Advances in animal breeding

Proceedings of the world symposium in honour of professor R.D. Politiek, organised by the Agricultural University, Wageningen, Netherlands, 11-14 September 1988

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PREFACE

Professor Rommert Douwe Politiek joined the staff of the Department of Animal Science, Animal Breeding section, at the Agricultural University, The Netherlands, in 1960 and became Professor and Head of the Department of Animal Breeding in 1968. After 20 years as Head, Professor Politiek retired on 1 September 1988.

For many years, Professor Politiek has had considerable influence on scientific research and education in animal breeding and on the breeding industry in The Netherlands and abroad. To honour the contributions he has made to animal production, and to dairy cattle production especially, this World Symposium on "Advances in Animal Breeding" was organised for 11-14 September 1988.

The symposium focussed on modern developments in animal breeding and on implications of biotechnology for animal improvement programmes. Scientists from Europe and North America delivered the principal papers, and researchers from The Netherlands presented shorter papers in the area of biotechnology and animal breeding. Other research projects in animal breeding were presented on posters.

The World Symposium and the articles contained in these proceedings of "Advances in Animal Breeding" are only a small expression of appreciation by colleagues and students to honour the many contributions of Professor Rommert D. Politiek.

Wageningen, The Netherlands
September, 1988

The Organizing Committee
S. Korver
H.A.M. van der Steen
J.A.M. van Arendonk
H. Bakker
E.W. Brascamp
J. Dommerholt
J. Wien

THE CONTRIBUTION OF ROMMERT POLITIEK AND HIS STUDENTS TO ANIMAL BREEDING

'The breeding goal is aimed at cattle producing milk and meat in the most economical way under present and prospected systems of herd management and demands of the market' (Politiek, 1962).

E.W. Brascamp

Research Institute for Pig Husbandry, P.O. Box 83, 5240 AB Rosmalen, The Netherlands

Rommert Douwe Politiek was born in 1926 on a farm in Wons near the Afsluitdijk, the dike which separates the IJssellake from the North Sea and connects the province of Friesland with that of North Holland. The farm was rather big for that time, with 30 dairy cows, some arable land and a few pigs. As suggested by the headmaster he went to secondary school and after that, during World War II, to the agricultural winter school, at that time the usual education for future farmers. Again a teacher (the later head of the Central Milk Recording Service, Mr S.R. Sijbrandij) suggested to continue education and Politiek went to college. Then, in 1950, after military service he went to the Agricultural University at Wageningen.

The Friesland period

During his studies he started to work on the protein content in milk. The interest in the subject was initiated by FRS, the Friesland Cattle Herdbook, and by the Association of Cooperative Dairies. Politiek finished his studies in Animal Production in 1955 and accepted a job with FRS. He continued to work on protein. He presented his first international paper in 1956 at the VIIth International Congress of Animal Husbandry of the European Association of Animal Production at Madrid on solids-non-fat-content in milk. In 1957 he got his PhD. degree on a thesis with the title 'The influence of heridity and environment on the composition of milk of Friesian cows and the practical possibilities of selection for protein content'. In the same year Friesland started with paying for protein content in the milk. Politiek was a enthousiastic stimulator of this. He saw clearly that paying for a trait is the most effective way to get it selected for. At that time the protein content was analysed using the so called Kofrani method. Analysis for protein content already started in 1958 also in other parts of the Netherlands, especially stimulated by the fact that the amidoblack dye binding method was developed, which turned out relatively easy to automise.

Other activities of Politiek in Friesland were the improvement of the method of progeny testing. Further he demonstrated special interest for cow size. He showed that since the beginning of the century the wither height dropped with 0.25 cm per year, going down to 1.25 m at the end of the fifties. Politiek encouraged selection for size, because of the positive correlation between size and milk yield.

The Institute for Animal Production

In 1958 Politiek changed job. He went to Utrecht, to the institute which later was moved to Zeist. Presently it's called Research Institute for Animal Production 'Schoonoord'. At this institute he participated in

research of S. Brandsma, dedicated to milking intervals. Politiek gave special attention to machine milking, machine stripping and to ease of milking. At the Max Planck Institute at Mariensee, FRG, he got ideas for a machine to measure ease of milking and in 1960 a system for performance and progeny testing was generally introduced.

The Agricultural University at Wageningen

In 1960 Prof ir W. de Jong died. Politiek went to Wageningen to take over Animal Breeding, within the Department of Animal Science of Prof dr Th. Stegenga. At that time the department had only a few staff members. From 1960 to now the Animal Sciences experienced a tremendous growth, as the whole University, in numbers of students, in staff and buildings. This is illustrated by the number of students annually starting Animal Science, 10 in 1960 and 110 in 1988. In 1968 Politiek became full professor in Animal Breeding and head of the meanwhile established Department of Animal Breeding.

Looking back at Politiek's carreer, his early years in Friesland and Utrecht suggest an explosive start. In Wageningen it looks like a growth curve, with a rather long, slow, start.

Politiek used the sixties to develop teaching in animal breeding and to make plans for an experimental farm in the polder (realised in 1968). He stimulated his first students and staff members to get a PhD degree (M.P.M. Vos in 1969 and H. Bakker and W.A.G. Cöp in 1974) and put a lot of effort in persuading the Dutch industry to adopt modern methods in their selection programmes.

Teaching Animal Breeding

Prof Politiek was not educated formally in quantitative genetics. In that respect he was a self-made-man. In 1970 a real acceleration was realised in the growth curve expressing the level of teaching animal breeding theory. In that year Prof J.E. Legates from Raleigh, North Carolina, USA, visited Wageningen on a Senior Research Fellowship. He teached animal breeding in a manner new for Wageningen and Politiek and Bakker picked up that level to be a general one for each animal breeding student to come. This change was supported by the inheritance of E.W. Brascamp's visit as a student to Prof H. Skjervold in Norway. An additional impulse was given in 1974, when Prof A.E. Freeman from Ames, Iowa, USA, visited Wageningen. Probably from the early seventies, a student taught animal breeding at the Agricultural University at Wageningen can compete with students taught anywhere else.

Influencing the Dutch Industry

In the sixties Politiek has been very active to encourage the industry to adopt improved methods of progeny testing and estimation of breeding values. Later on he stimulated J. Dommerholt to extend the subject further. In a box the development of the methods to estimate breeding values from 1960 onward are presented, showing an evolution from an unadjusted daughter average to Best Linear Unbiased Prediction.

Estimation of sire's breeding value in the Netherlands

In the fifties the genetic merit of a bull for dairy traits was expressed as a unadjusted daughter average. A first step of improving the estimation procedure was introduced in 1961 by comparing the daughter averages with the production of the dams. From 1963 to 1973 the 'melkindex' [dairy index] was used in which the daughter average was adjusted for the merit of the dams using the regression coefficient of daughter on dam.
In 1973 a method of Herd Mate Comparison was introduced. This method has been used until 1981. After that year sire's breeding values are estimated by BLUP in a model with sires (grouped according to breed class, including a relationships matrix) and classes of herd-year-season.
In 1985 the maternal grandsire was included in the model. Presently the technical and financial aspects are considered of an Animal Model to estimate breeding values for all individuals in the population.

Politiek presented important ideas how to optimize the collaboration of herdbooks, milk recording and A.I. In 1970 he published a report on this containing very useful ideas on the subject. Most of these ideas were only realised some ten years later, when a real integration of activities got shape. In the meantime Politiek continued to speak on numerous meetings of dairy farmers to stress the importance of short generation intervals and high selection pressure together with an accurate estimation of breeding values.

The initiatives of Politiek for experimentation on the experimental farm in the polder supported very much the discussions on breeding goals and selection procedures. This is particularly true for the first phase in Politiek's polder experiment in which Dutch Friesians of different regions and herd levels were compared. In later stages the usefulness of Holstein Friesians for the Dutch dairy industry was studied. In the late sixties various experiments were started with these cattle. Apart from the Agricultural University, the Institute for Animal Production 'Schoonoord' experimented with Holsteins in the polder. Also a field trial was started.

All these initiatives and continuing pressure highly influenced the present shape of the dairy industry, also due to his many students on relevant positions extending his ideas. In another box some of these developments are illustrated by some key data about A.I.

