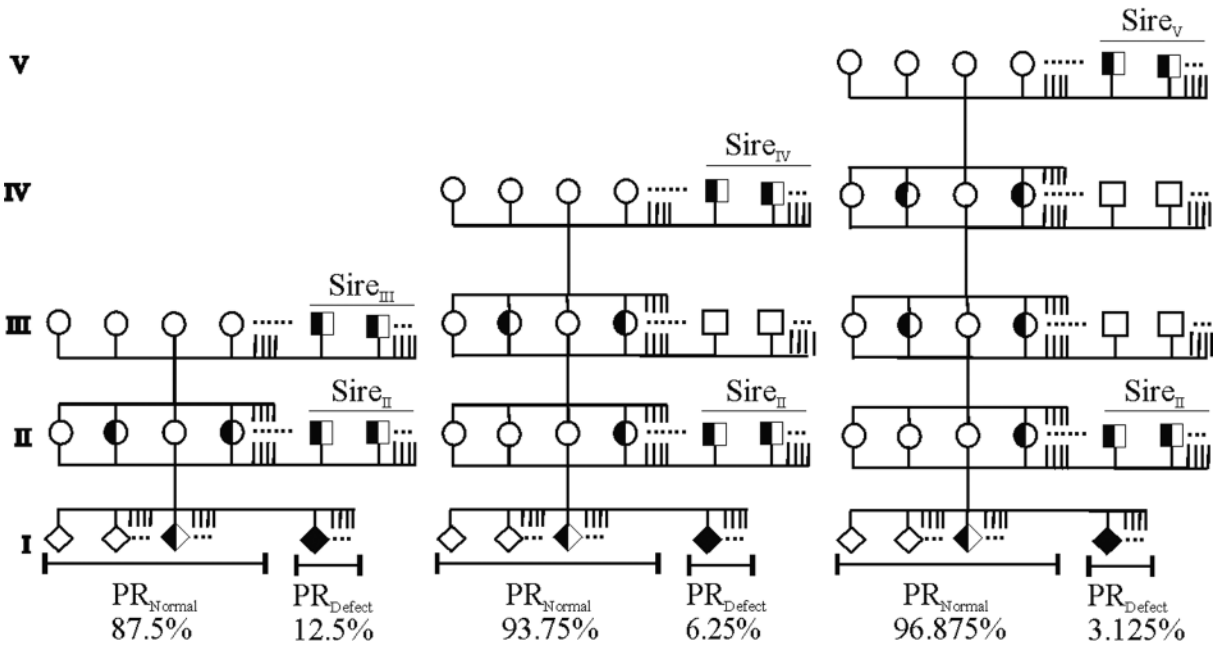


Fig. 3. Principles for extracting breeding data and analysing segregation ratios regarding autosomal recessively inherited disorders. The father ($Sire_{II}$) of all calves is a carrier of a specific disorder. When mated to daughters of carriers of the same disorder ($Sire_{III}$), 12.5% of the progeny will then have the diseased phenotype. Similarly, diseased progeny will be born with prevalences of 6.25% and 3.125% when a carrier ($Sire_{II}$) is mated to females that have a carrier as father to the maternal grandmother ($Sire_{IV}$) or to the great-grandmother ($Sire_V$), respectively. The numbers of each symbol do not necessarily correspond to the expected ratio. The female population in the oldest generation in each situation are expected to have a gene frequency of 0.

The number of affected progeny varied considerably according to the actual disorder (Table 3) and over time (Fig. 4a–f). Of the disorders occurring in Holsteins, complex vertebral malformation was the most numerous, with an estimated number of affected embryos around 12,000. Bovine leukocyte adhesion deficiency was less numerous, with an estimated number around 600 cases. In the Danish Red Dairy breed, animals suffering from spinal muscular atrophy or spinal dysmyelination numbered around 1,800 and 500 calves, respectively, while

TABLE 3. *Estimated number of affected progeny for some hereditary diseases in Danish cattle grouped according to combination of sires in different generations (see text for details)*

	Number of affected progeny			
	$Sire_{II} \times Sire_{III}$	$Sire_{II} \times Sire_{IV}$	$Sire_{II} \times Sire_V$	Total
Complex vertebral malformation[1]	7,966.7	3,323.9	789.5	12,080.1
Bovine leukocyte adhesion deficiency	546.9	84	10.5	641.4
Congenital erythropoietic porphyria	20.6	1.5	0	22.1
BPDME[2,3]	28.5	2.7	0.3	31.5
Spinal muscular atrophy	1,402.8	371.6	68.5	1,842.9
Spinal dysmyelination	432.8	60.8	7.0	500.6
Hereditary dilated cardiomyopathy[3]	98.6	112.4	60.0	271
Rectovaginal constriction[4]	285.5	34.6	3.4	323.5

[1] The number of progeny is given as embryos.
[2] Bovine progressive degenerative myeloencephalopathy.
[3] The number represents both males and females. Severe symptoms mostly develop after the usual slaughter age of males.
[4] The number represents both males and females, but severe disease is only seen in females.

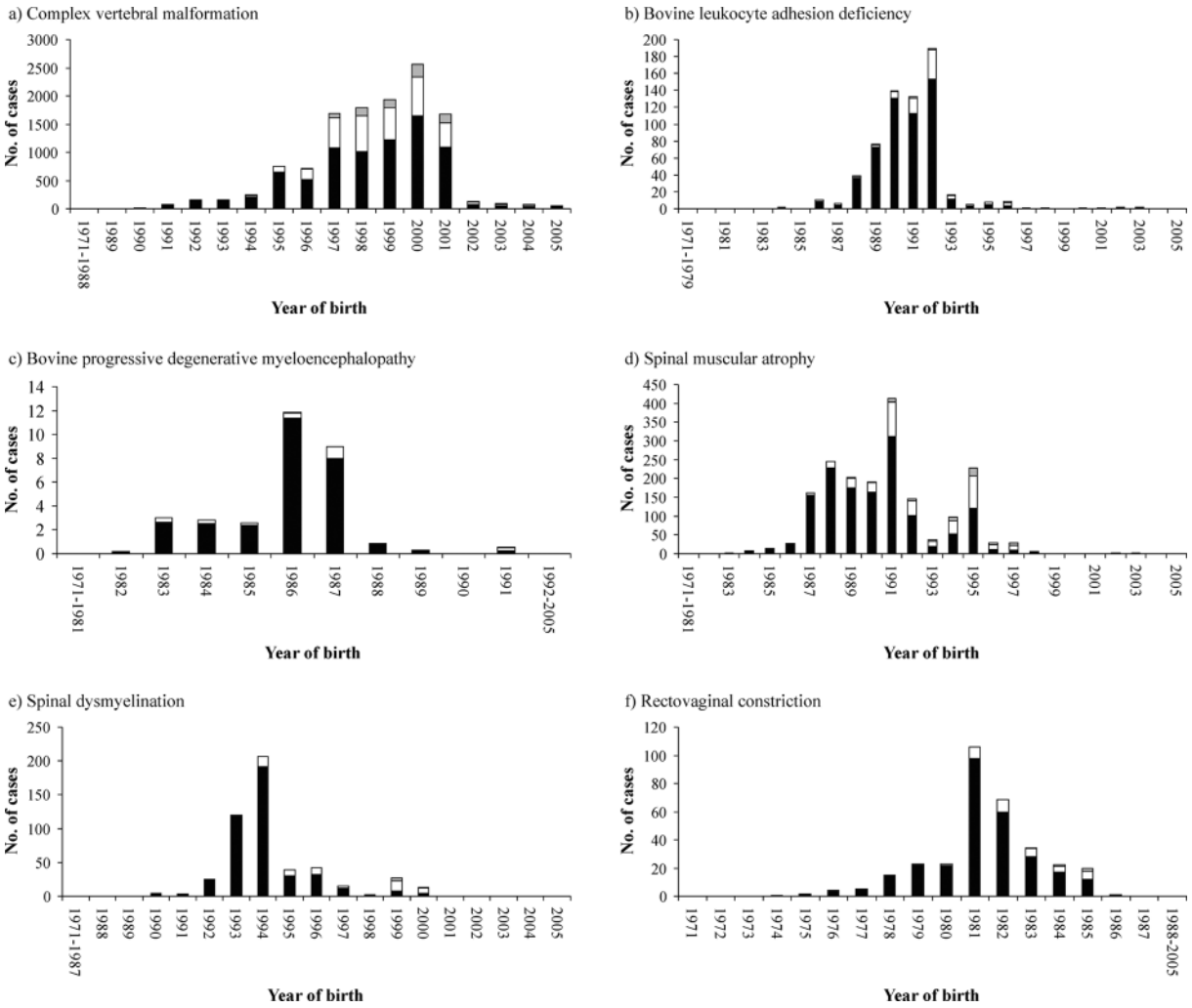


Fig. 4. Annual number of animals with a diseased phenotype according to year of birth and sire combination for a) complex vertebral malformation, b) bovine leukocyte adhesion deficiency, c) bovine progressive degenerative myeloencephalopathy, d) spinal muscular atrophy, e) spinal dysmyelination, and f) rectovaginal constriction. Contribution from sire combinations: $Sire_{II}$ mated to daughters of $Sire_{III}$ ■; $Sire_{II}$ mated to females related to $Sire_{IV}$ □; $Sire_{II}$ mated to females related to $Sire_{V}$ ▒, see text and Fig. 3 for details.

bovine progressive degenerative myeloencephalopathy remained almost insignificant. The estimated number of females with rectovaginal constriction was around 150 (Table 3).

A number of precautions influenced the accuracy of the estimations. The two most important factors were probably the impact of unidentified heterozygous sires and the quality of the data. Data on calves related to unidentified heterozygous sires were obviously not included in the data sets, and consequently the estimated numbers of affected calves are too low. A significant lack of heterozygous sires has been demonstrated (Table 2). The impact of these sires cannot be determined, but many sires are probably young sires culled after initial testing because of low breeding value. The lack of data from such sires might not greatly influence the number of defective calves.

The data quality had an important influence on the estimations. Estimations of the number of calves affected by syndactylism and hereditary zinc deficiency gave only 8 and 15 animals, respectively, while only a single calf of the Danish Red Dairy breed suffering from congenital paralysis or chondrodysplasia should have been born. Although the number of affected calves with these disorders is unknown,

an estimated number of only 15 calves with hereditary zinc deficiency appears to be much too low, as this disorder was considered a major problem in Danish Holstein in the 1970s. The poor estimations are probably due to lack of unambiguous identification of cattle until around 1983, when unequivocal identification by ear tags was made compulsory and registration of breeding was computerised. Therefore, estimations based on data through the 1970s are unreliable for all disorders, but as most disorders have been recognised in the 1980s or later, the influence on the calculations is limited for these diseases.

A few additional precautions should be mentioned, but many others may influence the estimated number. Errors in registration of parentage erroneously included some animals and excluded others depending on the disease status of the correct sire. Erroneous registrations occur with a frequency of 2–2.5% (data from 1986–1988). The estimations have not been corrected for perinatal mortality, which will reduce the actually observed number of affected calves for non-congenital disorders. Similarly, the actual number of affected calves is approximately 50% of the estimated number if the disorder is subclinical before the usual culling age of males of around one year or only of importance in one sex. This is relevant for diseases such as hereditary dilated cardiomyopathy and rectovaginal constriction.

5. Inherited disorders in Danish cattle

There has been research on inherited disorders in Danish cattle for around 80 years, but reports of malformations that later turned out probably to be inherited have been published for more than 140 years. Research focusing on this subject was started by *K. Løje*, who in 1930 published a review on inherited disorders (192). This was followed by the substantial research of *J. Nielsen*, who in 1950 published his dissertation on congenital paralysis in the Danish Red Dairy breed (217) and established the basis for reducing the prevalence of this disorder through breeding measures. Until 1989, when the present investigation was initiated, several researchers and research groups studied a variety of disorders, including hereditary zinc deficiency, congenital erythropoietic porphyria, and defects of spermatozoa. This led to a substantial number of publications in international scientific journals and established the scientific basis for the recognition and control of inherited disorders in Danish cattle.

Several comprehensive international reviews on inherited disorders in cattle have been published (65, 135, 180). In addition, a regularly updated and internationally acknowledged electronic database, Online Mendelian Inheritance in Animals (OMIA), is available on the worldwide web (http://omia.angis.org.au/) (215). The review presented in this dissertation focuses entirely on inherited disorders identified in Danish cattle and deals with three fundamental aspects of inherited disorders: morphology, inheritance, and affected breeding lines. It provides insight into the causes, pathogenesis, morphology, and present occurrence of inherited disorders in Danish cattle. Furthermore, it is the first review on this subject in Danish cattle written in English, making it available to scientists internationally. The review focuses only on inherited disorders with an established or likely genetic aetiology based on single genes. Some disorders, such as, for example, spastic paresis, progressive posterior paralysis, and segmental aplasia of the Wolffian duct in sires, which have been reported in Denmark (39, 40, 243, 261), have been omitted as they do not fulfil these criteria. However, a review of these disorders in Danish cattle has previously been provided (7). Syndromes that have been claimed to have a genetic aetiology because of a familial occurrence, but that have not been thoroughly examined, have also been omitted. Examples are foetal mummification (192) and a syndrome of pharyngeal swelling, anterior arthrogryposis, and seizure (named Baenster syndrome after the Holstein sire *Baenster* (DK6323)) (218, 219). Such findings have been evaluated, and it is evident from present scientific knowledge that there can be a wide range of causes.

Inheritance plays a role in many diseases. Disease often develops due to an interaction between a wide range of factors, including virulence of an infectious organism, immunity, management, environment, nutritional status, and inheritance. Such diseases occur in Denmark, but are not within the scope of this dissertation, nor are desirable defects such as muscular hypertrophy or genetic defects not associated with disease (i.e. abnormal coat colour and polledness). The natural subject of this dissertation is diseases due to the effect of single genes predominantly inherited in an autosomal recessive manner.

5.1. CHONDRODYSPLASIA

Chondrodysplasia (bulldog calves, achondroplasia, disproportionate dwarfism) is a designation used for a heterogeneous group of congenital skeletal malformations characterised by diminished endochondral osteogenesis. The morphological appearance shows wide variation, but the main feature of all cases is reduced length of bones with an endochondral growth pattern. Some types of chondrodysplasia are associated with foetal death and abortion. Others cause semilethal conditions, and several types produce viable but short-legged calves. Chondrodysplasia has been reported in many cattle breeds and at least nine different inherited types have been recorded (135). The aetiology may be either genetic or non-genetic. The molecular basis for hereditary chondrodysplasia in cattle is mostly unresolved, but it is probably

different for the various types. As the molecular basis is mostly unsolved, chondrodysplasia is generally categorised according to morphology. Although this is a less suitable method, it seems to be the only way until the molecular basis of a number of types has been established.

Three morphologically different types of chondrodysplasia with an established genetic basis have been recorded in Danish cattle: chondrodysplasia in the Dexter breed, chondrodysplasia in the Danish Red Dairy breed related to the sire *Thy Skov*, and chondrodysplasia in Danish Holstein related to the sire *Igale Masc*. The relation to specific sires (family clusters) is needed as other types of chondrodysplasia probably occur in these breeds. *Rasbech* (242) claims that chondrodysplasia occurs in all Danish breeds, but no evidence has been provided. A few cases have been examined since 1989, but these have been omitted because of an unsolved aetiology.

5.1.1. Chondrodysplasia in the Dexter breed

Chondrodysplasia in the Dexter breed is a classic malformation in cattle first reported in 1904 (258). It constitutes a prototype for chondrodysplasia.

Affected calves are aborted, mostly in the 6th to 8th month of gestation. The cows may have hydramnion with associated oedema of the foetal placenta. The affected foetuses are characterised by severe disproportionate dwarfism with prominent shortening of the spine and a compact body. There is a severe dysplasia of the splanchnocranium with palatoschisis and doming of the neurocranium, sometimes associated with hydrocephalus. Extreme tetramelic shortening of the limbs is seen. Longitudinal sawing of the bones reveals short diaphyses with prominent cartilaginous epiphyses. An abdominal defect with eventration of abdominal organs may be present (Fig. 5) (7, 57, 58, 123, 258).

The epiphyses are characterised histologically by hyaline cartilage. Distinct epiphyseal growth plates are lacking. Hypertrophied chondrocytes and chondrocyte alignment are irregular and almost absent. The diaphyses consist of dense, cancellous bone and compact bone (7, 57, 58, 123).

Inheritance of chondrodysplasia in the Dexter breed has been the subject of several studies. Although results have been conflicting, most studies have indicated an autosomal dominant inheritance with incomplete penetrance of the heterozygous genotype, maybe influenced by other genes. Aborted chondrodysplastic foetuses have a homozygous dominant genotype, while typical short-legged compact Dexter cattle have the heterozygous genotype (57, 304, 312). Recent genomic analysis of chondrodysplastic Australian Dexter cattle has identified a mutation (2266insGGca) in the aggrecan gene as the cause of this disorder, although other mutations are present in the gene (51). A genetic test is available for genotyping.

A single case of chondrodysplasia in the Danish Dexter breed has been diagnosed in the study period (Fig. 5) (7). However, this disorder has not been closely monitored and Dexter breeders have not been contacted separately for submission of defective calves. The prevalence of Dexter chondrodysplasia in Denmark is unknown. The first Dexter cattle were imported in 1986 (239) and the breed is a minor breed in Denmark with around 1,000 calvings in 2005.

5.1.2. Chondrodysplasia in the Danish Red Dairy breed related to the sire Thy Skov

This type of chondrodysplasia was originally reported in 1974; four cases were observed in a familial cluster with the sire *Thy Skov* (DK28440, born in 1962) as a common ancestor (18). An additional case belonging to the breeding line was found in 1992 (7) (Fig. 1).

This defect is characterised as a sublethal type of chondrodysplasia. Affected calves have bilateral symmetric shortening of the appendicular skeleton, mainly of the large bones, with joint instability and increased width of the metaphyses (Fig. 6). The pelvis and the bones of the cranial basis are reduced in length. Some calves have an additional palatoschisis, slight hydrocephalus, or a high interventricular defect in the heart. Only minor histopathological changes are present, mainly consisting of an irregular zone of chondrocyte alignment and scanty formation of primary trabeculae (7, 18).

The disorder occurred in a familial pattern with parents of normal phenotype (Fig. 1); findings that are consistent with autosomal recessive inheritance. Five heterozygous sires have been identified (Appendix 1).

Chondrodysplasia of this type is easily recognised by breeders and would probably have

been reported if it had occurred frequently. As this has not happened, it must be assumed that this disorder is of low prevalence. However, the defective allele is probably present in the population, which may give rise to isolated cases.

5.1.3 Chondrodysplasia in Danish Holstein related to the sire Igale Masc

This specific type of chondrodysplasia was recognised in Denmark after the French breeding association *Sercia France* released information about a defect in progeny of the French Holstein sire *Igale Masc* (F4493050102, born in 1993), which had been used in Denmark. The disorder was characterised as chondrodysplasia based on the examination of four cases in Denmark (VI).

Affected calves were delivered stillborn near or at term. The body weight was reduced and the carcasses displayed disproportionate dwarfism with a short and compressed body. The limbs had a bilaterally symmetrical compact appearance and a severely reduced length. However, the digits were of almost normal size. The splanchnocranium had severe dysplasia with palatoschisis, while the neurocranium was broad with bilateral exophthalmia and caudal displacement of the ears (Fig. 7). Longitudinal sawing of the long bones revealed prominent, non-calcified epiphyses and small irregular diaphyses, while the vertebrae had extremely prominent epiphyses, causing spinal cord compression. Additional malformations included umbilical eventration (one case), cardiac hypertrophy, and pulmonary hypoplasia (VI).

The epiphyseal histopathology was briefly characterised by irregular disorganized epiphyseal plates, which were dominated by hypertrophied chondrocytes and with almost complete absence of chondrocyte alignment, while the epiphyses appeared as a homogeneous hyaline cartilage without ossification (VI).

Studies on the inheritance of the defect have not been published. Genealogical examination of the Danish cases did not reveal any evidence regarding the mode of inheritance, but an autosomal recessive mode of inheritance was a possible explanation for the occurrence of defective progeny (VI). Apparently around 1% of the progeny of the sire are malformed. A marker-based test, which can test animals related to *Igale Masc*, has apparently been developed (136).

The prevalence of this specific type of chondrodysplasia in Danish Holsteins is probably low because of the limited number of heterozygous sires used (Appendix 1), and the limited number of inseminations with semen of these sires. However, the disorder might not be limited to the *Igale Masc* family, as a defect with a similar morphology has been reported in US Holsteins (138).

5.2. COMPLEX VERTEBRAL MALFORMATION

The complex vertebral malformation (CVM) syndrome is a congenital lethal malformation, which in late term aborted foetuses and perinatal calves is characterised by growth retardation and bilateral flexure of the carpal and metacarpophalangeal joints with rotation of the digits. In addition, most animals have malformation of the vertebrae (~98%), ribs (~94%), and arthrogryposis of the tarsal and metatarsophalangeal joints (~87%) (Fig. 8). The morphology, extent and location of the vertebral malformations varies between cases, with some having few malformed vertebrae, while others have extensive malformations causing shortening and scoliosis of the spine. Multiple vertebrae of the thoracic spine and posterior part of the cervical spine are misshapen and fused in typical cases (Figs. 9 and 10). A range of other malformations has been reported, of which cardiac interventricular septal defects, possibly combined with malformations of the great vessels and muscular hypertrophy, are the most common (~53% of cases). The morphological variation of the syndrome has been reported in detail (VII).

