Genetic resistance to bacterial diseases of animals

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Summary
Despite traditional disease control measures, losses attributable to infectious diseases continue to impede the livestock industries. An alternative approach to this problem is genetic disease resistance involving both immune and non-immune mechanisms, which is the inherent capacity of a previously unexposed animal to resist disease when challenged by pathogens. Although the nurturing environment influences variability in disease expression, natural resistance has been found to be inheritable and is transmitted from parent to offspring. Thus, an alternative approach to enhancing animal health management systems is to increase the overall level of genetic resistance at herd and population levels by using selective breeding programmes.

The purpose of this review is to bring veterinarians, regulatory officials, industry representatives and animal technicians up to date with the principles and applications of genetic resistance as an adjunct to traditional interventions to control bacterial diseases of livestock. Although genetic resistance to bacterial diseases is often regulated by multiple genes controlling different processes of the host-pathogen interaction, the genetics of natural resistance is being unravelled increasingly by identification and characterisation of candidate genes, microsatellite markers and comparative gene mapping, to develop more practical methods of application.

Keywords
Animals - Bacteria - Disease resistance - Genes - Genetics - Immunity - Naturally-acquired immunity.

Introduction
Natural resistance to bacterial diseases was first observed over one hundred years ago as familial tendencies in resistance or susceptibility to diphtheria in humans (83), but the genetic implications of this observation were not appreciated at the time, and another twenty years passed before the rediscovery of the studies performed by Gregor Mendel. With the renewed appreciation of the genetic principles proposed by Mendel, experimental animals were bred in the 1920s specifically to study natural resistance to a variety of infectious diseases (138, 177). The fact that disease manifestations rarely occur in all members of the population exposed to bacterial pathogens had long been observed in domestic livestock, and studies of resistance to Salmonella Pullorum in poultry and Brucella suis in swine confirmed a major role for genetic control (34, 138). Subsequent research on tuberculosis in twins confirmed the importance of genetics in determining the variability of susceptibility (45, 56, 84), while more recent studies have clearly differentiated the influence of genetics as compared to environment on premature death caused by infectious and non-infectious diseases in human adoptees (157).

These and similar early observations were largely ignored for several reasons. First of all, antibiotics were discovered in the late 1920s, and the usefulness of these new drugs was clearly demonstrated during World War II. Secondly, vaccines were rapidly being developed for several animal diseases. Lastly, the genetics of natural disease resistance seemed unduly complicated, and there was concern that planned breeding programmes to increase natural resistance would be too slow to have an impact and would compromise productivity.

If there is no shortage of evidence for genetic control of disease resistance, then why is genetic resistance not being used more
in modern livestock industries? Perhaps because regulatory officials, owners, producers and other industry managers do not recognise the potential for genetic resistance, not necessarily as the tool to replace traditional methods of disease control, but as another approach to reduce the impact of bacterial pathogens on animal health and to play a role in system-based approaches, such as the pre-harvest pathogen reduction programme. Significant losses caused by bacterial diseases continue to restrict livestock industries despite traditional control measures. Over the last decade, the excessive use of antibiotics has been criticised because of the possible development of antibiotic-resistant zoonotic organisms and the potential dangers of residual antibiotics in food animal products for human consumption. These problems and concerns suggest that other measures for the control of infectious disease should be sought to enhance animal health management programmes. Newer strategies to increase the overall level of resistance at herd and population levels which use selective breeding programmes to enhance natural resistance are expected to contribute significantly in this regard (3, 14, 59, 60, 81, 98, 158, 159, 161, 169, 176, 181).

This review will focus on progress in understanding genetic resistance to bacterial diseases in livestock species over the past two decades: readers are referred to previous in-depth reviews and texts for general and detailed knowledge of the genetics of resistance to bacterial diseases (3, 31, 81, 103, 122, 159, 163, 175, 176). Finally, the purpose of this review is to bring veterinarians, regulatory officials, industry representatives and animal technicians up to date on the principles and applications of genetic resistance as a new, alternative adjunct to traditional interventions in the control of bacterial diseases of livestock. In recent years, much progress on the identification and characterisation of candidate genes, microsatellite markers and comparative gene mapping has been made. Identification of individual candidate genes which control natural resistance and the actions of these genes will greatly expand the knowledge of genetic resistance to bacterial diseases and the possibilities for practical application.

**Background**

The animal genome always influences (and sometimes determines) susceptibility to bacterial diseases, yet because of the huge variety of pathogens and the multitude of complex host defence mechanisms involved, a simple understanding of resistance rarely emerges. Given this series of complex host-pathogen interactions, the fact that control of natural bacterial infection and resulting disease would rarely be exercised by a single gene is obvious, although expression of an allele at one locus can significantly affect disease pathogenesis in individuals. At the herd and population levels, where most livestock scientists are involved, many genes are operational in controlling the spectrum of disease expression.

The only way to understand genetically controlled resistance, and to reduce this understanding to practical application, is to investigate the sequential processes affecting the outcomes of host-pathogen interactions, and to identify in a step-by-step, reductionist manner the pattern of host responses to a pathogen in an attempt to reconstruct and define the genetic regulation of these processes. The fact that the successful co-existence of a bacterial pathogen with its host is the outcome of ancient co-evolutionary relationships and selection pressures must also be borne in mind. These developments have resulted in a stalemate in which the pathogen has evolved to survive within the biological systems of the host, and the host has evolved an immune system which allows survival of infection by the pathogen, thus ultimately supporting the survival of the host-pathogen system (60). The evolutionary development of innate, natural resistance preceded that of the adaptive, specific immunity, but as adaptive immunity evolved, its effector mechanisms combined forces with natural immune functions (122).

Indeed, recent findings suggest that innate immunity is essential to the optimal function of acquired, adaptive immunity, because most of the antigen receptors are not encoded in the germ line (53, 110). An awareness that approximately 10,000 years of domestication of livestock species has imposed artificial selection through management practices and procedures, which – for better or for worse – influence the balance of the host-pathogen systems, is also needed. To understand these relationships, many strategies are used to analyse genetic control of natural resistance with the following minimal requirements:

- variation in host response to the pathogen
- constant environmental conditions
- standardised discriminating challenge dose of the pathogen
- constant virulence of the pathogen
- constant route of challenge, preferably approximating the natural route of exposure
- consistent phenotyping procedures.