Until here, only Politiek's interest for cattle breeding has been touched upon. For cattle breeding he exhibited special interest. For other species his personal interest was less intense, but he very much stimulated interest in other species. In 1969, Cöp entered Politiek's group as first Wageningen researcher in pig breeding and in the same period M. Bekedam started his cross breeding experiments with sheep in the polder. From that time their has been a good balance between different species in teaching and research and Politiek's ideas affected breeding programmes in all species.

Developments in A.I. in cattle in the Netherlands

year	no of A.I.-studs	% A.I.	% frozen semen
1946	42	1.2	-
1950	151	24.1	-
1960	131	61.5	0.8
1970	79	61.7	25.5
1980	48	71.9	86.4
1987	19	83.3	>90

The diminishing number of A.I.-studs also can be illustrated by the fact that in 1987 62% of the inseminations was in the 4 bigger studs. In 1980 this was 33% and in 1970 23%.
From 1970 the proportion of black and white inseminations with Holsteins continuously increased to 16% in 1980 and 87% in 1987.

International contacts

Prof Politiek always cherished international contacts. He was a regular visitor of EAAP-meetings, visited colleagues in other countries and stimulated fellow scientists to visit the Netherlands and to stay some time at Wageningen. Here may be mentioned J.E. Legates and A.E. Freeman and further B.T. McDaniel, D.G. Grieve, R.B. Harrington, M. Grossman, G.E. Shook and B.W. Kennedy. Also, he invited lecturers from abroad as L.R. Schaeffer, E.J. Eisen and D. Gianola. In addition Politiek sent numerous students and staff members abroad to keep in touch with developments everywhere in the world.

A special word for Politieks contributions to EAAP. He was an early stimulator to improve the efficiency of the meetings by keeping time schedules and using higher quality slides and overhead sheets. He especially could do this as a President of the Cattle Commission from 1973 to 1979. He then also stimulated the phenomenon of working groups, given a year to evaluate the status of a particular problem. Together with E.P. Cunningham he initiated the studies on Livestock Production in Europe: Perspectives and Prospects, the results of which were published in 1982. Finally, since the beginning of this year, he is Editor-in-chief of Livestock Production Science.

Scientific Contributions

In appendix 1 a selection is presented of dr Politiek's scientific papers. His main areas were the genetics of protein content in the milk, calving difficulties and ease of milking. Science Citation Index (SCI) [SCISEARCH, Dialog information Retrieval Service] was analysed over the period from 1974 to 1988 to get an impression of the impact of these subjets on international scientific literature. Some 65% of citations of Politiek as first author are related to these three subject. Another 20% relates to the breed comparison experiments in the polder.

To get a fuller description of the research area of Politiek and his students in appendix 2 the titles are listed of theses by students getting their PhD with Prof Politiek.

SCI has been searched to study various aspects of the impact of the

work of Politiek and his students on the international scientific literature. The data used are all papers from 1974-1988 containing one or more references to Politiek or students of his. The list of students searched is listed in Appendix 3. Self-citations were excluded. In table 1 the main subjects cited are listed.

Table 1. Subjects of references to Politiek and his students (SCI, 1974-1988).

Subject		Of which:	
Accent on biology of traits	44%	Growth and feed intake	39%
		Reproductive traits	20%
		Calving difficulties	16%
Accent on methods	30%	Breeding goal & plans	30%
		Adjustment and estimation	25%
		Aspects of replacement	23%
Breed comparisons & crossing	17%	Cattle	71%
Miscellaneous	9%	Fish	68%

The table shows a prime interest for studies on growth and reproductive traits. This interest originates from Politiek's initiative to start selection experiments with mice on growth and litter size. It has been the main topic of study of Bakker. Already before that, M.P.M. Vos looked at weights and measurements of growing cattle. In the same period as Bakker, Cöp started his studies on the effect of feed intake on growth and the composition of growth in pigs. Related work recently was published by E. Kanis, while S. Korver and J.K. Oldenbroek studied related topics in cattle and F.R. Leenstra in broilers.

Bakker's work combined growth and reproductive traits. The subject of reproduction was taken further by H.A.M. Van der Steen, looking at the possibilities to select for litter size in pigs.

Calving difficulties have been studied by Politiek and recently by A. Meijering, who looked at the biology of the trait, but also at the theory of estimation in case of categorical traits. Fertility traits in dairy cattle also were studied by J. Jansen.

Research areas with relatively more emphasis on methods and theory have been cited less frequently. The area mainly consists of work on breeding plans, the adjustment of field data and estimation of breeding values. These subjects have been activily promoted by Politiek. His intention was to support a change of methods in the industry. In the early seventies the work of Brascamp and J. Dommerholt should be mentioned. The theory of breeding plans after that has had a constant attention in Wageningen, recently in the work of G. De Roo on small populations and of J.W.M. Merks, on the effect of GxE on breeding plans.

Dommerholt's work on adjustment and estimation of breeding values was extended by J.B.M. Wilmink.

Finally, S. Korver and J.A.M. Van Arendonk should be mentioned with their work on cow replacement. With this topic an intense relationship has been established with the Department of Economics, a relationship strongly supported by Politiek's general view on the function of animal breeding as an economic activity.

The entry 'miscellaneous' mainly concerns references to work of Kanis

when working in Norway as a student. Perhaps these references should not be included in a list of references to students of Politiek. It illustrates very nicely, however, that numbers of citations tend to increase if a paper has been published as part of the work of an important group. A similar case are references to Bakker, when working a year in Raleigh with Eisen.

Table 2 illustrates the growing contribution in time of Politiek and his students to the scientific world. The period from 1974 has been split in 3 intervals with clear differences in numbers of citations per year.

Table 2. Numbers of references (SCI) to Politiek and his students per year in three periods. The first period is set to 100.

Period	1974-78	1979-82	1983-87
Politiek and students	100	335	675

The clear increase of annual numbers of citations illustrated by table 2 partly is due to the simple fact that the number of publications increases. Compared to 1974-78, the figure for 1983-87 is about 200. It is to be expected that the number of references to Politiek and his students will continue to increase the coming years: For 1987 the relative figure is 1500.

The future

Now, in 1988, the Department of Animal Breeding is gradually moving its attention to biotechnology. Projects have been started on MHC with cattle and protein composition in cow's milk. 'Classical' animal breeding is expected to deserve continued attention but this attention will be shared with increasing emphasis on new biotechnological possibilities to aim effectively at the breeding goals.

Acknowledgement

Thanks are due to Siem Korver for useful comments on the draft and to Jan Dommerholt and Koos van Leeuwen for information on progeny testing and AI.

APPENDIX 1. A selection of publications by Prof dr R.D. Politiek

Politiek, R.D., 1956. Review of the present day problems posed by variations in the solids-non-fat-content of milk. VIIth International Congress of Animal Husbandry, Madrid.

Politiek, R.D., 1957. De invloed van erfelijkheid en milieu op de samenstelling van de melk bij Friese koeien en de praktische mogelijkheid van selectie op het eiwitgehalte. [The influence of heridity and environment on the composition of milk in Friesland cows and the practical possibilities of selection for protein content] PhD-thesis Wageningen, pp 174.

Politiek, R.D., 1961. De produktieverervingsbepaling bij stieren. [Progeny testing bulls for dairy traits] Landbouwk Tijdschrift 73: 481-495.

