Genetic disorders of sheep in New Zealand: A review and perspective

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Abstract

Genetic disorders of sheep that have occurred in New Zealand are reviewed and discussed with regard to phenotype, inheritance and, where known, genotype. Inbreeding was a major factor in the emergence of some of them. The various disorders reflect a continuum, ranging from simple monogenic diseases or malformations due to dysfunctional gene products, those monogenic disorders dependant on environmental interactions, malformations due to homoeotic gene dysfunctions, and multifactorial diseases for which genetic factors are associated with disease susceptibility. Chromosomal aberrations, although of limited importance, have contributed to an understanding of the physical chromosome map and derivative linkage map of sheep.

KEY WORDS: Genetic disorders, sheep, New Zealand, review

Introduction

There is a large wastage of sheep during their farmed life, most of which is concentrated in the neonatal period and then the first year. Major causes include infectious, parasitic, nutritional and toxic diseases. Although there is a tendency to think of these as due to external agents, they are in fact multifactorial diseases, being modified by a number of genetic factors affecting disease susceptibility. Monogenic disorders are more easily understood than multifactorial diseases because of their more apparent relationship to a single gene mutation and a dysfunctional gene product. However, a disease phenotype may have more than one genotype, or variable expression of a disease phenotype may be due to genetic variation in other genes related to the same area of metabolism or structure. This has given rise to terms such as digenic and oligogenic, to more accurately reflect the mode of inheritance (Badano and Katsanis 2002). In many genetic diseases, the expression of disease may also depend on secondary environmental factors. Thus, in human medical genetics, a continuity is now recognised between monogenic and multifactorial disorders due to varying interactions between genetic and environmental factors (Childs 2001). Examples of disorders in sheep across such a continuum are noted below.

The many genetic disorders of humans can be expected to be reflected in our animal populations. As within discrete ethnic or other subgroups of people, the number of entities in our sheep population will be much lower than encountered in the whole human population. This is because the sheep population in New Zealand is based on a limited number of breeds, each a distinctive subgroup derived from a restricted population in a geographical area. In contrast, the incidence of a particular inherited disorder may be higher than in most human populations because of a greater degree of relatedness between animals mated. This may be associated with both the hierarchical nature of livestock breeding whereby an individual, usually a male, may have numerous offspring, and close breeding between related animals, knowingly or unknowingly practiced.

This paper reviews and discusses genetic disorders of sheep that have occurred in New Zealand. Although some entities are not described in the literature or proof of inheritance may be lacking, the paper tends to be inclusive rather than exclusive, and draws at times on unpublished archival material, or analogy with similar disorders described in other countries. In such instances, this is made clear in the text and care should be taken in citing correctly the presumptive, or uncertain, nature of this information in consequent publications.

Monogenic disorders

Most inherited disorders of livestock are autosomal recessive traits, because dominantly inherited disorders, unless poorly expressed, tend not to be propagated as they are already manifested in the breeding animal. Some may arise de novo from mutations of germ cells, in which case a dominant mode of inheritance may be expected for an expressed phenotype.

Disorders of liver metabolism

Hyperbilirubinaemia and photosensitivity

A severe photosensitive disease with hyperbilirubinaemia was recorded in Southdown sheep (Cunningham 1942), and shown to be inherited as an autosomal recessive trait (Hancock 1950a). The same disease was later diagnosed in the same breed in California (Cornelius and Gronwall 1968; McGavin et al 1972; Cuppage et al 1979). There was a marked delay in plasma clearance of unconjugated bilirubin, phylloerythrin and other organic anions, but no defect in hepatic conjugation of bilirubin. Affected sheep lived for several years if they were protected from sunlight and tended to die from renal failure associated with progressive fibrosis of the kidney. Pigmentation of the carcass was mild but teeth, periostea, fascia, serosa and mucous membranes developed a green or yellow-green colouration due to accumulation of bilirubin and phylloerythrin. There were no gross structural abnormalities or pigmentation of the liver.

A similar disease was also recorded from California in Corriedale sheep and was likewise inherited as an autosomal recessive trait

MHC Major histocompatibility complex
PCR Polymerase chain reaction
PrP Prion-related protein
QTL Quantitative trait locus
(Cornelius et al 1965). In contrast to the disease in Southdowns, the functional defect was not in the uptake of unconjugated bilirubin and phylloerythrin, but rather its excretion from liver into bile. It affected lambs as they began to eat pasture and was associated with photosensitivity due to failure to excrete phylloerythrin. Lambs lived until 6 months of age if provided with some shade. Another difference was a severe melanin-like pigmentation of the liver. Although this disease has not been recorded in New Zealand, the putative mutant gene may have been present here as the Corriedale breed was developed in New Zealand from initial crosses of Merino and Lincoln sheep, with some input from Border Leicesters.

These two diseases are good examples of the involvement of external environmental disease factors in a genetic disorder, i.e. a diet of green fodder (chlorophyll), and sunlight, working in concert with the inborn error of metabolism to induce photosensitivity.

**Disorders of catabolism (lysosomal storage diseases)**

Lysosomal storage diseases mostly present as neurological diseases but, as they are in fact generalised disorders, they are dealt with here as a separate group. They are characterised by the accumulation of an undigested polymeric molecular substrate within the lysosomal system of cells (Jolly and Walkley 1997). In most instances, there is a direct relationship between the major accumulated substrate and the inherited enzyme deficiency: i.e. the accumulated material is the substrate of the deficient enzyme. In some instances, the relationship may be indirect. Nearly all lysosomal storage diseases are inherited as autosomal recessive traits and this would be expected for the diseases discussed below.

**Glycogen storage disease (Type II)**

A debilitating disease occurring in a flock of Corriedale sheep in Otago was first investigated in 1962. For a number of years, 7–10 animals from a flock of 1,800 ewes had been affected at 6–10 months of age. There was slight incoordination, lethargy, loss of condition and drooping ears. Some animals showing these signs died upon exertion. This disorder was retrospectively diagnosed as glycogen storage disease Type II by Manktelow and Hartley (1975). Excess glycogen was shown in neurons, and skeletal, smooth and cardiac muscle cells. Lysosomal compartmentalisation of this glycogen was shown by electron microscopy of archived, formalin-fixed nervous tissue. In this form of glycogen storage disease, muscle is the major tissue type functionally compromised. The enzyme deficiency expected in this disease is acidic α-glucosidase, but this was not confirmed experimentally for the disease in sheep. Recently, the disease was diagnosed in a 10-month-old Merino lamb.