Analyses of population-based breeding results have demonstrated a significant lack of calves born near term, thus indicating frequent intrauterine mortality of homozygous affected foetuses (33, 195, 225). Studies of Danish Holstein have shown that the extent of foetal mortality prior to gestation day 260 is approximately 77% (225). This is reflected in a significantly reduced ratio of CVM-affected calves in breeding studies (VIII).

CVM occurs in calves genetically related to the US Holstein sire *Penstate Ivanhoe Star* (US1441440, born in 1963), often through his

son *Carlin-M Ivanhoe Bell* (US1667366). CVM has only been reported in Holsteins and most confirmed cases have been reported from Denmark (VII). Similar, but genotypically unconfirmed, cases have occurred in the Netherlands (307, 308). Single cases have been reported from the USA (75), United Kingdom (245), Japan (211), and Sweden (33). The few reports do not reflect the extent to which CVM has occurred in Holstein cattle. *Berglund et al.* (33) estimated that 2,200 affected foetuses were produced annually between 1995 and 1999 in Sweden, while the annual loss in Germany was estimated to be more than 8,000 foetuses between 1997 and 2000 (160). Similar high figures were reported from the French region Brittany (195). The defective allele for CVM has been spread in Holstein populations worldwide though extensive exploitation of sires that later turned out to be carriers of the defect. For example, 13.2% of 957 sires used for insemination in Germany were diagnosed as carriers of CVM (160), while a prevalence of 31% and 32.5% was found in Denmark and Japan, respectively (211, 280).

Genomic analysis has identified a single base substitution (guanine to thymine) at position 559 in the gene *SLC35A3* as the cause of CVM. Defective calves have this mutation in both alleles, thus proving the autosomal recessive nature of the disorder. The gene *SLC35A3* codes for a nucleotide-sugar transporter in which the base mutation is reflected in an amino acid substitution at position 180 (valine to phenylalanine), thus inhibiting the function of the transporter. The nucleotide-sugar transporter plays an essential role in mechanisms controlling the formation of vertebrae from the unsegmented paraxial mesoderm. Consequently, the defective transporter molecule leads to vertebral malformations (280). The genomic analysis has formed the basis for the development of commercially available genotyping tests (31, 150).

Of all the genetic disorders, the CVM syndrome has probably had the greatest impact on Danish cattle breeding to date. Until 31 December 2005, a total of 544 heterozygous sires used for breeding had been diagnosed (Appendix 1) and around 12,000 homozygous affected foetuses had been produced (Table 3). The development of a genotyping test and its strategic use in selecting breeding sires has effectively reduced the number of affected calves (Fig. 4a) and prevented continued uncontrolled spread of the defective allele.

5.3. OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta (OI) is a congenital collagenopathy of type I collagen, the most abundant and ubiquitous collagen in mammals. Collagen type I constitutes an important component of bone, tendons, ligaments, skin and teeth. The protein is a heterotrimer made of two α1(I) and one α2(I) chains, which are coded by the *COL1A1* and *COL1A2* genes, respectively. The α-chains consist mainly of repeated tripeptide motifs, which all start with a glycine molecule. This construction is essential for correct formation of the collagen helix structure, but makes it vulnerable to functional mutations, resulting in anomalous chains. Although not all mutations result in abnormal collagen helix structures, a large number of dominant mutations in the *COL1A1* and *COL1A2* have been identified in human cases of OI (59).

OI in cattle is characterised by joint instability due to weakened tendons, ligaments and joint capsules leading to subluxation or luxation. A striking impairment of bone strength causes foetal fractures as well as multiple acute fractures in neonatal calves (Figs. 11 and 12). Additionally, the hardness of the dentine is reduced, predisposing the animals to tooth fractures. Reduced strength of skin is not a major sign in bovine cases. Severely affected calves are growth retarded. OI is a lethal disorder (64, 139, 277, II). Biochemical changes have been found in Australian and North American cases, but the molecular basis has not been identified for any bovine cases (83, 84, 277).

Four familial clusters of OI have been reported. Of these, three were in Holsteins in Australia (64), the USA (277), and Denmark (II), while the fourth cluster occurred in a Danish Charolais herd (139). In addition, an isolated case has been reported in a Danish Holstein calf (10).

The bovine clusters of OI have occurred as isolated familial cases. Affected calves have been the progeny of a single phenotypically normal sire mated to unrelated normal females and have occurred with frequencies of 9–50% in the

herds. Both females and males have been affected in equal ratios. Such occurrence does not correspond to simple Mendelian inheritance, but might be explained by the presence of a dominant mutation in a certain number of spermatozoa of the sire, thus displaying testicular mosaicism (64, II). Due to differences in the morphology and biochemistry among cases of the four clusters, different mutations of the *COL1A1* or *COL1A2* genes are likely to be involved.

Sporadic cases of OI are likely to occur in Danish cattle, but the overall prevalence is probably low. Family clusters of OI occur occasionally (139, II). So far, these occurrences have been in herds using natural breeding. However, if mutations causing OI were to occur in sires used for artificial insemination, considerable numbers of cases might arise.

5.4. SYNDACTYLISM

Syndactylism ("mulefoot") is a congenital malformation of the distal parts of one or more limbs characterised by complete or partial fusion or nondivision of the functional digits. The disease designation "syndactylism" refers to disorders where the digital malformation is the primary and most important defect. The following description refers to syndactylism used in this sense in Holsteins. However, syndactylism also occurs in other syndromes, such as in the facial-digital syndrome of Angus cattle, as well as in other breeds (229, 230).

Syndactylism develops due to fusion or nondivision of the foetal anlage of digits III and IV. Horizontal synostosis of the digits may – to a greater or lesser degree – be complete, with synostosis of the second pair of phalangeal bones as the most common. Additional morphological abnormalities, such as synostosis, may develop in other parts of the distal appendicular skeleton of affected limbs, for example, in metacarpal/metatarsal bones and carpal/tarsal bones. Concomitant adaptive changes are found in the muscles, tendons, nerves and vascular supply of the distal limb (4–6, 102, 124, 186).

Typical cases of syndactylism are externally recognised by the presence of a single hoof-like structure instead of the normally paired claws. A groove may be present in the dorsal midline (Fig. 13). The morphological variation reflects the underlying skeletal malformation. Thus, cases occur which have a narrow interdigital cleft and fusion of only the most proximal part of the claw capsules. Such cases may remain unrecognised unless the digits are carefully inspected. Furthermore, genetically affected but clinically normal animals are found. The limbs are not equally affected in diseased animals. Front limbs are more frequently affected than hind limbs, and right legs are more frequently affected than left legs. Both forelimbs are malformed in most animals (124, 134, 186). Affected animals are intolerant to high environmental temperatures and have developed lethal hyperthermia under experimental conditions (37 °C, 70% humidity) (182).

Syndactylism primarily causes concern in the Holstein breed, but has been recognised in several cattle breeds (177). The disorder has been a major problem in US Holsteins and has been spread through export of semen. However, scientific reports of its occurrence outside the USA are mostly lacking.

The inheritance of syndactylism in Holsteins has been determined as autosomal recessive by genealogical examination and breeding studies. However, the genotype has a variable expression, which is reflected in the morphological variation. Furthermore, the penetration of the diseased genotype is reduced, so genetically diseased but externally unaffected animals exist (25, 79, 124, 134). Sires have previously been genotyped by test breeding and progeny examination (124, 140). Initial studies mapped the syndactyly locus to chromosome 15 (52, 69). Recent studies in Holstein and Angus cattle have demonstrated several mutations in the low density lipoprotein receptor-related protein 4 gene (*LRP4*) impairing its function in distal limb development (72, 74, 141). Genotyping of cattle for these mutations is now available and such analyses have strongly indicated that the US Holstein cow *Raven Burke Elsie* (born 1947) is a common ancestor for a cluster of French, Belgian and US cases of syndactylism (74).

Syndactylism has been known to occur in Danish cattle for more than 150 years. A number of specimens were submitted to the Royal Veterinary and Agricultural University for inclusion in the collection of malformations (19–24). The specimen from 1886 had bilateral an-

terior syndactylism, while the dam had unilateral anterior syndactylism, thus indicating an inherited aetiology. Reports of several cases, including specimens from the collection, have been published (42, 237). The breed of these old cases is unknown. Later, the defect was introduced into the Danish Holstein breed by import of semen from the US Holstein sire *Pineyhill Carnation Star* (US1590283, born in 1970) and further spread through several of his sons born in Denmark. Sons and maternal grandsons of this sire could only be registered in the Danish herd book if they were bred to at least 30 of their own daughters without producing affected progeny (238). Other heterozygous sires, including *McCloe-Pond Trent* (US17226843, born in 1996), have also been used for insemination in Denmark (Appendix 1).

Syndactylism has been diagnosed twice in Denmark in the last 20 years. One case was diagnosed in 1984 and another in 1989 (223). The calves had different sires that were both tested free of the syndactylism allele by mating to their own daughters. The genetic basis for these cases is unsolved, and it emphasises that labelling of sires as carriers based on isolated diseased progeny is problematic. Although some cases of syndactylism need thorough clinical examination to be diagnosed and might be overlooked, it is expected that typical cases would be recognised and reported to the breeding associations. As only very few cases have been reported though the last two decades, the prevalence of syndactylism in Danish cattle is most probably very low.

5.5. ACROTERIASIS

Acroteriasis is a lethal congenital malformation morphologically characterised by severe facial dysplasia and tetramelic peromelia. Concurrent lesions, such as hydrocephalus and palatoschisis, are seen. Affected individuals are mostly aborted or stillborn. The disorder is inherited autosomal recessively as documented by segregation studies (247, 309).

The defect was originally reported in Swedish Holstein cattle (205, 309) and persisted for several years (76). The occurrence of this defect in Sweden followed importation of the sire *Gallus M 77* from East Friesland in Germany and inbreeding of his descendants. Additional cases were reported in Holsteins in Holland (100), Israel (256), France (172), Germany (247, 314), and the United Kingdom (35). Cases occurring outside the Netherlands have had Dutch ancestors.

Details of the occurrence of acroteriasis in Danish Holstein are lacking. *Hansen* (114) reported the occurrence of this defect and stated that it was introduced by breeding animals. *Rasbech* (242, 244) mentions that few cases have occurred in Denmark. Information on the number of affected animals, breeding lines affected, or their origin is not available. During the period when reports on acroteriasis were published from other countries, animals of the Holstein breed were imported to Denmark from East

Fig. 5. Chondrodysplasia in the Dexter breed. Aborted foetus, body weight 4.0 kg (reprinted from 7).

Fig. 6. Chondrodysplasia in a one-month-old calf of the Danish Red Dairy breed. The calf is genetically related to the sire *Thy Skov*.

Fig. 7. Chondrodysplasia in a Danish Holstein calf related to the sire *Igale Masc* (reprinted from VI; J Vet Diagn Invest 2004;16:293–8 with permission from the American Association of Veterinary Laboratory Diagnosticians).

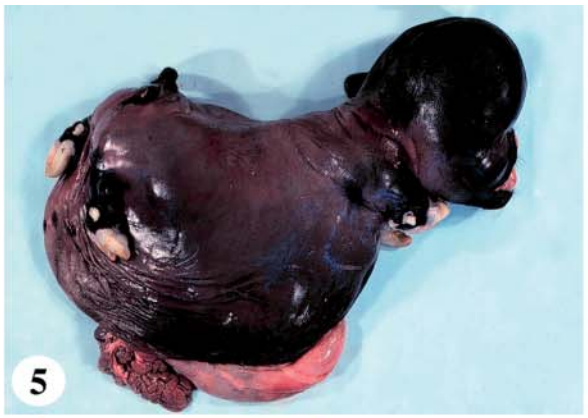
Fig. 8. Complex vertebral malformation in a Danish Holstein calf. Note the short neck and arthrogryposis of the distal joints (reprinted from V; J Vet Diagn Invest 2001;13:283–9 with permission from the American Association of Veterinary Laboratory Diagnosticians).

Fig. 9. Malformation of the thoracic vertebrae in a case of complex vertebral malformation in a Danish Holstein calf (reprinted from V; J Vet Diagn Invest 2001;13:283–9 with permission from the American Association of Veterinary Laboratory Diagnosticians).

Fig. 10. Radiograph showing malformation of vertebrae at the cervicothoracic junction, scoliosis and synostosis of the proximal part of several ribs in a case of complex vertebral malformation. Danish Holstein calf (reprinted from V; J Vet Diagn Invest 2001;13:283–9 with permission from the American Association of Veterinary Laboratory Diagnosticians).

Fig. 11. Osteogenesis imperfecta in a neonatal Danish Holstein calf. Note the severe joint laxity and diminished growth (reprinted from II, J Vet Med A 1994;41:128–38).

Fig. 12. Acute fracture of the left metatarsus in a case of osteogenesis imperfecta in a Danish Holstein calf (reprinted from II, J Vet Med A 1994;41:128–38).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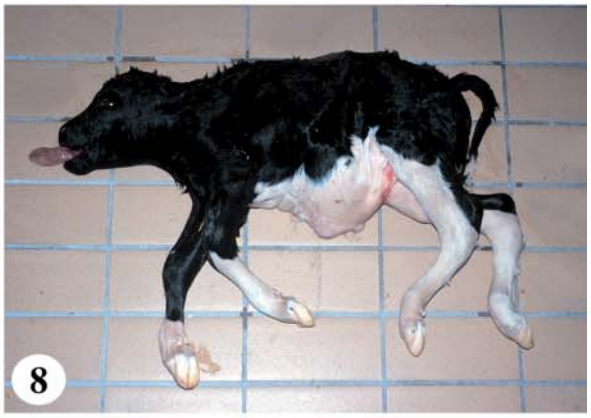
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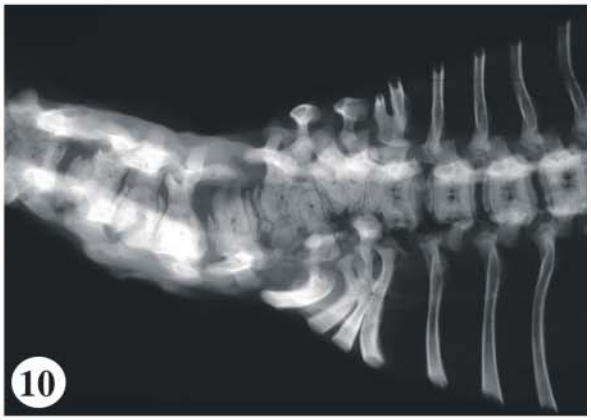
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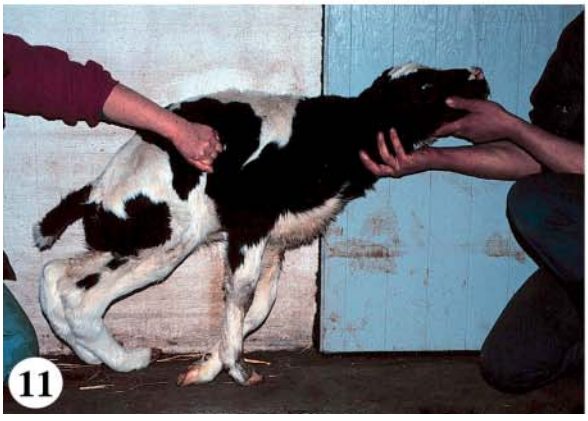
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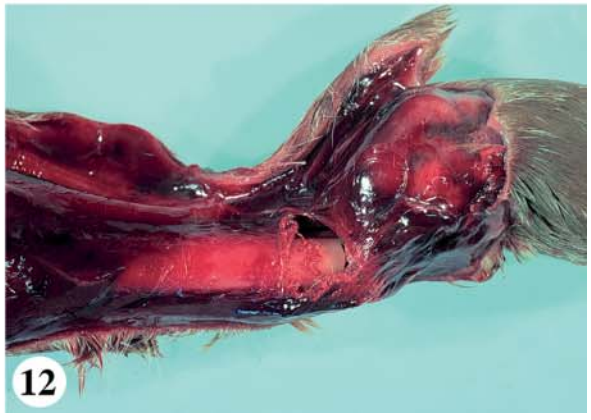
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Friesland (Germany), West Friesland (Holland), and southern parts of Sweden (299). The gene for acroteriasis might have been introduced by one or more of these imports. At present, the prevalence of acroteriasis in Danish Holsteins is probably low. No cases were recognised between 1989 and 2005.

5.6. CONGENITAL PARALYSIS

Congenital paralysis in calves of the Danish Red Dairy breed was originally reported by *Løje* in 1930 (192), but cases had occurred as early as 1924 (217). The disorder is characterised by congenital non-progressive lateral recumbency. Neurological dysfunction is limited to the hind limbs, which exhibit bilateral spastic extension. Affected calves are able to rise to the sternal position and are able to walk a few metres by use of their front limbs if supported by elevation of their hindquarters. The calves mostly die due to secondary infections, but may survive for some months if carefully nursed (54, 217). There is discrepancy regarding the pathology of the disorder. Six cases were examined at the Royal Veterinary and Agricultural University in Copenhagen, Denmark, by veterinary pathologists *I. P. Sjolte* and *A. F. Følger*, who were unable to identify any neuropathological changes (217). However, *Christensen* and *Christensen* (54) found neuronal atrophy and necrosis in the globus pallidus and in the reticular substance of the brain stem, medulla oblongata, and the cervical spinal cord of three calves, two of which were around 4-months old.

Extensive research into the inheritance and occurrence of congenital paralysis was performed from 1938 to 1948, and was published as a dissertation (217). Segregation studies demonstrated that congenital paralysis in the Danish Red Dairy breed was inherited autosomal recessively.

The sire *Tjalfe Kristoffer* (DK1343, born in 1913) was identified as the original source of the disease-causing allele (192, 217). Many sires, including elite sires such as *Højager* (DK2168) and *Højager Nakke* (DK2400), were identified as carriers of the defect as well and during the 1940s the estimated prevalence of heterozygotes was around 20% among elite sires and 15% in the general female population (217).

The current prevalence of congenital paralysis in the Danish Red Dairy breed is probably low. A search for inherited congenital neurological disorders in this breed was performed during the 1990s when the familial occurrence of spinal muscular atrophy and spinal dysmyelination was determined. Almost 500 calves were necropsied during this period (Table 1), and no cases with lesions similar to those reported by *Christensen* and *Christensen* (54) were detected. As clinical signs of congenital paralysis and spinal dysmyelination are considered to be indistinguishable by inexperienced observers, it is assumed that cases would probably have been found if the disorder had been common.

5.7. BOVINE PROGRESSIVE DEGENERATIVE MYELOENCEPHALOPATHY

Bovine progressive degenerative myeloencephalopathy (BPDME) ("weaver syndrome") is a neurodegenerative disorder, which was initially reported in purebred Brown Swiss cattle in the USA in 1973 (184). However, cases probably occurred already in the late 1950s (269).

The disorder is characterised by progressive hind limb weakness, ataxia, and dysmetria developing in calves aged 5 to 8 months. Other neurological abnormalities are absent. Progression occurs during the following months and severe ataxia and markedly diminished proprioceptive reflexes have mostly developed in 1.5- to 2-year-old animals. The speed of disease progression varies between cases, but recumbency is manifest before 4 years of age. Progressive muscular atrophy develops and terminally affected animals must be euthanised or they will die due to tympany or infections. Clinical cases are mostly found in females as males are often slaughtered before severe clinical signs have developed (68, 233, 270).

Significant gross lesions are absent and neuropathological changes are non-specific. Microscopic lesions are mainly confined to the spinal cord white matter and consist of degeneration and loss of axons and myelin (Wallerian-like degeneration). Lesions are most consistent and pronounced in the thoracic spinal cord, but not confined to specific fasciculi. Occasionally, swollen brain stem axons or degener-

ated or necrotic Purkinje cells of the cerebellar cortex are found (271). Ultrastructural, histochemical, and electrophysiological studies have demonstrated a variety of changes in brain, peripheral nerves, neuromuscular junctions, and muscles (12, 27, 80, 232, 234, 235, 288). It has been proposed that the neurological lesions are due to a dying back process, which may be founded in a metabolic defect of enzyme systems involved in energy production or normal integrity of the nerve cell body and its processes (234).

BPDME occurs in familial patterns consistent with autosomal recessive inheritance (27, 269). This mode of inheritance has been confirmed by microsatellite mapping. The locus for BPDME is closely linked to the locus for the microsatellite marker *TGLA116*, which makes genotyping possible (97).

