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Methodological aspects of the mapping of disease resistance loci in livestock

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Part I

Context

Chapter 1

The genetics of resistance to infectious diseases in livestock

This chapter gives an introduction to the genetic improvement of disease resistance to infectious diseases in livestock.

After a definition of the terms associated with resistance [1.2], the different kind of infectious agents are presented [1.3], and lists of diseases showing genetic variation in host resistance are given.

Then, the mechanisms underlying the host immune response are summarised [1.4], and some examples of known genetic variation between and within livestock breeds are given for bacterial, parasitic and viral diseases [1.5].

Chapter I: Genetics of resistance

1.1. Introduction

A major concern for animal breeders is the incidence of infectious diseases in their herds or flocks. Since infectious diseases adversely affect the production as well as the animal welfare, the costs of disease can be very high. These costs are estimated between 10% and 20% of total production values (OIE, 1998). Indeed, in terms of production costs, the labour of the breeders is increased: depending on the progress of the disease, animal breeders have to either apply a pharmaceutical treatment, or call a veterinarian, or possibly cull animals prematurely. The production level of affected animals is reduced in most of the cases, and prevention represents also a cost for animal breeders. Moreover, the action of the infectious agent itself as well as the symptoms of the disease can seriously reduce the animal's welfare. Finally, infectious disease may also affect the "image" of a product. The best example is the recent incidence of the Mad Cow disease on the cattle breeding industry.

Pathogens that are resistant to therapeutic agents (such as e.g. antibiotics, anthelmintics or insecticides) are emerging due to the intensive use of antibiotics in the past (e.g. Clausen *et al.*, 1992; Pillay & Zambon, 1998; Sangster & Gill, 1999; Teuber, 1999). This has led to calls for reduction in the use of antibiotics and other drugs throughout animal medicine. This emphasis is doubly important because of the between-species transfer of such resistance, particularly from livestock pathogens to human pathogens. The reduction in the use of antibiotics is consequently inevitable if one wants to avoid that the phenomenon gets out of control. Furthermore, this reduction is encouraged by the need to develop sustainable production systems and by consumer's increasing demand for products which are free of chemicals.

An alternative to the use of therapeutic agents, is to increase the disease resistance of animals. Nowadays, disease resistance can be achieved by two different ways: either by immuno/chemoprophylaxis (vaccines) or by genetic improvement (selective breeding).

In a number of instances, however, the application of prophylactic measures has been impossible due to either the non-availability of appropriate and safe products or logistic and management problems in extensive animal husbandry conditions. In addition, the results of certain control programmes have been unfavourable due to the inefficiency of the vaccine or drugs used or undesirable side-effects (OIE, 1998). Furthermore, pathogenic variants that are able to overcome previously successful vaccines are getting more frequent (e.g. Witter, 1997).

Genetic improvement of disease resistance

Genetic improvement of disease resistance implies that differences between animals or breeds exist in terms of resistance. Indeed, there are many documented instances of genetic differences between animals in resistance to specific diseases or tolerance to infection. Well-established examples exist in all major domestic species: e.g. Marek's disease and salmonellosis in chicken (Hutt & Scholes, 1941; Cole, 1968; Bumstead & Barrow, 1988), mastitis and trypanosomosis in cattle (Murray & Trail, 1984; Stanik & Vasil, 1986), and nematodiasis or footrot in sheep (Albers *et al.*, 1987; Raadsma *et al.*, 1993).

To improve the disease resistance of animals, one can either select on the general immune response of animals or select on indicator traits of specific diseases. On the one hand, the selection for enhanced immune response is based upon a combination of immune response variables, and is therefore difficult to implement. However, it allows to obtain animals resistant to a wide range of diseases (Boa-Amponsem *et al.*, 1997; Wilkie & Mallard, 1999). On the other hand, the selection on indicator traits is easier to implement but is restricted to resistance to specific diseases. One can for example select sheep on the number of eggs in their faeces to improve their resistance to parasitic diseases (Bishop & Stear, 1997) or select dairy cows on their somatic cell count to improve their resistance to mastitis (Heringstad *et al.*, 2000). In both cases, selective breeding of resistant animals on the basis of phenotypic traits is a slow process due to the long generation intervals of livestock species.