Politiek, R.D., 1961. Beobachtungen über die Möglichkeit zur Feststellung der Melkbarkeit und ihrer Variation bei Kühen, auch im Hiblick auf die Heritabilität dieser Eigenschaft. Hauptbericht IV, III International Tierzucht-Kongress, Hamburg, 148-166.
Politiek, R.D., 1962. Speenlengte en melkbaarheid. [Teat length and ease of milking] Veeteelt- en Zuivelberichten 5(11): 411-415.
Politiek, R.D. & M.P.M. Vos, 1964. Estimation of the breeding value of a young bull on the production figures of his parents. Zeitschr. Tierz. Züchtgsbiol., 79: 310-318.
Politiek, R.D., 1965. Fertility as a breeding problem. World Rev. Anim Prod, 4: 59-66.
Politiek, R.D., 1966. Probleme der Züchtung auf Milcheiweiss beim Rind. Wissenschaftl. Zeitschr. der Humboldt Univ. Berlin XV(3): 333-340.
Politiek, R.D., H. Vos, M. Milojic, & M.P.M. Vos, 1967. Het bepalen van de produktievererving van stieren. [Progeny testing bulls for dairy traits] Veeteelt- en Zuivelberichten 10(2): 48-58.
Politiek, R.D., 1968. Breeding dairy cows for better yields of milk protein. Proc. 2nd World Conf. Anim. Prod., Maryland, USA.
Politiek, R.D., 1968. Selection for ease of milking worth while? World Rev. Anim. Prod. 4 (16), 94-98.
Politiek, R.D., 1968. Prospects of increasing production of milk protein by breeding. Neth. Milk and Dairy J., 22: 179-191.
Politiek, R.D., 1970. De invloed van selectie en migratie op de FH-rundveepopulatie. [The influence of selection and migration on the Dutch Friesian cattle population] Bedrijfsontwikkeling, 1(7): 25-37.
Politiek, R.D. & J.E. Legates, 1971. Optimum utilization of genetic material, with special reference to crossbreeding in relation to other methods of genetic improvement; Dairy cattle. Proc. Xth Int. Congr. Anim. Prod., Versailles, France, 83.
Politiek, R.D., 1973. Comparison of Friesians from different origin. I. Comparison of the production of Dutch Friesians randomly sampled within two breeding districts and herd levels. Zeitschr. Tierz. Züchtgsbiol., 91: 1-10.
Politiek, R.D., 1974. Outlook on cattle production and research. Livestock Prod. Sci. 1: 261-264.
Politiek, R.D., 1974. The comparison of Friesians from different origin. II. Planning aspects of a dairy cattle breeding experiment. Proc. Working Symp. Breed Evaluation and Crossing Exp. with Farm Animals. September 15-21, Zeist, the Netherlands.
Bakker, H., R.D. Politiek, & J.H. Wallinga, 1976. Reproduction and body weight of mice after long term selection for litter size. 27th EAAP Congress, Zürich, Switzerland.
Politiek, R.D., 1978. Comparison of Friesians of different origins. Report for F.A.O., Warsaw, Poland.
Politiek, R.D., 1979. Sire evaluation for dystocia in Dutch cattle breeds. In: Calving problems and early viability of the calf. Current topics in Vet. Med. and Anim. Sci. Vol. 4. B. Hoffmann, I.L. Mason and J. Schmidt Ed.; Martinus Nijhoff Pub.
Politiek, R.D., 1981. Biedt selectie op kenmerken van uier, spenen, melkbaarheid en uiergezondheidskenmerken een perspectief voor de verbetering van de weerstand tegen mastitis? [Possibilities to improve resistance to mastitis by selection for traits of udder and teats, ease of milking and udder health] Tijdschr. voor Diergeneeskunde 106 (11): 546-553.
Politiek, R.D., H. Vos, & S. Korver, 1982: Comparison of the Friesian Cattle from different origins. II. Milk production traits in two subpopulations from the Netherlands and the progeny of Dutch Friesian,

Holstein Friesian an British Friesian proven bulls. Zeitschr. Tierz. Züchtgsbiol, 99 (4): 272-285.
Politiek, R.D. & J.J. Bakker, (Eds.) 1982. Livestock production in Europe: Perspectives and prospects. Amsterdam [etc.]: Elsevier, pp 335. (Livestock Prod. Sci. 9: 1-335).
Vecht, U., R.D. Politiek, G.E., Shook, G. Grootenhuis, W.J. Koops, & D.G. Grootenhuis, 1985. Effect of bull selection for somatic cell count in first lactation on cell counts and pathogens in later lactations. J. Dairy Sci. 68: 2995-3003.
Huizinga, H.A., R.D. Politiek, S. Korver, & B.T. McDaniel, 1986. Maternal effects due to cytoplasmic inheritance in dairy cattle. Influence on milk production and reproduction traits. Livestock Prod. Sci. 15(1): 11-26.
Politiek, R.D., 1986. Development of animal breeding research. Neth. J. Agric. Sci. 34: 421-426.
Politiek, R.D., O. Distle, T. Fjeldaas, J. Heeres, B.T. McDaniel, E. Nielsen, D.J. Peterse, A. Reurink, & P. Strandberg, 1986. Importance of claw quality in cattle. Review and recommendations to achieve genetic improvement. Report of the EAAP working group on claw quality in cattle. Livestock Prod. Sci. 15: 133-152.
Politiek, R.D., 1986. Milk production in the 3rd millenium. Prospects of the dairy cow. Int. Symp. Cattle for 3rd Millenium, Slusovice, Czechoslavakia.
Politiek, R.D., 1987. Selection for ease of milking in dairy cows. Proc. 3rd Symp. Automation in Dairying, 267-277. IMAG, Wageningen, The Netherlands.

APPENDIX 2. Theses of Politiek's students

1969 Vos, M.P.M. Het meten en wegen van runderen voor de selectie op vleesproduktie. [Weighing and measuring cattle to select for meat production ability]

1974 Tielen, M.J.M. De frekwentie en de zoötechnische preventie van long- en leveraandoeningen bij varkens. [The frequency and prevention by husbandry measures of lung and liver diseases in pigs]

Bakker, H. Effect of selection for relative growth rate and bodyweight of mice on rate, composition and efficiency of growth.

Cöp, W.A.G. Protein and fat deposition in pigs in relation to bodyweight gain and feeding level.

1975 Dommerholt, J. Correctie van de melkgift van koeien voor verschillen in leeftijd, seizoen en lactatiestadium. [Adjustment of milk yield of cattle for differences in age, season and stage of lactation]

Brascamp, E.W. Model calculations concerning economic optimalization of A.I.-breeding with cattle.

1976 Buis, R.C. Genetic polymorphism of blood proteins in a population of shetland ponies.

1979 Ketelaars, E.H. De vererving van onder praktijkomstandigheden geregistreerde kenmerken bij varkens. [The heritability of traits in commercial environments in pigs]

1980 Walstra, P. Growth and carcass composition from birth to maturity in relation to feeding level and sex in Dutch Landrace pigs.

1982 Korver, S. Feed intake and production in dairy breeds depending on the ration.

1983 Van der Steen, H.A.M. Maternal and genetic influences on production

and reproduction traits in pigs.

1985 Van Arendonk, J.A.M. Studies on the replacement policies in dairy cattle.

1986 Meijering, A. Dystocia in dairy cattle breeding (with special attention to sire evaluation for categorical traits.)

Van de Lagemaat, D. Onderwijzen in ondernemen. [Teaching farming]

Jansen, J. Studies on fertility in dairy cattle, based on analysis of AI data.

1987 Wilmink, J.B.M. Studies on test-day and lactation milk, fat and protein yield in dairy cows.

Leenstra, F.R. Fat deposition in a broiler sire strain.

1988 Merks, J.W.M. Genotype x environment interactions in pig breeding programmes.

De Roo, G. Studies on breeding schemes in a closed pig population.

Kanis, E. Food intake capacity in relation to breeding and feeding of growing pigs.

Oldenbroek, J.K. Feed intake and energy utilization in dairy cows of different breeds.

APPENDIX 3. Names of Politiek and his students included in the reference search 1974-1988 in Science Citation Index

Bakker,H; Bekedam, M.; Brascamp, E.W.; Buis, R.C.; Cöp, W.A.G.; De Jager, D.; De Roo, G.; Dommerholt, J.; Groen, A.F.; Kanis, E.; Ketelaars, E.H.; Knap, P.W.; Koops, W.J.; Korver, S.; Merks, J.W.M.; Meijering, A.; Oldenbroek, J.K.; Politiek, R.D.; Van der Steen, H.A.M.; Van der Werf, J.H.J.; Van Arendonk, J.A.M.; Van Steenbergen, E.; Vos, H.; Vos, M.P.M.; Wilmink, J.B.M.

Note that Jansen, J. has not been included because there were 1322 references to this author of which only a few were expected to refer to the relevant Jansen, J.