Natural disease resistance refers to the inherent capacity of an animal to resist disease when exposed to pathogens, without prior exposure or immunisation (81). Although some of the observed variation in natural resistance is related to environmental factors, a significant component of variation in natural disease resistance appears to be heritable and, therefore, to be passed stably from parent to offspring. Processes by which an animal might resist disease include both immune and non-immune mechanisms, as supported by important previous findings in the 1960s. These earlier discoveries of the role of genetics in susceptibility to mycobacterial infections were suggested by epidemiological studies (112), substantiated by twin studies (45, 84) and further documented by resistance to mycobacteria in strains
of inbred rabbits (99). Almost simultaneously with these studies, the cellular basis for specific immune responsiveness to mycobacteria was defined (101, 102). The combination of these findings then formed the basis for two major concepts. Firstly, the host response to mycobacterial infection has two phases: the innate stage of resistance to the establishment of infection, and the later development of specific, acquired cellular and humoral immunity, which results in either clearance of infection or disease progression. Secondly, host resistance mechanisms are under genetic control during both phases, but each phase is governed by different groups of genes.

These concepts established the foundations for the creation of recombinant inbred and congenic strains of mice to explore the genetics of natural resistance and to develop strategies for pursuing the molecular genetics of natural resistance in specific host-pathogen systems, particularly those of intracellular bacterial pathogens. Several approaches were successful, for example, positional cloning, candidate gene analysis, gene replacement knockout mice and other procedures. While questions and concerns regarding the traditional health management procedures are being raised, remarkable progress is being made in identifying specific genes which contribute to natural disease resistance. The creation of gene maps for domestic animals by identifying the chromosomal location of a large number of genes is also making significant progress (6, 18, 58, 182). In time, any gene involved in disease resistance should be genetically linked to a useful marker gene. Further advances in genetic technology should provide practical methods for using knowledge of disease resistance genes to improve the overall health of livestock. Together with current approaches to health management, genetic manipulation to increase natural disease resistance is predicted to contribute significantly to improvements in the health and productivity of domestic animals.

General mechanisms of genetic resistance

From the innate or natural non-specific immunity perspective, resistance to bacterial pathogens encompasses the following:

- resistance due to impenetrable barriers
- absence of appropriate receptors for binding and penetration of cellular membranes
- failure to survive after entering the host
- inability to replicate in the host
- killing and elimination by host defence mechanisms, especially by phagocytes.

These factors, although termed 'non-specific', are in fact dependent upon precise, genetically determined molecular interactions. Resistance to bacterial pathogens from the point of view of the 'acquired' or adaptive specific immunity involves the following:

- lymphocyte-mediated host responses, including cytotoxic T cells, helper/inducer T cells, delayed-hypersensitivity T cells and B cells
- non-lymphoid cells, natural killer (NK) cells and particularly macrophage- and granulocyte-mediated phagocytosis and inflammation
- humoral-mediated responses, including antibodies and complement
- production and regulation cytokines (175).

Importantly, the processes for both innate and adaptive immunity are genetically determined and controlled: innate immunity is controlled non-specifically or innate, immune mechanisms (103, 111). Cells involved in non-specific immunity include mononuclear-phagocytic system. With higher levels of macrophage activity, these low-response mice were also more resistant to infections with the intracellular pathogens B. suis, Mycobacterium bovis, Salmonella Typhimurium, Yersinia pestis, Listeria monocytogenes and others (16, 37).

The host usually employs at least three phases of host defence to overcome bacterial infections. The first defence mechanism encountered by the pathogen is the epithelial barrier. The epithelium provides a physical barrier blocking entry of potential pathogens, but also provides cell surface receptors for attachment of some pathogens, which is the first step in the establishment of many bacterial infections (86, 111, 175). Inappropriate conformation or absence of the receptor will prevent colonisation of the host. The second phase of host defence is non-specific, or innate, immune mechanisms (103, 111). Cells involved in non-specific immunity include neutrophils, macrophages and NK cells which lyse infected cells (141). Humoral mediators of non-specific host defences include the complement system (61) and the interferon...
system (80). The third phase of host defence is specific, or adaptive, immunity (111, 175). Stimulation of adaptive immune mechanisms is the goal of vaccination programmes, but these mechanisms may also be significant in speeding recovery and clearing the infection. However, in a primary infectious process, the development of this phase is delayed as it requires activation, proliferation, and differentiation of antigen-specific T and B lymphocytes (103). Several classes of T lymphocyte activity have been defined, including helper/inducer activity, suppressor activity, cytotoxic activity and activities inducing delayed hypersensitivity. Humoral mediators of immunity include the immunoglobulins secreted by plasma cells and lymphokines secreted by certain classes of activated T lymphocytes.

Host genes involved in resistance to bacterial pathogens

Interestingly, the best defined host-pathogen systems from the perspectives of effector mechanism and genetics are facultative or obligate intracellular bacterial pathogens (some of which are capable of extracellular replication). This may suggest that an evolutionary pathway was followed independently by a broad spectrum of bacteria, with selection in favour of organisms able to establish and sustain themselves inside host cells which had phagocytic and microbicidal function. All processes of host defence are subject to genetic control. Most of the natural defence mechanisms are controlled, at the molecular level, by proteins. Lipids and carbohydrates which contribute to host defence mechanisms are synthesised by enzymes. All proteins, whether enzymatic or structural, are synthesised from messenger RNA, which in turn is synthesised from the gene coding for the protein. Variant forms of a gene are called alleles, and alleles may give rise to different structural forms of the protein. Alterations in protein structure may affect the ability of the protein to function. If the protein is part of the host defence mechanism, then a decrease in its functional capacity may lower resistance to one or more infectious agents.

Theoretically, a defect in any single gene which controls the structure or regulates the expression of any host defence mechanism could modify the level of natural host resistance to a specific infectious disease, or to infectious diseases in general. In reality, many genetic defects would be so overwhelmingly disadvantageous that they would be rapidly selected out of the population, although selection pressure has diminished with the introduction of antibiotics and management procedures. There remain, however, other genes which strongly influence the level of host resistance in an individual, and several of these have already been identified. Most genes controlling specific processes of natural disease resistance have been identified using inbred strains of mice (Table I) (103, 105), due to the ease of creating mice for genetic experiments. Most genes identified in mice will probably be functional in domestic animals as well. Whether variation in any individual gene accounts for variations in disease resistance in domestic animals is known for only a few genes (Table II).