A faster alternative to increase the resistance of animals to infectious diseases is the use of molecular genetics. Indeed, the advent of new marker technologies has paved the way towards the identification of genes responsible for these differences in disease resistance and towards the subsequent selection of animals on the basis of their genotype at the identified loci (MAS, marker assisted selection). The selection for more resistant animals, either classical or marker assisted, has three types of consequences:

(1) For the animals, their welfare should be improved.

(2) For the breeders, it should result in increased profitability: more resistant animals should all in all produce more and costs should be reduced.

(3) When considered in an epidemiological context, there should be an epidemiological added value from selection, as the enhanced resistance ultimately reduces the disease transmission and the degree of challenge faced by animals (Bishop *et al.*, 2002).

However, it has to be mentioned that the selective breeding of resistant animals, marker assisted or not, can also have some drawbacks. Indeed, pathogens that are themselves resistant to the resistance of hosts can appear. Furthermore, the selection for the resistance to a specific pathogen can induce in hosts, susceptibility to other pathogens, as unfavourable associations can exist. Therefore, before any implementation of a selection for increased resistance, marker assisted or not, the sustainability of such a selection has to be carefully assessed (see e.g. Stear *et al.*, 2001).

1.2. Concepts

Two major concepts are used to define the action of hosts on infectious agents: *resistance* and *resilience* (or *tolerance*).

RESISTANCE is the ability of a host to initiate and maintain responses to prevent the establishment of an infectious agent and/or eliminate the load of this agent. This may comprise several components of the host-infectious agent interaction, e.g. the ability to lessen the probability of infection, or the

ability to moderate the lifecycle of the infectious agent by acting on specific developmental stages, or the ability to alter the latency of the infectious agent or to reduce its own infectivity towards other animals, etc (Bisset & Morris, 1996; Woolaston & Baker, 1996; Bishop *et al.*, 2002). Complete (as opposed to partial) resistance should thus result in freedom from clinical signs after challenge (Raadsma *et al.*, 1998a).

Another concept which complements the definition of *resistanc*e is the concept of NATURAL RESISTANCE, which refers to the inherent capacity of an animal to resist disease when exposed to pathogens, without prior exposure or immunisation (Adams & Templeton, 1998). Such a resistance can also be referred to as INNATE RESISTANCE.

RESILIENCE (or TOLERANCE) is the ability to maintain a relatively undepressed production while subjected to infection (Bisset & Morris, 1996), and therefore to withstand the effects (symptoms) of the disease (Bishop *et al.*, 2002). However, resilience is relatively impractical to quantify and measure, because costly and time-consuming measurements of production with and without a disease challenge are necessary (Raadsma *et al.*, 1998a).

1.3. Infectious agents

1.3.1. Introduction

Five major classes of infectious agents are known today to cause animal diseases: bacteria, parasites, viruses, prions and fungi. These infectious agents differ, among others, in terms of size and in terms of mode of transmission and multiplication. As few animals diseases are caused by fungal pathogens, this type of infectious agent will not be tackled.

1.3.2. Bacteria

As their genetic material is not enclosed in a cell nucleus, bacteria are prokaryote organisms, that are generally 0.0001-0.005 mm long; they may

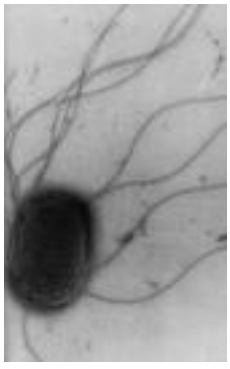
be spherical (coccus), rod-like (bacillus), spiral-shaped (spirillum), or filamentous and often occur in chains or clusters of cells. Most have a rigid cell wall, which may be surrounded by a slimy capsule, and they often have long whip-like flagella for locomotion and short hair-like pili used in a form of sexual reproduction (The Macmillan Encyclopedia, 2000).