**GM1 gangliosidosis**

A retrospective diagnosis of GM1 gangliosidosis, due to a putative deficiency of β-D galactosidase, was made using lectin histochemistry in a group of related 8-month-old lambs that had developed "ataxia that rapidly progressed to prostration" (Murnane et al 1991). The breed was not stated in this report, nor an earlier one, where the disease was described as a "lipid-like neuronal degeneration" (Hartley and Kater 1962).

GM1 gangliosidosis has also been reported from England in "Coopworth Romney" lambs closely related to a ram imported from New Zealand (Skelly et al 1995; WM Blakemore, pers. comm.).

**Ceroid-lipofuscinosis**

A recessively-inherited neurological disease was diagnosed in South Hampshire sheep, a composite breed developed from an initial cross between Southdown and Hampshire breeds. It was studied intensively over a 25-year period in an experimental flock established at Massey University, as a model of analogous diseases in humans. Clinical findings were mainly those of progressive loss of vision from 7–10 months of age, behavioural changes and facial manoeuvres that were interpreted as partial seizures that did not become generalised. Pathologically, there was cerebral cortical atrophy, particularly of the optic cortex, as well as retinal atrophy (Graydon and Jolly 1984; Mayhew et al 1985; Jolly et al 1989). These atrophic lesions due to neuronal loss, and lysosomal accumulation of a fluorescent lipopigment in remaining neurons and other cell types throughout the body, are the hallmarks of a heterogeneous group of diseases known as the ceroid-lipofuscinoses (Jolly et al 1999).

Analyses of isolated storage material showed that 50% was subunit c of mitochondrial ATP synthase, a highly hydrophobic protein making up much of the F0 complex of this important respiratory enzyme (Palmer et al 1989; 1992). Functional changes in ATP synthase activity relative to additional Ca2+ were demonstrated *in vitro* (Jolly et al 2001), but the relationship of this to the accumulation of its subunit c in lysosomes is unknown. However, the mitochondrial functional defect allows the hypothesis that neurodegeneration leading to brain atrophy is mediated by energy-linked excitotoxicity.

The South Hampshire form of ovine ceroid-lipofuscinosis maps to chromosome 7q13–15 (Broom et al 1998), which is syntenic with human chromosome 15q21–23, the site of human CLN6. An homologous disease, likewise linked to chromosome 7q13–15, occurs in Merino sheep in Australia (Cook et al 2002). A similar disease has recently been described in Borderdale sheep in New Zealand, but differences in the degree of brain atrophy and the ultrastructure of storage material suggest that it is due to a different mutation (Jolly et al 2002).

**Disorders of the nervous system**

**Lower motor neuron disease**

A disease of newborn lambs occurred in a small inbred flock of Romney sheep comprised of one ram, five founding ewes and ewe progeny. Lambs were apparently normal at birth but within 1 week they developed weakness and ataxia which progressed until they were unable to stand. Clinical examination showed poor muscle tone, depressed withdrawal reflexes and a slight medial strabismus. In lambs kept alive by hand feeding and nursing until 3–4 weeks of age, the principal histological lesions were degeneration and loss of neurons in ventral horns of the spinal cord and brain stem, Wallerian degeneration of ventral rootlets and motor nerves, and associated denervation atrophy of skeletal muscle fibres (Anderson et al 1999). Large fibrillar spheroids were found in white and grey matter including nuclei in the brain stem.

Subsequent breeding of the ram to unrelated ewes and their F1 progeny produced additional affected lambs in the F2 generation in numbers confirming inheritance as an autosomal recessive trait (HT Blair, unpublished). As many of these were dead at or near the time of birth, and others were not kept alive artificially, the lesions were not as severe as those described above. However,
pronounced spheroid formation in the oculomotor nucleus was found to be an important diagnostic observation and would be expected to be the lesion underlying strabismus.

A similar, though not identical, clinical disorder of newborn lambs was recorded in a small Dorset Down stud affecting approximately 20% of lambs. These lay with hindlimbs tucked under the body and forelimbs splayed sideways. Histologically, muscles showed group atrophy of fibres (Thornton and MacColl 1985). As the disorder did not occur in other breeds on the property, the authors suggested it was an inherited neuromuscular disease.

**Neuroaxonal dystrophy**

A heterogeneous group of diseases of genetic or acquired aetiology is characterised by spheroidal swellings of axons (Figure 1), the result of accumulation of axoplasmic organelles including neurofilaments. They tend to occur in proximal or distal extremities, but may also be seen along their length. Various entities in unweaned and weaned lambs characterised by ataxia affecting the hindquarters, trembling and weakness have been described in New Zealand Romney (Hartley and Kater 1962), Coopworth (Nuttall 1988; Anonymous 1991b), Perendale (Anonymous 1978), and South Suffolk breeds (Anonymous 1990). Nuttall (1998) likened the disorder in Coopworths to that in Suffolk sheep in California, where there was a strong presumption of an inherited aetiology (Cordy et al 1967). In a further investigation of the disorder in an inbred flock of Coopworth sheep where there was an incidence of up to 5% per year over several years, there were numerous proximal axonal swellings in nuclei in the brain stem (Figure 1) and ventral horns. Mating of a suspected heterozygous ram to 20 ewes known to have produced affected lambs previously resulted in 10/39 lambs born affected. This essentially confirmed inheritance as an autosomal recessive trait, at least in that flock (AC Johnstone, unpublished).

**Ovine spongiform leucoencephalopathy**

From 1961 to 1987, a neurological disease was recorded in New Zealand Romneys on at least six farms in Otago, affecting 2–3% of the lamb crop that were otherwise in good condition (Manktelow et al 1997). It affected 2–3-month-old lambs and was characterised by a rapidly developing and progressive posterior paresis leading to flaccid paralysis. There were no gross visible lesions. Histopathological studies showed a spongy vacuolation of brain and spinal cord. The earliest lesions were dilatation of myelin sheaths about a central axon, a change interpreted as due to intramyelinic oedema. Liver copper levels were normal and an inherited cause was suspected.