BPDME has been reported in purebred Brown Swiss cattle or their crossbreds in the USA (184), Switzerland (45), Canada (27), Italy (29) and Germany (68). The disorder has also been recorded in the Danish Red Dairy breed following crossbreeding with American Brown Swiss cattle (10)*

The gene for BPDME was introduced into the Danish Red Dairy cattle population by import of semen from the USA. The defect has been recorded in three breeding lines originating from the sires *Nakota Destiny Dapper* (US148460, born in 1965), *Norvic Larry's Lilason* (US131528, born in 1957) and *Rolley View Modern Strech* (US156458, born in 1969), respectively (7). A list of sires labelled with this disorder in Denmark is given in Appendix 1.

Four clinically suspected cases were examined from 1989 to 1991. One of these was diagnosed as affected (10). Suspected cases have not been recorded since then. Passive surveillance in Denmark is probably ineffective and cases may have remained unrecognised as it is difficult to diagnose clinically. However, the disorder is considered to be of low prevalence on account of breeding measures taken following its identification in the 1980s.

5.8. SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is a neurodegenerative disease belonging to the group of lower motor neuron diseases (199). The defective gene causing this disease was imported to Denmark through semen of American Brown Swiss sires and subsequently spread in the population of Danish Red Dairy cattle (121).

The disease affects calves up to 21 weeks of age, but most cases are found in calves aged 4 to 8 weeks. The age at disease initiation is difficult to determine and the speed of progression varies. The disorder is congenital in around 10% of cases. The clinical signs are dominated by progressive muscular weakness leading to recumbency and finally death. Muscular atrophy develops and is especially conspicuous in the hind limbs (Figs. 14 and 15). Most calves suffer from bronchopneumonia, possibly as a sequel to aspiration, and lesions associated with recumbency, including decubital lesions and chemically induced dermatitis on the ventral abdomen in male calves (8, 81, 267, 294).

Characteristic histological lesions are found in ventral horn motor neurons of the spinal cord. Lesions are present in all segments, but are generally most severe in the lumbar intumescence. The neurons display a progressive degeneration, which is initially characterised by swollen chromatolytic neurons that become successively necrotic. Finally, neuronophagia occurs and the neurons disappear leaving "empty beds". Focal as well as more widespread microgliosis is seen in the ventral horn grey matter (Fig. 16) (8, 81, 267). The cytoskeleton of the neurons disintegrates through this process (131, 132). Wallerian-type degeneration of axons within the spinal cord white matter, radix ventralis and peripheral nerves, briefly characterised by axonal swelling, loss of axons, infiltration by macrophages and distension of myelin sheets, is seen (8, 267, 293). Although SMA is mainly characterised by lower motor neuron pathology, upper motor neuron degeneration has been found as well (293). Progressive development of denervation atrophy of the skeletal

* Several authors refer to a publication by *Hansen* (116) as the first description of BPDME in Denmark. However, this publication is a review solely presenting US cases. *K.M. Hansen* did, in fact, diagnose the first case in Denmark and after this several cases of the disorder, though the results remained unpublished.

muscles follows the advancing neuronal loss (Fig. 17).

SMA has been found in American Brown Swiss in the USA (81, 293), as well as in several national European breeds upgraded with American Brown Swiss. SMA has been diagnosed in Denmark (7, 121), Germany (66), Switzerland (267), and Austria (305). The first case was diagnosed retrospectively in 1980 in the USA (294). Pedigree information has been provided for the Austrian, Danish, and Swiss cases, revealing a clear familial pattern with the American Brown Swiss sire *Meadow View Destiny* (US118619, born 1953) as the common ancestor. A single sire of the Danish Red Dairy breed (*VAR Vit-R*, DK31894) apparently not genetically associated with *Meadow View Destiny* has been identified. This might reflect the presence of another affected breeding line, phenocopies or be due to erroneous pedigree registrations. Pedigrees of the American cases have not been published in the scientific literature.

SMA occurs in a familial pattern consistent with autosomal recessive inheritance. This mode of inheritance has been confirmed by breeding studies (224). Recent molecular studies have strongly indicated that a missense mutation in the gene *FVT1*, coding for 3-ketodihydrosphingosine reductase, is the cause of SMA. This enzyme has housekeeping functions related to sphingolipid metabolism and is crucial for neuronal development and function. The missense mutation lowers the enzymatic activity of 3–ketodihydrosphingosine reductase to a level insufficient for survival of ventral horn motor neurons, which are selectively affected because of their high metabolic rate and extensive transport processes along the axons (163). Identification of the molecular cause for SMA provides the basis for development of genotyping tests.

SMA was a relatively common disorder in the Danish Red Dairy breed from around 1987 to 1995 (Fig. 4d), with an estimated number of affected calves of approximately 1,800 (Table 3). The prevalence of the disorder was reduced by extensive pathological examination of calves with neurological disorders (Table 1) and culling of heterozygous sires (Appendix 1). The spread of the defective allele was especially due to the use of heterozygotes, such as *MRS Abru* (DK81137), *RGK Focus* (DK81284), *Ka-Wa Westley* (DK32188), and *HV Hydro* (DK32960). The prevalence of SMA in the Danish Red Dairy breed is at present assumed to be low, though this cannot be proved as surveillance of calves with neurological disorders based on necropsy has been declining in recent years (Table 1) and surveillance based on clinical recognition of SMA is unreliable. The recent success in molecular characterisation of the disease should be use to genotype the sire population.

5.9. SPINAL DYSMYELINATION

Spinal dysmyelination (SD) is a lethal congenital neurological disorder of crossbred American Brown Swiss calves. This disorder was introduced into the Danish Red Dairy breed because of crossbreeding with American Brown Swiss.

Affected animals show congenital recumbency, often in a lateral position with opisthotonos and bilateral symmetric extension of the limbs (Fig. 18). The head and front limbs have a normal position, but the hind limbs are still extended if the calves are placed in the sternal position. Efforts of limb movement and support are absent when calves are raised manually (Fig. 19). Reflexes are either normal or increased. The calves are alert until they become debilitated due to infections (268, III).

Gross lesions are generally absent at necropsy, but some calves may have muscular atrophy, and the cervical and thoracic spinal cord segments might seem decreased in size on transverse section. Characteristic histological lesions are present in the gracile funiculus, dorsolateral spinocerebellar tract and the sulcomarginal tract, and consist of bilateral symmetric hypo- and demyelination (dysmyelination) with astrocytosis, oligodendrocyte necrosis and axonal degeneration (Fig. 20). These lesions are recognisable until lumbar segment 1, where the characteristic dysmyelination of the gracile funiculus disappears. The tract-associated lesions are no longer recognisable posterior to lumbar segment 4. Occasionally, a few neurons with central chromatolysis and swollen axons are seen in the brain stem. Variable degrees of denervation atrophy may be present in the skeletal musculature (109, III).

SD has been reported in crossbred cattle in Germany (109), Denmark (III), and Switzer-

land (268). A single case has been diagnosed in the USA (265).

Cases reported from Germany, Switzerland and Denmark occur in a familial pattern with the American Brown Swiss sire *White Cloud Jasons Elegant* (US148551, born in 1966) as the common ancestor. Cases in Denmark have occurred in a familial pattern consistent with autosomal recessive inheritance (III), and segregation ratios consistent with this mode of inheritance have been found in a breeding study (IV). Genomic analyses have identified the defective allele to bovine chromosome 11 in a region flanked by markers *BP38* and *BMS2569*, and a marker-based test for genotyping is available (226). As the lesions reflect an impaired oligodendrocyte function and maturation (109), a candidate gene should be associated with these functions.

A considerable number of cases occurred in the Danish Red Dairy breed during the 1990s (Table 3, Fig. 4e) mainly due to sires related to two sons of *White Cloud Jasons Elegant*: *Ka-Wa Balison* (US172466) (sire B in III) and *Prospect* (US173809) (sire C in III). Fifty-seven sires were identified as carriers of the defect (Appendix 1). The number of cases was reduced significantly at the end of the period although the detection of carriers based on progeny examination was ineffective (Table 2). Although the prevalence of SD in the Danish Red Dairy breed is probably low, a significant decline in the number of neonatal calves suffering from congenital neurological disorders submitted for necropsy in recent years (Table 1) has reduced the likelihood of detection of cases of SD.

5.10. SYNDROME OF ARTHROGRYPOSIS AND PALATOSCHISIS

The syndrome of arthrogryposis and palatoschisis (SAP) is a congenital malformation of Charolais calves. Affected calves are born at term but most calves are stillborn or die shortly after birth, probably due to respiratory failure. Live born calves have muscular hypotonia (251).

The full morphological variation of this syndrome is not known. The existence of genetically affected but phenotypically normal animals, and viable slightly affected animals, has been postulated (32, 99, 173, 174, 260). Furthermore, arthrogryposis and palatoschisis as two independent lesions, or in combination, are commonly recognised in calves (101). When such lesions appear in Charolais calves, it may be difficult to distinguish SAP from other syndromes (181). Typical cases of the syndrome are morphologically characterised by tetramelic bilaterally symmetrical arthrogryposis and palatoschisis (Figs. 21 and 22). A detailed description of joint involvement has been published (251). Briefly, flexion of the forelimbs, particularly due to flexion of the metacarpophalangeal joints and the carpus, rotation of the digits, and hyperextension of the metatarsophalangeal joints are found, but most joints of the appendicular skeleton may show flexion or extension. The extent to which each joint is affected varies considerably between cases. Malformation of the spine (scoliosis or kyphosis) is found in some cases. Skeletal muscles may be hypotrophic or partly replaced by adipose tissue (lipomatosis). Lesions in the central nervous system in some cases include cervical hydromyelia and syringomyelia (137, 178, 251). The basic mechanisms of this syndrome are not known, but it may be associated with a disturbed differentiation of the central nervous system causing an abnormal stimulation of the lower motor neurons. Consequently, an unbalanced muscle tone could develop, which could subsequently cause arthrogryposis (250, 251).

SAP was originally reported in Charolais cattle in France (171), but was later recognised in Canada (181), the USA (178), Australia (125), Belgium (122), the United Kingdom (137, 190), and Denmark (10). The widespread occurrence of this syndrome is probably due to export of carriers from France (170).

It is generally accepted that the syndrome is inherited in an autosomal recessive manner based on patterns of familial occurrence and segregation ratios between affected and unaffected progeny in Canadian Charolais (214, 251). However, different observations regarding the penetration of the homozygous affected genotype have been made. Complete penetration of the affected genotype was observed in one study (214). Other researchers (32, 99, 174) found reduced penetration and proposed the existence of genetically affected but phenotypically normal individuals. Furthermore, a vari-

ation in expression of the diseased genotype has been proposed by *Lauvergne* (170), who claimed that 30% of the cases have arthrogryposis without concomitant palatoschisis. Candidate genes for SAP have been identified based on comparative physiological studies, but need to be examined more closely (73).

Due to uncertainty regarding the morphological appearance of affected calves, a stringent diagnostic strategy has been applied in Denmark based on diagnostic criteria of tetramelic, bilateral symmetric arthrogryposis and palatoschisis. A single case was diagnosed in 1989 in a calf of unregistered descent (Figs. 21 and 22) (10). Very few malformed Charolais calves were necropsied from 1989 to 2005, and there has been no specific search for the disorder. The prevalence of the syndrome in Denmark is unknown, but is believed to be low.

5.11. ICHTHYOSIS FOETALIS

Ichthyosis foetalis (IF) is an ectodermal dysplasia, originally reported in Danish cattle by *Sand* (252). This lethal subtype of ichthyosis is characterised by the presence of hyperkeratotic epidermal plates of various sizes covering the entire body and enclosed by inflamed fissures. The presence of coat varies between cases. Ichthyosis in animals was reviewed by *Baker* and *Ward* (28) and *Huston et al.* (135), and additional cases have recently been published (241).

IF is generally referred to as an autosomal recessively inherited malformation. This is mainly based on a study by *Tuff* and *Gleditsch* (295) in Norwegian Red Poll cattle, demonstrating a familial occurrence following breeding between unaffected cattle and a segregation ratio corresponding to this mode of inheritance. *Lüps* (191) reported a familial occurrence of cases in German Pinzgauer cattle consistent with autosomal recessive inheritance. Other cases have mainly been reported as individual cases, omitting determination of inheritance. Extrapolation from the studies in Norwegian Red Poll cattle and German Pinzgauer cattle to other breeds is not advised, as although these cases may share a common morphology, a different molecular basis may mean they have different modes of inheritance.

IF has been observed in two Danish cattle breeds. According to *Rasbech* (242), the original case (252) was in the Danish Red Dairy breed and a few additional cases were seen in this breed and in Danish Holsteins. The exact diagnoses can be questioned, but according to the description of the original case, an illustration published by *Rasbech* (242, 244), and a specimen seen in the former collection of malformations at the Royal Veterinary and Agricultural University in Copenhagen, these cases most likely suffered from IF.

Cases have not been diagnosed during this study period, and the prevalence in Danish cattle is apparently very low.

Fig. 13. Syndactylism of the anterior limbs in a Danish Holstein calf (reprinted from 223; Dansk Vet Tidsskr 1990;73:699–701.).

Fig. 14. Spinal muscular atrophy in a four-week-old crossbred Danish Red Dairy/American Brown Swiss calf. Note the severe atrophy of skeletal muscles and the bilateral flexion of the anterior distal joints.

Fig. 15. Spinal muscular atrophy. Same calf as in Fig. 14.

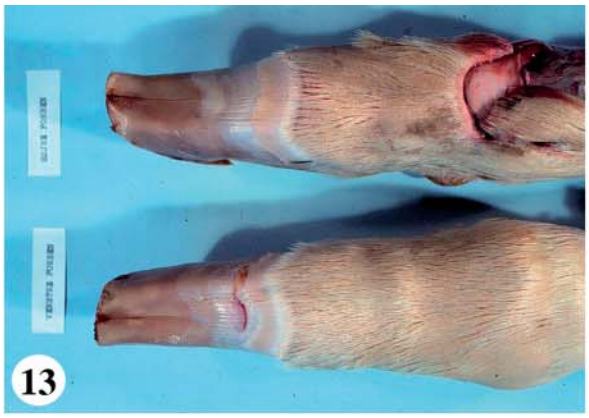
Fig. 16. Photomicrograph of the spinal cord ventral grey matter in a case of spinal muscular atrophy. A normal neuron (A) is surrounded by two necrotic neurons (B) and a chromatolytic neuron (C). Crossbred Danish Red Dairy/American Brown Swiss calf. Haematoxylin and eosin. Bar=50 μm.

Fig. 17. Photomicrograph of skeletal musculature (musculus semitendinosus) in a case of spinal muscular atrophy. Denervation atrophy characterized by groups of atrophic fibers and groups of hypertrophic or normal sized fibers. Crossbred Danish Red Dairy/American Brown Swiss calf. Haematoxylin and eosin. Bar=30 μm.

Fig. 18. Spinal dysmyelination in a neonatal crossbred Danish Red Dairy/American Brown Swiss calf. Note the lateral recumbency, opistothonus and extended hind limbs.

Fig. 19. Spinal dysmyelination. Note the absence of support to the body. Same calf as in Fig. 18.

Fig. 20. Photomicrograph of the cervical spinal cord in a case of bovine spinal dysmyelination. Note the symmetric dysmyelination of the gracile funiculus (↓), dorsolateral spinocerebellar tract (→) and sulcomarginal tract (↑). Crossbred Danish Red Dairy/American Brown Swiss calf. Luxol fast blue.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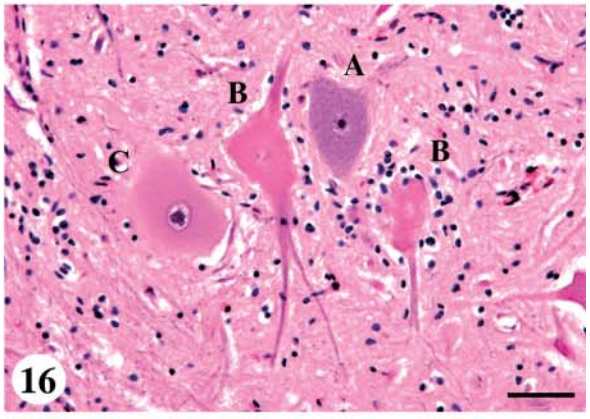

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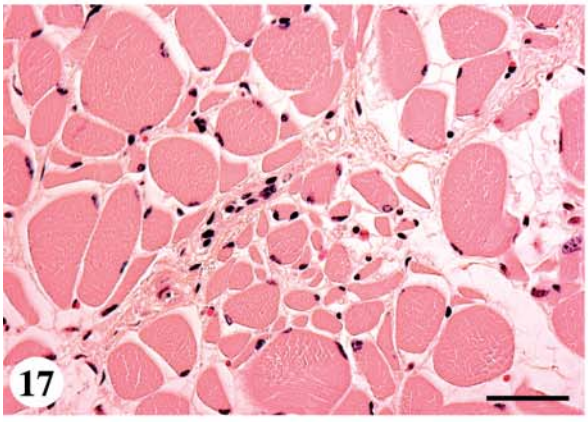
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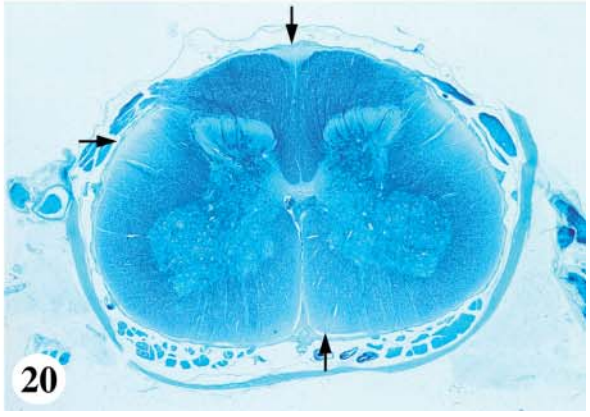
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5.12. EPITHELIOGENESIS IMPERFECTA

Epitheliogenesis imperfecta (EI) is a congenital malformation characterised by local agenesia of the skin. Several types of this disorder are known (135). The classic form (type 1) is lethal and characterised by lack of skin on the distal parts of the limbs, deformed ears due to auricular epithelial defects, defects in the integument of the muzzle, and a defective oral epithelium (Figs. 23 and 24). The basic defect may be associated with defective metabolism of fibroblasts impairing the nutrition of the epithelium (93).

EI type 1 has mainly been reported in Holsteins (135). Familial occurrence following breeding between unaffected parents indicates that some cases are due to an autosomal recessive gene, although segregation ratios between affected and unaffected calves differ from expected ratios (107, 108, 135, 179). The inheritance of recent cases in Holsteins is unsolved (60, 311).

Documentation of the occurrence of EI in Danish cattle is insufficient to draw definitive conclusions. *Rasbech* (242, 244) claims that a few sporadic cases have been observed, probably in Danish Holsteins and in the Danish Red Dairy breed. A case resembling EI type 1 in a calf of the Danish Red Dairy breed has been photodocumented by *K. M. Hansen* (in 242, 244). In 1991, EI type 1 was diagnosed in a female Hereford calf originating from a small herd (Figs. 23 and 24) (7, 10). In addition to the typical lesions present in the distal parts of the limbs, the muzzle, nostrils, and oral cavity, lesions were also found at the base of the ear and the teats. The ears were not malformed. The calf was the result of natural breeding between unaffected related parents, which is consistent with autosomal recessive inheritance, but no definitive conclusion could be reached as only one affected animal was born in the herd. Additional cases have not been submitted during the study period, and the prevalence of EI type 1 in Danish cattle is probably low.

5.13. HEREDITARY ZINC DEFICIENCY

Hereditary zinc deficiency (HZD) in Holsteins was originally reported from Scotland, where the disorder had occurred since at least 1951 (203). However, little attention was paid to the disorder until the 1970s when it was suddenly reported in national Holstein populations in several European countries, including Denmark (16, 103), Holland (297), Germany (272, 273, 282), and Italy (96 – referred in 272). Additional cases were reported in the 1980s from Ireland (200), the United Kingdom (78, 228), and France (254).

Several names have been proposed for this disorder. Lethal trait A46 was used by *Andresen et al.* (16) referring to the nomenclature originally proposed by *Lerner* (187). Adema disease was proposed by *Grønborg-Pedersen* (103) and referred to a carrier of the defect, the Danish Holstein sire *Hornshøj Adema* (DK8177). Designations referring to lesions observed in affected calves, such as parakeratosis and thymic hypoplasia, have been used by others (48, 272). The term "hereditary zinc deficiency" refers to a fundamental aspect of this disorder and has been used in recent publications (193, 276).

HZD is caused by impaired intestinal zinc absorption (85–87) due to abnormal function of a protein belonging to a family of zinc-uptake proteins. The molecular basis is a single nucleotide substitution in the gene *SLC39A4* (313). In acrodermatitis enteropathica, a human analogue of bovine HZD (50, 303), defects in the gene *SLC39A4* have also been identified (166, 300).

Affected animals can be reconstituted by continuous administration of supplementary zinc given at high doses (48, 164, 272, 297). As zinc is absorbed by passive diffusion and by a carrier-mediated process (130, 264), the increasing levels of zinc in the blood of treated calves may be due to passive diffusion across the intestinal barrier.