Most of the bacteria usually belong to one of two groups, Gram-negative or Gram-positive bacteria, depending on their dyeing ability. Examples of Gram-negative bacteria causing animal diseases are: e.g. *Escherichia coli* causing colibacillosis in calves, piglets and chicks; *Salmonella sp.* (see Box 1.1) causing salmonellosis in sheep (*Salmonella abortusovis*), chicken (*Salmonella pullorum*) or to a broad range of species (*Salmonella typhimurium*, *enteritidis*, …); and *Brucella sp.* causing brucellosis in cattle (*Brucella abortus* causing contagious abortion), human, pig, sheep and goats.

Box 1.1: *Salmonella*

Salmonella are Gram-negative bacilli found ubiquitously in nature. They are able to colonise the gastrointestinal tracts of domesticated and wild mammals, reptiles, birds, and even insects. *Salmonella* are capable of producing a spectrum of clinical illness in both animals and man ranging from asymptomatic carriage to life-threatening sepsis. Over 2000 *Salmonella* serotypes have been described through analysis of the cell wall and flagellar antigens. Individual *Salmonella* serotypes exhibit different patterns of host specificity.

Animals can become infected by contaminated feed or by chronic carriers introduced into the herd. The oral ingestion of the bacteria is followed by the colonisation of the intestine. *Salmonella* are capable of mucosal invasion which results in an acute inflammation of the mucosal cells. *Salmonella* can survive within macrophages and be transported towards other target organs such as spleen, lymphatic nodes, liver or lungs. The nature of the infected organ is depending on the invasion pathway of the pathogen, on its serotype and on the efficiency of its host to provide an appropriate immune response.



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Examples of Gram-positive bacteria responsible for animal diseases are: e.g. *Staphylococcus aureus* and *Streptococcus agalactiae* causing mastitis in cattle. Another independent group of bacteria is the group of actinomycetes which are non-motile filamentous anaerobic bacteria. The causative agents of ruminant diseases such as tuberculosis (most commonly caused by *Mycobacterium bovis*), paratuberculosis (*M. paratuberculosis*), as well as dermatophilosis (*Dermatophilus congolensis*), belong to this group.

Table 1.1: Livestock bacterial diseases with genetic variation in host resistance

Disease	Host	Causative agent	Group[a]
Atrophic rhinitis	pig	*Bordetella bronchioseptica, Pasteurella multocida*	g-
Bordetellosis	chicken, turkey	*Bordetella avium*	g-
Brucellosis	cattle	*Brucella abortus*	g-
Colibacillosis	pig	*Escherichia coli*	g-
Footrot	sheep	*Dichelobacter nodosus*	g-
Fowl typhoid	chicken	*Salmonella gallinarum*	g-
Pasteurellosis	chicken, turkey	*Pasteurella multocida, haemolytica*	g-
Pullorum	chicken	*Salmonella pullorum*	g-
Salmonellosis	cattle, sheep, chicken, pig	*Salmonella dublin, typhimurium, enteritidis, abortusovis, choleraesuis*	g-
Mastitis	cattle, sheep	*Staphylococcus aureus, Streptococcus agalactiae*	g+
Listeriosis	cattle, sheep, goat	*Listeria monocytogenes*	g+
Dermatophilosis	cattle, sheep	*Dermatophilus congolensis*	actino.
Paratuberculosis	cattle, sheep	*Mycobacterium paratuberculosis*	actino.
Tuberculosis	cattle	*Mycobacterium tuberculosis, bovis, avium*	actino.
Cowdriosis	cattle, sheep, goat	*Cowdria ruminantium*	rickett.

[a] g-, g+, actino. and rickett. respectively for Gram-negative, Gram-positive, actinomycetes and rickettsiales.

1.3.3. Parasites

When speaking about parasites causing diseases in livestock animals, one usually refers to diseases caused by helminths, protozoans, scabs or insects.