<table>
<thead>
<tr>
<th>Immune mechanism</th>
<th>Pathogen</th>
<th>Gene</th>
<th>Functional role</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbicidal</td>
<td>Mycobacterium</td>
<td>Nramp1</td>
<td>Endocytic membrane protein, effector transport in phagosome?</td>
<td>(63, 64, 70, 106, 171, 172)</td>
</tr>
<tr>
<td></td>
<td>Salmonella Typhimurium</td>
<td>[h2/Lsh/Bcg]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mycobacterium paratuberculosis</td>
<td>Nramp1</td>
<td>Endocytic membrane protein, effector transport in phagosome?</td>
<td>(57)</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium</td>
<td>NOS2</td>
<td>Inducible macrophage nitric oxide synthase</td>
<td>(100)</td>
</tr>
<tr>
<td></td>
<td>Gram-negative bacteria, Salmonella</td>
<td>Cyp</td>
<td>Panath cell defensins</td>
<td>(147)</td>
</tr>
<tr>
<td></td>
<td>Salmonella Typhimurium</td>
<td>Lps</td>
<td>Macrophage effector function</td>
<td>(118, 120)</td>
</tr>
<tr>
<td></td>
<td>Legionella pneumophila</td>
<td>Lgt1, Lps</td>
<td>Early inflammatory macrophages?</td>
<td>(10, 11, 184, 185)</td>
</tr>
<tr>
<td></td>
<td>Francisella tularensis</td>
<td>—</td>
<td>Macrophage function</td>
<td>(9)</td>
</tr>
<tr>
<td></td>
<td>Brucella abortus</td>
<td>—</td>
<td>Macrophage clearance &amp; MHC?</td>
<td>(38, 75)</td>
</tr>
<tr>
<td>T cell</td>
<td>Rickettsia tsutsugamochi</td>
<td>Ric</td>
<td>T-cell mediated elimination</td>
<td>(68)</td>
</tr>
<tr>
<td>Antibody</td>
<td>Salmonella Typhimurium</td>
<td>xid</td>
<td>B-cell controlled anti-polysaccharide immunoglobulins</td>
<td>(117)</td>
</tr>
<tr>
<td>Antigen processing, presentation</td>
<td>Mycobacterium, Salmonella</td>
<td>Nramp1</td>
<td>Enhanced macrophage antigen presentation</td>
<td>(20, 30, 92)</td>
</tr>
<tr>
<td></td>
<td>[h2/Lsh/Bcg]</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Listeria monocytogenes</td>
<td>Lsr1</td>
<td>Macrophage activation</td>
<td>(61, 154)</td>
</tr>
</tbody>
</table>

| Table I | Genetic resistance to bacterial pathogens in mice |

MHC: major histocompatibility complex
CD8+: cluster of differentiation antigen 8+
Nramp: natural resistance-associated macrophage protein
NOS2: nitric oxide synthase-2
Porcine K88\(^+\) receptor

The first defence barrier, the epithelium, provides receptor sites for attachment of many pathogens. Cell surface receptors for viral or bacterial attachment are a heterogeneous group of cell surface molecules, and some have been carefully defined and studied. Genetically determined variation in the structure of a cellular receptor would cause some individuals to be resistant to colonisation by a specific pathogen. The classic example of such genetic variability is the resistance of certain neonatal piglets to the K88\(^+\) strain of *Escherichia coli* (which causes colibacillosis) as a result of non-expression of an appropriate receptor for attachment of this organism to intestinal epithelium (146).

**Natural resistance-associated macrophage protein 1 (Bcg/lty/Lsh)**

Variations in the functional capacity of phagocytes, affect disease susceptibility (17, 64, 111, 141), an example of which is the expression of the natural resistance-associated macrophage protein-1 (*Nramp1*) gene. Studies over the last two decades have led to the identification of a gene, *Bcg/*lty/Lsh, on mouse chromosome 1 which alters the early stages of resistance to diverse and antigenically unrelated facultative and obligate intracellular pathogens, including *M. bovis* (bacillus Bilé-Calmette-Guérin) (Bcg), *M. intracellularare*, *S. Typhimurium* (Ity) and *L. donovani* (Lsh) (23, 47, 66, 127, 155), although these murine models do not usually discriminate between infection and disease. Resistance to one disease in animals was previously thought to be associated with late phosphoglycoprotein of *Nramp1* (106). Recent findings provide evidence that the membrane phosphoglycoprotein of *Nramp1* is associated with late endocytic (late endosome/lysosome) compartments (70) and is the expression of the natural resistance-associated macrophage protein-1 gene (171) and shown to encode an integral phosphoglycoprotein membrane protein, with 12 transmembrane domains, which is expressed only in the macrophages of reticuloendothelial organs (19, 82, 105). Other sequence motifs of *Nramp1* include predicted extracellular glycosylated loops, sites for phosphorylation by protein kinases, a proline-rich src homology 3 (SH3)-binding domain and a 'binding-protein-dependent transport system inner-membrane component signature' motif in one of the intracellular loops. Gene disruption (knockout) experiments have confirmed that *Nramp1* and *Ity/lty/Bcg* are the same gene (172, 173), and that this gene acts early to regulate the pathway priming/activation for anti-microbial activity, particularly generation of NO (nitric oxide) following tumour necrosis factor α (TNF-α)-dependent, sustained expression of Nos2 encoding inducible nitric oxide synthase (NOS) (7, 9, 92, 135, 137). *Nramp1* has many pleiotropic effects influencing phenotypic expression, which include the following:

- inhibition of bacterial growth
- granuloma formation
- production of reactive oxygen and nitrogen products
- antigen processing and MHC class II molecule expression
- enhanced phago-lysosomal fusion
- regulation of production and release of KC chemokine and TNF-α and interleukin-1β (IL-1β) cytokines (19, 43, 48, 92).

Susceptibility to *M. bovis* BCG infection in inbred strains of mice is caused by a recessive deficiency allele associated with a single glycine to aspartic acid substitution at position 169 of the putative transmembrane region of the protein (106). Recent findings provide evidence that the membrane phosphoglycoprotein of *Nramp1* is associated with late endocytic (late endosome/lysosome) compartments (70) and α- and β-tubulins (89), is constitutively expressed in professional phagocytes of the myeloid line (44, 186) and is also inducible by interferon-γ (IFN-γ) followed by lipopolysaccharide (LPS) (42, 62), while the *Nramp1* form of the protein is degraded and is not expressed (174).