**Cerebellar cortical atrophy (‘daft lamb’ disease 1)**

A “cerebellar cortical atrophy” was recorded in a group of newborn Corriedale lambs in the South Island of New Zealand (Anonymous 1991a) and in 15 newborn Drysdale lambs in a flock of 130 ewes (Cox 1992). In this latter flock, affected lambs were the progeny of a single ram, and the disease was considered to be inherited as an autosomal recessive trait. These disorders were clinically and pathologically similar to those described as ‘daft lamb’ disease in inbred flocks of Welsh Mountain sheep in Wales (White and Rowlands 1945) and Corriedales in Canada (Innes and Saunders 1962). Lambs were weak, unable to rise without assistance, or if they did rise, walked with difficulty by straddling their legs on a wide base. In some, there were opisthotonous and coarse tremors. Histologically, there was loss of Purkinje cells of the cerebellum, decreased cells in the granular layer, glosis of the granular layer and proliferation of Bergmann glia. In the original description, the disease in Welsh Mountain sheep included data on sire/daughter matings and the disorder was considered inherited as an autosomal recessive trait. In Corriedales in Canada, breeding data led to the conclusion “that the disease was conditioned by a recessive gene, but was not a simple case of homozygous recessive” (Innes and Saunders 1962). Those authors also noted that “private communications intimated the occurrence of the same disease in Australia and New Zealand”.

**Cerebellar abiotrophy**

A disorder characterised by fine head tremor and hindlimb weakness developing at several weeks of age was diagnosed in 2002 in progeny of sire/daughter matings in a hobby flock of Wiltshire sheep and also in the flock from which the parent sheep were derived. Histologically, there was severe loss of Purkinje cells of the cerebellum and proliferation of Bergmann glia (AC Johnstone, unpublished). The history suggested an autosomal recessive mode of inheritance. Although histopathologically this resembled the “cerebellar cortical atrophy” described by Innes and Saunders (1962), the disease was not present at birth and clinical signs differed. To distinguish it from the congenital disorders, it is tentatively named ‘cerebellar abiotrophy’.

**Star-gazing lambs (‘daft lamb’ disease 2)**

An hereditary disease clinically similar to cerebellar cortical atrophy (see above), and also called ‘daft lamb’ disease, was described in newborn Border Leicester lambs in the United Kingdom, but without histological evidence of Purkinje cell loss or reactive changes, considered the hallmark of “cerebellar cortical atrophy” (Bradley and Terlecki 1977; Terlecki et al 1978). These lambs displayed a “dorsal arching of the neck with the head being pressed backwards” that has been also described as “star-gazing” (Bradley 1983). Histological lesions were noted in neck muscles and nerves but it was uncertain if these were primary lesions reflecting abnormal neuromuscular transmission, or secondary to a primary central neurological defect. Approximately 10 similar star-gazing lambs (Figure 2) were born in a Coopworth flock in 2001 and no central nervous system lesions were noted (AC Johnstone and RD Jolly, unpublished). A further six were born the following year. As this closely resembled the disease in Border Leicesters, and as Coopworths are derived from an initial cross of New Zealand Romney and Border Leicester breeds, it may be the same disease. An autosomal recessive mode of inheritance would be expected from the history, but is unproven.

**Endocrine disturbances**

**Hypothyroidism (congenital goitre)**

A congenital goitre was recognised in an inbred composite breed derived from Pollled Dorset, New Zealand Romney, Perendale and Cheviot breeds. It was postulated to be inherited as an autosomal recessive trait (Davis et al 1979), an hypothesis later confirmed by controlled breeding experiments (Jones et al 1986). Affected lambs were found dead after birth or succumbed in the first few days of life. Neonatal respiratory distress syndrome due to low levels of thyroid hormone affecting fetal lung development was thought to be a factor in these deaths. One lamb was maintained on oral thyroxin and thrived until development of the rumen, when it ceased to be effective. Biochemical investigations allowed the conclusion that the primary defect was in thyroglobulin synthesis (Jones et al 1986).

**Disorders of the integument**

Skin is a complex tissue, subject to a number of inherited anomalies affecting its stratified epithelium, basement membrane, un-
derlying dermis, feet and wool (hair). Of these, some give rise to skin fragility, others to bullous and erosive diseases or abnormalities of wool.

**Ehlers-Danlos syndrome**
Skin fragility was noted in approximately 12 lambs in a flock of 1,400 ewes over a 3-year period (Clark et al 1977). It was seen in newborn lambs, at tailing or at crutching. The skin was loose and present in excessive amounts, with folds over the carpal joints and lower regions of the legs. In some lambs, there was separation of epidermis from dermis with blood-filled cavitations and intact skin that could be easily torn (Figure 3). Their fetlock joints were overextended. The type of lesion and clinical history is indicative of a genetic cause but with insufficient information to deduce its mode of inheritance. Of the 10 phenotypic types of Ehlers-Danlos syndromes in human beings to which it can be likened, inheritance may be dominant or recessive, depending on whether the mutation affects the structural elements of collagen (dominant) or the process of post-translational modification by enzymic cleavage of procollagen, or enzymic cross linking (recessive) (Byers 2001). If it was dominantly inherited, then a new mutation of male germ cells in a ram would be expected as the parents were normal. Skin fragility was also listed by Hartley and Kater (1964) as a congenital defect of neonatal lambs.

**Epidermolysis bullosa**
Clinically identical bullous diseases occurred in Suffolk and South Dorset Down flocks (Alley et al 1974). In the Suffolks, 5/32 affected lambs were born to 3- and 4-year-old ewes mated to their sire, or one of his progeny. In the South Dorset Down flock, the disorder was noted over a 5-year period, with an incidence of one in four in the 200 ewes mated. All the dams of affected lambs were thought to share a common Dorset Down ram as a sire or grandsire. The lesions were confined to areas of skin and mucous membranes exposed to frictional trauma early in life. The earliest were erosions on the oral mucosa, particularly midline of the hard palate, tongue, lips and nasolabium. Red vesicles up to 5 mm in diameter occurred on the lower lips and nasolabium before ulcerating. In lambs several days old, there was loss of skin and an exudative dermatitis on exposed areas of limbs and feet. The coronary border and hooves were usually involved and there was a thick crusty scab above the hooves. In most cases, the hooves became loose and were shed leaving a raw exposed corium. The wool could be plucked with relative ease and in some such cases a thin layer of epidermis separated and remained attached to the base of the plucked wool fibres.

Histologically, cleavage occurred between the basement membrane and dermis. By comparison with human forms of inherited bullous disease, it is analogous to epidermolysis dystrophica, which reflects defects in collagen VII (Uitto and Pulkinen 2001). A great many mutations in the human gene for this disorder are described, giving rise to both recessive and dominant forms of disease; the latter mainly being mutations associated with codons for glycine. From the history, an autosomal recessive mode of inheritance in both breeds of sheep would be expected.