Zinc is an essential trace element. It has a structural role in tissues such as bone, teeth, muscle, and integument, and is involved in the metabolism of proteins, nucleic acids, and carbohydrates through its role as an essential part of many metalloenzymes or as an enzymatic cofactor (127, 168). Calves are born with normal levels of zinc, as they are nourished through the placenta during intrauterine development. Serum concentration of zinc decreases during the first weeks of life and precedes development of lesions and clinical signs. Diarrhoea,

probably due to disturbed turnover of enterocytes and deficiency of functional intestinal enzymes, develops prior to other symptoms (193). Well-developed lesions are mainly characterised by parakeratosis and dermatitis, and occur in areas of continual skin flexion or in regions particularly subjected to abrasion. Hence, lesions are most extensive around the mouth, eyes, base of the ear, joints, and lower parts of the thorax, abdomen and limbs (Figs. 25 and 26). Parakeratosis and ulceration of the non-glandular part of the intestinal tract occurs and is mostly expressed clinically as stomatitis. Diminished eating ability and growth retardation occur (193, 272, 282). Thymus, lymph nodes, and gut-associated lymphoid tissue are hypoplastic, and affected calves are immunosuppressed due to impaired function of the immune system (49, 236). Animals often develop bronchopneumonia. Lesions are progressive and, if left untreated, calves die within 4 to 8 weeks after initial symptoms are observed (46, 47).

The genetic aetiology of the disorder was proposed by *McPherson et al.* (203), who recognised that cases occurred following inbreeding and were segregated in a manner similar to an autosomal recessively inherited defect. This mode of inheritance was proven by additional segregation studies (16, 17). Most reported cases are of Dutch Holstein origin and genealogical studies have traced the origin of the disease-causing allele to the Dutch Holstein sire *Egbert N.R.S. 13110* (born 1932) (164).

Thirty-five sires used for insemination in Denmark have been diagnosed as carriers of HZD based on progeny examination (Appendix 1). These sires have not been used for at least the past 20 years. Pedigree analysis has demonstrated that 28 of the heterozygous sires are genetically related to *Egbert N.R.S. 13110*, while the pedigree of the remaining seven sires is incomplete. The prevalence of calves suffering from HZD has been reduced since the 1970s. *Bauer et al.* (30) state that only one calf was included in their study due to lack of affected calves, and *Agerholm* (7) diagnosed only four cases, all of which occurred in a single herd due to inbreeding between a sire (*Moesgård Chapel*, DK224785) and closely related females. At present, the prevalence of HZD in Danish Holsteins is probably low.

5.14. RENAL LIPOFUSCINOSIS

Renal lipofuscinosis (RL), which is also referred to as "black kidneys", is a disorder characterised by cytoplasmic accumulation of the pigment lipofuscin in the renal tubular system, predominantly in the proximal tubular epithelium. Macroscopically, the kidneys have a bilateral diffuse brown to black discoloration of the cortex (Fig. 27) and outer strip of the outer medulla. The disorder is mostly diagnosed in cattle aged 3 years or older. The disorder is apparently not associated with clinical disease and is generally not diagnosed before slaughter. However, the culling rate differs from that of unaffected cattle; thus, indicating an adverse effect on health or production (X).

Epidemiological studies (X) have shown that RL occurs in Danish Holsteins and Danish Red Dairy cattle and crossbreds, involving at least one of these breeds, but apparently not in other cattle breeds in Denmark. Cases are recognised in family clusters and statistical analyses strongly indicate an autosomal recessive mode of inheritance.

There is a high prevalence of RL in Danish Holsteins and in the Danish Red Dairy breed. The incidence of the disorder in slaughter cattle aged 3 years or older has been calculated to be 0.44% and 2.51% for Danish Holsteins and the Danish Red Dairy Breed, respectively (X).

5.15. HEREDITARY DILATED CARDIOMYOPATHY

Hereditary dilated cardiomyopathy (HDC) is a disease of adult cattle of Canadian Holstein origin. Affected animals are mostly around 3 years old, but variation from 2 months to 8.5 years is seen. Disease progression is subclinical, but once clinical signs have developed, there is rapid deterioration due to progressive cardiac insufficiency. Signs include severe subcutaneous oedema located ventrally on the body and between the mandibles, ascites and hydrothorax. These symptoms are consistent with right-sided heart failure. At necropsy, cardiac lesions are characterised by diffuse induration of the myocardium, cardiomegaly, and dilatation of all compartments. Lesions due to chronic stasis and hypertension are present macroscopically

and microscopically in several tissues. Myocardial histopathology is characterised by interstitial fibrosis, myocyte necrosis, myofibre hypertrophy, and myocyte vacuolation (94, 197, 212, 213, 281).

HDC was originally reported from Switzerland, where the disorder became endemic (197). In addition, cases have been reported from Japan (262), Canada (26), Australia (202), the United Kingdom (43, 44, 212), Germany (165), Austria (62) and Denmark (IX).

HDC is likely to be inherited autosomal recessively as cases have been reported in familial patterns consistent with this mode of inheritance (26, 94, 253, IX) and breeding studies have demonstrated the expected segregation ratios (67). Recent studies have shown that the locus for HDC is located on chromosome 18 (106) When details of genealogy were provided, a genetic relationship to the Canadian Holstein sire *Montvic Rag Apple Sovereign* (CAN155159) born in 1942 or his son *A B C Reflection Sovereign* (CAN198998) was found (94, 198, IX). In most scientific publications, sires have been referred to by coded names, thus preventing any detailed insight into the familial occurrence of the disorder. However, detailed pedigrees of Danish cases of HDC have been published (IX).

HDC has been reported in Holsteins and Red Holsteins, as well as in national crossbreeds (62, 165, 281). In Denmark, the disorder has been observed in the Danish Red Dairy breed, Red Holstein breed and Holstein breed (IX). The disorder may have been present in the Danish Red Dairy breed since the 1960s. Five cases of myocardial fibrosis were reported in 1964 (110, 220). A retrospective examination of archived materials from these cases has demonstrated histopathological changes consistent with HDC (IX). A genetic basis for this disorder was apparently not considered in the original studies.

The prevalence of HDC in Danish cattle is unknown. Fourteen cases were diagnosed during a 13-year period (1991–2003) (IX). Additional cases have not been diagnosed since then, thus indicating a low prevalence. However, this is most likely erroneous. The diagnosed cases consisted mainly of animals referred to the Royal Veterinary and Agricultural University in Copenhagen. As animals are mainly referred to the University from the eastern part of Denmark, where cattle density is low, the figures only reflected a subpopulation of Danish cattle. Furthermore, an estimate of the number of cases based on pedigree information of only these 14 cases revealed that almost 150 cases had probably appeared (Table 3). As the estimate was based on animals acquired almost fortuitously and mainly from a subpopulation, the real number of cases may be considerably higher. The high number of Danish Red Dairy cattle diagnosed with HDC might reflect that this breed is most prevalent in eastern Denmark rather than a higher prevalence of the disorder in this breed than in Danish Holsteins and Red Holsteins. A search for clinical cases was initiated in 1994 through a publication in the journal of the Danish Veterinary Medical Association (175). Only one clinical case, which turned out to suffer from endocarditis, was referred to the authors. There has been no active search for cases since then.

5.16. BOVINE LEUKOCYTE ADHESION DEFICIENCY

Bovine leukocyte adhesion deficiency (BLAD) is an immunological defect due to a molecular aberration in CD18. CD18 constitutes a part (β-subunit) of the CD11/CD18 glycoprotein complex located on the surface of neutrophils. Consequently, the three subtypes of CD11/

Fig. 21. Syndrome of arthrogryposis and palatoschisis in a Danish Charolais calf. Note the tetramelic bilateral symmetric arthrogryposis (reprinted from 7).

Fig. 22. Palatoschisis in the syndrome of arthrogryposis and palatoschisis. Same calf as in Fig. 21 (reprinted from 7).

Fig. 23. Epitheliogenesis imperfecta. Note the absence of epithelium in the distal parts of the limbs, seperation and loss of claw capsules and intense inflammation of the corium. All four limbs were affected to an equal degree. Hereford calf (reprinted from 10; Acta Vet Scand 1993;34:245–53).

Fig. 24. Epitheliogenesis imperfecta. Extensive loss of epithelium in the tongue exposing acutely inflamed subepithelial tissue. Same animal as in Fig. 23.

Fig. 25. Hereditary zinc deficiency. Extensive parakeratosis around the muzzle and the eyes. Danish Holstein. Courtesy of *T Flagstad.*

Fig. 26. Hereditary zinc deficiency. Parakeratosis, dermatitis and alopecia on the distal part of the limbs. Danish Holstein. Courtesy of *T Flagstad.*


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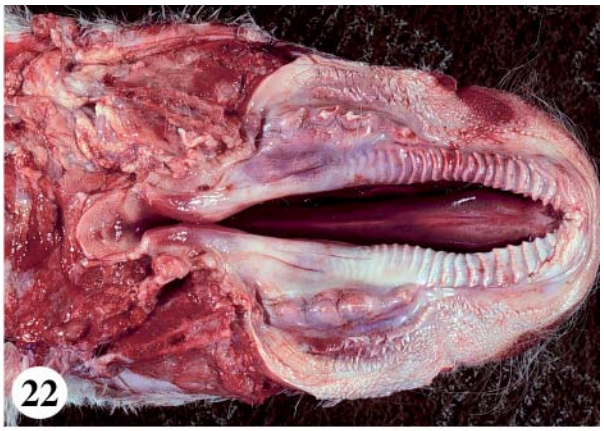
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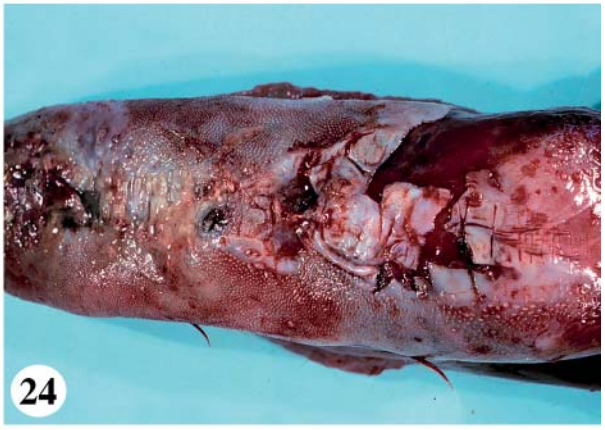
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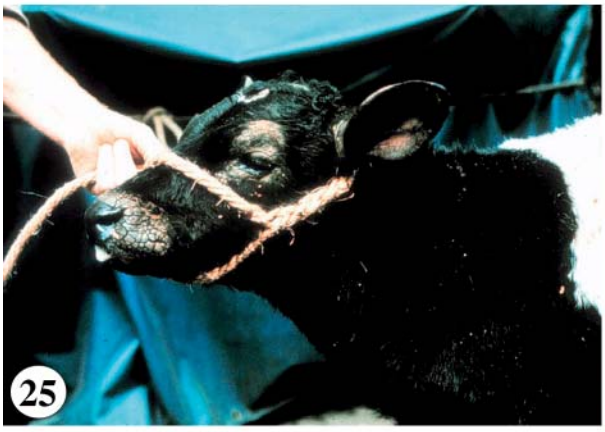
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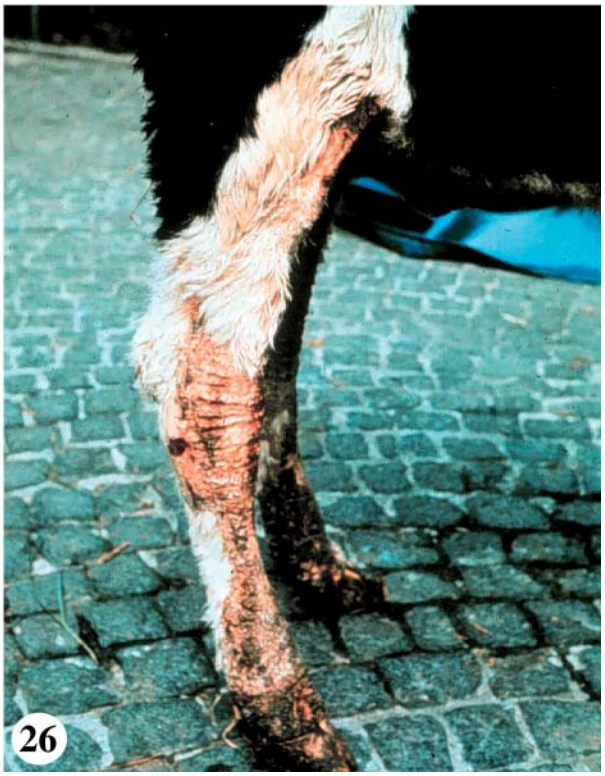
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CD18 (CD11a/CD18, CD11b/CD18 and CD11c/CD18) are functionally deficient. These glycoproteins play an important role in the inflammatory response to infections as they interact with receptors on the vascular endothelium, thus making adhesion between neutrophils and endothelium possible. Such adhesion is mostly a prerequisite for extravascular migration of neutrophils, and affected individuals therefore lack extravascular neutrophils in most tissues. In addition, functional defects in neutrophils have been recorded (209). Consequently, such individuals are predisposed to recurrent and prolonged mucosal and epithelial infections (155–157, 210).

BLAD is lethal for most calves within one year, but individuals may live longer if managed well and treated properly for infections (3). The animals display signs of immunodeficiency, but the appearance of affected animals varies. A common finding is a total leukocyte number of more than 40×10^9 cells per L blood, but often considerably higher. The leukocytes are predominantly neutrophils (>80%) (98). The haematological changes in combination with stunted growth may be the only clinical sign of BLAD, at least at certain stages of disease development (Fig. 28) (I). BLAD-affected calves contract a range of opportunistic bacterial and fungal infections, and a wide range of lesions may consequently be seen. Widespread ulcerative and necrotising stomatitis with periodontitis, loss of teeth, and alveolar periostitis are frequent lesions in the oral cavity. Extensive dermatophytosis may occur (Figs. 29 and 30). Multifocal chronic ulcerative and necrotising enteritis, rhinitis and suppurative bronchopneumonia are frequent additional necropsy findings. The inflammatory response in the alimentary tract, upper respiratory system and skin is characterised by granulomatous inflammation and a striking absence of infiltrating neutrophils despite their huge intravascular presence. Granulation tissue is often present due to the chronic stage of inflammation. In contrast to these lesions, pathological changes in the lung are dominated by suppuration to the alveoli as migration across the blood-air barrier is CD11/CD18 independent (1–3, 95, 98, 129, 207, 210, 231, 255, 274, 275, I).

BLAD is inherited in an autosomal recessive manner and occurs in a clear familial pattern. The disease is due to a single base substitution of adenine with guanine at nucleotide 383 in the CD18 gene (*ITGB2*), which subsequently leads to replacement of aspartic acid with glycine at position 128 in the corresponding protein (D128G). The molecular studies have made genotyping of animals possible and the US Holstein sire *Osborndale Ivanhoe* (US1189870, born 1952) has been identified as the common ancestor (259).

The defective allele for BLAD has been spread to many Holstein populations through widespread use of semen of sires genetically related to *Osborndale Ivanhoe*, i.e. *Penstate Ivanhoe Star* (US1441440), *Ugela Bell* (US1920807), and *Carlin-M Ivanhoe Bell* (US1667366). Consequently, cases of BLAD have been reported from Austria (255), Denmark (I), Germany (129, 274), Japan (i.e. 210), Netherlands (34, 95), South Africa (263), and the USA (i.e. 98). However, cases have probably gone unrecognised or unreported in other countries.

Cases of BLAD in Denmark were reported in 1993 (I) and a large number of Holstein sires were analysed for the functional mutation in the CD18 gene. This identified 108 heterozygous sires used for breeding out of 405 tested sires, including the extensively used sire *NJY Hubert* (DK18382) (149). At present, 338 sires used for artificial insemination in Denmark have been shown to be carriers (Appendix 1). The estimated number of BLAD-affected calves in Denmark has been calculated to be around 650 (Table 3), with most cases occurring from 1989 to 1992 (Fig. 4b). However, the actual number is higher, as 346 sires with an undetermined genotype that were sons of a known carrier (Table 2) were omitted from the calculations. Fifty per cent of these were expected to be heterozygous for the BLAD allele. A rapid decline in the number of BLAD-affected calves occurred after the introduction of systematic genotyping of sires (Fig. 4b). At present, BLAD is considered to be of low prevalence due to the measures implemented by the Danish breeding associations.

5.17. CONGENITAL ERYTHROPOIETIC PORPHYRIA

Congenital erythropoietic porphyria (CEP) in cattle is an inherited enzyme deficiency in the

pathways of haeme biosynthesis. Haeme, which is a fundamental part of haemoglobin, is synthesised by a number of successive enzymatic steps, starting with the formation of δ-aminolevulinic acid from glycine and succinyl-CoA, which is further metabolised to porphobilinogen. Porphobilonogen is subsequently synthesised to uroporphyrinogen III by the action of two enzymes, uroporphyrinogen I synthetase and uroporphyrinogen III cosynthase. CEP is caused by deficiency of one of these, uroporphyrinogen III cosynthase (188, 249). An intermediary metabolite (hydroxymethylbilane) in this enzymatic step is converted to uroporphyrinogen I, some of which may be further metabolised to coproporphyrinogen I. These porphyrinogens are oxidised to their end products, uroporphyrin I and coproporphyrin I, which accumulate in the body and are excreted in urine and faeces (151). The excretion of porphyrins varies and porphyrin metabolites other than uroporphyrin I and coproporphyrin I, such as protoporphyrin, are also excreted (56, 146, 151, 248, 302). Determination of the ratio between urinary coproporphyrinogen isomers I and III may allow differentiation between unaffected homozygotes, heterozygotes and affected homozygotes (206).

The molecular basis for CEP in cattle has not been investigated. In man, several mutations in the uroporphyrinogen III cosynthase gene have been associated with CEP (310).

CEP is clinically and morphologically characterised by photosensitization, congenital brown discoloration of the skeleton and teeth, chronic haemolytic anaemia, and reduced growth.

Clinically, the most striking lesion is photosensitization, which may cause subepidermal blistering and dermal necrosis of unpigmented areas (82, 91, 257). These lesions are due to the photodynamic properties of the porphyrins deposited in the skin. These porphyrins absorb energy when exposed to ultraviolet light and become unstable. When porphyrins return to the ground state, energy is released, which in the presence of molecular oxygen forms free radicals (i.e. singlet oxygen), and subsequently cell components are damaged (92, 151). As this process requires ultraviolet light, lesions are only seen in animals housed outdoors and mainly during periods of intense sunlight. There are individual differences, probably reflecting the level of porphyrins deposited in the skin (302). In geographical regions with limited exposure to high levels of ultraviolet radiation, as in Denmark, photosensitization may be sparse (146).

A characteristic lesion of CEP is diffuse systemic brown discoloration of bones and teeth (Figs. 31 and 32). The colour changes affect the compact and callous bones, and although both enamel and dentine of teeth are affected, much higher concentrations are found in the dentine. Porphyrins are deposited in bands of higher and lower concentration, probably reflecting cycles of exacerbation and remission of the disease during foetal development (Fig. 33). Bony discoloration can be seen in affected foetuses around the third month of gestation (146, 148, 283). Some cases may remain undiagnosed until slaughter, when systemic brown discoloration of bones and teeth is recognised. However, discoloration can be so sparse that inexperienced meat inspectors may overlook it. The incorporation of photodynamic substances into the skeleton and teeth can be visualised by exposing these structures to ultraviolet light, as with the use of a *Wood*'s lamp (Fig. 34). This will result in a bright red fluorescence even in slightly discoloured cases. Abnormal coloration of internal organs may be present due to accumulation of porphyrins or other forms of pigment, i.e. haemosiderin (146–148, 151).

Affected animals are born with haemolytic anaemia and an intense erythrogenic response (152). Anaemia of variable severity persists but may be subclinical. The erythrocyte survival time is reduced and is associated with increased erythrocyte porphyrin content, probably reflecting porphyrin toxicity (151, 153, 246, 316).

CEP was originally reported in South African Shorthorns (90), but most reported cases have been of the Holstein breed. However, ancestors of the Shorthorn breed have been identified in some cases. A few cases have been reported in other breeds, such as Canadian Ayrshire cattle (126). The disorder has been reported in Holsteins in the USA (194, 246, 301), South Africa (88, 89, 91), and Denmark (145, 147). The cases apparently occur as isolated familial clusters although this might be due to incomplete pedigree information. Investigations of some clusters by analysis of segregation ratios between

affected and phenotypically unaffected animals have demonstrated an autosomal recessive inheritance (145, 301), while this mode of inheritance has been indicated by the presence of inbreeding loops in other clusters (82, 194).

The inheritance of CEP in Danish Holsteins with ancestors of the Shorthorn breed has been determined by breeding studies. Segregation ratios demonstrated an autosomal recessive mode of inheritance (145). *Jørgensen* (145) found cases in a familial pattern and claimed to have identified the common ancestor, which unfortunately was only referred to by the code *L.W.* Additional pedigree analyses were not possible, so the occurrence of this defect in the Danish Holstein and Shorthorn breeds was not completely resolved (148). Although most cases have been seen in the Shorthorn or Holstein breeds or their crosses in Denmark, a single case in a red coloured cow has been reported (240).

