GENETICS OF DISEASE RESISTANCE

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INTRODUCTION

Instead of making a complete summary of all the papers of this session, the moderator will make a general introduction or overview and restrict his comments on the papers for two main reasons: 1) Delay in receiving the manuscripts expected and changes in the list of speakers due to renouncements and replacements. 2) The workshop papers cover necessarily a restricted part of this comprehensive field.

There are two major issues connected with the subject "genetics of disease resistance" in the context of livestock production. Firstly the basic issue: How to identify the genetic basis or the genes behind disease resistance or susceptibility and possibly to identify the actual causative mechanisms involved. Secondly, the applied issue: How to employ the acquired knowledge in breeding strategies to improve genetic resistance in livestock. A lot of research has been and is still being carried out specifically aimed to answer the above questions. This is clearly reflected in the present workshop. Also research projects with objects different from the present one provide spin off knowledge for understanding the genetics of disease resistance. Examples of such projects are gene mapping programmes, studies on: defence molecules and defence mechanisms, pathogenesis, regulation of gene expression together with transgenic experiments, and last but not least molecular modelling and protein engineering, creating new genes and new gene products with novel properties.

The concept "disease resistance" within the framework of this workshop embraces resistance or susceptibility to infections, parasite invasions included. Non infectious diseases and disorders are not included for the reason of space and time.

IDENTIFICATION OF THE GENETIC BASIS.

Genetic variation in disease resistance and susceptibility.
Almost from the beginning of this century, studies in mice have revealed genetic variation in resistance or susceptibility to infections. Some fifty years ago evidence for specific disease resistance was produced based on the finding that mice which were highly resistant to one infective agent could be highly susceptible to another.

Specific disease resistance or susceptibility is restricted to a certain disease or pathogen, is usually influenced by a major single locus but may still be moderately to fairly strongly influenced by unidentified loci, regulatory elements included,as well as environmental factors. The gene is a specific predisposing or conditioning factor among a series of other factors, environmental ones included. The mechanism behind is often based on the presence or absence of certain molecules or variants of such in the host which are 1) critical for the recognition of, and the specific response to non-self, 2) critical for the specific adherence of the pathogen, and its access or not, to the body or 3) responsible for eliciting a pathogenic process when an infective agent, or aggressive part of it, generates in the body. Genetic and antigenic drift of the pathogen, affecting determinants of importance for recognition, adherence, response and toxicity exerts a significant influence on this type of host resistance. This trait is therefore very determinant or agent dependent. Typical examples are the MHC associations with resistance and susceptibility to Gross leukaemia virus (GLV) and Schistosoma mansoni infection in mice. The H2b and the H2k haplotypes are associated with resistance and susceptibility, respectively to the former (Lilly et al., 1964), whereas vice versa to the latter (Claas & Deelder, 1979).
General disease resistance is relatively pathogen non restricted and is influenced by the accumulative effects of many genes together with the blending effects of environmental factors. Antigenic drift of the pathogens will have minor effect, or no effect at all on this polygenic type of defence which embraces all possible physiological and anatomical properties that may contribute to the protection. Hence, this trait

is very little dependent upon origin, type or design of the infective agent. Such resistance can still be seen in the tropics where natural selective forces have influenced a number of genes due to pressure from a wide range of severe infectious diseases. This can be examplified by the recognition that the capacity to tolerate heat, the ability to conserve water, low maintenance requirements together with the ability to resist a series of important infectious diseases are also characteristics attributed to trypanotolerant breeds e.g.: the taurine cattle like N'Dama and West African Shorthorn. (Murray & Trail, 1984).

It is clear that there are types of resistance or susceptibility which may not conform to the two defined. Prime example are major gene influenced non specific killer mechanisms like the activity of lysozymes, interferons, macrophages etc, besides monogenetic deficiencies leading to general susceptibility (e.g.: severe combined immunodeficiency, SCID in man and horses).

An immense number of studies through the whole of a century have provided convincing data on genetic variation in resistance or susceptibility to a series of diseases as well as variation in general fitness or survival among terrestrial and aquatic species. Evidence for the latter is also given in the present workshop by Fjalestad et al.
They report significant family differences and heritabilities (h^2) for general survival rates (losses from various causes) as well as survival after natural and induced specific infections in Salmonid spp., with specific disease giving the highest estimates.

The genetics of disease resistance is reflected in the absolute non-host or species restricted resistance (e.g. MD/VD attacking cattle and EIA horses and not vice versa), striking breed variation (e.g. trypanotolerance), marker associated resistance (MHC and disease) and a series of within breed family studies revealing significant h^2 for almost all known or investigated diseases. In this context it is a bit surprising why this recognition has not been employed to a greater extent in animal breeding, especially when one realizes the enormous economical consequences of diseases to the livestock industry . (Gavora & Spencer, 1983; Lie, 1985). There has not been the same degree of hesitation in breeding for improved production, although adverse effects of onesided yield-selection have been confirmed (Emanuelsson, U. 1988).