**Lustrous wool**
A dominantly-inherited gene occurred in New Zealand Romney sheep, conferring a lustrous appearance to the fleece, reduction of follicle density and a deficiency of glycine-/tyrosine-rich proteins (Blair 1990; Gillespie and Darskus 1995). The gene may be a regulatory one as it affects the expression of several genes encoding these proteins. Affected sheep have lower bodyweight and fleece weight, even after adjustment for the former.

**N-type wool**
The dominantly-inherited N gene has pleiotropic effects causing both increased fibre diameter, increased medullation of fibres, and the presence of horns in both sexes (Dry 1955a). Originating in New Zealand Romney sheep, it has been developed into distinct breeds for the carpet-wool industry. A number of alleles exist (Robards et al 1993) and a non-allelic recessive nr gene produced similar effects except that homozygous ewes did not produce horns, although rams did (Dry 1955b).

**Disorders of bone**

**Osteogenesis imperfecta with skin fragility**
Approximately 50 lambs affected with fragile bones and multiple fractures of ribs and long bones were born in a New Zealand Romney flock of 450 ewes (Arthur et al 1992). Long bones were orange/pink in colour, had thickened diaphyses and almost complete absence of a medullary cavity. Other consistent gross findings included moderate brachygnathia inferior, subcutaneous oedema, extreme joint laxity, dark blue sclera, small pink teeth (dentinogenesis imperfecta) and pink tendons.

Histopathology and electron microscopy of skin showed deficient and abnormal collagen. In bones, growth plates were essentially normal but bone trabeculae were very thin and calcified cartilage persisted deep into the diaphyseal region. The cortices were thin and composed of porous irregular bony trabeculae separated by loose fibrous tissue. Electron microscopy of skin and tendon showed fibrillar and electron-dense material in dilated cisternae and in the cytoplasm of fibroblasts.

The sire of the affected lambs was identified from five possible rams, by DNA fingerprinting. Mating to a further group of unrelated ewes on another property produced further cases of osteogenesis imperfecta. These results showed that not only was the disease inherited as an autosomal dominant trait, but it was due to a new germ cell mutation, as the ram himself was normal. Such new mutations create germ cell mosaicism and are well-recognised causes of inherited connective tissue defects, of the type described here.

The term osteogenesis imperfecta covers a heterogeneous group of connective tissue diseases caused by quantitative or qualitative defects in Type 1 collagen. This is the predominant type in bone, dentine, tendon and sclera. In human beings, a phenotypic classification does not clearly coincide with genotype, which is associated with many potential mutations in COL1A1 or COL1A2 molecules that make up Type I collagen. The present cases were likened to Type II osteogenesis imperfecta. Although skin fragility is not normally associated with this disorder in human beings, other mutations in COL1A1 or COL1A2 of Type I collagen involving deletion of an N-proteinase cleavage site, result in Ehlers-Danlos syndrome Type VII A and B, respectively, which are associated with skin looseness and fragility.

An osteogenesis imperfecta, but apparently without skin fragility, had previously been described in approximately 20 lambs (breed unstated) in a flock of 200 ewes (Kater et al 1963). Although the authors did not suggest a genetic cause, this can probably be assumed in retrospect and could likewise have been the result of a new mutation.
Figure 1. Swollen proximal segment (spheroid) of the axon of a multipolar neuron in the ventral spinal cord of a Coopworth lamb with neuroaxonal dystrophy (H&E, bar=100 µm).

Figure 2. Opisthotonus (star-gazing) in newborn Coopworth lambs.

Figure 3. Skin fragility, manifested by its easy tearing and separation from underlying subcutaneous tissue, in a lamb with Ehlers-Danlos syndrome (photo courtesy of RG Clark, Wanaka, NZ).

Figure 4. Suffolk lambs with spider syndrome (chondroplasia) showing long limbs and facial deformity (Roman nose) which are features of this disorder (photo courtesy of KG Thompson, Massey University, Palmerston North, NZ).

Figure 5. Abdominal viscera of lamb with congenital polycystic kidneys. The bisected kidney shows a multitude of small 1–3 mm-diameter cysts and gross enlargement of the organ.

Figure 6. Newborn Perendale lamb with truncated appearance due to a deficient number of vertebrae (photo courtesy of RG Clark).
Hereditary chondrodysplasia (‘spider syndrome’) of Suffolk sheep

The semi-lethal malformation known as 'spider syndrome' was first described in America in the 1970s and was introduced to Australia by importation of both rams and ewes (Phillips et al 1992) and from there to New Zealand (West et al 1995). The trait is inherited in an autosomal recessive manner but with varying degrees of expressivity. The high prevalence of spider syndrome lambs in America was thought to be associated with breeding for long-legged animals which may have been heterozygous for the defect. Such partial expression of disease in the heterozygous state (overdominance) is not uncommon in other chondrodysplasias.

Spider syndrome lambs may be aborted or stillborn, but most are born alive showing various degrees of skeletal abnormalities. Some may appear essentially normal only to develop evidence of the syndrome during their first month of life, being manifested by long limbs and neck, scoliosis and/or kyphosis, a shallow body as well as other boney defects of the head (Figure 4). Histopathological examination showed abnormal ossification centres in bones developing from endochondral ossification (Vanek et al 1986, 1989; Rook et al 1988; West et al 1995; Oberbauer et al 1995). These, and irregular thickened growth plates, allow convenient diagnosis by radiology.

At the molecular level, spider syndrome is caused by a mutation in the fibroblast growth factor receptor 3 gene (FGFR3) involving an A→T point mutation causing a valine-to-glutamic acid substitution (Beever et al 1998). A DNA, polymerase chain reaction (PCR)/restriction enzyme-based test is available to detect heterozygosity (Beever et al 1998). A DNA, polymerase chain reaction (PCR)/restriction enzyme-based test is available to detect heterozygous individuals in stud flocks (I Anderson2, pers. comm.).

Chondrodysplasia of Texel sheep

In contrast to the disease above, a chondrodysplasia resulting in a dwarfing phenotype has occurred in a Texel flock over 4 years, and in two other related flocks (Thompson et al 2003). It appears probable that it is inherited as an autosomal recessive trait.

‘Inherited taillessness’

A malformation varying from complete absence of a tail to a short and frequently kinked tail occurred in a commercial Romney x Southdown flock. Breeding experiments led to the conclusion that the defect was inherited as a simple dominant factor causing variable hypoplasia of the coccygeal vertebrae. The homozygous tailless embryos underwent degeneration and died at 3–4 weeks gestation (Carter 1977/78).