### Table II

<table>
<thead>
<tr>
<th>Animal species</th>
<th>Disease</th>
<th>Phenotype</th>
<th>Pathogen</th>
<th>Gene</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>Brucellosis</td>
<td>In vivo</td>
<td><em>Brucella abortus</em></td>
<td><em>Nramp1</em></td>
<td>(54)</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td>In vivo</td>
<td><em>Mycobacterium bovis</em></td>
<td>–</td>
<td>(124)</td>
</tr>
<tr>
<td></td>
<td>Salmonellosis</td>
<td>In vivo</td>
<td><em>Salmonella Dublin</em></td>
<td><em>Nramp1</em></td>
<td>(132)</td>
</tr>
<tr>
<td>Swine</td>
<td>Calibacillosis</td>
<td>In vivo</td>
<td><em>Escherichia coli K88</em></td>
<td>–</td>
<td>(146)</td>
</tr>
<tr>
<td></td>
<td>Brucellosis</td>
<td>In vivo</td>
<td><em>Brucella suis</em></td>
<td>–</td>
<td>(32, 33, 34, 35)</td>
</tr>
<tr>
<td>Chicken</td>
<td>Pullorum</td>
<td>In vivo</td>
<td><em>Salmonella Pullorum</em></td>
<td><em>Sal</em></td>
<td>(26, 138)</td>
</tr>
<tr>
<td></td>
<td>Fowl typhoid</td>
<td>In vivo</td>
<td><em>Salmonella Gallinarum</em></td>
<td><em>Sal</em></td>
<td>(26)</td>
</tr>
<tr>
<td></td>
<td>Salmonellosis</td>
<td>In vivo</td>
<td><em>Salmonella Enteritidis</em></td>
<td><em>Sal</em></td>
<td>(26)</td>
</tr>
<tr>
<td></td>
<td>Salmonellosis</td>
<td>In vivo</td>
<td><em>Salmonella Typhimurium</em></td>
<td><em>Sal</em></td>
<td>(25)</td>
</tr>
<tr>
<td>Sheep</td>
<td>Footrot</td>
<td>In vivo</td>
<td><em>Dichelobacter nodosus</em></td>
<td>–</td>
<td>(51, 121, 133, 156, 179)</td>
</tr>
</tbody>
</table>

?: preliminary evidence
Subsequently, Nramp1 has been shown to belong to a family of related proteins, including Nramp2 (69), which is expressed in many tissues in mice and humans and has also been found recently in divergent cation transporter (DCT1) (71), which is expressed primarily in duodenum and kidney of mice. Several polymorphisms of the human homologue (41, 87), Nramp1, have been described (21, 97), but no association has been found with tuberculosis (115), leprosy (93, 148) or leishmaniosis (178), although an association with rheumatoid arthritis has been demonstrated (149). Moreover, controversy exists regarding the role played by Nramp1 in natural resistance to tuberculosis, because in other studies which compared antimicrobial resistance to Mycobacterium tuberculosis or BCG, M. tuberculosis-infected Nramp1 mice actually had reduced survival times when compared to congenic Nramp- mice (107, 109, 116); however, Nramp1 mice were able to stabilise BCG pulmonary infections (108). Extensive controversy continues over the mechanism of action of the Nramp1 gene as a possible nitrate (or other substance) transporter, SH3-binding domain-associated cell signal transducer, cytoskeletal attachment mechanism or tyrosine kinase phosphorylation associated with macrophage activation (19, 21, 43, 88, 171).

In domestic animals, homologues for Nramp1 have been identified, sequenced and/or mapped in cattle (54), chickens (78, 79), swine (168) and sheep (126, 125), although at present, associations with disease resistance have been documented only in cattle (54). Other homologues for Nramp1 have been identified in Drosophila melanogaster (fly), Caenorhabditis elegans (nematode), Oryza sativa (rice), Saccharomyces cerevisiae (yeast) and M. leprae (bacteria), thus indicating conservation of an ancient origin for the NRAMP family associated with a common membrane structure and possible transport activity (43).

**Major histocompatibility complex**

The third phase of host defence on the primary encounter with a pathogen is the specific immunological response. The MHC is an important genetic complex controlling immune responses (12, 77, 98), and consists of a series of closely linked genes coding for at least three classes of proteins in all mammalian species studied. There are multiple copies of the class I genes, which encode glycoproteins that associate non-covalently with a second protein, β2-microglobulin, on the surface of all nucleated somatic cells. Cytotoxic T lymphocytes use these class I MHC molecules in recognising infected cells (144). Thus, the antigen and the class I MHC molecule together constitute an antigenic complex recognised by the cytotoxic T lymphocyte. There are also multiple copies of the class II MHC genes. These consist of genes for the α-chain and the β-chain of class II glycoproteins. The two chains associate non-covalently on the surface of B lymphocytes and cells of the mononuclear-phagocytic system. T lymphocytes of the helper/inducer and delayed-hypersensitivity classes use class II molecules for recognition of foreign antigens (144). For these T lymphocytes, both the foreign antigen and the class II MHC molecule make up the antigenic complex required for T lymphocyte recognition. The recent characterisation of human MHC peptide-binding motifs and the identification of peptides from pathogens binding these MHC molecules and eliciting protective immune responses provide novel approaches to optimise vaccines (4). Additionally, peptide-binding motif analysis offers new rationales for understanding hyporesponsiveness in certain individuals (152).

An important characteristic of the class I and class II MHC genes is their high degree of polymorphism. Polymorphism indicates that a gene exists in more than one allele in a population. For most genes, only one to a few alleles exist in a population. By contrast, over fifty alleles have been serologically identified for each of two class I genes in both man and mice (77). Additional alleles are being defined by improved serological techniques and by other, more precise, techniques. A similar degree of polymorphism exists for class II genes (77). The result of the multiplicity of MHC genes is that each individual has a number of class I and class II molecules with which its T cells recognise foreign antigens. The consequence of the high degree of polymorphism for each gene is that the set of MHC class I and class II genes is unique to each individual; over 100 million combinations are possible. The ability of an individual to respond to certain antigens is under genetic control of the MHC. This was shown most clearly in mice using simple synthetic antigens (12). Most of these effects are determined by the class II genes, and presumably relate to the ability of the class II molecules available to the individual to form an immunogenic complex with the foreign antigen, and thereby to activate helper/inducer T lymphocytes to initiate an immune response (144).

In humans, genetic associations between the MHC and susceptibility to certain infectious diseases have been identified (129). A striking example is that of leprosy. Two polar forms of leprosy exist: lepromatous and tuberculoid. Lepromatous leprosy is associated with a minimal T-cell response, disseminated lesions and a poor prognosis. Tuberculoid leprosy is associated with a strong T-cell response, multiple confined granulomata and a good prognosis. The tendency to develop lepromatous or tuberculoid leprosy is inherited and is associated with certain MHC class I and class II alleles (170).

In mice, some immune response defects are associated with the gene complex for the immunoglobulin heavy chains (IgH) (13). The IgH complex consists of gene segments for the variable region and for the constant region of the antibody molecule. The variable region of the antibody binds to specific antigens, and the constant region carries out other biological functions, such as complement fixation. Presumably, immune response defects are caused by an absence of variable region genes capable of forming antibodies which effectively interact with the antigen. In some human diseases, association with
certain allelic variants, or allotypes, of immunoglobulin heavy chains has been reported (65). The genes encoding the T-cell antigen receptor have recently been identified and mapped (90).

Hereditary immunodeficiency syndromes are clear examples of genetic alteration of susceptibility to infectious diseases. In humans, horses and mice, inherited forms of severe combined immune deficiency, in which the individual lacks functional T and B lymphocytes, have been defined (123). Specific defects in T- or B-cell function have also been identified in humans and mice. In mice, the xid gene, on the X chromosome, controls certain aspects of B-cell maturation, and in humans, X-linked defects in B-cell function have also been characterised (55, 150). In mice and rats, the nude gene controls thymic development and, consequently, T-cell immune functions (151).