By far the most frequent helminth infections of livestock are infections of grazing ruminants by nematodes residing within the gastrointestinal tract of the vertebrate host. Because these are the most economically important helminth parasitoses (nematodiasis), they have received the bulk of attention in terms of research efforts (Gasbarre & Miller, 2000).

Nematodes

Nematodes are spindle-shaped colourless worm, also called roundworm, belonging to the phylum Nematoda (about 80000 species). Most nematodes are less than 3 mm long and have a mouth at one end, sometimes containing teeth or stylets, and usually a short muscular pharynx leading to the intestine. The sexes are generally separate. Nematodes live almost everywhere in soil, fresh water, and the sea. Some are parasites of plants or animals; others feed on dead organic matter. Many damage crops or parasitize domestic animals and man (The Macmillan Encyclopedia, 2000).

In sheep, the three most frequent species of gastrointestinal nematodes responsible for nematodiasis are *Haemonchus contortus*, *Ostertagia circumcincta* and *Trichostrongylus colubriformis*, whereas in cattle, the most frequent species is *Ostertagia ostertagi*. All four are members of the *Trichostrongylidae* family (see Box 1.2). Finally, *Ascaridia galli* is the major specie causing nematodiasis in chicken (Table 1.2).

Protozoans, ticks and insects

Another important group of parasites is the group of protozoans, among which one finds the agents responsible for trypanosomosis in cattle and sheep (*Trypanosoma congolense*), East Coast fever (*Theileria parva*) in cattle or coccidiosis in sheep or chicken (*Eimera sp.*). Finally, other important diseases in sheep such as liver fluke, flystrike or scab are respectively caused by a trematode (*Fasciola hepatica*), the blue blowfly, and the sheep scab mite (*Psoroptes ovis*).

A special feature of some of these parasitic diseases is their mode of transmission which is vector-borne: e.g. trypanosomosis is transmitted is by the tsetse fly (genus *Glossina*) (for a review see d'Ieteren *et al.*, 1998), the agent of liver fluke is vectored by a snail, while the agent of the East Coast fever is borne by ticks.

Box 1.2: Life cycle of *Trichostrongylidae*

The life cycle of the *Trichostrongylidae* family has two phases: a pre-parasitic phase followed by a parasitic phase. During the pre-parasitic phase, the larval development happens out of the host. Eggs are first evacuated in the faeces of infected hosts. Contained embryos can develop on pasture into first (L1) larval stage and hatch if temperature and humidity are optimal (22-26°C and 100% humidity). First and second (L2) larval stages feed on faecal and soil bacteria but the third stage (L3) cannot feed because it is enclosed in the L2 cuticle, which is a protective and impermeable sheath. These unsheathed L3's survive by utilising nutrients stored by the actively feeding L1 and L2 stages.

The parasitic phase begins when L3 larval stages are ingested by hosts as they graze on pasture. The L3 stage is the infective stage of trichostongylids. Exsheathment (losing of old cuticle) is the next event in the parasitic phase of this life cycle.

Exsheathment sites are species-specific and are always proximal to the predilection site of each particular trichostrongylid species.

Exsheathment is immediately followed by movement of parasitic L3's to the predilection site where growth and development to adults occurs (L3 to L4, and then to adults). Following sexual reproduction, mature females lay eggs approximately 2-3 weeks after infection (Johnstone *et al.*, 1998).

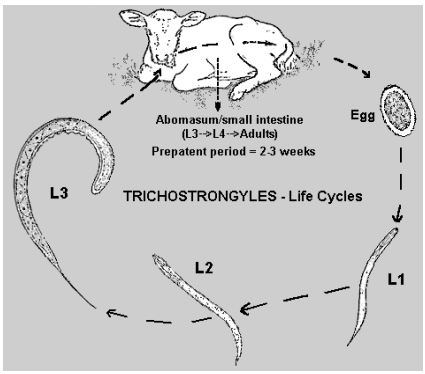

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Table 1.2: Livestock parasitic diseases with genetic variation in host resistance