Disorders of the reproductive system

Numerous defects of the male and female reproductive organs are known to occur but the genetic basis for many of them are unknown and not investigated in New Zealand. Some not clearly defined in Mendelian terms are discussed later, under the heading ‘Malformations’.

Inverdale streak ovary

An X-linked fecundity gene (Inverdale or FecX) occurs in New Zealand Romney sheep which, in the heterozygous state, results in increased numbers of ovulation sites in females and increased numbers of multiple births. Paradoxically, in the homozygous state the sheep are sterile. Germ cell development, formation of the follicle and early stages of follicular growth occur, but development beyond the primary stage is impaired. These sheep have small ‘streak’ ovaries but include cystic or semi-solid tumour-like masses made of “granulosa-like, or fibroblast and luteal-like cells” (Galloway et al 2000; Juengel et al 2000). This anomaly is associated with a point mutation in the BMP15 gene, a member of the transforming growth factor β (TGFβ) superfamily that is expressed in the oocytes. A second unrelated family of New Zealand Romney sheep has similar phenotypes due to an independent germline mutation of the same gene (FecX3).

Disorders of the kidney

Mesangiocapillary glomerulonephritis in Finnish Landrace sheep

An immune-based glomerulonephritis occurs in Finnish Landrace sheep (Angus et al 1973, 1974ab). It is associated with a deficiency of complement C3 (Gardiner 1976) which is normally important in retarding the formation of large immune complexes in plasma. Lambs are normal at birth, but within a few weeks they cease to suckle, stand apart from others and have fine muscle tremors. Palpation of the abdomen is painful and reveals kidneys up to six times larger than normal. A recessive mode of inheritance was considered likely (Young et al 1981) but the pattern of inheritance is confused by reports of the disease in out-cross lambs with other breeds (Frelier et al 1990). A case of this disease was diagnosed in a New Zealand-born Finnish Landrace lamb imported as an embryo (AF Julian3, pers. comm.).

Polycystic kidneys

Congenital polycystic kidneys is a well-recognised lethal defect in newborn lambs that has occurred regularly throughout New Zealand for more than 50 years (Hancock 1950b; Hartley and Kater 1964; Anonymous 1991a, 1995). Lambs are born dead with very enlarged kidneys containing a multitude of 1–3 mm-diameter cysts (Figure 5). Two outbreaks involving multiple cases, brought to our notice in 2002, involved a Coopworth flock and a flock where Perendale rams were mated to their cross-bred daughters. Apart from renal cysts, there is profound biliary dysplasia with some consequent cyst formation. An autosomal recessive mode of inheritance has been shown by controlled breeding trials. The distinctive phenotype of this disease is homologous with that of autosomal recessive polycystic kidneys of children (Sessa et al 2001). As a mutated gene is known for this disease in humans (Ward et al 2002), it may be a likely candidate gene for the disease in lambs.

Organs of special sense

Cataract

Bilateral cataracts occurred in a stud New Zealand Romney flock. Controlled breeding experiments showed that the defect was inherited as an autosomal dominant trait (Brooks et al 1982). In affected lambs, partial cataracts were usually noted at 2–4 months of age as discrete focal anterior or posterior opacities which could be central or peripheral in the lens. These opacities grew and tended to fuse with the formation of radial spokes more or less radiating from the centre of the lens. By 10–12 months, the entire lens was diffusely opaque. The histopathology, including ultrastructural changes, has been described by Brooks et al (1982/1983). In two progeny of matings between affected animals, severe cataracts were present at birth. These animals were considered homozygous for the mutant gene.

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Microphthalmia

Microphthalmia is a well-recognized inherited disease in Texel sheep in Europe, with an autosomal recessive mode of inheritance (Hámori 1983). Following importation and ‘breeding up’ of the breed in New Zealand in the 1990s, animals were released from quarantine for further expansion of the breed. Microphthalmia has occurred in a number of Texel flocks and an experimental breeding flock is maintained by AgResearch to study the molecular genetics (AM Crawford4, pers. comm.). Derivatives of each embryonic component of the eye were noted on histological examination (Roe et al 2003). The retina was composed of an irregular mass attached to and continuous with the ciliary apparatus at one pole, and connected to the optic nerve posteriorly by a short stalk. Organisation varied from quite discrete differentiation with inner and outer nuclear layers in normal configuration, to rosettes of similar cells deeper within the mass. Photoreceptor cells had well developed outer segments but little connection with a normal layer of pigment epithelium. Short rows of ganglion cells were sometimes noted within the dysplastic retina more or less in normal spatial relationship with the other layers. These gave rise to myelinated fibres that exited the eye via the optic nerve.

Congenital deafness

An advertisement for deaf sheep for medical research purposes elicited a number of replies (DF Hill5, pers. comm.). Consequently, one deaf ewe gave birth to another deaf lamb when mated back to her sire. A further deaf lamb was sired by the same ram in the flock of origin. ‘Click stimulus’ testing resulted in no electrophysiological response in any brain stem structures of one deaf animal tested. The history suggests an autosomal recessive form of deafness in sheep.

Monogenic predisposition to infectious disease

Genetic susceptibility to infectious disease is usually polygenic and is commented on below. However, there are examples where susceptibility is controlled by a single gene as in scrapie, a neurological disease twice introduced to New Zealand and twice eradicated (Davidson 2002). Scrapie is the prototype of an enigmatic group of diseases known as the transmissible spongiform encephalopathies (Prusiner and Scott 1997). It is regarded as an infectious disease as it is caused by a transmissible agent known as a prion, but there is such a strong genetic basis to the disease that it is appropriate to discuss it here, as part of the continuum of genetic contributions to disease.

Prions are non-traditional infectious agents that do not appear to contain DNA or RNA. They are part of a ‘prion-related protein’ (PrP) that has undergone conformational change, with a greater proportion of β-sheets and fewer α-helices. In the infected animal, they seem to act as a template and induce the formation of similar conformational change in the host’s PrP protein that leads to the formation of further transmissible prions (PrPSc) and cellular disruptions. Susceptibility to scrapie is largely determined by three polymorphic amino acid codons at positions 136 (valine “V” or alanine “A”), 154 (arginine “R” or histidine “H”) and 171 (arginine “R” or glutamine “Q”) in the PrP protein. Each is associated with a single base substitution at the relevant genetic locus (Hunter 2000). In one combination of the amino acid codons at these loci (ARR/ARR), sheep are mostly resistant to scrapie and varying degrees of susceptibility or resistance are associated with other combinations; VRQ/VRQ, VRQ/ARQ, ARQ/ARQ genotypes are the most susceptible. There is now widespread testing of sheep in some European countries and resultant selection for resistant genotypes as a means of controlling scrapie. Limited testing of more than 1,000 sheep of varying breeds showed that the full range of genotypes are present in New Zealand (AM Crawford5, pers. comm.).