Systemic diffuse brown discoloration of the skeleton in cattle has been recognised in Danish cattle for around 100 years. *Poulsen* (240) mentions that such disorders are seen once or twice a year at the public abattoir in Copenhagen, while *Møller-Sørensen* (208) reports that fewer than 2 cases were found per 20,000 slaughtered cattle on the island of Funen. Regionally, the disorder became more prevalent during the 1950s (145).

During the present study period, seven cases of the Danish Holstein breed with severe photodermatosis were examined at slaughter. Of these, four cases had brown discoloration of bones and teeth, displaying bright red fluorescence when subjected to ultraviolet light. Haematological analyses were not performed. Although these findings are not pathognomonic, these animals were considered to suffer from congenital erythropoietic porphyria. Three animals were progeny of the Holstein sire *Klaus 323* (DK 226735), while one animal was a daughter of *T Ingslev* (DK 235145). Pedigree analyses demonstrated inbreeding and identified the Holstein sires *Black 18* (DK 18004) and *SK Black* (DK 11516) as likely carriers of the defect, with *MJY Black* (DK 8744) and *VE Klaus* (DK 15613TL) as possible carriers (Fig. 35).

A further search for cases has recently been performed. In a survey of 111,796 cattle, including 70,199 Danish Holsteins admitted to four major abattoirs from 1 August 2005 to 31 December 2005, no cases were detected. This study is planned to continue until September 2007. Additional Danish bovine practitioners were requested to report cases of severe photodermatosis in Holsteins in 2003, but no more cases were found. It can be concluded that CEP occurs with low prevalence in the Danish Holstein breed.

5.18. RECTOVAGINAL CONSTRICTION

Rectovaginal constriction (RVC) is a connective tissue disorder associated with modification and exaggeration of normal structures in the wall of the vestibulum and the large intestine at the junction between the rectum and the anus. In the anorectal junction, the structure consists of the internal anal sphincter muscle and the anal fibromuscular coat, which is where the levator ani muscle is inserted into the longitudinal smooth layer of the rectum. This combined structure is ultrastructurally abnormal and forms a fibrous inelastic band around the anus, which can only be distended a few centimetres. In addition, the amount of collagen in the external anal sphincter is increased and the collagen subtypes may be changed. A fibrous inelastic

Fig. 27. Bovine renal lipofuscinosis.

Fig. 28. Bovine leukocyte adhesion deficiency. Growth retardation and unthriftiness in an 8-month-old Danish Holstein calf (reprinted from I; Acta Vet Scand 1993;34:237–43).

Fig. 29. Bovine leukocyte adhesion deficiency. Extensive chronic dermatophytosis and unthriftiness. Danish Holstein.

Fig. 30. Bovine leukocyte adhesion deficiency. Extensive chronic dermatophytosis. Detail of the animal shown in Fig. 29. Danish Holstein.

Fig. 31. Congenital erythropoietic porphyria. Diffuse brown discoloration of compacta and spongiosa. Humerus, Danish Holstein.

Fig. 32. Congenital erythropoietic porphyria. Diffuse brown discoloration of the teeth. Part of the mandible. Danish Holstein.

Fig. 33. Congenital erythropoietic porphyria. Note the rings of brown discoloration of different intensities. Femur, Danish Holstein.

Fig. 34. Congenital erythropoietic porphyria. Pink fluorescence of teeth exposed to ultraviolet light (*Wood*'s lamp). Part of the mandible. Danish Holstein.


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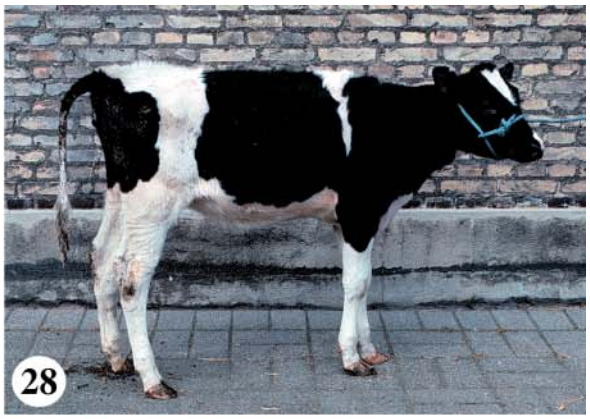
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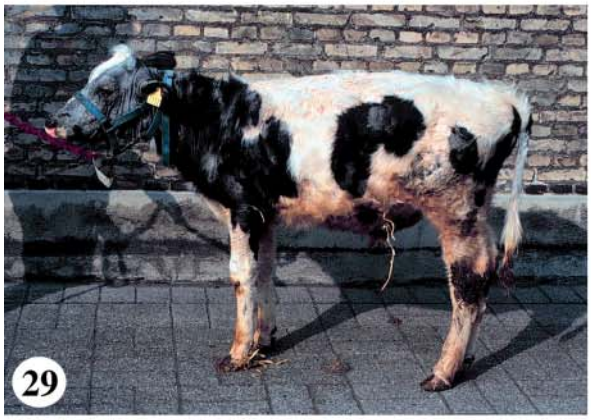
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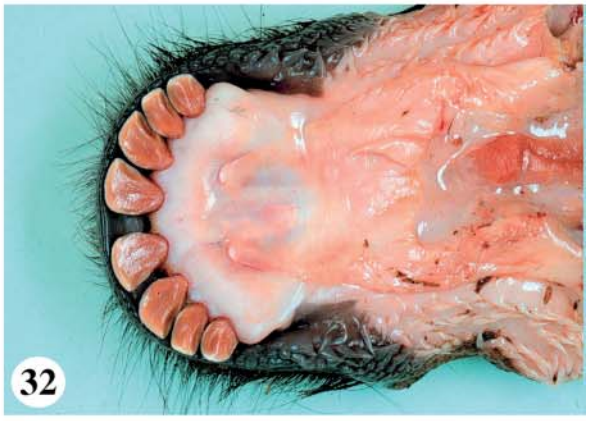
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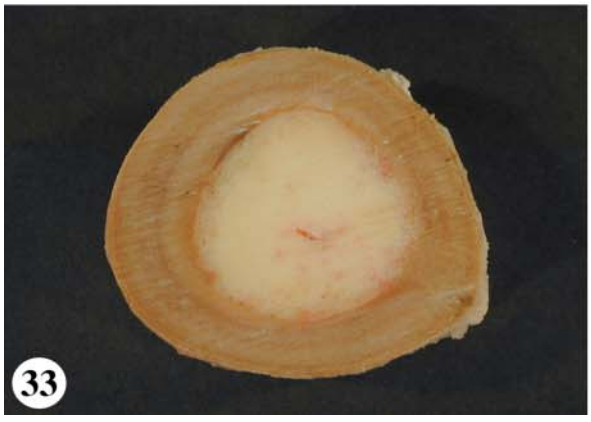
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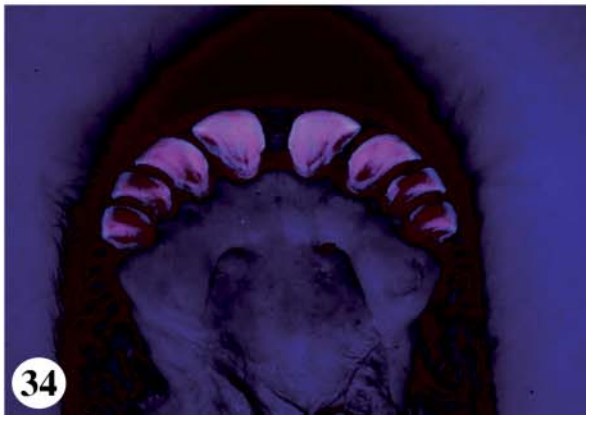
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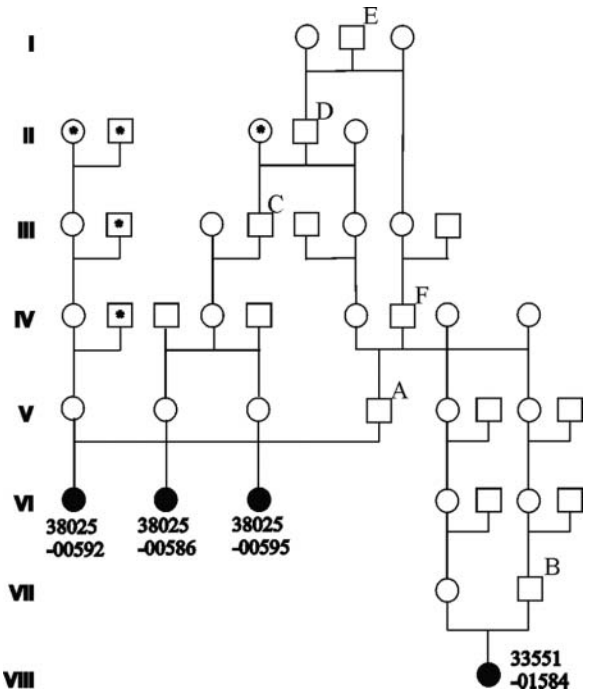

Fig. 35. Genealogical diagram showing the genetic relationship between four Holstein heifers affected by congenital erythropoietic porphyria (cases 38025-00586, -00592, -00595 and 33551-01584). The sires *Klaus 323* (A), *T Ingslev* (B), *Black 18* (C) and *SK Black* (D) are likely carriers of the defect as they are part of an inbreeding loop. The sires *MJY Black* (E) and *VE Klaus* (F) might be carriers.

constricting ring is also present in the tunica muscularis of the vestibulum (63, 201, 286, 292). Furthermore, bilateral stenosis of the milk veins (vena epigastrica cranialis superficialis dexter et sinister) at their penetration site though the abdominal wall is found (13). Increased amount of collagen may be present in the head and in the perineal region (284, 285).

The clinical signs of RVC are primarily associated with the effects of the vestibular and venous stenoses. The vestibular stenosis causes dystocia, which mostly must be resolved by Caesarean section (183). This is mainly a problem associated with natural breeding, as the disorder is generally identified if the animal is inseminated. The stenosis of the milk veins causes stasis and increased intravascular pressure in the vein, which results in udder oedema and ischaemic necrosis of the udder skin and subsequently mastitis (13, 14). As the anal stenosis is not associated with clinical signs, RVC is mainly a disorder of adult females and is only accidentally diagnosed in males. Several unsuccessful attempts have been made to develop laboratory methods for identification of heterozygous individuals (63, 169, 287, 289–291, 296). At present, only breeding trials are reliable.

RVC was first reported in the Jersey breed in the USA in 1975 (176), but may have occurred more than 40 years earlier (133). The disorder occurred in a familial pattern consistent with autosomal recessive inheritance. This was later confirmed by breeding studies (185).

RVC was diagnosed in the Danish Jersey breed in 1984 after Danish veterinary surgeons were made aware of this disorder (115, 118). Several sires were identified as carriers of the disorder based on clinical examination of affected animals or specimens from them, or a clinical history consistent with the disease and familial relation to known carriers (118, 119). Identified heterozygous sires were genetically related to the US Jersey sire *The Trademark* (US585350) or the Danish Jersey sire *Rosenfeldt Favorit* (DK4250) (119, 266). These sires have a common ancestor, the US Jersey sire *FAV Commando* (US457631) (7). The prevalence of affected animals was reduced though the 1980s by a restrictive breeding policy (144).

Four suspected cases of RVC were examined from 1989 to 1991. One of these was probably affected (10). No cases have been examined since then. As RVC in females is associated with severe symptoms and as technicians probably diagnose the disorder in association with insemination or pregnancy testing, a lack of reports of affected cases probably reflects a low prevalence of the disorder in the Danish Jersey breed.

5.19. CHROMOSOMAL ABERRATIONS

Three transmissible chromosomal aberrations have been diagnosed in Danish cattle: tandem fusion translocation, translocation t(1;8;9)(q45; q13;q26), and translocation 1/29. These defects reduce the animal's fertility due to development of gametes with unbalanced chromosome numbers leading to non-viable embryos. The chromosome aberrations, which are mostly identified in cultured blood lymphocytes, can be present in one or two copies, designated as heterozygous and homozygous states, respectively.

The translocations reduce the number of chromosomes from the normal 60 to 59 or 58 in the heterozygous and homozygous state, respectively. The centromere of one chromosome may be lost during the conjunction of the chromosomes, but the coding DNA is conserved (189). Animals that carry these chromosome defects are therefore phenotypically normal.

5.19.1. Tandem fusion translocation

This translocation is characterised by the fusion of two chromosomes at the free end (opposite the centromere), with simultaneous loss of one centromere. This aberration was reported by *Hansen* (111–113) in the Danish Red Dairy breed, but the chromosomes involved were not identified. The defect was identified in sires used for insemination and heterozygous individuals had a decreased fertility of around 10% measured as 30–60 day non-return to service rate. The prevalence of this defect is at present unknown.

5.19.2. Translocation t(1;8;9)(q45;q13;q26)

This is a complicated translocation where chromosomal segments have been exchanged among chromosome nos. 1, 8 and 9 (162). This defect was originally found in the American Brown Swiss sire *Sunburst Hill Combo Fabian* (US184214) (161, 162). Semen of this sire had been used to a limited extent in Denmark.

The t(1;8;9)(q45;q13;q26) translocation has a severe negative influence on fertility, exemplified by the observation that 223 inseminations only resulted in 11 calves (4.9%). The non-return to service rate at gestation day 56 was 26%. Compared to the usual rate of 65% this demonstrates that most progeny were lost during early development (55). The defect was trasmitted to 5 of 10 progeny. The prevalence of this disorder is assumed to be low in Danish cattle as the severe impact on the fertility of affected individuals will normally result in slaughter, thereby interrupting transmission of the defect.

5.19.3. Translocation 1/29.

Chromosome translocation 1/29 is a centromere fusion of chromosome nos. 1 and 29. This defect is the most common chromosome translocation in cattle and has been identified in cattle breeds worldwide (104, 105). The defect is associated with a decreased fertility of 5–10%. This is due to a certain level of spermatozoa and eggs with unbalanced chromosome number as the separation of chromosomes during meiosis may be disturbed (77, 104, 105).

Translocation 1/29 has been recognised in Danish Blonde d'Aquitaine, Limousine and Danish Red Dairy breed crossed with American Brown Swiss (55, 117, 221, 222). The prevalence was highest in the Danish Blonde d'Aquitaine population. By combining the results of *Agerholm et al.* (10) and *Hansen* and *Hansen* (120), who performed their studies around 1990, a prevalence of 28.1% and 0.5% can be calculated for heterozygous and homozygous affected animals, respectively. The prevalence of animals having a 1/29 translocation in the Danish Limousine population was 12.2% (10). The respective breeding associations initiated a programme to reduce the prevalence of translocation 1/29. Samples from animals of these breeds have continuously been examined and translocation 1/29 seems to be of low prevalence (53).

5.20. DEFECTS OF SPERMATOZOA

Several defects of spermatozoa have been identified in Danish cattle, but an inherited basis has only been established for the "Dag-defect" in Jersey sires.

The "Dag-defect" is characterised by spermatozoa with tails that are strongly coiled, extensively folded, or split into fibres, and is present in at least 25% of the spermatozoa. These abnormalities inhibit controlled motility. The fertility of affected sires reflects the level of abnormal spermatozoa. The sires often have severely reduced fertility, as the percentage of defective spermatozoa is mostly high (36, 38). A disturbed arrangement and lack of central and peripheral fibres in the tail has been observed ultrastructurally (38, 158, 317). The tail abnormalities are not present in the spermatozoa as long as they are within the testicles, but develop during passage through the epididymidis. This has led to the hypothesis that the spermatozoa are normal, but are damaged by an unfavourable biochemical environment within the tubules of the epididymides. It has, in fact, been demonstrated that sires with the "Dag-defect"

have an elevated semen zinc concentration (41), which may damage the spermatozoa. The pathogenesis has not been clarified, but may involve an inherited biochemical defect in the tubular epithelium of the epididymidis.

The "Dag-defect" was named after the Danish Jersey sire *Fåborg Dag* (born 1962), which was the first animal identified with this defect (37, 38). However, the defect probably originated from a Jersey sire born in 1934, but his identity has not been revealed. Fifteen bulls diagnosed as having the "Dag-defect" between 1963 and 1979 were maternally and paternally related to this sire, thus demonstrating a familial pattern consistent with autosomal recessive inheritance (159). A breeding study between an affected sire and his own daughters revealed a segregation ratio of 6 affected males to 32 unaffected males, which is in accordance with the expected 1:7 ratio ($\chi^2=0.376$, df=1).

Systematic data on the prevalence of the "Dag-defect" in sires entering breeding stations are not available, but laboratory technicians claim not to have seen the defect for years (15). The disorder was last reported in 1987 in three Jersey sires (227). The present prevalence of the "Dag-defect" is apparently low.

6. Conclusions

A wide range of inherited disorders has been identified in Danish cattle since 1989. However, intervention in breeding plans by culling or restrictive use of heterozygous sires has successfully reduced the number of affected progeny and controlled further spread of defective genes for most disorders. A specific programme to reduce the spread of hereditary dilated cardiomyopathy has not commenced, but as a considerable number of animals may be affected, a surveillance program for this disorder is recommended. Hereditary dilated cardiomyopathy is a lethal disorder of adult cattle with rapid deterioration, which is difficult to differentiate clinically from other causes of right-sided heart failure. Achieving sufficient cases to survey the disorder will be expensive and there are practical obstacles that must be overcome before an efficient surveillance programme can be established. In addition, control of the disorder is expected to be prolonged, especially as the disorder is not expressed until adulthood. For these reasons, development of a molecular test for genotyping of animals must have high priority. It is also important to confirm initial findings that cows with renal lipofuscinosis have an apparently increased risk of early culling. If the disorder is associated with adverse effects on health or production, the economic implications may be considerable due to the high prevalence of the disorder. Determination of the molecular basis may be of importance in understanding the mechanisms leading to lipofuscin accumulation and in helping control the disorder.

Although many inherited disorders have been found in Danish cattle, it is recognised that a number of these disorders have also been found in several other countries, demonstrating the clear international perspective of bovine inherited disorders. Several reports have been published from Germany, Switzerland, the USA and Denmark, but this does not necessarily reflect the actual occurrence of specific disorders. Disorders such as complex vertebral malformation and bovine leukocyte adhesion deficiency are likely to be distributed worldwide and have probably occurred in most national Holstein populations despite there being few published reports. Reports of hereditary disorders are clearly associated with the distribution of certain breeds. However, they are probably also closely associated with the presence of scientists with an interest in investigating inherited bovine disorders and the capacity to identify and describe such disorders. To postulate that inherited disorders are more prevalent in the countries mentioned than in other countries is most probably erroneous.

Inherited disorders in Danish cattle have mostly been found in Danish Holstein and Danish Red Dairy breeds. Although this might be associated with breeding strategies and therefore reflect a higher prevalence of inherited disorders in these breeds than in other Danish breeds, it is more likely due to the high number of animals in these breeds and especially the awareness of the breeders. In contrast to the situation in these dairy breeds, few inherited defects have been recognised in Danish beef cattle. This may reflect not only the low number of animals but also problems in determination of inheritance when isolated congenital syndromes occur in small herds using natural breeding.

Statistical evaluation of the progeny-based identification of heterozygous sires showed that this method had a low sensitivity as significantly fewer heterozygous sires than expected were identified (Table 2). It is likely that most heterozygous sires that passed the initial breeding evaluation undetected – and subsequently were used more extensively – were identified later on simply because of a higher number of progeny. Therefore, most extensively used carriers were probably detected and any delay in reduction of the prevalence of diseased calves caused by undetected carriers is assumed to be limited. The detection of diseased calves was based on the farmer's and veterinarian's ability to recognise an inherited disorder without preceding notice. The results indicate the inadequacy of their ability and it is recommended that breeders of animals at high risk be informed of a specific inherited disorder, thereby increasing their awareness. This will probably lead to a higher level of carrier detection.

Estimations of the number of progeny

affected by an inherited disorder showed that generally less than 1,000 calves were diseased. This could be interpreted such that inherited disorders were almost insignificant compared to other causes of calf mortality. However, the numbers must be compared to the breeding population. An example of the significance of an inherited disorder can be given for spinal dysmyelination in 1994, where 26,600 calvings were recorded. As 206 defective calves were born that year (Fig. 4e), spinal dysmyelination contributed 0.77% to calf mortality. This example demonstrates that inherited disorders may have significance for a breed even though the total number of defective calves seems low. It is also important to note that the estimations included the effects of interventions in the use of heterozygous sires once the undesirable genotype was recognised by the breeding associations. The sudden and rapid annual increase in the number of defective animals that occurred before interventions commenced, as seen for several disorders (Fig. 4), indicates the seriousness of these defects and the potential impact on the breeds.