Disease	Host	Causative agent	Group[a]
Ascaris	chicken	*Ascaridia galli*	nemat.
Nematodiasis	cattle	*Ostertagia ostertagi, Cooperia oncophora*.	nemat.
Nematodiasis	sheep	*Haemonchus contortus*, *Ostertagia circumcincta* and *Trichostrongylus colubriformis*	nemat.
Babesia	cattle	*Babesia bigemina, divergens*	protoz.
Coccidiosis	sheep	*Eimeria sp.*	protoz.
Coccidiosis	chicken	*Eimeria tenella, necatrix, brunetti*	protoz.
East Coast Fever	cattle	*Theileria parva*	protoz.
Theileria	cattle	*Theileria annulata*	protoz.
Trypanosomosis	cattle, sheep	*Trypanosoma congolense, vivax, brucei*	protoz.
Flystrike (myasis)	sheep	Blue blowfly (*Lucilia cuprina*)	insect
Ticks	cattle, sheep	*Boophilus microplus*	insect

[a] protoz., nemat. respectively for protozoans and nematodes

1.3.4. Viruses

Viruses are minute non-cellular particles that can reproduce only in living cells. They consist of a core of nucleic acid (either DNA or RNA), surrounded by a protein coat (capsule) and, in some types, a lipid-containing envelope. Some bacterial viruses have tails (e.g. bacteriophage). They may be spherical, ellipsoid, rod-shaped, or polyhedral, with sizes in the range 20-450 nanometres (nm), although some tailed forms may reach 800 nm. Viruses alternate between an inert virion stage and an infective stage, in which the capsule binds to the host cell and the viral nucleic acid (containing its genes) enters the cell and directs the components of the host cell to assemble replica viruses. These are finally liberated, often with damage to or death of the host cell (The Macmillan Encyclopedia, 2000). Viruses are

classified into families according to three patterns: the type of nucleic acid, the architecture of the capsule and the presence or absence of an envelope.

Table 1.3: Livestock viral diseases with genetic variation in host resistance

Disease	Host	Family of causative agent	Type[a]
African swine fever	pig	*Iridoviridae*	DNA
Aujeski	pig	*α-Herpesviridae*	DNA
Infectious laryngotracheitis	chicken	*Herpesviridae*	DNA
Marek's disease	chicken	*Herpesviridae*	DNA
Avian infectious bronchitis	chicken	*Coronaviridae, genus Coronavirus*	RNA
Avian leucosis	chicken	*Retroviridae*	RNA
Bovine leukosis	cattle	*Retroviridae, sub-family Oncoviridae*	RNA
Maedi-Visna	sheep	*Retroviridae, genus Lentivirus*	RNA
Foot and mouth disease	cattle, pig	*Picornaviridae, genus Aphthovirus*	RNA
Infectious bursal disease	chicken	*Birnaviridae*	RNA
Neonatal and post-weaning diarrhoea	pig	*Coronaviridae, genus Coronavirus*	RNA
Newcastle disease	chicken	*Paramyxoviridae, genus Paramyxovirus*	RNA
Rous sarcoma	chicken	*Retroviridae*	RNA

[a] type of nucleic acid (DNA or RNA)

Many viruses are causative agents of important animal diseases (Table 1.3). For example, viruses from the *Herpesviridae* family are causing e.g. Marek's disease in the chicken, IBR (infectious bovine rhinotracheitis) in calves or Aujeszky's disease in pig. Another important family is the *Retroviridae* family to which the agent of the bovine leukosis and avian leukosis belong. Finally, the causative agent of the foot-and-mouth disease in cattle and pig is a member of the *Picornaviridae* family.

1.3.5. Prions

Prions are agents thought to be responsible for a group of degenerative brain disorders, the transmissible spongiform encephalopathies, that includes BSE in cattle, scrapie in sheep and Creutzfeldt-Jakob disease in humans; the name PRION is a shortened and altered form of *pro*teinaceous *in*fectious particle. Small amounts of prion protein (PrP) occur normally in the brain, but the brains of affected individuals contain large amounts of an abnormal form of prion, resulting from a gene mutation or transmitted by accidental consumption or injection of infected tissue. Highly resistant to heat and radiation, this abnormal prion damages and destroys surrounding brain cells (The Macmillan Encyclopedia, 2000).