Other anatomical malformations

Some monogenic malformations that are reasonably well understood in terms of inheritance have been discussed above. Additionally, there are many other developmental defects occurring regularly in the national flock, but for many of them their aetiology is unknown. Whereas some common defects may be due to teratogenic agents and others may be due to somatic mutations of the embryo, still others can be expected to be due to mutations of homeotic genes (regulatory genes controlling tissue differentiation) as well as those coding for structural or functional proteins. It is also noteworthy that some teratogens depend for their effect on the genotype of the embryo and act on a gene at specific times of development, when a tissue is differentiating under the control of specific regulatory genes (Harding and Copp 1997). Because many of the malformations that are observed in lambs in New Zealand are not described adequately in the literature, they are briefly outlined here, particularly if there is evidence that a defect may be inherited in sheep in other countries.

A major survey recorded approximately 1% of neonatal lambs necropsied were affected with a malformation (Table 1; Hartley and Kater 1964), some of which are described in more detail here.

<table>
<thead>
<tr>
<th>Table 1. Congenital developmental abnormalities of sheep (reprinted from Hartley and Kater 1964, with permission).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Integument:</strong> Congenital skin fragility; hairlessness; hairy fleeces (often associated with congenital chorea); thickened skin (associated with agenesis of the corpus callosum and hippocampus)</td>
</tr>
<tr>
<td><strong>Musculo-skeletal system:</strong> Arthrogryposis; torticollis; kyphosis; amputated limbs; twisted limbs, cleft palate; agnathia; osteogenesis imperfecta; diaphragmatic hernia</td>
</tr>
<tr>
<td><strong>Respiratory system:</strong> Agenesis of the lungs; adenoma of the lung</td>
</tr>
<tr>
<td><strong>Cardiovascular system:</strong> Patent intraventricular septum; patent foramen ovale</td>
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<tr>
<td><strong>Alimentary system:</strong> Imperforate ileocaecal junction; megacolon; imperforate anus; umbilical hernia; cystic bile ductules; cystic pancreas; haemangioma of liver; congenital Southdown photosensitization</td>
</tr>
<tr>
<td><strong>Urogenital system:</strong> Agenesis of one or both kidneys; polycystic kidneys; hydronephrosis; lobulated kidneys; hypospadias; patent urachus; scrotal hernia</td>
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<tr>
<td><strong>Nervous system:</strong> Microencephaly; cerebellar hypoplasia; agenesis of the corpus callosum and hippocampus; spina bifida and Arnold Chiari defect; congenital chorea; hydrocephalus; meningocele (Hartley and Kater 1962)</td>
</tr>
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</table>

Other abnormalities rarely seen include conjoined twins and miniature lambs

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Testicular defects

The term cryptorchidism refers to failure of one, or less commonly both, testicles to descend into the scrotum and is a common, across-species defect, with an incidence of approximately 1%. The defect occurs in many breeds of sheep and is considered inherited, but the mechanism is unclear (Warwick 1931; Bruère 1970). In some horned breeds, it may also be linked to the polled gene (Hámori 1983).

Testicular hypoplasia is associated with cryptorchidism, itself an inherited defect (see above). Unilateral testicular hypoplasia may be part of this syndrome as it occurs in the same flock and may reflect delayed maturity of a late-descending testicle (Bruère 1970). Testicular hypoplasia also accompanied segmental aplasias of the epididymis, but there were insufficient cases to decide whether these were hereditary (Bruère 1970).

Micro-orchidism (testicular weights 30–40 g) was also recorded by Bruère (1970) and in two cases was associated with an XXY genotype (Klinefelter's syndrome) due to non-dysjunction of the X chromosome. Bruère speculated that the incidence of this mosaicism in rams could be 0.2%, similar to that in man. In six such rams, libido was similar to that of normal rams (Bruère and Kilgour 1974).

Intersexes

A single male pseudohermaphrodite has been described in New Zealand (Brüere et al 1969). In contrast, freemartin intersex malformations are acquired genetic aberrations occurring in genetically female lambs born co-twin to a male lamb. In such cases, there has been fusion of the placentas and an exchange of haemopoietic cells between fetuses prior to immunological competence, so that each twin developed with sex chromosome chimerism 54XX/54XY (Kennedy and Miller 1992; Broad et al 1997). More importantly, there are also developmental abnormalities affecting females born co-twin to a male. In these, the gonad is a cord-like thickening in the cranial border of the ovarian ligament but it may show varying differentiation towards a testis. The tubular Müllerian duct-derived structures tend to be hypoplastic and do not connect with an hypoplastic vagina. The Wolffian duct-derived structures give rise to seminal vesicles and sometimes epididymis and spermatic cord. Six cases were described in New Zealand (Brüere and McNab 1968), but they are probably common. Unlike cattle, where twin placental fusion occurs in 90% of twin pregnancies, it occurs in approximately 1–2% of twin sheep pregnancies. Offsetting this, however, is the much greater preponderance of twins in sheep.

Defects in conformation of the jaw

There is considerable variation in the relationship of incisor teeth with the dental pad that comes within the normal range. However, severe undershot jaws (brachygnathia) or less commonly overshot jaws (prognathia), are both considered to have an hereditary basis under the control of several genes (Hancock 1950b; Hámori 1983; Brüere and West 1993). There is considerable variation in expressivity.

Entropion

Entropion of newborn lambs occurs in various breeds of sheep in New Zealand and has an hereditary basis, possibly as a dominant trait (Brüere and West 1993). There may be considerable variation in expression (Hámori 1983). In England, experimental matings with Suffolk rams showed progeny of different rams had varying incidence and expressivity of the disorder and this was also affected by the different breeds with which they were crossed (Taylor and Catchpole 1986).