The economic consequences of inherited disorders can be significant for cattle breeders. With disorders in the neonatal calf, expenses are mainly related to lost calves, treatment before the diagnosis is established, and the cost of restocking with females. Other disorders not obvious in neonates, such as hereditary dilated cardiomyopathy and rectovaginal constriction, have a greater impact, and disorders where abortion is common, such as complex vertebral malformation, may mean additional losses from reduced milk production. Estimations of the economic impact of inherited disorders have been made on a few occasions. British researchers estimated the total costs, including lost milk production and premature culling associated with a case of complex vertebral malformation, to be £ 419 (2005 level) (154). The economic impact on Danish breeders can subsequently be calculated to be around £ 5 million or DKK 50 million, if it is assumed that the costs per case are at the same level in Denmark and that there are around 12,000 cases (Table 3). The widespread occurrence of complex vertebral malformation and its economic consequences emphasises the need for continued surveillance to detect inherited disorders of cattle.

Estimations of the number of defective calves were performed by a simple and transparent method, and documented the disease magnitude and annual fluctuations in disease occurrence. The most significant contribution to the number of affected animals was derived from the mating of carrier sires and daughters or granddaughters of heterozygous sires, respectively (Fig. 4). It is recommended that similar estimations be made when future inherited disorders are recognised in Danish cattle, thereby showing the number of affected calves over the years and the actual disease extent. Estimations can even be done before comprehensive genotyping data are present as recently demonstrated by *Man et al.* (196). Such data can be included as part of the basis for making decisions on intervention in breeding programs.

The present investigations have shown the importance of accurate research and diagnostic methods. Pathological studies have been an important part of these methods due to the nature of inherited disorders seen in Danish cattle during recent years. However, many scientific disciplines, including radiology and molecular biology, have provided valuable information and shown that research into inherited disorders of cattle is a multidisciplinary task.

Determining the cause of a disorder may appear straightforward if the disorder shares morphology with known inherited disorders. However, the existence of phenocopies indicates that great caution is required regarding such interpretations. Examples are the case of syndactylism reported in Danish Holstein in 1990 (223) and cases of malformations indistinguishable from the complex vertebral malformation syndrome (142, VII). Even if cases occur in patterns consistent with simple Mendelian inheritance, conclusions must be drawn with caution as such patterns may occur fortuitously (V). Another potential pitfall is the adaptation of results regarding inheritance from one breed to another or from another species. It is important to stress that a common morphology does not imply a similar aetiology or mode of inheritance. It is well known from human medicine that a range of mutations can be associated with a shared phenotype and similar observations have also been made respecting bovine diseases (70, 71), although larger studies of family clusters of cattle with shared disease phenotype are

lacking. In this dissertation such uncertain conclusions have been minimised as each section has focused on a single breed or family cluster. That breeding associations demand high quality research before intervention in breeding schemes is understandable due to the potential pitfalls and the far-reaching economic implications of erroneous interventions.

7. Perspectives

This dissertation provides a review and describes the *status quo* regarding inherited disorders in Danish cattle. However, it does not cover the topic exhaustively as obviously it can only include recognised disorders. It is most likely that unrecognised inherited abnormalities have occurred and still occur in the cattle population. Recently, a familial congenital syndrome in Danish Holstein calves designated "brachyspina syndrome" was reported (11). This syndrome occurs in a familial pattern consistent with autosomal recessive inheritance. It was originally identified in Denmark, but cases have later been reported in the Netherlands and Italy, thus demonstrating international perspectives for the Holstein breed (9, 278). It is beyond doubt that other disorders will also be identified in the future. Consequently, research on bovine inherited disorders is a "neverending story".

Recognition of inherited disorders and congenital syndromes in cattle depends on the skills of the breeder and the veterinary practitioner. These limitations make it necessary for passive surveillance to focus on disorders that can actually be recognised. These disorders include skeletal malformations, severe neurological disorders, and skin defects. Danish breeders and veterinarians should be requested to report animals suffering from such disorders, with representative cases being submitted for laboratory examination. Functional surveillance is important in order to identify hereditary syndromes in time to prevent a severe impact on livestock economy and on animal welfare.

Most sires are probably carriers of one or more recessive defects (204, 216), so the spread of defective alleles and the occurrence of defective calves is an inevitable part of modern cattle breeding. An efficient breeding policy is necessary for a remunerative farm economy and for the availability of dairy products and meat at reasonable prices. High-ranking sires are extensively used by breeders and semen suppliers despite the simultaneous spread of their defective genes. Few semen suppliers and breeders are interested in knowing which defective genes their sires spread before a problem is recognised in the general population. The reason for this is an understandable concern regarding the value of breeding animals and semen once it is known which defective genes the animals carry. This phenomenon could be called "the paradox of knowledge". As all sires are carriers of unfavourable recessive genes, would it not be better to know which undesirable traits a sire spreads, so that the effects can be measured and appropriate and timely breeding interventions can be initiated to prevent a severe impact on livestock economy and animal welfare, than just to wait and see what happens? It is generally required that negative effects of compounds or procedures are known so that this information can be included in the overall assessment. Why should this not apply to the commercial semen trade? This is, meanwhile, not a scientific matter but a matter between semen suppliers and semen buyers. The attitude of several breeding associations towards inherited disorders has progressed towards openness and evidence-based decision making. The World Holstein Friesian Federation is an example of an association facing the undesirable effects of intensive cattle breeding; it states that the full disclosure of named genetic defects in the Holstein population provides useful information when making breeding decisions on farms, giving the opportunity to minimize the impact of any associated problems (306). Evidence-based decisions require that the impact on the breed can be measured. However, it does not mean that a sire must be culled or used restrictively just because he carries a recessive inherited disorder.

Testing high-ranking sires for undesirable recessive genes would make it possible to develop molecular genotyping tests before the recessive genes are expressed in the general population in the form of large numbers of defective progeny. Relevant sires could be genotyped and the prevalence of defective progeny could be measured prospectively by analysis of breeding combinations using the retrospective method applied in this dissertation (Chapter 4). This would provide a solid foundation on which breeders and breeding associations could base their decisions. In addition, such an approach would allow the breeding associations to reduce

the prevalence of the disorder by introducing breeding restrictions whenever they wanted and simultaneously to exploit the superior traits of the breeding lines by using homozygous normal sires. Such research projects could be carried out in a partnership between semen suppliers, breeding associations and research institutions.

Progress in genome mapping and methods for genomic analysis has made it possible to elucidate the pathogenesis of inherited disorders, and this will lead to increased knowledge respecting the action of many genes. Genome analysis is mostly applied when a major disease problem is recognised, with the aim of developing molecular tests. However, genome analysis should be applied more widely to characterise sporadically occurring disorders. One of the major obstacles is the lack of DNA from such sporadic cases. Researchers and diagnosticians should be encouraged to publish reports on sporadically occurring defects and routinely store tissue or DNA for further analysis. Meanwhile, such stored tissue is often lost within a few years due to lack of storage capacity or changes in employment and priorities. Establishment of an international bank for storage of DNA from defective animals could solve such problems, making it possible to obtain multiple cases of sporadically occurring defects on which research projects could be based. As international biological banks for microorganisms have already been founded, establishing a bank for DNA of defective animals appears an achievable objective.

8. Summary

Inherited disorders are of great concern in cattle breeding as the breeding systems and the extensive use of genetically related sires predispose to increased frequency of recessively inherited disease genes in the population and subsequently the occurrence of diseased animals. Inherited disorders may in this way contribute significantly to the extent of calf diseases and mortality as elite sires may produce hundreds of thousands of progeny. Furthermore, high numbers of defective animals may be reached due to international trade with semen, which links national cattle populations together genetically.

Several inherited disorders have been recorded in Danish cattle, mainly in Danish Holsteins and the Danish Red Dairy breed. These two breeds are the first and third most common breeds in Denmark, which may partly explain this observation. The structure of the beef cattle industry in Denmark – with few purebred animals and many small herds – makes recognition of inherited disorders in beef cattle difficult.

Sires used for breeding purposes in Denmark are labelled for specific inherited disorders if they are genetically related to known carriers or if they have been genotyped. The labelling system includes disorders such as complex vertebral malformation, bovine leukocyte adhesion deficiency, spinal muscular atrophy, and spinal dysmyelination. Animals may be labelled as non-carrier, confirmed carrier, likely carrier or possible carrier based on, for example, molecular genotyping, progeny examination or pedigree information. A complete list of sires that are carriers of an inherited disorder and have been used for breeding in Denmark is provided.

The genotype of sons of heterozygous sires used for insemination was evaluated to determine if all carriers had been detected. The analyses demonstrated that labelling of sires based on examination of diseased progeny reported by breeders or veterinarians was insufficient to detect carriers. A targeted search for specific inherited disorders is therefore recommended in the future, i.e. through contact with owners of animals at high risk of developing disease. Such animals can be picked out based on breeding and pedigree information, which is available from the Danish Cattle Database. Molecular genotyping is an efficient way to distinguish between carriers and non-carriers, but this method is only applicable once the molecular basis of a disorder has been established.

The number of animals suffering from a range of inherited disorders was estimated based on breeding results, pedigree, and data on the genotype of sires. It was estimated that around 12,000 embryos had suffered from complex vertebral malformation. The total costs related to these cases came to £5 million (2005 level) if estimations of the costs associated with a single case of complex vertebral malformation from the United Kingdom were adapted. Spinal muscular atrophy was the most important disease in the Danish Red Dairy breed with around 1,800 cases. The number of animals suffering from inherited disorders during the 1970s or earlier could not be estimated due to poor data quality. The annual number of affected progeny was determined for each disease and the efficiency of the control measurements implemented by the breeding associations was evaluated. The number of diseased animals had been reduced to around zero for most disorders, but the time span needed to achieve this varied considerably. A rapid decrease in the number of affected progeny was observed if control measurements were based on molecular genotyping, while a prolonged decrease was seen if control measurements were based on progeny examination. The findings demonstrate the superiority of molecular genotyping to progeny examination in programmes to identify heterozygous sires and reduce the negative effects of inherited disorders. Estimations of the number of animals suffering from hereditary dilated cardiomyopathy showed that more than 100 cases had occurred. Hereditary dilated cardiomyopathy has only been diagnosed fortuitously and information on affected breeding lines is probably faulty. The number of cases may therefore be considerably higher and increased surveillance of this disorder is recommended. Renal lipofuscinosis is highly prevalent in Danish Holsteins and the Danish Red Dairy breed. Further research is needed to evaluate whether the in-

creased culling rate of affected cows is a real or merely an accidental finding.

A review of inherited disorders and their present significance in Danish cattle is given, focusing on the morphology and inheritance of the disorders, and providing information on affected breeding lines. Other important aspects of the disorders are described, especially the aetiology and pathogenesis. The review includes chondrodysplasia, complex vertebral malformation, osteogenesis imperfecta, syndactylism, acroteriasis, congenital paralysis, bovine progressive degenerative myeloencephalopathy, spinal muscular atrophy, spinal dysmyelination, syndrome of arthrogryposis and palatoschisis, ichthyosis foetalis, epitheliogenesis imperfecta, hereditary zinc deficiency, renal lipofuscinosis, hereditary dilated cardiomyopathy, bovine leukocyte adhesion deficiency, congenital erythropoietic porphyria, rectovaginal constriction, chromosomal aberrations, and defects of spermatozoa.

9. Sammendrag (summary in Danish)

Arvelige sygdomme er af stor betydning i kvægavlen, da avlssystemerne og den udbredte brug af familiært relaterede tyre disponerer for en øget frekvens af recessivt nedarvede sygdomsgener i populationen og deraf følgende forekomst af syge dyr. Da elitetyre kan få hundredetusinde stykker af afkom, kan arvelige sygdomme bidrage væsenligt til omfanget af kalvesygdomme og -dødelighed. Der kan yderligere optræde et stort antal syge dyr som følge af international handel med sæd, som gør nationale kvægbestande genetisk beslægtede.

Adskillige arvelige sygdomme er blevet registreret hos kvæg i Danmark, især i dansk holstein og rød dansk malkerace. Disse er den hyppigste og trediehyppigste kvægrace i Danmark, hvilket delvist kan forklare observationen. Strukturen af den danske kødkvægsindustri med få renracede dyr og lille besætningsstørrelse vanskeliggør erkendelsen af arvelige sygdomme hos denne type kvæg.

Avlstyre, som anvendes i Danmark, markeres i stambogen for specifikke arvelige sygdomme, hvis de er beslægtede med kendte bærere af sådanne, eller hvis de er blevet genotypet. Mærkningssystemet inkluderer blandt andet sygdommene complex vertebral malformation (CVM), bovine leukocyte adhesion deficiency (BLAD), spinal muskelatrofi (liggekalvesyndromet) og spinal dysmyelinering (medfødt lammelse). Baseret på blandt andet molekylær genotypning, undersøgelse af afkom eller afstamningsoplysninger, kan dyr blive markeret som ikke-anlægsbærer, anlægsbærer, sandsynlig anlægsbærer eller mulig anlægsbærer. En komplet oversigt over tyre som er anlægsbærere af arvelige sygdomme og som har været anvendt i Danmark gives i afhandlingen.

Genotypen af sønner af heterozygote inseminеringstyre blev evalueret for at undersøge om alle anlægsbærere var blevet påvist. Analysen viste, at påvisningen af heterozygote tyre var utilstrækkelig, hvis denne blev baseret på undersøgelse af sygt afkom udpeget af besætningsejeren eller dyrlægen. En målrettet søgen efter specifikke arvelige sygdomme er derfor anbefalet i fremtiden, for eksempel ved kontakt til ejere af høj-risiko dyr. Sådanne dyr kan udpeges ud fra afstamnings- og avlsregistreringer i kvægdatabasen. Molekylær genotypning er en effektiv metode til at skelne mellem anlægsbærere og ikke-anlægsbærere, men denne metode er kun anvendelig, når den molekylær genetiske baggrund for en sygdom er kendt.

Antallet af afficerede dyr blev estimeret for en række arvelige sygdomme baseret på avlsresultater, afstamning og tyres genotypningsdata. Det blev estimeret, at omkring 12.000 embryoner havde haft complex vertebral malformation. De totale omkostninger forbundet med disse tilfælde udgjorde 50 millioner kroner (2005 niveau), hvis estimated blev baseret på omkostningsberegninger fra Storbrittanien. Spinal muskelatrofi var den vigtigste sygdom hos rød dansk malkerace med omkring 1.800 tilfælde. Antallet af dyr, som havde haft en arvelig sygdom i 1970erne eller tidligere, kunne ikke beregnes på grund af utilstrækkelige data. Det årlige antal afficeret afkom blev beregnet for hver sygdom, og effektiviteten af kvægavlsforeningernes avlsforanstaltninger blev vurderet. Antallet af sygt afkom var blevet reduceret til næsten nul, men tidsperioden, der var nødvendig til at opnå dette, varierede betydeligt. Et fald i antallet af sygt afkom skete hurtigt, såfremt kontrolforanstaltningerne var baseret på molekylær genotypning, mens en langstrakt reduktion sås, hvis foranstaltningerne var baseret på undersøgelse af afkom. Dette viser, at molekylær genotypning er overlegent i forhold til afkomstundersøgelse til identificering af heterozygote tyre og til at reducere den negative effekt af arvelige sygdomme. Estimatet af antallet af dyr, som havde haft arveligt betinget dilateret kardiomyopati viste, at mere end 100 tilfælde var forekommet. Arveligt betinget dilateret kardiomyopati var kun blevet diagnosticeret tilfældigt og kendskabet til afficerede avlslinier er sandsynligvis ufuldstændigt. Antallet af tilfælde kan derfor have været betydeligt højere og en øget overvågning af denne sygdom anbefales. Renal lipofuscinose (oksens sorte nyrer) er høj-prævalent hos dansk holstein og rød dansk malkerace. Det er nødvendigt med yderligere forskning for at vurdere om den observerede øgede udsætningsrate af afficerede køer er reel eller tilfældig.

Afhandlingen giver en oversigt over arvelige sygdomme og deres nuværende betydning hos dansk kvæg. Der fokuseres på sygdommenes morfologi og arvelighed, og der gives oplysninger om afficerede avlslinier. Andre vigtige aspekter ved sygdommene omtales, specielt ætiologi og patogenese. Oversigten omhandler kondrodysplasi, complex vertebral malformation, osteogenesis imperfecta, syndactyli, acroteriasis, kongenital paralyse, bovin progressiv degenerativ myeloencefalopati, spinal muskelatrofi, spinal dysmyelinering, syndrome of arthrogryposis and palatoschisis, ichthyosis foetalis, epitheliogenesis imperfecta, arveligt betinget zinkmangel, renal lipofuscinose, arveligt betinget dilateret kardiomyopati, bovine leukocyte adhesion deficiency, kongenital erytropoietisk porfyri, rektovaginal konstriktion, kromosomfejl og spermiedefekter.

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11. Appendix 1

This appendix provides a list of sires used for breeding in Denmark and which have been determined as carriers of an inherited defect. The list is mostly adapted from the labelling of sires in the Danish Cattle Database. This labelling is performed by the Danish Cattle Federation or the breeding associations and the accuracy of the data is their responsibility. The appendix must be read together with the description of each disorder in Chapter 5. The appendix is a research tool. Breeders and breeding associations must have the status of carriers confirmed by the owner of the sire or the breeding association before taking any action against individual sires or including the data as part of the basis for making any decisions. Data were extracted from the database on January 26th 2006.

The data have been expanded with results obtained since 1989 regarding disorders for which labelling is not performed. Parentage control has not been performed in all cases. Sires that have an unconfirmed paternity to a defective calf have only been included if the case occurred in a familial cluster.

As labelling is based on progeny examination or genotyping (see Chapter 3), heterozygous ancestors are mostly not included in the appendix. DNA of such ancient animals may not be available or affected progeny may not have been recorded. However, the identity of ancestors is mostly given in Chapter 5.

The sires are identified by their name and herd book numbers. Foreign sires have a Danish herd book number in addition to their original number. Both numbers have been provided throughout this appendix to improve the usefulness of the appendix internationally.

The appendix documents the basis on which estimations made in Chapters 3 and 4 were made.

TABLE 4. *Carriers of chondrodysplasia in Danish Dexter*

No registered carriers.

TABLE 5. *Carriers of chondrodysplasia in the Danish Red Dairy breed*

Danish herd book no.	Original herd book no.	Name
28440		*THY Skov*
29559		*NØ Gerber*
29851		*NOF Kel*
29852		*NOF Lød*
32566		*HV Flid*

TABLE 6. *Carriers* of chondrodysplasia in Danish Holstein*

Danish herd book no.	Original herd book no.	Name
240726	F4493050102	*Igale Masc*
244129		*Igale 891*

* The mode of inheritance has not been reported.