Likely major reasons for the delays and the restricted progress in resistance breeding are: lack of efficient tools and recording systems (its easier to measure yield than disease in a standardized way), selection for specific resistance to one disease may enhance susceptibility to another (see above), lack of good criteria to select for overall resistance. A measure that to some extent has met these challanges is the Norwegian nationwide health card system. In addition to production traits, bulls have included in their indexes current information on specific as well as total disease in their daughters and thus hopefully achieving genetic progress for fitness and longevity. (Solbu et al.,1987). A comprehensive treatment of this subject is given by Solbu et al. at the present workshop.

Marker gene candidates, genes and mechanisms involved.
A classical marker for infections in livestock is the resistance of B^{21} haplotype of the chicken MHC with the neural lymphoma, Marek's disease (MD). This was first reported by Hansen et al. (1967) and Brewer et al. (1969) and later followed up by Pazderka et al. (1975), Longenecker et al. (1976) and Briles et al. (1976, 1977). Apart from the B^{21} -MD association and the chicken MHC haplotype influence on progression and regression of Rous sarcoma virus (RSV) induced tumors (Collins et al., 1977), there is now reasonable evidence for MHC association with the following farm animal disease candidates: Caprine arthritis encephalitis (CAE) (Ruff & Lazary, 1988), equine sarcoid (Lazary et al., 1985), in swine: reproductive disorders and piglet mortality (Vaiman & Renard, 1980; Mallard et al., 1987), resistance and responsiveness to Trichinella spiralis (Lunney & Murrell, 1988),increased expression of Sinclair swine cutaneous malignant melanoma, SSCM, Tissot et al. (1989) and possibly susceptibility and resistance to African swine fever indicated by a Swiss group (Ackermann et al., personal communication), bovine mastitis (Solbu et al., 1982; Lunden et al.; 1990; Lie et al., 1990), bovine leucosis virus (BLV) infection (Bortolozzi & Hines, 1982; Lewin & Bernoco, 1986; Lewin et al. 1988), susceptibility to infestation with bovine ecto-and endoparasites (Stear et al., 1989) and a debatable scrapie association in sheep: Millot et al., (1985) reported an OLA linked scrapie susceptibility locus whereas Cullen et al., (1984) could find no association of the sheep MHC with either natural or experimental scrapie.

In this workshop Lewin et al. will give details from their studies providing evidence of BoLA association with subclinical progression of BLV together with the identification of resistant and susceptible haplotypes and genetic correlation between BLV and production potentials.

Solbu et al. are following up the pilot study from 1982 (comprising 14 sires and approx. 3000 daugthers with health card records) now on a bigger body of data (245 sires and approx. 50 000 cows), confirming prior results of BoLA association with mastits. Resistant and susceptible haplotypes are identified. Moreover, BoLA association with ketosis and production traits are found.

Stear et al. review studies on genetic control of nematode infections in ruminants and provide evidence of MHC being one of the genetic systems contributing to the variations in resistance or susceptibility.

Blankert will present data from a project aimed to map the MD resistant haplotype more closely and possibly localize the actual gene involved by employing challenge experiments with recombinants.

For very few infectious disease candidates has the genetic locus involved in the defence or pathogenesis been identified. Examples from experimental animals are susceptibility to LCM, Gross virus leukaemogenesis and autoimmune thyroiditis in mice due to H-2 linked dominant immune response genes (see review of Oldstone et al., 1973) and the Rsm-1 locus controlling protective immunity against Schistosoma mansoni in mice (Correa-Oliveira et al., 1986). In farm animals one knows that dominat alleles are responsible for receptors providing access to the host (or host cells) for ALV and RSV in chicken (Piraino, 1967; Crittenden, 1975) and for enterotoxic E.coli in swine (Sellwood, 1975; Rutter et al., 1975; Sellwood, 1979), whereas the genetic factors behind trypanotolerance in cattle, associated either with reduced parasite multiplication (availability of growth factors) or host antibody response, are not yet identified (see review of Murray et al., 1986).

Hope & Hunter confirm at the present workshop prior evidence (see Dickinson et al., 1968, Nussbaum et al., 1975) for a single locus (Sip) dominant control of scrapie susceptibility in sheep. A candidate product (PrP-protein) of the host control locus is suggested and there is allelic association (linkage disequilibrium) of PrP alleles (RFLP) with Sip alleles in sheep and with homologous loci in mice and man. Surprisingly, the same RFLP can reflect both susceptibility and "resistance" depending on the population studied. The value of RFLP-analysis in predicting the response of unselected sheep to scrapie exposure is under investigation. For the bovine spongiform encephalopathy, a similar test may be developed. Scrapie has also apparently much in common with the human neurodegenerative disorders, kuru and Creutzfeld-jacob disease. Hope & Hunter review this topic in general.

Further details of this topic, i.e. identification of genes and mechanisms, are outlined by Dr. Gavora in the present workshop together with research strategies.