DEVELOPMENTS IN THEORY AND APPLICATION OF ANIMAL BREEDING

J.E. Legates

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Summary

Practical breeders were already fashioning their animals in accord with their desires before the scientific foundations for animal improvement were laid. Robert Bakewell is most often cited for his practical accomplishments as the founder of animal breeding. While it is impossible to recognize all who made significant contributions, Darwin and Galton clearly dominated early thinking even before the rediscovery of Mendelism in 1900. Once Mendel's postulates were in place, substantial progress was made on many fronts. Foremost was the accommodation of Mendelism to the inheritance of continuously varying traits. Many individuals have made mammoth contributions to the theory on which animal breeding practice is based today. Informed breeders are aware of genetic variance, genetic correlations, selection indexes, heterosis, and BLUP, as these concepts have moved from the research arena to appreciation in the field. Truly we have a rich heritage and a solid foundation for future developments in animal breeding.
Keywords: animal breeding, animal, improvement, genetics, selection, heterosis

Introduction

Animal breeding, as the application of science to the genetic improvement of animals, implies a close inter-relationship between theory and its application. Genetics has provided the matrix from which logical principles could be developed and tested by experimentation and practice.

During the 20th century, genetics has assumed a broader meaning and numerous subdivisions of the discipline have emerged. Advances in animal breeding also have drawn heavily on contributions from statistics, biochemistry, physiology, economics and other disciplines. Animal breeding and reproductive physiology have been uniquely interwoven.

Animals with superior genotypes can not contribute to succeeding generations unless their reproductive capacity is maintained at satisfactory levels. Developments such as artificial insemination, embryo transfer and cloning have and will continue to stimulate new theory and applications in animal breeding.

Livestock production is an economic enterprise. Hence, animal breeding recommendations must withstand the scrutiny of economic, as well as genetic considerations, before they are accepted and integrated into enterprises by breeders. As a consequence, a close relationship between the breeder and the science, application and theory, has been nurtured.

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It is appropriate and fitting to review these advances in honour of Professor Politiek, who has so completely dedicated himself to the advancement of animal breeding theory and practice. His concern and encouragement of his students will continue to yield rich dividends.

Beginnings

Pre-Mendelian

Even before Mendel's principles were uncovered, the mystery of the transmission of hereditary material from parent to offspring was recognized although not understood. Robert Bakewell of Leicestershire, England who lived from 1725 to 1795, is generally credited as the founder of animal breeding. He contributed much to the development of the Longhorn cattle, Leicester sheep and Shire horses. Bakewell reportedly purchased animals from different sources which he thought met his goals and utilized inbreeding and intense selection to develop the kind of animals he desired. His animals were much in demand, and he appears to have been among the first to conduct systematic progeny tests of rams and bulls. He let these out for a fee with the option of bringing the best back for use in his herd.

Apparently Bakewell told little about his mode of operation, and some were obliged to think that there was something mysterious about it. At that time there was a strong prejudice against inbreeding, and it may have been that he did not want to invite criticism. Many stockmen did come to work with Bakewell on his estate at Dishley. Perhaps the most noted, the Colling brothers, are credited with founding the Shorthorn breed.

Herdbooks provided records of identification and parentage of foundation stock. The first herdbook was published in 1791 for Thoroughbred horses. The Coates Shorthorn herdbook appeared in 1822, accepting for registry only what were judged as outstanding animals. The herdbook fever reached a peak in the 1870's and 1880's when importers particularly wanted to declare that their animals could be traced to a known foundation. Herdbooks and breed societies have been a part of animal breeding with nobly stated purposes, yet on occasion, hindering real genetic progress.

Practical breeding moved ahead even without the benefit of a scientific foundation. Darwin's studies of populations drew upon the experience of practical breeders. Conversely, reports suggest that the philosophy and writings of Darwin on organic evolution and natural selection were certainly known by some British breeders. Darwin explained the impact of reproductive fitness logically, but his insights into the process of hereditary transmission was flawed. Under the blending hypothesis the variation in the population would be halved each generation as pointed out by Jenkins (1867). A tremendous infusion of new variability would be required to reconcile the continuing variation observed in panmictic populations. Hence, favourable circumstances were provided for the acceptance of De Vries (1910) mutation theory.

Darwin (1859) underscored the importance of continuous variation to evolutionary and directed change in animals and plants. Galton (1889), without the benefit of Mendel's findings, added quantitative precision to the characterization of the variation which Darwin had drawn upon to formulate his theory of natural selection. Galton's law stated that given a correlation of .50 between parent and offspring in a population with minimal inbreeding and for a highly hereditary trait, the correlation between an animal and a more remote ancestor is halved for each inter-

vening generation. Lush (1945) pointed out that practical breeders in Britain had used this concept as early as 1815.

A second component of Galton's law was that the square of the correlation coefficient measures the proportion of the variance in one variable which disappears when the other is held constant. Yet Galton failed to recognize that this postulate was not true when bridging over generations. Each of the four grandparents do not account for 1/16 of the variance of their individual independent of the parents. It was Yule (1906) who corrected this view of Galton with his multiple regression technique. At the 3rd International Congress on Genetics, Yule presented a multiple correlation interpretation which demonstrated that with the full knowledge of the parents the contribution of the grandparents to the variance is nil.

Mendelism rediscovered

Mendel (1865) had already provided the answer to the flaw in Darwin's theory of blending inheritance; although, as we now know, the scientific world had not at that time recognized the moment of his findings. His conclusion that the basic hereditary mechanism was particulate and not blending, with the capability for independent assortment and recombination, gave substance to Darwin's theory of natural selection. According to Wright (1967), Mendel accepted the theory of natural selection; although neither Darwin nor Mendel recognized this in their time.

The veil of ignorance about the fundamental postulates of heredity was lifted in 1900 when De Vries in Holland, Correns in Germany and Tschermak in Austria recognized the impact of Mendel's 1865 publication. A flurry of investigations moved forward to uncover examples of inheritance which followed the postulates of Mendel. Bateson was an active investigator in this arena at Cambridge. His study of the inheritance of comb types in chickens brought forth one of the first and most interesting examples of gene interaction. Bateson (1902) is credited with suggesting genetics as the name for the new discipline. He also proposed the terms homozygote and heterozygote.

The Danish botanist, Johannsen (1903) had been working with beans, which are naturally self-pollinated, and developed a number of pure lines. He made the distinction between genotypes and phenotype and is credited with the first use of these terms, as well as the designation of the gene. In his publication of 1903, he refers to the work of Galton and his law, plus the work of Pearson in recognition of the contribution of biometrics. Goldschmidt (1951) has stated that Johannsen revealed that "Genetics must be studied with mathematics, not as mathematics."

Mendelism and the biometrical approach

Expected parent-offspring and maternal correlations under Mendelism with random mating were developed by Pearson (1904). He expressed concern that a discrepancy existed between expected and observed correlations, which Yule (1906) explained was due to Pearson having assumed complete dominance was always expressed. Yule further postulated a swarm of genes affecting a trait, which had small but similar effects, as a contribution to reconciling Mendelism with the emerging biometrical analysis of genetic variation.

One of the cornerstones of animal breeding and population genetics was revealed independently by Hardy (1908) and Weinberg (1908), which has become known as the Hardy-Weinberg law. This finding further showed how

population variability was maintained in a large random mating population with the genotypic or zygotic frequencies being equal to the square of the gametic frequencies. Wright (1967) relates that one of his earliest contributions to population genetics and animal breeding was in the use of the Hardy-Weinberg principle of random recombination within and among loci to distinguish among genetics hypothesis for coat color in Shorthorn cattle (Wright, 1917).

Weinberg (1909) continued to explore the expected correlations between relatives, accounting for multiple alleles, varying degrees of dominance, various gene interactions, plus environmental variance. His results and the demonstration of Yule's multiple gene hypothesis by Nilson-Ehle (1909) with wheat had provided the framework for compatibility between the Mendelian and statistical viewpoints. However, the accommodation of both points of view was long in being realized by many, chief among them was Bateson. It required a newly schooled scientific generation to accept the merging of the statistical and Mendelian approaches. Fisher's (1918) oft quoted but less frequently read publication, restated and expanded the earlier analysis of the correlation between relatives under the assumption of random mating by Weinberg (1909). He demonstrated that the results of the statistical analyses were embedded in the principles of Mendel.