TABLE 7. *Carriers of complex vertebral malformation syndrome*

Danish herd book no.	Original herd book no.	Name
17001	US1667366	*Carlin-M Ivanhoe Bell*
18382		*NJY Hubert*
19804		*VE Nelson*
44293	NLD316419721	*Delta Cleitus Jabot*
82190	US1441440	*Penstate Ivanhoe Star*
82634	US1875896	*Lutz-Brookview Bell Rex-ET*
82658	US1891196	*Nowerland Trifecta*
82685	US1920807	*Ugela Bell*[#]
224302	US1875356	*Kashome Bell Jurist-Twin*
224515		*RGK Jure*
225200	US1892913	*Ca-Lill Belltone*
226804	US1964484	*Southwind Bell of Bar-Lee*
227511		*VE Thor*
229874	US1882141	*Stan-Bitzie Kirk Bell Boss*
230104		*T Burma*
230429	CAN371115	*Sunnylodge Sammy*
230961	US2021095	*Paradise-R Roebuck*
231341	US2065871	*Highlight Converse-ET*
231642		*VAR Ute*
231665		*RGK Olie*
232755	NLD316419721	*Delta Cleitus Jabot*
233579		*RGK Parbo*
233883		*T Havndal*
234036	US2089381	*Mar-Bil Command Geoffry*
234042		*KOL Nixon*
234113		*RGK Pust*
234277	NLD460942030	*Etazon Labelle-ET 528*
234344	US1912270	*Emprise Bell Elton*
234604	US2071247	*De-Su Secret Jetson Top Gun*
234898	US1819119	*Bossir Glen-Valley Starlite Al*
234981	US2080263	*Paradise-R Cleitus Mathie*
234984	F2989026154	*Esquimau*
235145		*T Ingslev*
235514	US2049679	*Heinz Liberty-ET*
235769	US2094527	*Ameldin II Pontiac Hunter*
235921	NLD776437936	*Havep Marconi*
236199	US2145234	*Londondale Swind Merv-ET*
236328	US2154310	*Mel-Ham Dixie-Lee Sand-ET*
236398		*T Klassy*
236503	NLD319957882	*Delta Lava*
236598	F2290038601	*Fatal*
237017	NLD780180664	*Etazon Lord Lily*

TABLE 7 *(continued). Carriers of complex vertebral malformation syndrome*

Danish herd book no.	Original herd book no.	Name
237018	NLD790545532	*Zandenburger Royal*
237022		*V Amster*
237314	S44358	*Häradsköp*
237454		*T Laluffe*
237626		*V Balling*
237800		*RGK Skalp*
237865		*Var Brint*
238094	US2076574	*Agi Spencer*
238098	NLD115467480	*Sperwer*
238127	NLD167957274	*T Limba*
238138	NLD864484246	*T Monark*
238139		*T Minerva*
238147	S620327618	*T Medox*
238149	NLD167388690	*T Mabelle*
238150		*T Moulder*
238160		*T Mitra*
238176		*VE Domino*
238246		*T Mikado*
238253	NLD785532529	*Holim Stans Tornedo-ET*
238270	2014517	*Highlight Mr Mark Cinder-ET*
238340	F2990000428	*Fecamp*
238349		*T Molok*
238359	D340227796	*VE Domonit*
238392	US2193611	*Wells Catalyst-ET*
238486		*V Bolivar*
238538		*RGK Tippe*
238584		*ØDA Lyre*
238624		*T Mogul*
238626		*T Metope*
238628		*T Money*
238652		*VE Demo*
238654	NLD177526248	*VE Dokaan*
238821		*V Bjerg*
238833		*V Bond*
238837		*RGK Telius*
238839		*Rgk Tilst*
238852		*TVM Hole*
238866		*VE Dekan*
238869		*TVM Hugev*
238876		*T Marimba*
238886	NLD176204639	*T Nektar*
239113		*T Norbert*
239114		*T Neptun*
239116		*T Nobilik*
239120		*T Narkisos*
239128		*T Nappa*
239130		*T Negro*
239177		*V Cassini*
239262		*T Neon*
239321	NLD340964542	*T Natan*
239322		*T Nota*

TABLE 7 *(continued). Carriers of complex vertebral malformation syndrome*

Danish herd book no.	Original herd book no.	Name
239325		*T Nasturia*
239326	NLD198344197	*T Navajo*
239375		*RGK Tao*
239445	NLD340968994	*T Nirman*
239450		*T Nokra*
239468		*V Congo*
239531		*RGK Thure*
239532		*RGK Tusty*
239561		*V Chaplin*
239563		*V Cheng*
239567		*V Cypres*
239568		*V Cognac*
239570		*V Ceres*
239574		*V Ceylon*
239578		*V Crosby*
239581		*V Chile*
239610	S330250115	*T Olle*
239611		*T Oporto*
239635		*VE Elta*
239671		*VAR Dalar*
239677		*RGK Talk*
239682	NLD168778126	*RGK Arnold*
239690		*V Carlton*
239693		*V Claes*
239699		*V Cola*
239700		*V Colbert*
239701		*V Chardon*
239730		*RGK Alan*
239765		*T Ommelund*
239770		*T Ofalia*
239784		*T Otroy*
239786		*T Onzelot*
239789	NLD206189055	*T Osterink*
239828		*VAR Daniel*
239829		*VAR Danilo*
239830		*VAR Danner*
239918		*V Casper*
239919		*V Claude*
239925		*V Caudius*
239945		*RGK Akke*
239966		*V Corola*
239977		*VAR Darwin*
239978	D577317764	*VAR Davis*
240014		*VE Etala*
240049	NLD173169722	*Lord Sunshine 102*
240051		*V Council*
240059		*T Orion*
240060		*T Orolo*
240065		*T Odessa*
240111		*V Clive*
240112		*V Chianti*
240114		*V Cremona*
240116		*V Chirac*

TABLE 7 *(continued). Carriers of complex vertebral malformation syndrome*

Danish herd book no.	Original herd book no.	Name
240131	NLD829877874	*Holim Boudewijn*
240134		*V Daimler*
240136		*V Dental*
240174		*RGK Alex*
240179		*RGK Amor*
240182		*RGK Agro*
240187		*RGK Alfons*
240223		*T Officer*
240224		*T Oxon*
240225		*T Otto*
240230		*T Orient*
240237		*T Osvaldo*
240248		*ØDA Mild*
240249		*ØDA Leman*
240272	NLD777133097	*Lucky Leo*
240276		*VAR Derek*
240279		*VAR Difko*
240290		*V David*
240291		*V Daniel*
240292		*V Diesel*
240298		*VE Edom*
240378		*ØDA My*
240404		*T Polka*
240406	D341440527	*Fabian*
240409		*Picasso*
240411		*T Pampas*
240414		*T Prins*
240415		*T Puma*
240418		*T Parade*
240421		*T Paxo*
240491		*RGK Alpe*
240492		*RGK Almue*
240497		*V Delta*
240519		*V Direktor*
240520		*V Demand*
240521		*V Depot*
240523		*V Detroit*
240525		*V Dalgas*
240553	NLD831375195	*Holim Apollo*
240557		*VAR Donner*
240558		*VAR Dons*
240567		*VE Epoke*
240575		*T Pingo*
240628	NLD202428341	*T Pajero*
240631	NLD204399328	*V Dacapo*
240653		*T Pedro*
240669		*ØDA Fortun*
240671		*ØDA Altag*
240714		*V Dana*
240721		*V Dissing*
240727	F5191005833	*Gelpro*
240743		*T Paris*
240744		*T Pokal*

TABLE 7 *(continued). Carriers of complex vertebral malformation syndrome*

Danish herd book no.	Original herd book no.	Name
240745		*HMT Jyde*
240803		*T Panter*
240806		*T Perle*
240809	D577788833	*VAR Dorf*
240826	D342567647	*VE Ell*
240827	F5497015024	*TVM Hapell*
240875		*RGK Alaska*
240901		*V Dirch*
240933		*V Dollar*
240936		*V Dixi*
240937		*V Doge*
240941		*V Duma*
240943		*V Demokrat*
240948	NLD211251167	*V Danton*
241001	D577691423	No registered name
241054		*VAR Duncan*
241063		*V Dam*
241064		*V Dairy*
241069		*V Deuntzer*
241071		*V Dekan*
241074		*V Diktator*
241078		*V Djabot*
241079		*V Donau*
241082		*V Diadem*
241089		*VE Elsam*
241090		*VE Elba*
241094		*VE Format*
241095	D343023474	*VE Fro*
241098		*RGK Andre*
241103		*RGK Andrew*
241104		*RGK Auto*
241124		*VAR Dybbøl*
241136		*HMT Jalte*
241149		*T Rebus*
241151		*T Rotor*
241152		*T Retto*
241155		*T Rup*
241160		*T Rasmus*
241171		*VAR Dyb*
241172		*VAR Ebro*
241187		*RGK Bolt*
241190		*V Duet*
241193		*V Decamp*
241196		*V Dexthor*
241216		*HMT Jeppe*
241228		*T Rosen*
241229		*T Røn*
241231	F4493050135	*Italie Mas*
241233	US2266008	*Ricecrest Lantz*
241234	US2249055	*Wa-Del Convincer-ET*
241318	F5898002010	*TVM Hilton*
241386	D342919848	*V Dorky*
241388	D343085106	*V Dalvero*

TABLE 7 *(continued). Carriers of complex vertebral malformation syndrome*

Danish herd book no.	Original herd book no.	Name
241390		*V Dingo*
241393	US2257212	*Garjo Elton Gabe-ET TL*
241400		*V Datal*
241403		*RGK Bøg*
241410		*T Roslev*
241412		*T Reform*
241414		*T Rambo*
241415		*T Ratal*
241419		*T Rocket*
241423	D578133187	*VAR Effen*
241427	US2261720	*De-Su Luke Casino-ET*
241486	NLD207490198	*Homerun*
241493		*V Ecamp*
241495		*V Ege*
241507		*T Rekrut*
241513		*T Repro*
241556		*VAR Eggers*
241632	NLD112538714	*Carrousel Sierra TL*
241638		*RGK Bo*
241642		*RGK Bertel*
241648	F2998012101	*TVM Habon*
241695		*V Elton*
241697		*V Engels*
241751		*T Staun*
241870	US2253348	*Sim-Co Liberty Chance-ET*
241917		*RGK Ben*
241920		*RGK Bob CV*
241921		*V Ego*
241936	NLD173319699	*V Emsen*
241939		*Var Elmo*
241949	US2271665	*Ladys-Manor El Temptor-ET*
241950	US2276216	*Wa-Del Elton Bugleboy-ET*
241952	NLD856070222	*Delta Largo*
241954	F4494050236	*Jarny Jabo*
242099		*V Ero*
242142	NLD864110860	*Gryphus Simon Tl*
242146		*T Stof*
242160		*T Slalom*
242169		*T Spolar*
242211	US2256388	*Cedar-Creek Bergwil-ET*
242213	NLD118522472	*Bobstar 50 TI*
242275	US2251487	*Regancrest Elton Dante-ET*
242293		*V Espholm*
242302		*V Esprit*
242305		*V Estragon*
242309		*V Eskholm*
242347		*T Stuntman*

TABLE 7 *(continued). Carriers of complex vertebral malformation syndrome*

Danish herd book no.	Original herd book no.	Name
242395		*RGK Bodo*
242436	US2289548	*Ricecrest Brett ET*
242466		*V Elan*
242471		*V Emmedsbo*
242493		*VE Fantom*
242502	NLD141079778	*Woudhoeve Russel*
242511		*VAR Estrup*
242513	D344688449	*VAR Ferro*
242515	D344666684	*VAR Filip*
242554		*T Tank*
242557		*T Tebel*
242559	NLD232807253	*T Tucky*
242562		*T Think*
242570		*T Terry*
242572		*T Tesk*
242585		*RGK Dennis*
242643		*VAR Facet*
242644		*VAR Facon*
242649	D344688473	*VAR Falk*
242755		*Ejst Funki*
242766		*V Erotik*
242772		*F Ullits*
242777		*V Eufori*
242778		*F Farsø*
242785	D344666669	*V Epsilon*
242786	D342409897	*V Elamain*
242793		*RGK Dingo*
242834		*V Fix*
242846	US2289080	*Webb-Vue Int Boy Wonder-ET*
242861		*T Teknik*
242870		*T Tavle*
242885		*VAR Fangel*
242891		*Var Felix*
242897	NLD129187369	*Tolhoek Glory Box Tl*
243021		*Nixon 1008*
243065		*T Tyson*
243066		*T Tenerif*
243084		*RGK Dam*
243094	NLD219170930	*RGK Dumle*
243096		*F Tirsvad*
243101		*HMT Loft*
243112	US2282520	*Peckenstein Elton Curtis*
243121		*V Facet*
243124		*V Farty*
243145		*Esqui 140*
243158	NLD149310675	*Delta Bentley Tl*
243219		*VAR Folmer*
243284		*T Ugilt*
243285		*T Uldahl*
243306		*V Flint*
243369		*T Urban*

TABLE 7 *(continued). Carriers of complex vertebral malformation syndrome*

Danish herd book no.	Original herd book no.	Name
243372		*T Urth*
243373		*T Ullman*
243374		*T Urias*
243377		*T Upolo*
243381		*T Ubiq*
243382		*T Utopia*
243385		*T Ursus*
243387		*T Ubbesen*
243391		*T Uggerhøj*
243393	NLD265548044	*T Uno*
243459	F5994022699	*Jesther*
243518	NLD167388760	*Nab Evert*
243524		*RGK Drille*
243528		*RGK Dumbo*
243532		*V Finbo*
243533		*V Frøy*
243539		*V Frey*
243545		*V Fasmark*
243549		*V Follo*
243556		*V Francis*
243560		*Holin*
243575		*HMT Ludo*
243673		*V Fin*
243675		*V Faris*
243680		*VAR Fregat*
243681		*VAR Fremad*
243682		*VAR Fresko*
243685		*VAR Friso*
243687		*F Halling*
243705		*F Rækby*
243738		*T Uniq*
243744		*T Utah*
243748		*T Unipac*
243760		*T Utica*
243762		*T Ungarn*
243772		*T Ulitsa*
243781		*T Uffe*
243782		*T Uranus*
243787		*Ribe Apoll*
243795		*Pust 1072*
243817		*V Fagale*
243819		*V Fakkel*
243821		*V Flantz*
243822		*V Forky*
243913		*Nixon 2423*
243914		*Rud Pabs*
243924		*VAR Galant*
243935		*V Fence*
243937		*V Funtex*
243940		*HMT Lixon*
243946		*F Bevtoft*
243972		*VAR Gamma*
243973		*VAR Gamst*

TABLE 7 *(continued). Carriers of complex vertebral malformation syndrome*

Danish herd book no.	Original herd book no.	Name
244004		*Lund*
244019		*T Urtime*
244025		*T 2000-5*
244027		*T 2000-7*
244032		*T 2000-12*
244033		*T 2000-13*
244034		*T 2000-14*
244038		*T 2000-18*
244040		*T 2000-20*
244041		*T 2000-21*
244053		*V Farma*
244055		*V Foton*
244060		*V Fokus*
244100		*Ø S Rup*
244117		*T 2000-34*
244120		*T 2000-37*
244121		*T 2000-38*
244170	US17001863	*Pride-Of-Iowa Will Carl-ET*
244173		*T 2000-42*
244178		*T 2000-47*
244195		*Addesqve*
244214		*Søgd Apol*
244267	NLD263010279	*Morpheus*
244285		*Nix Boj*
244374	US2289624	*Whittail-Valley Zest-ET*
244393	US17112421	*Lylehaven Sand Gaston-ET*
244408		*DG Convin*
244421	F1095001791	*Lorak*
244429		*RGK Ede*
244439		*S Asmus*
244440		*S Asger*
244454		*Rav Nix*
244469		*Høng Lantz*
244470		*Høn Apollo*
244476		*T 2000-56*
244493		*T 2000-74*
244499		*Klassy1068*
244539		*Døl Klassy*
244542		*Eisson*
244553		*Gyrup Lanz*
244582		*Peter*
244631		*Hovg Huxle*
244741		*Gabe 1797*
244752	NLD188347542	*Horst Maistein*
244840		*Lynggaard*
244869		*Høvet*
244893		*T 2000-112*
244914	D2261528773	*Dancy ET*
244957	US2250783	*Regancrest Elton Durham-ET*

TABLE 7 *(continued). Carriers of complex vertebral malformation syndrome*

Danish herd book no.	Original herd book no.	Name
244960	NLD170658722	*Eemvelder Osmond*
244961	NLD180884717	*Rocker*
245017		*Valtain*
245018		*Val 997*
245025		*Eksport*
245027		*Nimbus*
245037		*Klassy1008*
245040	NLD194532495	*Delta Dacca CV*
245049		*L Lily 899*
245073		*Kozak*
245103		*Hux 2686*
245105		*Convin2723*
245164		*Simon*
245187		*Homo Polle*
245252		*Klassy1030*
245255	US18040136	*Windsor-Manor Machoman-ET*
245294		*Vand Lily*
245355		*Ecco Storm*
245358		*Houg Webst*
245359		*Houg Bobst*
245360		*Houg Klass*
245373	US1920807	*Ugela Bell*[#]
245383		*ÅM Conwi*
245403		*ØH Bojer*
245423		*Curtis 914*
245448		*Klassy*
245463		*Søgd Lantz*
245582	NLD202428505	*Isidorus Icon*
245591	US122185573	*Vison-Gen Ozzie-ET*
245592	US17188116	*Glen-Toctin Pippen-ET*
245631		*St. Conv*
245712		*Ub Boj*
245719		*Hovg Web*
245782		*WebsterBoj*
245900	NLD168175055	*Leroy Abrian Tl*
245904		*Glory 1619*
245915		*961 Hukas*
245927		*L Lil Boj*
245961		*Hovg Deweb*
245964		*Hovg Pasen*
245966		*Hovg Deltw*
246075		*Nixon 1209*
246250	D340717908	*Emil CV*
246357		*Boj Rav*
246440		*FB Laluffe*
246636		*Hovg Summe*
246678		*Lambada 1361*
246679		*Bossen*
246715	NLD176187525	*Morgenster Chuck*
246751	NLD217851172	*De Crob Dynasty*
246772		*Bysk Mars*
246877		*Ting Shall*

TABLE 7 *(continued). Carriers of complex vertebral malformation syndrome*

Danish herd book no.	Original herd book no.	Name
246880		*E 2003*
246965	NLD232136885	*Katshaar Kirby*
246991		*Bibi*
247169		*Debel Jock*
247312		*Bathau Do*
247425		*TIR-AN Ridler Sabel ET*
247571	F2298044708	*Orcival CV*
247609		*Havers Ned*
247789		*Debel Curt*
247793		*Ladin Boj*
247839		*Jurmel 915*
247841		*Curtis 2011*
247855		*Dansire Ridler Rocker*
247982		*Ting Inqui*
248100	D1401263093	*Lucifer CV*
248131		*Curtis Boj*
248294		*Luffe 1491*
248410	NLD262656584	*Holim Rafael*
248466		*Holm Manat*
248568	NLD232138906	*Welser Uruguay CV*
248587		*Manor2186*
248588		*Jest2023*
248633		*S. Svane*
248634	NLD170943976	*Janson*
248660		*Vest*
248901		*Debel Conca*
248905	US131102143	*Bo-Irish Alton ET*
248928		*Svane1914*
249001		*Timer Rit*
249025	US17093333	*Sikkema-Star-W Hi Metro ET*
249042		*Jensen 5*
249114		*Champ 1157*
249116		*Holme Oman*
249131		*Lkm Lancelot 1*
249138		*Lkm Kimmer 32*
249139		*Lkm Lancelot 2*
249199		*Ølgod Bob*
249401		No registered name
249451		*Svane2304*
249512		*Svan1914*
249592		No registered name

[#] The sire *Ugela Bell* is registered under two Danish herd book numbers: 82685 and 245373.

TABLE 8. *Carriers of osteogenesis imperfecta*

Danish herd book no.	Original herd book no.	Name
228239		*Guldager Fantastic*

TABLE 9. *Carriers of syndactylism*

Danish herd book no.	Original herd book no.	Name
12346		*SDJ Kran*
12361		*VE Byg*
12818		*NJY Star*
13229		*HV Puns*
15425		*SDJ Dallas*
82023	US1590283	*Pineyhill Carnation Star*
82532	US1417290	*Rincon Var Skyview Lad*
82630	US1590582	*Wayne-Spring Fond Apollo*
235424	CAN362017	*Hurtgen-Vue Marathon*
240552	NLD456911499	*Ulkje Fari's Wayne 403*
241592	I908017670	*Olmo Prelude Tugolo*
244667	US17226843	*McCloe-Pond Trent*
244751	NLD175029341	*Agus Coolcat*

TABLE 10. *Carriers of acroteriasis*

No registered carriers.

TABLE 11. *Carriers of congenital paralysis*

Danish herd book no.	Original herd book no.	Name
28836		*VE Leo*
31221		*Syf Fort*

Additionally, the identities of a substantial number of heterozygous sires have been published elsewhere (217).