1.4. Mechanisms of disease resistance

1.4.1. Introduction

The host usually employs at least three phases of host defence to overcome an infection. The first defence mechanism encountered by the pathogen is the epithelial barrier. The second phase of host defence is non-specific, or innate, immune mechanisms, while the third phase is specific, or acquired, immunity.

Most microorganisms proceed no further than the epithelial barrier. Once past this host-environment interface, many potential pathogens fail to establish a foothold. This may be due to innate or acquired immune responses or, much more commonly, to a range of innate non-immunological factors, such as lack of essential nutrients/substrates, lack of receptors for potential intracellular parasites, incompatible intracellular processing mechanisms, etc. At the third level, potential pathogens may establish, but not cause significant disease (Figure 1.1).

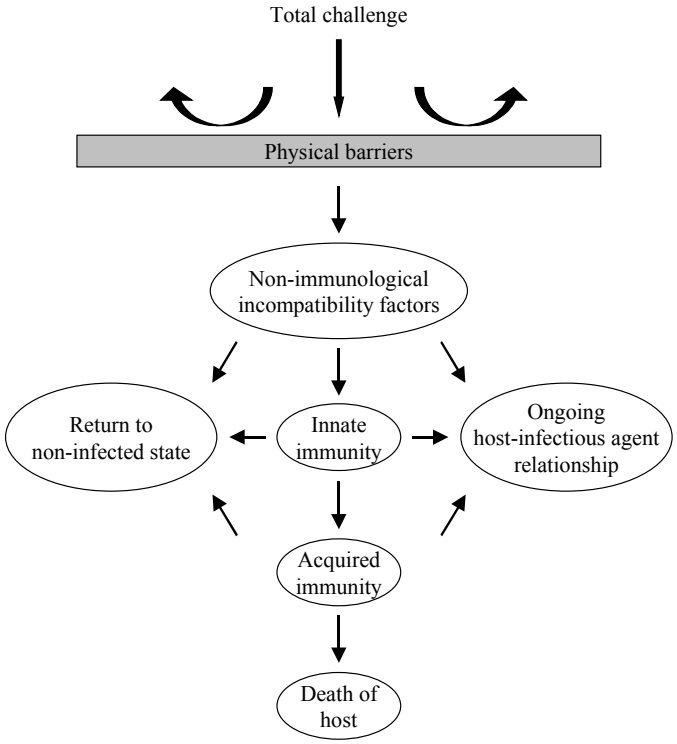

Figure 1.1. Mechanisms of host resistance (adapted from Teale, 1999).

1.4.2. Epithelial barrier

The epithelium provides a physical barrier blocking entry of potential pathogens, but also provides cell surface receptors for the attachment of some pathogens. At this level, one can already observe differences between hosts in terms of skin thickness (which can also play a role for some vector-borne diseases), or in terms of presence or absence of appropriate receptors for binding and penetration of cellular membranes (Adams & Templeton, 1998; Bishop *et al.*, 2002).

1.4.3. Innate immunity

Innate immunity is rapid, non-specific and acts as a second line of defence. It predominantly involves two types of defence: cellular and humoral defences (Mammerickx, 1995; Adams & Templeton, 1998; Bishop *et al.*, 2002).

- the cellular defence first involves neutrophils (leukocytes), then come the microphages and macrophages, finally come the natural killer cells (large granule-filled lymphocytes) acting without the recognition of a specific antigen.
- the humoral factors for the non-specific defence are diverse: e.g. lysozymes, inhibiting factors of enzymes, anti-viral factors such as the interferon (a product liberated by virus-infected cells and acting non-specifically), the complement system, as well as factors such as acute phase proteins that are activated by cytokines.