Partitioning hereditary variance

The logical partition of hereditary variance into an additively genetic component or that due to gene by gene effects, a residual attributed to intrallelic interaction or dominance deviations, and the remainder due to interallelic interaction has provided a framework to attack many problems.

The impact of dominance variance has been examined for the most part assuming no epistasis. Comstock and Robinson (1952) proposed experimental designs to clarify the nature of dominance effects with particular concern for evidence of over-dominance. Most of these were applicable to monoecious plants. Wright (1935b) provided insights into the contribution of two gene epistatic deviations to the correlation between relatives as he considered deviations from an optimum. Cockerham (1954) presented an extension of the concept of partitioning the epistatic component of variance and the contribution of the several partitions to the correlation between relatives. This drew upon the partitioning of individual degrees of freedom for an n loci model, recognizing additive effects, dominance deviations, and epistatic effects.

Fisher's (1925) contribution of the analysis of variance has been one of the most useful to statistical methodology in animal breeding. Apart from its use to test mean differences, its application for the estimation of components of genetically and environmentally caused variation has been widespread. Wright (1918) earlier had developed the path coefficient analysis to relate the correlation between variables in an interacting system of causal relationships. Statistically the path coefficient is a standard partial regression coefficient, and its square represents the portion of the total variance accounted for directly by a specific variable. Recognition of joint paths could provide for an assessment of covariance. The flexibility of the analyses of variance and its many modifications, however, has provided the foundation for genetic analyses for parameter estimation in animal breeding.

The intraclass correlation, introduced by Harris (1913), has had much applicability in animal breeding. Variance ratios have been used widely with the concepts of repeatability and heritability as introduced by Lush

having most common usage. Fisher (1918) had introduced the dominance ratio, the ratio of the dominance variance to the total hereditary variance, in an attempt to determine a generalized relationship between the magnitude of dominance variance to the expected correlation among relatives.

Estimation of variance and covariance components has been an important technique in animal breeding research. Unequal and disproportionate subclass numbers, being the rule for animal data, has required special adaptations of the analysis of variance procedures (Harvey, 1975). Winsor and Clark (1940) were among the first to provide expectations of mean squares for data with unequal subclass numbers. Yate's (1934) method of fitting constants was adapted for testing mean differences, and Henderson (1953) expanded this approach to account for adjustment of fixed effects, plus the adaptation of maximum likelihood in variance component estimation.

Advances in the estimation of variance and covariance components has been a key to devising effective breeding strategies. Where randomness of all elements in the model is realized, simpler estimation techniques provide unbiased estimates. Henderson's (1953) Methods II and III provided approaches to adjust for the fixed effects in a linear model. Subsequently methods of maximum likelihood estimation with a general mixed linear model were advanced by Hartley & Rao (1967), Patterson and Thompson (1971) and Rao (1971). Maximum likelihood and REML modification, while biased, avoid the troubling negative estimates of components. Choice of the desired procedure is not based on precise criteria, and with large data sets even computational requirements can be a determining factor.

Estimation of breeding values

Animal breeding practice consists primarily of predicting breeding values, selecting animals on the basis of these estimates, and designating their mates. Prediction of average breeding values has commanded most attention, recognizing that the need for consideration of special breeding values merits consideration under specific circumstances.

The use of repeatability to project expected future performance, when multiple expressions of a trait are concerned, provided an early prediction equation for what Lush termed "most probable producing ability". Heritability in the context of the regression of average breeding values on phenotypic values, provides the basis for a comparable prediction of average breeding values. A variety of adjuncts to individual selection have been drawn upon as aids to individual selection. The performance of related individuals and combinations of information on the individual and its relatives can be utilized in the estimation of breeding values. Lush (1947b) explored the relative weights to be given individual records and family averages to predict additive breeding values. The notion that on occasion the family average may properly receive a negative weight emerged. Such was the case where the environmental correlation among family members exceeded the genetic relationship or correlation.

Maternal influences common to litter mates can be a source of an environmental correlation between relatives, potentially obscuring the genetic differences among litters. The crossing of breeds with widely divergent body sizes, as with the Shetland pony and the Shire horse (Walton and Hammond, 1938) documented maternal effects. Dickerson (1947) pointed out the impact of the direct maternal effects of the dam and the effect of the genes transmitted to the young on maternally influenced traits. Venge (1950) sought to separate the impact of uterine environment

versus maternal cytoplasmic effects with the reciprocal transfer of fertilized rabbits ova between large and small breeds.

Expectations of the contributions of additive and dominance effects to the covariance among relatives to estimate variances due to direct and transmitted influence on maternal traits were developed by Willham (1963). Utilizing the "coefficients of parentage" and the dominance coefficient of relationship the expected contribution to covariances among relatives can be assessed. Van Vleck (1976) has developed selection procedures for simultaneous consideration of direct and maternal genetic effects. Some further evidence suggests that cytomplasmic effects could be an important component of maternal influence (Bell et al., 1985); although, conclusive evidence from experiments including embryo transfer are not yet available.

The progeny test has been heralded as a means of accurately estimating breeding values. Developed largely for sex-limited traits, many modifications have been made since Nils Hanson in 1903 proposed the equal parent index as a method of expressing progeny test. Lush (1935) did much to put the relative accuracy of the progeny test and individual selection into perspective. While of tremendous value in the advancement of animal breeding, Dickerson and Hazel (1942) also recognized its limitation in respect to progress per unit of times as it lengthened the generation interval. This concept for the analysis of expected genetic progress from alternate breeding plans was further extended by Robertson and Rendel (1950) to identify the potential annual contribution of each of the four grandparental lines of the pedigree.

Significant advances in the precision of expressing the progeny test have been made with the use of the contemporary comparison (Robertson and Rendel, 1954) and the appropriate regression of daughter's records on herdmates (Henderson et al., 1954). The Modified Contemporary Comparison (Dickinson et al., 1976) for dairy cattle and the Best Linear Unbiased Predictor approach, BLUP (Henderson, 1973) represent further advances.

Selection indexes and selection

Reflection thus far has been couched in terms of selection for one primary trait. Animals are a composite of many genes and numerous expressed traits. Only rarely can the appropriate breeding goal be confined to a single trait. Smith (1936) approached the problem of multiple traits with the development of a discriminant function for choosing among strains or varieties based on the totality of genetic differences among them. He introduced the important concept of the relative worth or economic value of improvement in each of several desired traits. Smith et al., (1986) have provided additional insights to the derivation of economic weights. They have argued that extra profit that could accrue merely from rescaling the size of the breeding operation should not be credited to the value of genetic improvement, per se. Further, the fixed costs attendant to attaining a given level of output must be included; thereby reconciling equivalency of derived economic weights from various profit equations (Dickerson, 1970).

Hazel (1943) approached the problem with the path coefficient analysis focusing on an index for aggregate average or additive breeding value for the desired traits. He developed the concept of the genetic correlation with the subdivision of the covariance between two traits into their genetic and environmental components. The concept of the selection index has provided much guidance in animal breeding theory and practice. The generality of the concept to accommodate multiple traits, information on relatives, and where the means and variances are unknown was underscored

by Henderson (1963).

The BLUP methodology has become a standard for prediction of breeding values in animal breeding practice. The initial conceptual framework for this mixed model methodology was presented by Henderson (1949b), and its further extension suggested (Henderson, 1973) in the symposium honoring Dr. Jay L. Lush for his contributions to animal breeding. The procedure combines the desirable features of selection index and least squares techniques. It is adaptable to varying computer capabilities and additional intricacies, including the animal model, have been accommodated as computing capacity and economy have advanced. Although the system does involve linear equations and had usually been applied to an additively genetic model, Henderson (1977) has illustrated applications where estimated values involving dominance variances and covariances are utilized.