TABLE 12. *Carriers of bovine progressive degenerative myeloencephalopathy*

Danish herd book no.	Original herd book no.	Name
32382		*ØJY Lynbru*
32710		*ØJY Hans*
32994		*ØJY Højbo*
33018	US181608	*H Brigeen D Lancer*
81057	US156458	*Rolling View Modern Stretch*
81087		*ØJY Ingbru*
81116		*VAR Brun*
81206	US171547	*Johann Proud Matthew*
81226	US160195	*West Lawn Dorset Improver*
81250	US175105	*Mort Modern Click*
81289	US172391	*Century Acres Hollys Answer*
81303		*JMS Søbru*
81313	US175783	*H Brigeen Elegant Lou*
81314	US175928	*Twin Oak Jordan*
81339		*VAR Dobru*
81601	US175545	*Ventures Esp Babaray*

TABLE 13. *Carriers of spinal muscular atrophy*

Danish herd book no.	Original herd book no.	Name
31894		*VAR Vit R*
32188	US177055	*Ka-Wa Westley*
32409	US178634	*Fox Trail Anchorman*
32685		*FYN Smid*
32913		*HV Garde*
32960		*HV Hydro*
33326		*JMS Balkan*
33391		*RGK Larm*
33436		*HJ Ager*
33456		*FYN Bio*
33463		*RANO April*
33473		*JMS Calm*
33486		*SYD Knut*
33491	US182822	*Johann Lemmerman*
33499		*RGK Lad*
33506		*ØDA Fidus*
33531		*RGK Luxus*
33559		*SYD Krølle*
33561		*FYN Tem*
33562		*FYN Visir*
33589		*HJ Foca*
33602		*RGK Mouse*
33606		*SYD Kato*
33607		*SYD Kæk*
33608		*SYD Komet*
33635		*SYD Klint*
33636		*SYD Krone*
33637		*SYD Krake*
33639		*FYN Malko*
33674		*JMS Dest*
33721	US184303	*Lone Oak Bvc Desperado*
33732		*FYN Dolfus*
33749		*ØJY Vind*
33750		*ØDA Wold*
33804		*HJ Kvist*
33838		*SYD Lido*
33842		*FYN Hasle*
33858		*RGK Nyt*
33863		*SYD Lyn*
33898		*HJ Day*
33903		*ØJY Buk*
33917		*SYD Muld*
33937		*FYN Best*
33938		*RANO Eg*
33940		*JMS Ekko*
33957		*SYD Mely*
33970		*HJ Kridt*
33974		*ØJY Bob*
33979		*RGK Nermi*
33986		*SYD Mego*
33992		*SYD Mango*
33999		*ØDA Whist*
34004		*SYD Mejle*
34015		*RGK Obo*

TABLE 13 *(continued). Carriers of spinal muscular atrophy*

Danish herd book no.	Original herd book no.	Name
34016		*RGK Omak*
34063		*RANO Bæk*
34091		*T Fosen*
34136		*FYN Fjord*
34157		*T Spros*
34294		*T Sneco*
34297		*VEST Plank*
34338		*FYN Lakmus*
34411		*VEST Pil*
34412		*VEST Pup*
34443		*FYN Gejs*
34541		*SYD Cap*
34551		*SYD Carlo*
34592		*ØDA Luton*
34670		*T Vold*
34785		*VEST Sne*
34865		*T Pøst*
34870		*SYD Draken*
35009		*SYD Ebru*
35047		*VEST Tatum*
35113		*T Frisbjer*
35120		*FYN Asger*
35147		*VEST Uno*
35152		*T Knustrup*
35318		*ØDA Idum*
35843		*R Aston FG*
35917		*R Bistro*
81137		*MRS Abru*
81205	US171713	*Johann Evilo Rocket*
81208	US163153	*West Lawn Stretch Improver*
81284		*RGK Focus*
81297		*FYN Knubru*
81301		*KOL Vilo*
81352		*HV Dur*

TABLE 14. *Carriers of spinal dysmyelination*

Danish herd book no.	Original herd book no.	Name
32649		*KOL Bali*
33222	US182072	*Towpath Jupiter*
33434		*HJ Kibo*
33549		*ØJY Rim*
33790	US179303	*Rolling View Conductor*
33995		*ØDA Wampyr*
34013		*ØJY Plou*
34063		*RANO Bæk*
34123		*SYD Andy*
34140		*VEST Oli*
34168		*SYD Ajax*
34178		*VEST Old*
34182		*SYD Ali*
34203		*SYD Aks*
34209		*VEST Poker*
34222		*SYD Ahorn*
34231		*SYD Assam*
34233		*SYD Alex*
34234		*SYD Astru*
34263		*VEST Pro*
34264		*VEST Præst*
34269		*T Gærum*
34283		*SYD Aura*
34292		*FYN Erot*
34294		*T Sneco*
34325		*SYD Biki*
34327		*SYD Agn*
34333		*T Reng*
34335		*T Knud*
34362		*ØDA Condor*
34384		*ØDA Jaco*
34406		*T Fred*
34414		*ØDA Empire*
34421		*SYD Bold*
34423		*SYD Bruno*
34429		*ØDA Jevo*
34479		*VEST Point*
34484		*ØDA Cafir*
34498		*ØDA Em-92*
34553		*SYD Como*
34579		*SYD Ceres*
34656		*FYN Pit*
34662		*ØDA Lanza*
34672		*T Lars*
34718		*SYD Cruso*
34788		*T Hejn*
34826		*FYN Taro*
34864		*T Årslev*
34880		*SYD Dito*
34882		*SYD Dylan*
34942		*ØDA Julius*
34970		*Herman*
34991		*T Eng*
35140		*T Moritz*
35230		*ØDA Master*
35595		*T Tejo*
35681		*FYN Dandy*

TABLE 14 *(continued). Carriers of spinal dysmyelination*

TABLE 15. *Carriers of syndrome of arthrogryposis and palatoschisis*

No registered carriers.

TABLE 16. *Carriers of ichthyosis foetalis*

No registered carriers.

TABLE 17. *Carriers of epitheliogenesis imperfecta*

No registered carriers.

TABLE 18. *Carriers of hereditary zinc deficiency*

Danish herd book no.	Original herd book no.	Name
7095		*Ham Hoorn*
7097		*Hob Agi*
7136		*Hhj August*
7200		*Ska Presid*
7252		*Hhj Odin*
8177		*HHJ Adema*
8236		*RDS Thor*
8965		*KOL Hoff*
8982		*VAR Kæk*
9105		*ØJY Astor*
9210		*Hob Gordon*
9928		*NJY Vim*
9990		*VE Star*
10231		*VAR Telsta*
10461		*VE Daniel*
10581		*NJY Pel*
10945		*HV Komet*
11238		*KOL Pabst*
11300		*RGK Corr*
11526		*JY Emyl*
11561		*HJ Lars*
11667		*NJY Mark*
11893		*JY Skjold*
12065		*SDJ Løkke*
13219		*RGK Uran*
13221		*RGK Tito*
13497		*NJY Bay*
13726		*NJY Bison*
15913		*VAR Jenle*
15957		*NJY Fritz*
17090		*NJY Golf*
82134	NLD57700	*Niertjes Adema 12*
82146	NLD60721	*Emyl 2 V D Emmahoeve*

TABLE 18 *(continued). Carriers of hereditary zinc deficiency*

Danish herd book no.	Original herd book no.	Name
82149	NLD35953	*Emyl 33 V D Emmahof*
82150	NLD57544	*Frans Ij 256*

TABLE 19. *Carriers of renal lipofuscinosis*

No registered carriers.

TABLE 20. *Carriers of hereditary dilated cardiomyopathy*[#]

Danish herd book no.	Original herd book no.	Name
10326		*GJ Oskar*
11516		*SK Black*
16175		*SDJ Eksil*
33068		*SDJ Calmo*
33288		*ØDA Kro*
33385		*SYD Jason*
33805		*ØDA Wopper*
33852		*ØDA Sum*
34052		*FYN Rock*
34462		*Pilg Debut*
35514		*SYD Grease*
43977		*DRK Nego*
81066	CAN331034	*Maplelawn Cincinnati-Red*
81177		*FYN Banca*
81181		*SDJ Otca*
81219		*ØDA Solo*
82167	D9010361761	*Tejo*
82168	CAN267150	*Rosafe Citation R «RC*
82270	CAN260008	*Romandale Reflection Marquis*
82477	CAN198998	*A B C Reflection Sovereign*
82553	CAN290516	*Agro Acres Marquis Ned *RC*
84018	CAN326692	*Narfa Western Star-Red*
84020	CAN311569	*Branderlea Citation Topper-Red*
84025	CAN331034	*Maplelawn Cincinnati-Red*
84104	CAN312731	*Romandale Royal-Red*
84112	CAN327403	*Mapel Wood Prince-Red*

[#] This table is based on the study by *Leifsson* and *Agerholm* (IX). It includes not only the sire of affected animals but also the common ancestor and the sires at the root of the genealogical diagram. There is no definitive proof that these sires are carriers of hereditary dilated cardiomyopathy, only a strong indication.

TABLE 21. *Carriers of bovine leukocyte adhesion deficiency*

Danish herd book no.	Original herd book no.	Name
14249		*NJY Cheri*
14452		*RGK Lori*
14872		*Basse Tvil*
16046		*VE Knop*
16224		*ØDA Sherif*
17001	US1667366	*Carlin-M Ivanhoe Bell*
17037		*HJ Daniel*
18382		*NJY Hubert*
18582		*ØJY Lerche*
18706		*HV Vagon*
19881		*VAR Malu*
82028	US1512026	*Harrisburg Gay Ideal*
82070	US1719192	*Arnold Acres Chief*
82085	CAN327279	*Puget-Sound Sheik*
82129	US1702759	*Penn-Dell Gay Jess*
82190	US1441440	*Penstate Ivanhoe Star*
82220	US1563453	*Willow Farm Rockman Ivanhoe*
82266	US1189870	*Osborndale Ivanhoe*
82642	US1842389	*Lekker Ivanhoe Bell Jesse-ET*
82668	US1954217	*Dixie-Lee Ivanhoe Henry-Et*
82685	US1920807	*Ugela Bell*[#]
82694	US1790625	*Potts Southern Man-Twin*
82701	US1799693	*Arlinda Carl-Twin*
82715	US1753897	*Yard-O-Ute Milu Bookie*
82728	US1608425	*Arlinda Cinnamon*
220270		*VAR Mikro*
220415		*NJY Ivanho*
221058		*NJY Ibsen*
222300	US1856904	*Thonyma Secret*
222345		*ØDA Busk*
223083		*NJY Karat*
223241		*SK Drøn*
223303	US1874645	*Pond Oak Pappy-ET*
223355		*SDJ Jan*
223419		*ØDA Bech*
223556		*SDJ Jolle*
223601		*CEN Sølv*
223678		*ØDA Bertel*
223685		*HMT Pilot*
223697		*SDJ Jessor*
223699		*SDJ Jubel*
223816		*VE Ronson*
223818		*VE Red*
223902	CAN369995	*Lamport Hawkeye*
223987		*CEN Alber*
223992		*ØDA Ny*
224126		*SDJ Jels*
224132		*SDJ Jaket*

TABLE 21 *(continued). Carriers of bovine leukocyte adhesion deficiency*

Danish herd book no.	Original herd book no.	Name
224202		*NJY Laks*
224204		*NJY Leopol*
224207		*NJY Loft*
224234		*RGK Jajla*
224251		*ØDA E T*
224304	US1882797	*Ripvalley Na Bell Troy-Et*
224337		*VAR Pasca*
224429		*FYN Flis*
224542		*VAR Paso*
224543		*VAR Pauli*
224544		*VAR Pelro*
224833		*HV Apon*
224837		*HV Agern*
224894		*HMT Rola*
224899		*VAR Pepsi*
225010		*SK Eli*
225054		*SDJ Kerne*
225113		*RGK Jepsen*
225192		*SK Fregat*
225245		*NJY Mads*
225246		*NJY Mozart*
225253		*NJY Multi*
225323		*HMT Rival*
225375		*SDJ Konto*
225384		*RGK Jolly*
225398		*RGK Jes*
225481		*HV Banjo*
225500		*VAR Pirat*
225602	US1903604	*Relay Arise Swd Vanguard-ET*
225633		*VAR Pors*
225700		*CEN Stedy*
225746		*KOL Dingo*
225800		*NJY Mobil*
225850		*VAR Rabbi*
225870		*SDJ Klink*
225976		*SDJ Korup*
225988		*JY Dors*
226154		*HMT Shag*
226156		*Per*
226190		*VAR Pårup*
226202	US1927586	*Tikvah Bc Julius-ET*
226311		*RGK Kras*
226321		*US Florida*
226322		*US Alaska*
226323		*RGK Kenja*
226353		*CEN Imbel*
226365		*VE Sonda*
226384		*JY Secre*
226624		*SDJ Lokal*
226643		*US Oregon*
226671		*NJY Makron*

TABLE 21 *(continued). Carriers of bovine leukocyte adhesion deficiency*

Danish herd book no.	Original herd book no.	Name
226724		*VE Sella*
226776		*US Illinoi*
226817		*KOL Finale*
226847		*NJY Nexø*
226982		*VAR Ringo*
227200		*RGK Lans*
227275		*VAR Ronson*
227347		*NJY Nihof*
227349		*NJY Nestor*
227365		*SK Glob*
227379		*VAR Rival*
227586		*CEN Cling*
227787		*VAR Salto*
227895		*SDJ Lur*
227897	D105655294	*SDJ Lebøl*
227926		*HV Diskos*
227950		*SK Gokart*
228067		*VAR Sigurd*
228070		*VAR Sirius*
228131		*NJY Ocean*
228165		*ØDA Tay*
228200	CAN384848	*Hanoverhill Stardom*
228218		*VAR Sonny*
228227		*SDJ Milt*
228262		*HV Domi*
228295		*NJY Ole*
228308		*NJY Ozon*
228326		*SK Horn*
228352		*Hess Hub*
228386		*VAR Sober*
228396		*SDJ Mango*
228398		*SDJ Mesa*
228429		*HMT Vidne*
228430		*KOL Nibøl*
228467		*RGK Lunk*
228576		*HV Design*
228646		*HV Depot*
228685		*SDJ Malle*
228807		*Hubert 856*
228830		*CEN Imy*
228906		*HMT Vang*
228908		*HMT Veike*
228941		*SDJ Mode*
229003		*VAR Sultan*
229006		*VAR Svend*
229009		*VAR Tango*
229013		*VAR Tax*
229035		*VE Utopi*
229036		*SK Hof*
229121		*HMT Vagn*
229123		*HMT Vilje*
229151		*RGK Marabu*
229153		*RGK Marv*

TABLE 21 *(continued). Carriers of bovine leukocyte adhesion deficiency*

Danish herd book no.	Original herd book no.	Name
229155		*RGK Mamut*
229158		*RGK Mentor*
229166		*SDJ Nap*
229201		*HV Dennis*
229202		*HV Dakota*
229225		*T Amerika*
229228		*T Allegro*
229235		*T Andy*
229299		*Hubert 624*
229302		*ØDA Vakka*
229311	US1936474	*Belmont*
229332		*KOL Viva*
229335		*VAR Tebal*
229337		*VAR Terry*
229342		*VAR Tjep*
229349		*FYN Inka*
229350		*FYN Ir*
229351		*SDJ Nis*
229352		*ØDA Bobcat*
229353		*ØDA Mugge*
229402		*RGK Medusa*
229430		*T Anglia*
229436		*T Ambell*
229447		*Bodils Hub*
229518		*HV Duplo*
229551		*T Alling*
229553		*T Asa*
229558		*T Aris*
229566		*VAR Thomas*
229586		*HMT Vups*
229609		*KOL Key*
229617		*Gun Hubert*
229628		*VAR Tippo*
229631		*VAR Tofte*
229634		*VAR Tolk*
229637		*VAR Tot*
229648		*ØDA Varig*
229658		*SDJ Notat*
229659		*SDJ Nil*
229662		*SDJ Neksø*
229663		*SDJ Nøk*
229712		*RGK Milt*
229713		*RGK Mask*
229732		*HV Ebbe*
229743		*Thor*
229754		*Slots Uhre*
229780		*SDJ Nepal*
229781		*SDJ Njal*
229785		*SDJ Nørup*
229795		*SDJ Nibe*
229803		*T Bio*
229809		*T Barbi*
229871		*Drengs Hub*

TABLE 21 *(continued). Carriers of bovine leukocyte adhesion deficiency*

Danish herd book no.	Original herd book no.	Name
229874	US1882141	*Stan-Bitzie Kirk Bell Boss*
229893		*VAR Tone*
229972		*RGK Mølle*
229976		*RGK Nild*
229980		*RGK Nør*
230043		*ØDA Salom*
230110		*T Blunk*
230125		*SDJ Nivå*
230169		*ØDA Visum*
230172		*RGK Nørst*
230261		*T Bern*
230284		*Gamst Vang*
230303		*FYN Jeppe*
230363		*Højg Wilow*
230709		*HV Ergo*
230773		*Vejr Tong*
230915		*Graum Vang*
230928		*Lerche 645*
231147		*Abs Annan*
231187		*Bor Pontus*
231191		*Møns Centa*
231289		*Hou Hubert*
231311		*Lindsø*
231402		*Uffe*
231730		*Hebo Hub*
231890		*Høstrup*
231973		*Mosl Laust*
232065		*Westh*
232143		*Nyrup 1278*
232147		*Nyrup*
232219		*Stardom702*
232222		*Brøns Vang*
232268		*Ares 491*
232318		*Syd Hawkey*
232640		*Otto 524*
232654		*Otto 1052*
232665	NLD314390431	*Oudkerker Constantijn*
232718		*Bertus*
232726		*Us Herbert*
232885		*Nørg Hub*
232895		*Steines*
233156		*Hub 1618*
233567		*Bit Holm*
233611		*Hub 650*
233643		*Hub 942*
233854		*Bell 431*
233927		*Dum*
234057		*Højager*
234277	NLD460942030	*Etazon Labelle-ET 528*
234280		*Holm 429*
234290		*Astre 1601*
234344	US1912270	*Emprise Bell Elton*

TABLE 21 *(continued). Carriers of bovine leukocyte adhesion deficiency*

Danish herd book no.	Original herd book no.	Name
234426		*Øst Weis*
234443	US2038151	*Zee-Cal Commotion-ET*
234755		*Bork Huber*
234990		*Vagn*
235049		*Lun Stardu*
235224		*Aero 582*
235286	CAN355454	*Newlands Detective*
235593		*Stamp Ast*
235777		*Gj Bra*
235823	US2051549	*Blackcrest Karmel-Red-ET*
235859	US1626173	*Eng-Amer Ivanhoe Jerry*
236377		*Dane Inspi*
236444		*Birk Mount*
236503	NLD319957882	*Delta Lava*
236534		*Bor Vulcan*
236598	F2290038601	*Fatal*
236975		*Astre 913*
237028		*Moun 720*
237087		*Vej Hubert*
237428		*Hubert 450*
237429		*Hubert 472*
237569		*Lubert*
237787	D107174081	*Sturm*
237822		*Mounspi*
238056		*ØH Juror*
238446	NLD461308877	*Etazon Lutz*
238647		*Eksport*
238793	F5189001700	*Enehould*
238865		*Bellis*
238891		*Thor 625*
238984		*Låstrupgdr*
239438		*F Labelle*
239726		*Vil Fatal*
239749		*Label 1401*
239946		*Dissing 2*
240190		*Fatal 1205*
240325		*Blakihu*
240387		*Ring Fatal*
240589		*Fatal 899*
240622		*Tirs Fatal*
240636		*Eksport*
240647		*Eksport*
240667		*Fatal 1205*
240808		*Høj Burma*
240957		*Eksport*
241027		*Burma 661*
241061		*Lily Holm*
241265		*Søren*
241375		*Fatal 514*
241376		*Fatal 1582*

TABLE 21 *(continued). Carriers of bovine leukocyte adhesion deficiency*

Danish herd book no.	Original herd book no.	Name
241570		*Labell*
241626		*Årre L Leo*
241899		*Kær Fatal*
241907		*Ho Labell1*
241934	US397763	*Haldrey Leadership*
241953	US2271271	*Ricecrest Emerson ET*
242109		*Eksport*
242236		*Celsi 1419*
242266		*Fecamp1159*
242529		*Funki 1219*
243076		*Tirs Marty*
243241		*Hovg Boude*
244142		*BGH Roscas*
244282		*Uhre Basar*
244388		*Tirs Emer*
244441		*S Anton*
244442		*S Anker*
244443		*S Aksel*
244444		*S Abel*
244793		*Delta 1958*
244796		*Tønnin Leo*
244858		*V GroovyBL*
244891		*Tirsvad Emerson Cassius*
245051		*P N Stone*
245373	US1920807	*Ugela Bell*[#]
245457		*Houg Emers*
245509		*Tir Fatal*
246759		*Pors Marsh*
247097		*Inquirer 1173*
247168		*Manat 773*
247233		*Tir-An Magna Clapson*
247716		*Hes-Stoneham*

[#] The sire *Ugela Bell* is registered under two Danish herd book numbers: 82685 and 245373.

TABLE 22. *Carriers of congenital erythropoietic porphyria*

Danish herd book no.	Original herd book no.	Name
11516		*SK Black*
18004		*Black 18*
226735		*Klaus 323*

TABLE 23. *Carriers of rectovaginal constriction*

Danish herd book no.	Original herd book no.	Name
4205		*Onkel Sam*
4250		*Rosenfeldt Favorit*
4419		*SKÆ Trad*
4420		*SKÆ Mark*
4432		*Trademølle*
4452		*HJ Kær*
4718		*HJ Navr*
4843		*Rosenfeldt Oktav*
4844		*Rosenfeldt Fos*
4973		*SKÆ Knap*
5037		*ØDA Lux*
5095		*SKÆ Kaj*
5339		*SKÆ Ling*
5386		*SKÆ Mors*
5519		*SKÆ Bargo*
5528		*Expert*
5587		*ØDA Sambo*
5785		*FYN Noes*
5829		*Kildg Mark*
5940		*Mors 72*
5992		*HJ Giv*
6002		*ØDA Alsam*
6056		*Lervang 74*
6134		*Østerg Sam*
6147		*MRS Oks*
6253		*SKÆ Fut*
45427		*FYN Dres*
45479		*Såhøj Lux*
45491		*HJ Tuby*
45492		*HJ Stof*
45510		*ØJY Lopa*
45635		*Søgrd Mark*
46030	US627500	*Sargent Plus*
83001	US585350	*The Trademark*
300439	US630261	*Mayfield Volunteer Bruce Twin*
300850	US580714	*Tristram Nevada*

TABLE 24. *Carriers of tandem fusion translocation*

No registered carriers.

TABLE 25. *Carriers of translocation t(1;8;9)(q45;q13;q26)*

Danish herd book no.	Original herd book no.	Name
33720	US184214	*Sunburst Hill Combo Fabian*

TABLE 26. *Carriers of translocation 1/29*

Danish herd book no.	Original herd book no.	Name
68001	F4683132159	*Ukrainien (heterozygous)*
68005	F6485015667	*Agenais (homozygous)*
	F4786011835	*Balthazar (heterozygous)*

TABLE 27. *Carriers of the "Dag-defect"*

Danish herd book no.	Original herd book no.	Name
–		*Fåborg Dag*
–		*Fåborg RU*[#]

[#] *Fåborg Ru* is most likely the full-brother to *Fåborg Dag* mentioned by *Blom* (36). Other carriers have been diagnosed but their identity is no longer available.