BREEDING STRATEGIES

Direct method.
The major advantages of a selection based on field disease records are: 1) all genetic host factors influencing resistance or susceptibility are automatically included 2) the animals are selected for the "correct trait" regardless of shift in management and disease profile over time. The principal disadvantages of the method are: 1) low heritability of the disease trait (especially when recorded as an all-or-non trait) necessitating expensive progeny testing systems with prolonged generation intervals, 2) the disease trait can be age and sex-restricted, which may also affect the generation interval, 3) the disease trait can be heterogenous and moderately defined. All these factors will have a negative impact on the genetic gain.

Marker assisted selection.
Strategies to circumvent these problems are: Identify major marker genes or the actual genes involved in defence or pathogenesis and employ these as selection criteria. For resistance to well-defined specific diseases under the influence of a major locus and/or for simple inherited deficiencies the marker may be restricted to one, whereas for polygenically influenced diseases (probably accounting for the majority of

diseases) a series of markers for socalled quantitative trait encoding loci QTL (Geldermann, 1975) have to be identified for the purpose to carry out a balanced marker assisted selection (MAS). Given knowledge of such marker-QTL relationships, MAS for polygenically influenced diseases would seem cost-effective for several reasons: much less expensive than traditional strategies (e.g. progeny testing), more secure and balanced than single marker based selection and last but not least, accelerated genetic progress. By this strategy of dissecting quantitative traits into several discrete Mendelian factors, one has been able, employing RFLP, to map several QTL's controlling quantitative traits in tomatoes like water use efficiency, fruit mass etc. (Paterson et al., 1988; Martin et al., 1989). This approach is also broadly applicable to economically important quantitative traits in farm animals, disease resistance included, (Beckmann et al., 1987; Beever et al., 1990). The progress will crucially depend on the rate of the evolvement of the physical genomic maps (Fries et al.,1989). With new powerful techniques (e.g. PCR), highly informative locus specific polymorphic probes (e.g. VNTRs), typing of extreme groups and crosses with respect to a trait (e.g. trypano-tolerance /-sensitivity, N'Dama/East African zebu) and/or haplotyping of variant single sperm and eggs together with the employment of the new common map language or landmark called sequence tagged sites (STS) (Olson et al., 1989), the speed of mapping will increase dramatically.

Breeding strategies are in particular discussed by Solbu et al. besides Fjalestad et al., the latter considering the specific problems related to aquacultured species.

TRANSGENIC STRATEGIES

Most of the transgenic approaches in the disease resistance field so far have been carried out to study regulation of expression of candidate genes related to immune responsiveness. Examples of successful achievments are: integration and expression of swine MHC (SLA) class I genes in mice, partly explained by the fact that transacting regulating factors have been conserved between species (Frels et al., 1985) and the correction of immune response deficiency in an inbred mice line by creating E-α-gene transgenic mice after injection of the "correct" responder gene (Le Meur et al., 1985). Transgenic approaches with defence molecules to improve disease resistance have potentials but are still premature. The transfer techniques can still be refined and one needs better control of transgene expression. A strategy to circumvent these problems may be to insert and express genes of a defective pathogen into the host genome and thus producing resistant hosts by specific interaction between products of the integrated harmless pathogen with the native attacking pathogen: "inherited vaccines" (Crittenden & Salter, 1986). This strategy has been successfully carried out by Salter et al. (1987), Salter & Crittenden (1989), Crittenden et al. (1989) and is reported in the present workshop by Crittenden & Salter. They have produced trangenic chickens with molecularly modified low pathogenic avian leukosis viruses (ALV) as a retroviral gene transfer vector. One line of chickens expressed ALV envelope antigen on the cell surface but did not produce complete ALV or other viral gene products. These chickens were very resistant to pathogenic ALV, most likely because the cell surface receptors were saturated by the envelope protein and hence interferring with viral adherence and penetration. Next step is the refinement of replication-defective retroviral vectors that can deliver a variety of gene candidates to the chick germ line without pathogenic side effects. This model should be applicable to all livestock species, fish included, and represents at present the likely most promising and realistic approach towards transgenic resistant animals.

FINAL COMMENTS, FUTURE PROSPECTS

There is a lot more to learn and consequently a lot more to achieve. An enormous biological landscape is still fragmentary known and understood, physically and functionally, embracing the genetic architecture (physical gene maps with regulatory elements included), regulation of gene expression, defence molecules and mechanisms with their interplay, network of pathogenesis etc.

With regard to the employment of the evolving knowledge and modern tools in animal breeding (e.g. MAS of QTL , transgenes etc.), we are still in our starting blocks. Genetic progress in disease resistance will no longer entirely be based on selection of existing diversity. The transgenic approach presented at this workshop confirms this. Moreover, novel properties are likely to be created by molecular modelling and mutagenesis. New molecules with defence properties or ability to block receptor and/or pathogenic

processes are thus already on the stage. Provided such molecules are used as therapeutics or their genes are somatically transfected, this is fairly unsensitive. It may, however, be more controversial if mutated molecules are introduced to a population via the germ line, the transgenic route. Thus, much biological research is needed before such systems can be routinely implemented, not to mention all the social, ecological and ethical implications involved.

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