Experimental demonstration of the effectiveness of index selection has not been definitive. When several traits are included in the selection goal, it is difficult to achieve the dramatic response often noted with single trait selection. However, long term selection studies such as the 70 generations of selection in maize for oil and protein content (Dudley 1977), and numerous subsequent studies with laboratory and other species (Robertson 1980) have underscored the resourcefulness of the hereditary mechanism to provide the essential variability required for continuing response to selection. Demonstrated correlated responses have confirmed the manifold effects of selection. Robertson (1960) has provided us with an analysis of the selection limits under the additive model. All of these facets of information give assurance that our animal populations should, for the most part, be far from their ultimate limits of improvement for important economic traits.

Inbreeding, relationship and heterosis

The general effects of inbreeding were noted and recorded long before experimentation began. Bakewell is credited with recognizing the concentration of breeding associated with close-breeding. Darwin's (1868) statement "The consequences of close inter-breeding carried on for too long a time are, as is generally believed, loss of size, constitutional vigor, and fertility, sometimes accompanied by a tendency to malformation". Prior to the close of the 19th century inbreeding experiments with mice demonstrated the adverse effects of inbreeding on fertility and litter size in rats. However, no measure of inbreeding was available, and the degree of inbreeding was reckoned in terms of the number of generations of brother-sister mating that had accumulated.

Inbreeding and relationship

When Wright joined the U.S. Department of Agriculture in 1915, he took charge of the inbreeding experiments with guinea pigs initiated by Rommel in 1906. Analyses of data from these experiments led to the development of a general theory of inbreeding and to studies of the actual amount of inbreeding that had occurred in certain breeds of livestock. Wright (1921) developed the coefficient of inbreeding which permitted evaluating inbreeding studies on a comparable basis of expected change in heterozygosis. Earlier (Pearl, 1913) and subsequent attempts (Fisher, 1949) to improve upon this measure did not meet with universal success, and the coefficient F of Wright continues in general usage. Wright (1921) referred to F as the correlation between uniting gametes, and he developed the concept in more detail in his later publication (Wright, 1922).

Malecot (1948) has expressed the coefficient of inbreeding as a probability rather a correlation context, which simplifies many developments.

The coefficient of relationship measuring the probable proportion of genes that are the same for two individuals due to common ancestry also was developed by Wright (1922). As was the case for the inbreeding coefficient, the relationship coefficient gave a proportion over and above that existing in a base population. The quantification of relationship and inbreeding allowed for a logical assessment of effects occurring from a mixture of regular and irregular matings. The covariance matrix of the numerator of the relationship coefficient, as twice the expected inbreeding of offspring of these two parents, has provided a basis for many practical developments. The development of the ingenious computing algorithm for the A^{-1} matrix by Henderson (1976) represents a penultimate application of these concepts.

Efforts to integrate the impacts of inbreeding, crossbreeding, and selection was published in Wright's monumental work on "Evolution in Mendelian Population" (Wright, 1935a). We draw heavily on his analysis of inbreeding in a closed random mating population in experimental design, now more for the avoidance of inbreeding rather than to increase homozygosity. The relationship between population size, inbreeding and gene extinction have provided the foundation for further inquiry into this field. Lush's (1947a) examination of chance as a cause of gene frequency change in breeds of livestock is a cogent example.

Heterosis

Heterosis is the phenotypes difference between the progeny mean and the average of the parents, with the potential for positive, negative or no heterosis. Hybrid vigor is often used interchangeably, yet we al,most never speak of negative hybrid vigor. Dominance, overdominance and epistasis may contribute to the expression of heterosis. Heterosis is a much used but basically little understood phenomenon that had been noted and its effect empirically recorded before Mendel published his findings. Zirkle (1952) reports that hybrid vigor in crop production was known over two centuries ago. The donkey is evidence of the knowledge of hybrid vigor among animals. Mendel (1865) describes hybrid vigor in that the taller of the two parent strains was exceeded by the hybrid. Darwin (1876) stated, "The first and most important conclusion which may be drawn from observations given in this volume, is that cross-fertilization is generally beneficial and self-fertilization injurious."

Realization that heterosis was a special result of the principles of inbreeding and outbreeding, came with the work of Shull (1952); although, he personally states that unraveling the heterosis concept was not the purpose of their early research. Controlled parentage in maize was the primary concern. East and Jones (1919) gave further substance to the genetic concept. An important addition to the application of heterosis was that of general and specific combining ability among crosses as presented for maize by Sprague and Tatum (1942) and for swine by Henderson (1949a). This recognized the important contribution of additively genetic merit as a foundation for the expression of heterosis or specific effects in the success of practical breeding programs.

With the understanding of the mechanistic basis for heterosis, procedures were sought to maximize gain for selection for heterozygosity. Hull (1945) proposed recurrent selection as a means of selecting for specific combining ability. His proposal for intra-population selection included the use of a tester strain to which the recurrently selected population was to be mated. Comstock et al., (1949) proposed reciprocal recurrent

selection as a breeding procedure to utilize advances in additive merit and specific combining ability, particularly if overdominance was operative. Numerous variations of such a scheme have been devised. Their comparative response is directly dependent on the causal nature of the hereditary variance; additive, dominance, overdominance and epistasis. Such knowledge has not been available, a priori. Direct selection for specific combining ability, with the usually lengthened generation interval and demand for additional resources, appears warranted only after it is determined that response to selection for additive genetic merit has become meager.

The utilization of hybrid vigor has been a major component of applied breeding programs, particularly with poultry and meat animal enterprises. Maternal heterosis in cattle and swine has been of sufficient magnitude to dictate the use of crossbred females in commercial production (Dickerson, 1973). The trend toward specific sire and dam lines has been an encouragement for the entry of commercial breeding companies, especially into poultry and swine breeding.

Conclusion

Application of fundamental principles has advanced markedly in developing local, national and regional breeding strategies. Positive results from programs already are occurring. Investments in many schemes are large, and the dramatic rise in inflation and interest rates in recent decades has prompted a more careful examination of the return on investment along the lines suggested by Brascamp (1973). With the extensive movement of deep frozen and embryos, some breeding programs have become internationalized. This has prompted a recurring concern regarding genotype-environmental (country) interactions. Falconer (1952) has provided a valuable insight in the context that a trait measured in two different environments could be considered as two different traits genetically. Within temperate areas of the world, such interactions have not been of major significance on the basis of limited current experience. More dramatic evidence for such interactions has been recorded in tropical and subtropical climates.

All of the valuable contributions to the advancement of the theory and development of animal breeding are not included, herein. Apology is extended for critical omissions. Yet it is hoped that the major foundation principles have been brought to your attention.

Many findings now can be catalogued neatly in their appropriate classifications and categories, as if they were uncovered in an orderly fashion. Insights, experimentation, analyses and interpretation come slowly. They also come with much uncertainty, concern and often loneliness, especially when a new tenet is advanced. We are indebted to many persons, indeed many that have not been mentioned, for the exciting developments that have shaped animal breeding from the past to the present. Many of you here will carry the mantle of responsibility for insuring the development of animal breeding theory and applications in the future.

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BIOTECHNOLOGY WITH SPECIAL REFERENCE TO GENE TECHNOLOGY IN ANIMAL PRODUCTION/ANIMAL BREEDING

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Summary

In the present paper, recent findings in molecular genetics are summarized. The opportunities offered by monoclonal antibodies and recombinant DNA technology to improve animal production are discussed. Comments are given on some Norwegian biotechnology/gene technology projects in animals.
Keywords: "keystones", monoclonal antibodies, recombinant DNA technology, projects, ethics, prospects, resources.

Introduction

There has been a strong desire among scientists working in the field of genetics to be able to exert control over the genes which are combined in new individuals. Consequently, much effort has been spent during the last decade in developing techniques to achieve this aim. In molecular genetics, one is speaking of genetic engineering or gene technology. At the same time, we know that much progress has also been made within the field of embryo technology. In the following an attempt will be made to give a brief survey of new developments and relate these to prospects for future application in animal production/animal breeding.

Some biotechnological techniques such as embryo transplantation and their applications will, however, not be dealt with here, but in other papers.