Agenesis of cerebellar vermis (Dandy-Walker defect)

This defect occurs across species and has multiple aetiologies including several different genetic causes (Murray et al 1985). First described in two lambs in New Zealand (Table 1), it has recently been recorded in two white-face lambs in a flock in the Manawatu region (WD Roe6, pers. comm.). Outbreaks of the Dandy-Walker defect, including hydrocephalus, which occurred in the United Kingdom in four Suffolk flocks, led to the conclusion that it was probably an inherited defect in that breed (Linklater 1994; Pritchard et al 1994). This, and the sporadic nature of the defect, suggests that the defect in lambs (breed(s) not identified) in New Zealand could also have a genetic origin, but this should not be assumed.

Defects of the gastrointestinal tract

There are many defects of the gastrointestinal tract seen from time to time including cleft palate, atresia of the intestine/colon and anus. In medical biology, these defects may have several causes including genetic. No studies are reported that indicate cause in the sporadic cases seen in sheep in New Zealand, but genetic aetiologies are likely.

Amputated limbs

This defect was described as a “well-established lethal disorder” of the Southdown breed (Hancock 1950b).

Short spine in Perendale sheep

A congenital malformation of the spine was recorded in 22 Perendale lambs in a flock of 1,000 ewes over a 5-year period (Clark and Twine 1983). Breeding records were not kept but the epidemiology suggested a recessively-inherited trait. One lamb necropsied had a shortened vertebral column (Figure 6) comprising four cervical, 10 thoracic, four lumbar, three sacral and eight coccygeal vertebrae, compared with the norm of seven, 13, six, four and 16–18, respectively.

Congenital dropsy

Southdown lambs with congenital dropsy were so oedematous that they could only be born by caesarian section. The results of breeding experiments performed were confused, but tended to indicate a dominant mode of inheritance (Hancock 1950b). As the sire himself was normal, a new germ cell mutation may have been responsible.

Chromosomal aberrations

The methodology used in cytogenetics originally allowed characterisation of the chromosomes (karyotypes) of various species. The normal diploid number (2n) in domestic sheep is 54, of which 23 are pairs of acrocentric or telocentric (depending on whether the centromere is at or close to one end, respectively) and three pairs are metacentric (centromere in the middle). Further characterisation is achieved by various staining reactions which
stain chromosomes in characteristic light, dark and fluorescent bands that help to further define the physical chromosome map (Ansari et al 1993; Broad et al 1997). This has been essential for development of the current linkage map of the sheep's genome (Maddox et al 2001).

These cytogenetic techniques also allowed recognition of abnormal karyotypes arising from errors in chromosomal replication in early cleavage divisions of a fertilised egg (Nicholas 1987; Broad et al 1997). The most common aberrations involve the sex chromosomes X and Y, with the formation of unbalanced chromosomes such as XO (monosomy; i.e. lacking a chromosome); XXX (trisomy; i.e. an extra chromosome), XXY, and variations on these. Cases of XXY genotype in rams resulting in micro-orchidism (Klinefelter's syndrome) are discussed above. The other aberrations can be expected to occur in sheep but probably go unrecognised and are relatively unimportant. Similar defects affecting autosomal chromosomes are also likely to occur and would be expected to be a cause of embryonic loss, being mainly incompatible with viability of the embryo or fetus. The prevalence of these expected embryological defects has not been investigated in sheep in New Zealand.

Another type of chromosomal aberration known as a translocation is where one part of a chromosome is interchanged with part of another (Nicholas 1987; Broad et al 1997). These may be balanced or unbalanced, the latter being incompatible with a viable embryo. Of particular interest to New Zealand were the classical studies of Bruère and colleagues, who recognised three balanced centric-fusion (Robertsonian) translocations (M1–3; later changed to t1,2,3) in New Zealand Romneys and their derivative Drysdale breed (Table 2). This type of translocation involves two acrocentric chromosomes fusing at the centromere to form a metacentric type of new chromosome with a consequent reduction in the number of chromosomes. In extensive breeding experiments, various numbers and combinations of these centric-fusion chromosomes were bred into individual progeny with resultant decreasing chromosome numbers of 2n=52, 2n=50, 2n=49 and 2n=48 (Bruère 1974; Bruère and Ellis 1979). The latter were a ewe and ram, homozygous for all three of the translocations. The authors concluded that there was no evidence to suggest that these centric-fusions, in a variety of combinations, affected the overall total reproductive fitness of domestic sheep as unbalanced spermatids failed to mature and take part in fertilisation. More recently, two further similar translocations have been recognised in New Zealand Romney sheep, t4 and t5 (Pearce et al 1994). Two lambs have now been bred homozygous for four centric-fusion chromosomes (t1,2,3,5; 2n=46) (Broad et al 2000). The Robertsonian translocations discovered by Bruère and colleagues are ‘marker’ chromosomes that have been extremely useful in sheep gene-mapping studies (Ansari et al 1993).

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Reference</th>
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<tbody>
<tr>
<td>t1 (6;24)*</td>
<td>Bruère et al 1969</td>
</tr>
<tr>
<td>t2 (9;10)*</td>
<td>Bruère and Mills 1971</td>
</tr>
<tr>
<td>t3 (7;25)</td>
<td>Bruère et al 1972</td>
</tr>
<tr>
<td>t4 (5;6)</td>
<td>Pearce et al 1994</td>
</tr>
<tr>
<td>t5 (9;22)</td>
<td>Pearce et al 1994</td>
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</table>

* Chromosome numbers have been restated from the original reports in line with present international conventions (Ansari et al 1993).

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**Genes and multifactorial diseases**

It is beyond the scope of this paper to discuss multifactorial diseases in detail, but as they are part of the ‘continuum’ of genetic aspects of disease mentioned in the Introduction, general comments are pertinent. Infectious diseases caused by macro- and micro-pathogens are considered multifactorial as the processes of infection and pathogenesis of disease are influenced by the interaction of common alleles of several genetic polymorphisms, each a quantitative trait locus (QTL), as well as environmental factors. In contrast to dysfunctional gene products in monogenic diseases, QTL gene products are variable within the normal functional range.

Pathogenic agents and their hosts have co-evolved by developing sophisticated multiple mechanisms to co-exist in relatively stable host-parasite relationships. However, these have been disturbed through domestication and development of intensive animal husbandry regimes which may favour the agent leading to overt disease. With relatively few exceptions, factors governing host susceptibility are polygenic, and understanding these gene/protein interactions with an infectious agent is an important area of current research because of interest in breeding for greater resistance or tolerance (resilience) to these diseases.