Genetic resistance in domestic animals

As stated earlier, resistance may be associated with a single gene but usually is associated with several. Studies which demonstrate genetic control of natural disease resistance in domestic animals are highly dependent on methodology. Important methodological parameters include the nature of the exposure to the pathogen, the method used to assess resistance and the type of genetic analysis used. Exposure to a pathogen may be by natural (field) exposure or by an experimentally controlled and discriminating inoculum. The advantages of the latter include the certainty that all animals in the study are exposed and that the exposure is uniform for all animals. For these studies, the dose of the pathogen used for challenge is chosen to maximise differences between resistant and susceptible animals, while approximating a natural exposure. Resistance and susceptibility may be graded according to the severity of disease induced in the animal or according to isolation of the pathogen from lesions, or both. Examples of studies of genetic resistance to specific bacterial diseases in which some of the above criteria have been used are illustrated in Table II. If isolation is a criterion, relative differences in susceptibility may be assigned qualitatively (i.e., any isolation of the pathogen implies susceptibility) or quantitatively (i.e., isolation of a minimum number of organisms implies susceptibility; this method will include a class of animals with intermediate susceptibility). If severity of disease manifestations is used as the criterion for assessing relative susceptibility, additional genetic mechanisms are likely to be measured. This arises from the fact that three classes of animals are involved in these experiments, as follows:

- infected and diseased
- infected and disease-free
- uninfected and disease-free.

Thus, one would be measuring genes which allow, or prevent, infection, in addition to those genes which allow, or prevent, disease manifestations in infected animals.

Different types of genetic analyses are also possible. All types of analysis assume that animals can be identified as resistant or susceptible. (Indeterminate types are also included, but cannot be analysed.) The examples given below were selected to represent the various methodologies and approaches which have been used to identify genetic control of disease resistance and susceptibility. Two examples have been noted above: brucellosis and K88+ colibacillosis in pigs. The study of susceptibility to B. suis in pigs represents the ultimate goal of most studies of natural disease resistance: the ability to breed selectively to increase herd resistance to disease (34). Here, the mechanisms by which some pigs were more resistant were not determined, and genes controlling resistance were not identified. By contrast, the mechanism for resistance to K88+ colibacillosis is well characterised and relates to genetic variability in the expression, or non-expression, of a receptor for K88+ E. coli on the intestinal epithelium of neonatal pigs (146).

Bovine brucellosis

Studies to determine whether resistance to B. abortus is heritable and to identify genes controlling resistance to brucellosis in cattle began in the late 1970s (165). Unvaccinated and previously unexposed sexually mature bulls or heifers at mid-term gestation (150 ± 30 days) were challenged with a standardised, discriminating challenge inoculum of B. abortus S2308, then scored for the outcome of parturition, and quantitative cultures were collected from tissues and secretions three to five months later. Resistant cows did not abort, and no Brucella organisms were cultured from the cow or calf. Resistant bulls similarly gave negative culture results for Brucella in semen and at slaughter. Immune correlates with respect to macrophage function, bovine leucocyte antigen (BoLA) alleles and immunoglobulin allotypes associated with natural resistance to Brucella were determined retrospectively (Table III) and breeding experiments were begun to identify the genes which control differential immune responses.

The expression of anti-LPS immunoglobulin G2a (IgG2a) allotypes in the two groups of heterozygous cattle was significantly different from the IgG2a A1 allotype predominating (P < 0.05) in B. abortus-susceptible cattle (2, 52). However, previous studies have disputed the role that antibodies play, if any, in natural resistance to B. abortus in cattle (72, 167). No association of resistance with BoLA class I alleles was demonstrated; however, mammary macrophages from resistant cows, and monocyte-derived macrophages from resistant cows and bulls, were significantly more active than macrophages from susceptible cows and bulls in terms of:

a) respiratory burst in response to opsonised B. abortus (74)
b) ability to control replication of B. abortus (36, 130, 132).
The differential response between macrophages from resistant and susceptible cattle was similar to the differences observed in mice strains resistant and susceptible to *M. bovis* BCG, *L. donovani*, *M. paratuberculosis* and *S. Typhimurium* (48, 134, 135). Furthermore, macrophages from cattle which were selected for *in vivo* resistance to *B. abortus* restricted the intracellular replication of *B. abortus, M. bovis* BCG and *Salmonella* Dublin significantly better than macrophages from cattle which were susceptible to *B. abortus* challenge (132). By assaying the brucellacidal capacity of macrophages before challenge, resistance or susceptibility to *B. abortus* cattle which were susceptible to *B. abortus* were challenged with *B. abortus*. In classical breeding studies, natural resistance to *Brucella* was demonstrated to be increased dramatically by simple mass selection in one generation of selective breeding (164). The frequency of natural resistance to brucellosis in challenging unvaccinated cattle was 20% (30/150). Mating a naturally resistant bull with naturally resistant cows increased the frequency of natural resistance in their progeny to 58.6%

**Table III**

Characteristics of macrophages, T cells and antibody responses in cattle naturally resistant or susceptible to *Brucella abortus*

<table>
<thead>
<tr>
<th>Biological activity</th>
<th>Activity in resistant cattle</th>
<th>Activity in susceptible cattle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercellular growth of <em>Brucella abortus, Mycobacterium bovis, Salmonella Dublin</em></td>
<td>Restrictive</td>
<td>Permissive</td>
</tr>
<tr>
<td>Phago-lysosomal fusion</td>
<td>Increased</td>
<td>Reduced</td>
</tr>
<tr>
<td>Production of reactive oxygen intermediates</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>LPS + IFN-γ induced nitric oxide production</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><em>B. abortus</em> binding to macrophages</td>
<td>RGDS tetrapeptide, <em>B. abortus</em> LPS and Mab anti-LFA-1 inhibit 90% binding</td>
<td>Minimal inhibition</td>
</tr>
<tr>
<td>Antibody response to <em>B. abortus</em> LPS</td>
<td>Minimal, short duration</td>
<td>Massive, long duration</td>
</tr>
<tr>
<td>IgG&lt;sub&gt;2a&lt;/sub&gt; A1 and A2 allotypic response to <em>B. abortus</em> LPS at 6 wks</td>
<td>Only <em>B. abortus</em> stimulates response</td>
<td>95% A1</td>
</tr>
<tr>
<td>Oligoclonal T-cell response</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- *LPS* : lipopolysaccharide
- *IFN-γ* : interferon-γ
- *IgG<sub>2a</sub>* : immunoglobulin G<sub>2a</sub>
- *RGDS* : tetrapeptide of asparagine-glycine-glutamine-serine
- *LFA* : CD11a/CD18, lymphocyte function-associated antigen