Definition

Several definitions of biotechnology can be found in the literature, one of these being as follows: "All technology which systematically uses micro-organisms, or plant and animal cells, or parts here of, to create or modify products, to change plants and animals, or to develop micro-organisms for specific purposes" (Nordiska Ministerrådet, 1987).

Recent knowledge as a base for application - a short review.

If we try to summarize the molecular genetical "keystones", and the cell culture techniques the following may be listed: (see e.g. Old & Primrose, 1982):

1. The DNA-molecule (DNA = deoxyribonucleic acid) carries all the inheritable information.
2. The sequence and the number of amino acids give the proteins their geometric structure.
3. The genetic code programmes protein synthesis.
4. Restriction enzymes are available to cleave the DNA-molecule at sites with defined base sequences.
5. The cloning of a fragment of DNA allows indefinite amounts to be

produced from even a single original molecule. A clone is defined as a large number of cells or molecules all identical with an original ancestral cell or molecule. Cloning of DNA is made possible by the ability of bacterial plasmids and phages to continue their usual life-style after additional sequences of DNA have been incorporated into their genomes.

6. Since 1980, several attempts have been made to introduce genes into animals. An animal that gains new genetic information through the addition of foreign DNA is described as transgenic. In the progeny, expression of the donor gene is extremely variable, - it may be extinguished entirely, reduced somewhat, or even increased. Even in the original parents, the level of gene expression does not correlate with the number of tandemly integrated genes. Probably only a few of the genes are active. What could be responsible for the variation in gene expression? One possibility that has often been discussed in connection with transfected genes, and which also applies to integrated retroviral genomes, is that the site of integration may be important. A gene may perhaps be expressed if it integrates within an active domain, but not if it integrates in another area of chromatin. Another possibility is the occurrence of epigenic modification. Some of the transfected genes in the mouse are methylated, and changes in the pattern of methylation might perhaps be responsible for changes in activity. Alternatively, the genes that happened to be active in the parents may have been deleted or amplified in the progeny.
7. Hybridoma (MAb) technology. This modern variant of cell culture technique was first described by Köhler & Milstein (1975). The technique, still "young and promising", is under constant development both with regard to improvement and field of application. The principle consists of merging (fusing, hybridizing) an antibody-producing cell with a myeloma cell (malignant plasma cell). The hybrid cell, the so called hybridoma cell, thus created, combines the properties of both parent cells i.e. it produces antibodies and grows continously in culture. Cloning consists in culturing (selecting) identical offspring (a clone) of a hybridoma mother cell with an uniform monoclonal antibody as the result (Figure 1).

The use of biotechnology/gene technology in animal production/animal breeding

Monoclonal antibodies (MAb)

Antibodies which can neutralize e.g. bacteria and viruses are used in diagnosis, prevention and therapy of infectious diseases in human - and veterinary medicine. Such antibodies are produced in animals by special cells, the lymphocytes. The need for pure, unmixed antibodies has been met through the technique of cell hybridization. This technique is based on the fact that each antibody secreting cell (lymphocyte) produces and secretes one type of antibody. Mab is a tool which plays a central role in modern biotechnology and which has a vast range of applications.
Among he major of these are: 1) Diagnostics, 2) Bioseperations and chromatography, 3) Development of vaccines, including antigen characterization and "antigen copying" (anti-idiotype), 4) Cell seperation, 5) Blood and tissue typing, 6) Therapy, 7) Immuno-assays and immunological research etc. (see Lie & Hellemann, 1986). Concerning applications in veterinary medicine, the following may be stated (see e.g. Hauge & Rönningen, 1985).

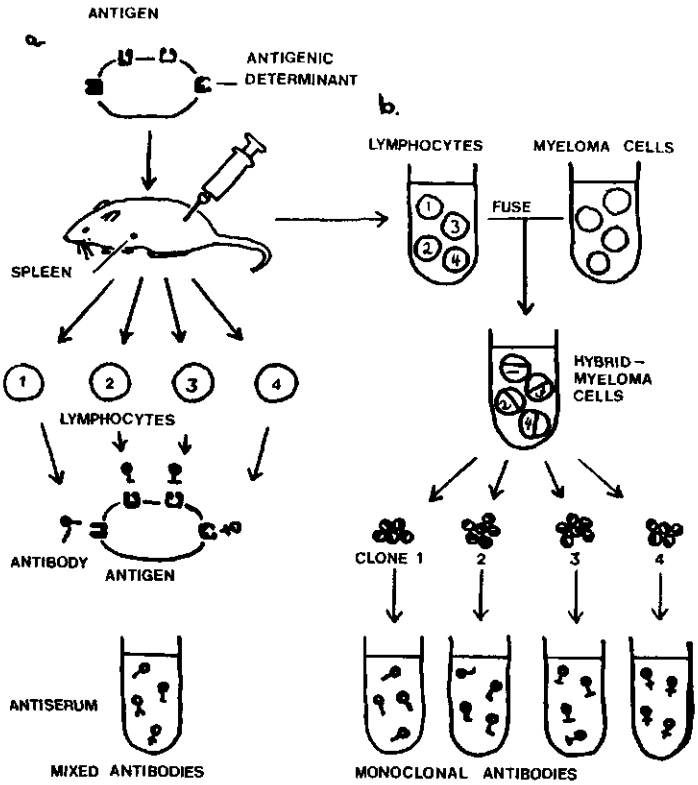

Fig.1. Immune response is initiated (a) when an antigen molecule carrying several different antigenic determinants enters the body of an animal. The immune system responds: lines of B-lymphocytes proliferate, each secreting an immunoglobulin molecule that fits a single antigenic determinant (or a part of it). A conventional antiserum contains a mixture of these antibodies. Monoclonal antibodies are derived by fusing lymphocytes from the spleen with malignant myeloma cells (b). Individual hybrid cells are cloned, and each of the clones secretes a monoclonal antibody that specifically fits a single antigenic determinant on the antigen molecule (Milstein, 1980).

Infectious disease-causing agents

Because of their specificity and uniformity, MAbs are ideal as diagnostic reagents. It may soon be possible to use commercial kits to identify viral respiratory tract pathogens of horses. Specific MAbs can be produced against rare or minor antigens, and these therefore have the potential to distinguish closely related strains of viruses. MAbs that distinguish canine parvovirus from feline panleucopenia virus have been produced recently (Antczak, 1982).

Cell surface antigens

The availability of MAbs against blood group antigens would increase the efficiency of blood typing and genetic identification of livestock. MAbs against histocompatibility antigens are of interest, and these antigens hold promise as markers for immune response genes in domestic animals.

Another exciting prospect in this area is the possibility of developing tumour specific MAbs that do not crossreact with normal tissue antigens. Such MAbs could then be used, appropriated labelled, for determining the location of a tumour with scanning devices. The MAbs may also be used either directly in immunotherapy, or indirectly to carry cytotoxic drugs to the tumour (Collin & Kaplan, 1984).

Proteins and other small molecules

MAb can be used in the milk progesterone test for confirmation of oestrus and pregnancy diagnosis in cattle (Robertson & Sarda, 1971; Heap et al., 1973). The use of monoclonal antibodies leads to improvements in test standardization and avoids the dependency upon animals producing high quality antisera. In pigs, increased levels of oestrone sulphate in plasma have been demonstrated early in pregnancy starting from day 16, with a maximum on day 40 (Robertson & King, 1974). MAbs have a potential advantage in that they might have the desired specificity for oestrone sulphate whereas polyclonal antibodies are mostly directed against oestrone.Another typical application in animal reproduction is the use of monoclonal antibodies against H-Y antigen for sexing bovine embryos before transplantation (Booman, 1986). The affinity of the developed monoclonal antibodies appears to be low. It seems unlikely that H-Y antigen will be used as a means for selection of X or Y chromosome bearing sperm. Success would depend on haploid expression of H-Y antigen by Y-bearing spermatozoa. Use of MAbs to detect pesticide or drug residues in carcasses, and illegal drugs in the blood or urine of race-horses, can also be envisaged (Antczak, 1982).