1.4.4. Acquired immunity

Acquired immunity involves antigen specific responses via lymphocytes, i.e. B cells and T cells, which are produced through unique genetic mechanisms. B cells play a role in humoral defence by secreting soluble substances called antibodies (immunoglobulins) into the body's fluids, or humors, while T cells carry out cellular defence and produce lymphokines which are inter-cellular messengers playing an auxiliary role in the production of antibodies.

In livestock animals, the actions of antibodies is depending on the type of infection: (1) neutralisation of exotoxins from bacteria or killing of bacteria themselves; (2) degradation of the cuticle of nematodes or precipitation at the level of their mouth or anus; and (3) inhibition of the binding and penetration of pathogens into sensitive cells (Mammerickx, 1995; Bishop *et al.*, 2002).

1.4.5. Genetic basis of immunity

Resistance to many common infections is often the result of a combination of innate and acquired systems. Due to the multiplicity and to the complexity

of the mechanisms involved, immunity can be assumed to be under the control of multiple genes.

For example, regarding acquired immunity, the repertoire of T cell and B cell receptors is very large and come from a combination of gene segment re-arrangement, point mutation and gene conversion (for example in genes coding for immunoglobulins or T receptors). Another important genetic component of the immune system is the major histocompatibility complex (MHC), which derives its complexity from the large number of allelic variants at more than 200 loci.

1.5. Sources of genetic variation

1.5.1. Introduction

There is considerable evidence that part of the natural variation in resistance is under genetic control: see reviews by Adams & Templeton (1998) for bacterial diseases, Gasbarre & Miller (2000) and d'Ieteren *et al.* (1998) for parasitic diseases, and by Schat & Davies (2000) for viral diseases. Incorporation of resistant breeds into breeding programs or selection of resistant animals within breeds are available options. An additional option is the exploitation of identified gene polymorphisms known to influence resistance of domestic animals to specific diseases in marker assisted selection programmes.

1.5.2. Differences between breeds

Many studies were carried out to evidence genetic variation between breeds. Most of them involved exposure of animals from different breeds to pathogens under uniform conditions. Some examples are given below.

Bacterial diseases – Chicken lines that are more resistant than others to *Salmonella* infection exist. Bumstead & Barrow (1988) evidenced differences between lines in susceptibility to mortality using inoculation of chicks at 1 day of age with *Salmonella typhimurium*: inbred lines W, 6_1 and

N were highly resistant to challenge, whereas lines C and 15I were highly susceptible. In the same model, but using outbred chicken lines, Guillot *et al.* (1995) also observed differences in *Salmonella enteritidis* (SE) susceptibility. For the same bacteria (SE), differences in contamination of spleen, intestine, ceca, and ovary were observed in adult hens inoculated orally (Protais *et al.*, 1996). Regarding the susceptibility to Dermatophilosis, West African *Bos taurus* cattle such as N'Dama are more resistant than Zebu-type populations such as Ghana Sanga, Gudali and Gobra Zebu (Ambrose *et al.*, 1999).

Parasitic diseases – Some breeds of sheep are more resistant than others to nematode infection. In France, Romanov sheep were more susceptible than Lacaune sheep to infections with *Nematodirus spathiger* and *Ostertagia circumcincta* (Gruner *et al.*, 1986). In the tropics, Red Maasai ewes were more resistant to gastrointestinal nematode infections that Dorper ewes as shown by their significantly lower faecal egg counts (Baker *et al.*, 1999). In Louisiana (USA), the Gulf Coast Native sheep breed was more resistant than the Suffolk sheep breed to *Haemonchus contortus* infection (Bahirathan *et al.*, 1996; Miller *et al.*, 1998). Another well documented example is the trypanotolerance in cattle, particularly in N'Dama cattle and the West African shorthorn (d'Ieteren *et al.*, 1998).

Viral diseases – There are lines of chicken that are more resistant than others to viral infections. Bacon *et al.* (2000) reported the existence of resistant and susceptible lines at the Avian Disease and Oncology Laboratory (Michigan): line 6_3 is resistant to Marek's disease virus, while line 7_2 is resistant to Rous sarcoma virus.