Consequently, the bovine homologue to the murine *Nrampl* gene (designated bovine *NRAMP1*) was cloned and the complementary DNA (cDNA) sequenced (54). The DNA sequences of the murine *Nrampl*, human *NRAMP1* and bovine *NRAMP1* have remarkable conservation of DNA sequence and predicted amino acid sequences. The predicted amino acid homology for murine *Nrampl* and bovine *NRAMP1* is 87%, and that between human *NRAMP1* and bovine *NRAMP1* is 89% (41, 54). All three of the predicted *Nrampl* proteins are polytopic membrane proteins which are expressed predominantly in the macrophages or reticuloendothelial cells. Common features in all three species are a conserved protein of approximately 60 kiloDaltons (kDa) with an N terminus SH3 motif, four phosphokinase C (PKC) phosphorylation sites and a 'binding protein-dependent transport system inner-membrane component signature', all predicted to be expressed on the inner membrane (19, 54, 171). The hypothesis was further supported by the conservation of the Bcg/Lsh/Ity-bovine *Nrampl* amino acid sequences and the conservation of the linkage group on mouse chromosome 1 (19, 104, 128, 178) and bovine chromosome 2 (6, 18, 58, 183). Northern blotting confirmed that bovine *Nrampl* was primarily expressed in macrophages of the reticuloendothelial system (RES). As discussed previously, there is a point mutation at position 169 of the murine *Nrampl* which distinguishes the resistant (Gly-169) and susceptible (Asp-169) alleles of the murine Bcg gene. Neither cattle nor any other species (including humans, rats, chickens, bovine, bison, water buffalo, sheep, red deer and moose) sequenced for the *Nrampl* homologue by the authors or other researchers have the coding region mutation at position 169. Single-stranded conformational analysis (ssCA) (142) disclosing a highly significant association of a single-stranded conformation polymorphism located in the 3' untranslated (UT) portion of bovine *NRAMP1* with cattle naturally resistant to brucellosis (Table IV). The only difference found in *NRAMP1* sequences from cattle, bison, water buffalo, goats, sheep, red deer, white-tailed deer, fallow deer and moose is an imperfect dinucleotide (GT)<sub>n</sub> DNA microsatellite in the 3' UT portion of bovine *NRAMP1* homologues. These data also indicate that more than a single gene influences susceptibility to *B. abortus* infection and abortion in cattle.
A total of 73% (24 of 33) of the progeny from the resistant naturally resistant (R) to brucellosis. The progeny of these boar which did not develop antibody titres when exposed to swine were resistant to the challenge infection, compared to their antibody titres to B. suis were compared to control were saved for breeding. These swine were classified as B. al. (32, 33, 34). In the first experiments, two sows and one subsequent breeding challenge-infection studies, R X R groups of unselected pigs, which were also challenge-infected. was conducted by Cameron £ suis control of resistance to B. abortus and in large populations of naturally exposed cattle which have been phenotyped for disease expression and confirmed by bacteriological culture to be free or infected with M. bovis, S. Dublin or B. abortus as a method for genetic selection against these diseases. This study indicates that natural resistance involves interacting genes, which leads to complex genetic types and consequently to the need to identify other genes contributing to natural resistance. The study also illustrates that individual genes, or gene effects, which have an effect on natural resistance can be identified in spite of complex patterns of inheritance, and that the frequency of these genes realistically could be increased through selection or gene manipulation procedures.

Porcine brucellosis

In regard to swine brucellosis, a series of studies of genetic control of resistance to B. suis was conducted by Cameron et al. (32, 33, 34). In the first experiments, two sows and one boar which did not develop antibody titres when exposed to B. suis were saved for breeding. These swine were classified as naturally resistant (R) to brucellosis. The progeny of these three apparently resistant swine were challenge-infected and their antibody titres to B. suis were compared to control groups of unselected pigs, which were also challenge-infected. A total of 73% (24 of 33) of the progeny from the resistant swine were resistant to the challenge infection, compared to 9% resistant (3 of 24) progeny in the control group. In subsequent breeding challenge-infection studies, R X R matings produced 128 progeny, of which 76.6% were R, 22.6% were of uncertain status and 0.8% were susceptible. Thus, in one generation of mass selection, resistance to B. suis could be increased remarkably by approximately 54% over unselected controls. Another important observation of natural disease resistance was the demonstration that pigs which did not develop brucellosis in a natural outbreak of B. suis were naturally resistant to the disease, and that 76.6% of their progeny were also resistant to an experimental challenge with B. suis (34). Obviously, very few genes are involved in controlling resistance to B. suis in swine.

Bovine tuberculosis

Natural resistance to tuberculosis in cattle has been observed and statistically evaluated in families and breeds exposed to M. bovis under field conditions (39, 40, 124, 136). No association between the expression of tuberculosis and the Latvian Brown or Mottled Black breeds was found (124). Zebu cattle were observed to be much more resistant to M. bovis than European breeds (Jersey, Holstein and Brown Swiss) and Ankole cattle in another study (40, 136), which is somewhat analogous to the findings of racial differences in tuberculosis susceptibility in humans (160). Additionally, Zebu cattle derived more protection from BCG vaccination against experimental virulent M. bovis challenge than Sussex cattle (50). From extensive family studies, the coefficient of heredity of resistance to M. bovis in cattle was estimated to be 0.18 (124). Families having low levels of tubercular disease and high productivity were documented in these extensive studies over time and in different climatic zones. Recently, macrophages from cattle phenotyped for in vivo and in vitro resistance to B. abortus (36, 130, 132) were found to be significantly superior (P = 0.009) to macrophages from susceptible cattle in their ability to restrict the growth of M. bovis (BCG) (132). The previously mentioned monozygotic and dizygotic twin study of human tuberculosis gave the first clear evidence that disease expression was genetically influenced (45, 56, 84). The Bcg gene was subsequently identified and characterised in mice (22, 67) and documented to control mycobacterial infections (28, 39, 143), including M. bovis (BCG) and M. paratuberculosis (57). Bcg was confirmed to be identical to the Ity and Lsh genes controlling salmonellosis and leishmaniosis and to be allelic with Nramp1 by gene disruption (173). Considering these observations and discoveries, the data from cattle, mice and humans are highly suggestive that resistance to M. bovis is genetically influenced by the candidate gene, Nramp1 (166).