The majority of mechanisms associated with genetic susceptibility/resistance/tolerance to infectious disease reflect gene/protein variations responsible for innate natural mechanisms of immunity, be they associated with barriers of skin and mucous membranes, mediators of the inflammatory reaction and their receptors, naturally occurring carbohydrate or lipopolysaccharide lectins, enzymes or phagocyte-associated membrane proteins, and so on (Hill 2001). In the acquired immune system, genes (proteins) of importance are those of the major histocompatibility complex (MHC), particularly Class II. MHC genes are at closely-linked loci and individual alleles are highly polymorphic. The MHC-glycoprotein complexes which occur or are induced on the surface of cells (particularly macrophages and dendritic cells), bind with different degrees of avidity to antigens expressed on pathogenic organisms. They present these to populations of T- or B-cells which are likely to contain variant members with many more specific receptors capable of binding to specific short antigenic amino acid sequences, so initiating the cellular and/or antibody-mediated immune responses. Degrees of genetic susceptibility to infection may depend on the initial binding of antigen with MHC glycoprotein which may be favoured, or otherwise, by certain allelic polymorphisms for one or more of the MHC-glycoprotein complex gene products. There are a number of known associations between MHC haplotype (the MHC allelic profile inherited from a parent) or specific allele and enhanced resistance to a particular disease, but these are likely to be only one of a number of protein (gene) variations that govern the optimal degree of genetic resistance capable of being expressed naturally. In New Zealand, a genetic test based on MHC typing is offered in Merino flocks with footrot problems (Hickford and Zhou 2003).

With regard to environmental toxins, breeding for enhanced tolerance (resilience) is also possible. The principles are the same but instead of genetic variation in the innate and acquired immune systems, it is variations involving innate mechanisms of clearing, detoxifying and/or excreting the toxin that will be important. Much has been learnt from the discipline of pharmacogenetics which is based on variations in an individual's abil-
ity to metabolise complex endogenous or exogenous molecules including certain drugs (Kalow and Grant 2001). Those authors listed 28 drug-metabolising enzymes, or enzyme systems known to be genetically variable, which could be involved. They include esterases, transferases, reductases, oxidases and those of the cytochrome P450 system. The latter is a complex system involving a large number of peroxisome membrane-bound haemoproteins (enzymes) that have evolved to biotransform chemical substrates of widely divergent structure.

Discussion

The incidence and cost of monogenic disorders to the sheep industry are not known. The only indicators are (1) the 1% incidence of malformations recorded by Hartley and Kater (1964; see Table 1); (2) the common emergence of recessive disorders in new composite breeds, particularly within individual flocks; and (3) the emergence of genetic diseases in flocks derived from a limited number of importations of an exotic breed (founder effect). Whereas some of the abnormalities noted in the survey of 1964 may not have been inherited, it is still likely that monogenic disorders noted at or subsequent to birth may affect up to 1% of lambs, this being of the same order of magnitude as those in human beings. The smaller number of lethal or sub-lethal mutants carried by a sub-population of sheep is likely to be offset by a greater degree of relatedness, and hence a relative greater incidence of an inherited disorder than overall prevalence of heterozygotes might imply. Manifestation of disease or malformation will represent only the ‘tip of the iceberg’ in regard to the prevalence of collective mutant genes present in the population. We conclude that a relatively high proportion of sheep may be heterozygous for one or more of such genes, many of which will be rare and seldom recognised in the homozygous state. This would explain the emergence of a disorder when close- or in-breeding (e.g. sire/daughter matings) occurred, this being a common denominator behind the emergence of a high proportion of the entities described above. This tended to occur in development of composites within a single flock, with ‘breeding up’ an exotic breed from a small number of founders, or when a breeder used rams obtained from the same stud each year without consideration for their degree of relatedness.

Given the low economic value of most individual sheep, control of genetic disorders is often not practical. However, if a problem is recognised, simple procedures such as culling and changing the source of rams may be a practical means of reducing incidence of the disorder. Individual sires may not be known but they may be identified by genotyping polymorphic markers in affected lambs and possible sires, as described for osteogenesis imperfecta (see above), and such tests are commercially available. If the mutant gene is known, then PCR-based mutation testing may be warranted in stud animals. This supposes a single mutation, which is usual because of the breed structure and patterns of breeding in the sheep industry, but it should not always be assumed. Such a service is available and being used for testing Suffolks for the ‘spider lamb’ mutation in New Zealand.

With few exceptions, testing for genetic factors associated with resistance/tolerance to infectious and toxic diseases is in its infancy but this is a major area of current research. Although selection for a number of desirable resistance-associated polymorphisms may one day be a reality, present breeding programmes are mainly more traditional with resistance traits measured by more direct measurements of disease resistance. Those for cattle and sheep in Australia and New Zealand are reviewed by Morris (2000).

Inheritance patterns of developmental defects such as entropion and brachygnathia are often difficult to interpret in Mendelian terms. This is because development of tissues is under the control of a complex array of homeotic genes, that are switched on and off in an orderly manner to regulate complex sequential developmental processes. Minor genetic changes may perturb regulatory functions and result in variable expression of development of a tissue, that obfuscates interpretation in Mendelian terms. There may also be an interplay between certain genotypes and environmental factors.

Many reports on genetic diseases of animals are accompanied by a comment on their potential use as models of analogous human diseases. Of the diseases discussed above, an in-depth study of ceroid-lipofuscinosis in South Hampshire sheep over 18 years has been critical to the present understanding of the analogous diseases in humans. The sheep is an experimental animal par excellence, being low cost, easy to handle under New Zealand conditions, has a genome remarkably similar to the human, and interacts well with human beings because of long-term domestication. In contrast, the vast amount of detailed anatomical, metabolic and molecular information available on inherited disorders and developmental anomalies in humans and laboratory animals is an invaluable research resource to help further define the analogous genetic anomalies that occur in sheep and other domestic animals.

Although the discipline of cytogenetics has been largely replaced by molecular genetics as a means of describing genetic disorders, this branch of genetics played an important role in developing the genetic maps as we know them today (Ansari et al 1993). The banding technique allowed localisation of known genes or other markers to fairly precise locations on individual chromosomes by fluorescent hybridisation techniques. Modern DNA technology extended this by using expressed overlapping DNA sequences generated in yeast (Yac) or bacterial (Bac) libraries to build up longer expressed sequences that could be localised to the many genetic markers already determined for each chromosome. For sheep, there are currently over 1,000 markers and because many genes are closely linked and conserved during evolution, markers or gene localisations derived from another species such as cattle may also be useful in extending the sheep map. The sheep linkage map (Maddox et al 2001) owes much to studies on animals in New Zealand.

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