1.5.3. Differences within breeds

Evidence for genetic variation within breeds comes from studies of pedigree populations in which offspring have been assessed for resistance under uniform conditions of exposure and at the same age. The within breed variation is best described by estimates of HERITABILITY (h^2), which is the

proportion of total variance attributable to genetic variance. Some examples of within genetic breed variation are given.

Bacterial diseases – Within the same line or breed, variation in bacterial carrier state between chickens were evidenced by Berthelot *et al.* (1998). These authors showed that the extent of caecal colonisation (after enrichment) in the L2 line was an inheritable trait: heritability was estimated at 0.20 ± 0.12 (mean ± s.e.). In chicken broiler lines, selected divergently for high (H) or low (L) antibody titre to *Escherichia coli*, Yonash *et al*. (1996) estimated the heritability of antibody titre to 0.44 and 0.42 in H and L, respectively.

Parasitic diseases – The nematode burden varies between individual sheep in a flock grazing the same pastures. The distribution of burdens (and faecal egg count, FEC) is overdispersed; that is, a minority of the individuals harbour the majority of the nematodes (Gasbarre & Miller, 2000). As for all diseases, heritability estimates are varying according to the type of indicator trait that is measured (FEC, haematocrit, worm size, …), as well as according to the age of animals and to the type of challenge (natural or artificial) that is performed (Table 1.4).

Table 1.4: Heritability estimates of faecal egg counts in lambs

Authors	Population	Type of challenge	h^2
Albers *et al.* (1987)	Merino (*n*=882)	artificial challenge with 11,000 *Haemonchus contortus* larvae	0.34 ± 0.10
Douch *et al.* (1995)	Romney (*n*=1547)	natural challenge	0.23 ± 0.07
Bouix *et al.* (1998)	Polish long-wool (*n*=659)	natural challenge with *Haemonchus contortus* and *Teladorsagia circumcincta*	0.33 ± 0.05
Stear *et al.* (1997b)[a]	Scottish blackface (*n*=501)	natural challenge with *Ostertagia circumcincta*	0.33 ± 0.14

[a] in this study, worm size was shown to be the most heritable trait (0.62 ± 0.20)

Viral diseases - In lines of chickens selected for nine generations for high or low antibody response, Pinard *et al.* (1993) estimated the heritability of mortality from Marek's disease virus to 0.40.

1.5.4. Gene polymorphisms

Beside variation between breeds and within breeds, another source of genetic variation is explained by a few identified gene polymorphisms known to influence resistance of domestic animals to specific diseases:

- evidences have been shown that the *Ity-NRAMP1* gene (on Chr. 7) and the *Lps-Tlr4* gene (on Chr. 17) are involved in the resistance to *Salmonella* infection in chicken (Leveque *et al.*, 2003; Beaumont *et al.*, 2003).
- *Mx* proteins were identified as being involved in the susceptibility to influenza and other viral diseases in chicken and pigs (Haller *et al.*, 1998).
- The *ARR* allele (136/154/171) of the PrP gene (Prion Protein gene) was identified as conferring resistance to scrapie in sheep (Belt *et al.*, 1995; Hunter, 2000).

Such gene polymorphisms can be used in marker assisted selection programmes. For example in France and United-Kingdom, a selection at the national level on the *ARR* allele is carried out as a mean to eradicate scrapie in sheep populations (and to prevent transmission of BSE).

1.6. Conclusion

From this small bibliographical survey, it appears that breeding animals for increased disease resistance is a realistic and profitable perspective. Although environmental differences account for most of the variation observed, differences between breeds of within herds in terms of disease resistance can be explained by a genetic component. Due to the multiplicity and to the complexity of the mechanisms involved, the genetic control of this resistance is certainly multigenic.

As the variation observed between animals in terms of resistance to infectious diseases is mainly quantitative (e.g. variation in the concentration of immunological factors in blood), rather than dichotomous (animals are neither clearly resistant nor clearly susceptible), mapping methods aimed at locating genes underlying complex traits can be applied to indicator traits of disease resistance. The theory behind those methods is the focus of the following chapter.