Avian salmonellosis

Some of the earliest observations of natural resistance to bacterial diseases of domestic animals were made in elegant, long-term experiments in the 1920s and later years by forward-thinking poultry scientists who convincingly demonstrated that resistance to S. Pullorum (138) and S. Typhimurium (64) is under genetic control. More recently, studies of not only S. Typhimurium but also S. Gallinarum and S. Enteritidis in inbred lines of chickens have extended the earlier findings and provided clear evidence of natural resistance to clinical disease and mortality due to salmonellosis (25, 26). Other studies have demonstrated that survival of S. Typhimurium in the liver and spleen was significantly lower in susceptible than in resistant inbred lines.
of chickens (8); these findings are parallel to the murine salmonellosis resistance (95, 96, 119). Linkage analysis in segregating backcross chicken progeny suggested a major dominant autosomal gene not linked to the MHC (25), which certainly implies that a homologue of the murine Nram1 should be considered as a candidate, as recently proposed (78). With the availability of the chicken gene maps (25, 94) and inbred lines of resistant and susceptible chickens (8, 25), this hypothesis will certainly be tested.

**Ovine footrot**

Genetic factors for natural resistance to *Dichelobacter nodosus*-induced footrot have been observed in sheep under various climatic and management conditions (24, 51, 179) in addition to breed-associated resistance (51, 133, 156), although some studies had limited numbers of observations. One study suggested that development of footrot lesions was inversely related to the humoral immune response to membrane antigens of *D. nodosus* (179), while others imply that resistance may be related to non-immune mechanisms, e.g., receptors (24). The mechanism of resistance remains largely undefined, as does the mode of inheritance, although resistance to footrot did respond to selection pressure (24), but is difficult to phenotype accurately because of the extreme sensitivity to variable challenge inocula. Other studies conclude that insufficient data exist to permit inclusion of selection for resistance to footrot in production-oriented breeding programmes (49).

**Future strategies for developing genetic resistance in domestic animals**

Since breeding for resistance to all bacterial pathogens will not be possible, should the selection for resistance be specific or general (59)? Should selection be for resistance to infection or to disease (122)? Can selection for optimal disease resistance be achieved without compromising productivity (59, 60, 122, 169)? These basic questions provoke major controversy, some aspects of which will be discussed.

**Caveats**

Clearly, any form of resistance to an infectious disease is relative rather than absolute. This is true for vaccine-induced resistance as well as for natural resistance. Thus, breeding animals to increase their level of natural resistance will not completely prevent infectious diseases. However, the increased level of natural resistance conferred by selective breeding would reduce morbidity and economic losses caused by infectious diseases. In combination with a vaccination programme, inherited natural resistance could provide even better protection than the use of either measure alone. Indeed, a strategy could include selection for appropriate immune responses to vaccination. Another concern is that, in selecting for natural resistance, production traits may be compromised, even though information on correlations between disease resistance, immune parameters and important production is practically non-existent. A compromise might occur if there were a negative correlation between enhanced disease resistance and one or more production traits. On the other hand, selection for high egg production and other related traits in chickens resulted in slightly improved resistance to Marek's disease (60). Additionally, the predicted relative economic benefits will need to be determined to justify the inclusion of selection for resistance in a breeding programme for maximum productivity.

If a negative correlation between disease resistance and production is observed, at least three approaches might be used to avoid negative selection for the production traits. One simple approach would be to test unrelated breeder stock for correlation between resistance and production traits; a negative correlation in one set of breeder stock does not imply a correlation in all stock. An alternate approach would be to survey the breeding stock for animals which have undergone genetic recombination which reassorted the genes for disease resistance and production traits. This approach is being greatly facilitated by the rapid development of linkage and physical gene maps of domestic animals, cattle, chicken and swine (27, 58, 139, 182, 183), particularly microsatellite saturated maps, in which selection for maximal polymorphism on each chromosome and genetic diversity would be possible. These maps are a major resource for comparative genetic analysis for homologues of resistance genes in other species (46). A third approach could be taken if the specific gene conferring resistance were identified and isolated. This would involve transferring the resistance gene into an embryo, so that the resistance gene would effectively be added to the desirable production traits determined by the genome of the embryo. This last approach will be feasible only when resistance genes are isolated and the technology for transferring genes efficiently has been developed.

The generality of disease resistance is also a major concern. Several studies have demonstrated the feasibility of breeding animals resistant to a single pathogen. Some have been able to demonstrate that animals bred for resistance to one pathogen are also more resistant to another pathogen, for example, *Ostertagia circumcincta* and *Haemonchus contortus* in sheep (145). As noted above, both the *Lsh* and *Lps* genes in mice confer resistance to several unrelated intracellular pathogens (47, 118, 140, 155). In addition, Biozzi *et al.* bred mice for high and low antibody titres in response to immunisation with sheep erythrocytes, and were able to demonstrate segregation of resistance and susceptibility to a variety of pathogens in those strains (17), thereby demonstrating that different immune functions play crucial roles in resistance to different pathogens. Chickens selected in the same way also differed in their levels of natural resistance to various infectious diseases (153).
These findings indicate that the ability to select for resistance to a group of pathogens is possible, but may not be probable, particularly given the complexity of bacteria and the multitude of host defence mechanisms. Perhaps selection for resistance to a reduced spectrum of bacterial diseases could be tailored for pathogens of cold, temperate or tropical climatic conditions or specific management systems, because selection for all pathogens will not be feasible. Efforts to enhance the general immune response through selection would be less likely to contribute to the generalised enhancement of the disease resistance but rather would be expected to enhance the quantity and quality, as opposed to the specificity, of the immune response (15, 16, 17). This possibility is further supported by the fact that selection on components of a trait is rarely as effective as selection on the whole trait. In addition, the carrier state at the population level is frequently associated with low levels of persistent infection concurrent with protective immune responses, which leads to the idea that the adaptive immune response is in reality a modulator of the host-pathogen relationship; as a result, good immunity allows life to continue with infection, i.e., a successful co-existence. Thus, selection should be made preferably for resistance to disease rather than for resistance to infection.

**Strategies for application of genetic resistance**

Remembering that under natural conditions, host, pathogen and environment are normally interacting in expression of disease, careful approaches are necessary to understand the basis for genetic resistance. Several strategies for improving genetic disease resistance have been proposed previously from various perspectives (1, 59, 169), as follows:

- variation in host response to the pathogen
- environmental conditions
- standardised discriminating challenge dose of the pathogen
- constant virulence of the pathogen
- constant route of challenge, preferably the natural route of exposure
  - constant phenotyping procedures of the resistant trait
  - methods to measure components of innate and adaptive immune responses
  - defined strains or families of the host.

Current techniques of animal breeding, using direct marker-assisted genetic selection for measurable traits as illustrated above for bovine brucellosis, could be applied to the problem of increasing natural disease resistance. This would require that the gene, a linked marker, the gene product, or an in vitro correlate of resistance be identified in individual animals. Animals which possess the resistance trait would then be selected for breeding, and this procedure would be followed until a high proportion of animals carry the gene for the resistance trait. This could be accomplished by using a marker gene closely linked to the resistance gene, by identifying the gene product using monoclonal antibodies or by directly identifying the gene using specific DNA probes. Gene products involved in controlling resistance to infectious diseases, e.g., specifically class I MHC gene products, can be identified on embryos (162). This should enable the selection of only those embryos which have inherited the appropriate gene for transfer to surrogate mothers.

Recent developments in the area of molecular biology are certainly enhancing the utilisation of known genes for natural disease resistance. With the current molecular genetic technology, more bacterial resistance genes will be identified and cloned in mice and humans, and given the extensive domestic animal (especially cattle)-human and domestic animal-mouse homology, identification of domestic animal resistance homologues will be greatly facilitated. Furthermore, the recent progress in the isolation and characterisation of candidate genes and new microsatellite-based markers for family linkage studies of the entire genome are expediting the identification of new resistance genes. With the progress in development of genetic and physical maps of domestic animal genomes (27, 58, 182, 183) which have informative markers throughout the genome, identity-by-descent and identity-by-state analyses of affected sib pairs become very powerful tools to identify major disease resistance loci (75), which can then be confirmed by gene disruption (knockout) procedures (85). These methodologies are making the candidate gene approach preferable to the positional cloning approach for identifying new resistance genes. In this way, the linked markers or the gene can be used to determine the relative risk of clinical disease in exposed individuals. The accuracy of predicting relative risk is affected by the distance between the linked marker and the resistance gene, in addition to the relative contribution of the resistance gene to the overall disease phenotype on the variable genetic and environmental backgrounds of outbred domestic animals.

The transfer of innate and adaptive disease resistance genes into embryos taken from animals which have superior production traits by microinjection of pronuclei, retroviral insertion and stem cell insertion is becoming increasingly possible (113, 114, 131). The transgenic animal derived from that embryo would then have a probability of approximately 70% of carrying the desired gene in its germ cells, and therefore would have an approximately 50% likelihood of passing the gene to its progeny (131). Understanding of gene regulation will be necessary to make the system more efficient. The technology for transferring genes to embryos is being improved for all species of domestic animals, and controls for assuring the safety of such experiments are being carefully clarified and applied. The application of direct gene transfer technology for genetic resistance to bacterial diseases depends upon public support for the introduction of appropriate laws permitting use of transgenic animals in animal production (113).
Conclusions

Without doubt, vaccination programmes, antibiotics and other modalities have contributed significantly to the reduction of losses from bacterial pathogens. However, with the exception of a few diseases in specific geographical areas, bacterial diseases have not been eradicated and remain a major cause of animal and economic loss. The aim of applying genetic selection to the problem of controlling infectious diseases in domestic animals is not so far into the future. Of necessity, a significant part of this review has been devoted to comparative studies in mouse or other models from which much information has been gleaned for application to bacterial diseases of domestic animals at genetic and functional levels. Poultry breeders have successfully applied selective breeding programmes to produce stock with increased genetic capacity to resist specific diseases (59, 60, 169). Investigators in several branches of veterinary science are bringing the realisation of this aim even closer by providing basic information about the genetic constitution of domestic animals and about specific genes controlling mechanisms involved in natural and adaptive resistance to bacterial diseases. Utilisation of such basic information to enhance herd health would be a significant adjunct to current and future bacterial disease control methods for diseases of domestic animals such as brucellosis, tuberculosis and salmonellosis within the next decade.

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Résistance génétique des animaux aux maladies bactériennes

L.G. Adams & J.W. Templeton

Résumé

Malgré les mesures de prophylaxie traditionnelles, le secteur de l'élevage continue de subir de lourdes pertes du fait des maladies infectieuses. Or la résistance génétique aux maladies pourrait être un autre moyen de faire face à ce problème. Faisant intervenir à la fois des mécanismes immunologiques et non immunologiques, elle correspond à la capacité innée d'un animal non précédemment exposé à un agent pathogène, de résister à la maladie normalement causée par cet agent. Même si l'expression de la maladie est influencée par les facteurs environnementaux, la résistance naturelle à la maladie est héritable et se transmet à la descendance. L'autre solution pour améliorer la santé animale consistait donc à améliorer la résistance génétique globale aux niveaux du troupeau et de l'ensemble du cheptel grâce à des programmes de sélection.

L'objet de cette étude est d'apporter aux vétérinaires, aux services officiels, aux responsables des filières de production et aux techniciens d'élevage les connaissances les plus récentes sur les principes et les applications de la résistance génétique comme volet complémentaire des méthodes traditionnelles de prophylaxie des maladies animales d'origine bactérienne. Certes, la résistance génétique aux maladies bactériennes dépend souvent de nombreux gènes contrôlant différents processus de l'interaction hôte-agent pathogène. Cependant, les mécanismes génétiques de la résistance naturelle sont de mieux
Resistencia genética a las enfermedades bacterianas de los animales

L.G. Adams & J.W. Templeton

Resumen
Pese a las medidas tradicionales de control sanitario, las pérdidas achacables a enfermedades infecciosas siguen constituyendo un pesado lastre para la industria agropecuaria. Una solución alternativa a este problema podría hallarse en la resistencia genética a la enfermedad ligada a mecanismos tanto inmunológicos como no inmunológicos, esto es, la capacidad inherente a un animal de resistir a la presencia de patógenos en su organismo sin haber tenido contacto previo con ellos. Aunque los modos de alimentación y cría influyen sobre la variabilidad en la expresión de la enfermedad, ha podido observarse que la resistencia natural es hereditaria y se transmite de un progenitor a su descendencia. Por ello, una posible alternativa para mejorar los sistemas de gestión zoosanitaria reside en la aplicación de programas de selección que permitan aumentar el nivel general de resistencia a la enfermedad, en términos tanto de rebaños como de poblaciones.

Esta reseña intenta proporcionar a veterinarios, funcionarios de órganos reglamentarios, representantes de la industria y técnicos de producción animal información actualizada sobre los principios y aplicaciones de la resistencia genética, concebida como accesorio a las medidas tradicionales de control de las enfermedades bacterianas del ganado. Aunque en la regulación de la resistencia genética a las infecciones bacterianas suelen intervenir numerosos genes, con control sobre distintos procesos de la interacción entre huésped y patógeno, la identificación y caracterización de genes candidatos, el uso de marcadores microsatélite y la cartografía genética comparada están permitiendo desentrañar progresivamente los mecanismos genéticos de la resistencia natural, lo que a la postre ha de conducir al desarrollo de métodos aplicados más eficaces.

Palabras clave
Animales — Bacterias — Genes — Genética — Inmunidad — Inmunidad natural — Resistencia a la enfermedad.
References