Recombinant DNA technology

Recombinant DNA technology is characterized by new combinations of inheritable material created by inserting nucleic acids molecules produced outside the cell, into a plasmid or a virus vector. This vector is introduced into a host where it will reproduce (see Figure 2). The technique can be used in different fields and/or strategies, the major ones being:

1) Formation of recombinant DNA-products (either cloned naturally occuring or "mutant" proteins produced by means of protein engineering) such as subunit vaccines, therapeutic agents etc.
2) Production of diagnostic probes.
3) Reprogramming of fermentation microbes or cells for efficient production of various metabolites e.g. antibiotics.
4) Transfer of genes for
   a) creation of cells for specific production or for the study of gene regulation and expression,
   b) creation of transgenic individuals to study gene regulation/expression and also effect on population level,
   c) somatic gene therapy (humans).

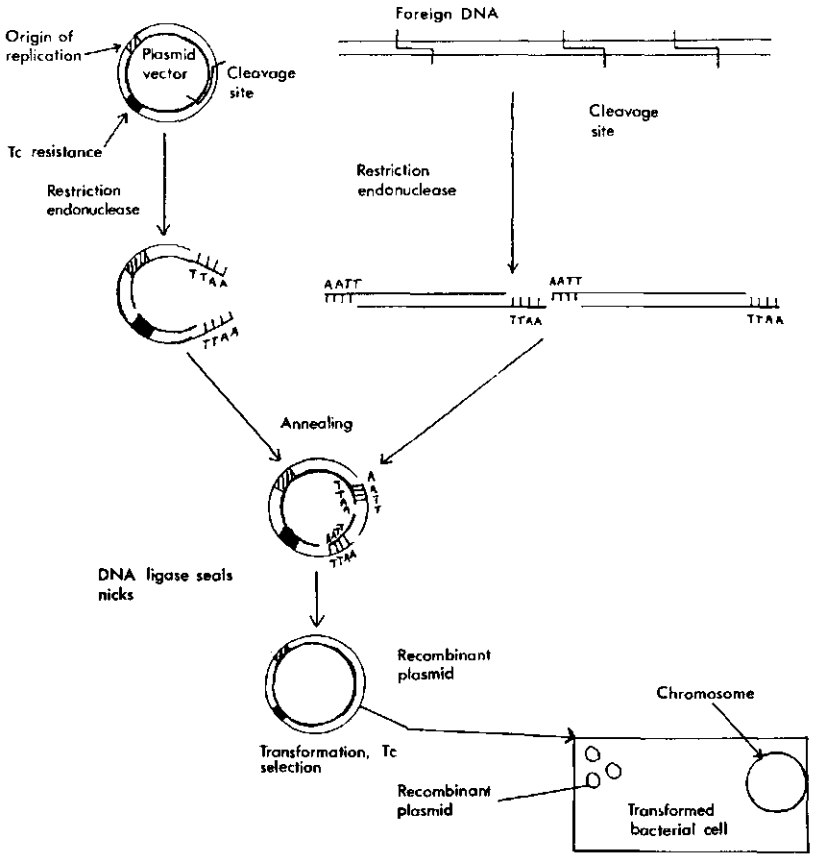

Fig. 2. Use of DNA ligase to create a covalent DNA recombinant joined through association of termini generated by Eco RI.(Old & Primrose, 1982).

Production of vaccines.

The conventional methods of vaccine production are not only expensive but also sometimes pose a certain risk. Vaccines produced by recombinant DNA technology have compared to conventional methods the following advantages:

a) The risk of infection when producing and using the vaccine is reduced because the vaccine does not include infectious material.
b) The vaccine may be produced at a lower cost.
c) The vaccine will be cheaper and easier to handle if e.g. storing at lower temperature can be avoided.

The main drawback associated with modern subunit vaccines is low immunogenicity. Though the solution of this problem has proven to be quite a challenge, several promising techniques for potentiation of immunogenicity have recently been presented (Franke et al., 1985, Morein et al., 1984. For review see Lie & Hellemann, 1986).

Genes for virus subunits have now been cloned for the following animal viruses: Herpes virus, canine parvo virus, foot-and-mouth disease, fowl

plague, rabies, and vesicular stomatitis, while several others are in the process of being cloned (Bachrach, 1982). In the area of bacterial vaccines, attempts are being made to transfer pili genes from enterotoxicogenic E. coli causing diarrhoea in livestock into E.coli K12, with the aim of producing a pilus vaccine (Bachrach, 1982).

The ability to separate functional antigens from irrelevant antigens, and to produce specific proteins, opens up the possibility of also developing vaccines against helminths and hemoprotozoa. Furthermore, it may now become possible to produce vaccines against agents which are too dangerous to grow on a large scale using conventional methods.

A survey of the potential for new biotechnology in vaccine production is given in Table 1.

Table 1. Viral animal diseases and potential vaccine production.

Disease	Potential for new biotechnology	Current vaccine status	Potential for new vaccine
Viral diseases:			
Foot-and-mouth disease.....	+	Medium	Replacement
Rabies.....	+	Variable	Replacement
Parvovirus:			
Swine.....	+	Poor	Replacement
Canine.....	+	Medium	Replacement
Bovine leukosis virus.....	+	N.A. *	Replacement
Bovine papilloma virus.....	+	N.A.	Export animals
Rift valley fever.....	+	Good	Replacement
Marek's disease (fowl)	+	Medium	Replacement
Infectious bovine:			
Rhinotracheitis.....	+	Medium	Replacement
Pseudorabies.....	+	Medium	Replacement
African swine fever.....	+	None	New product
Rota viruses.....	-	None	New product
Bluetongue.....	+	Poor to medium	Export animals
Hog cholera.....	-	Good	Replacement
Newcastle disease.....	+	Poor in some areas	Replacement
Bacterial diseases:			
Tuberculosis.....	N.A.	None	New product
Neonatal diarrhea.....	+	Poor	Replacement
Bacterial respiratory disease.	N.A.	Poor	Replacement
Anaplasmosis	N.A.	None	New product
Parasitic diseases:			
Babesiosis.....	+	None	Replacement
Trypanosomiasis.....	+	None	New product
Coccidiosis.....	+	Good	Replacement
Helminithic diseases.....	+	Fair	Replacement

* N.A. =Information not available.

Source: Board of Science and Technology for International Development, et al.. "Priorities in Biotechnology Research for International Development-Proceedings of a Workshop" (Washington, D.C.: National Academy Press and the Office of Technology Assessment).

Production of hormones

The first pharmaceutical products resulting from the application of this new technology were the hormones somatostatin, insulin and growth hormone, and the antiviral agent interferon. The testing of microbially produced growth hormone from swine and cattle and of interferon from cattle is well underway. Remarkable results have recently been reported in connection with the use of synthetic growth hormone in lactating cows. A daily injection of 40 mg hormone led to a 40 percent increase in milk yield compared to the control group (Hauge, 1985). Given to heifers, hormone increased growth of the udder. It also appears promising with regard to obtaining more efficient meat production. Another hormone the availability of, which might be valuable, is parathyroid hormone. This is because of its potential as a prophylactic agent in cows with a history of milk fever, one of the common production diseases.

The following results have been reported from experiments in USA in which pigs were given a daily injection of 200 mg growth hormone, starting at about the 40 kg live weight stage:

15-18 % increase in growth rate.
20-30 % increase in feed efficiency.
55 % reduction in the amount of carcass fat.

Manipulation of micro-organisms in the rumen to increase feed efficiency

An interesting question related to animal production is the following: Is it possible to increase the genetic capacity of enzymes of ruminal bacteria by recombinant DNA technique? We know that e.g. reindeer and musk oxen possess rumen organisms which depolymerize hemicellulose/-cellulose/lignin more efficiently than those in high yielding milk cows. Efforts are being made to induce bacteria in the pig stomach to produce cellulose degradation enzymes, using recombinant DNA technology (Pond, 1983). See also Smith & Hespell (1982), and Rutledge & Seidel (1983).

Diagnosis of microbial infections

Hybridization using a radioactive, isolated DNA fragment can also be used to identify genes of infectious organisms. Such DNA probes for several human viruses are now being produced on a commercial scale. A further account is given by e.g. Olsvik & Fossum (1986).

Animal breeding

The application of traditional animal breeding strategies in e.g. cattle, pig and sheep results in a genetic progress per year of approx. 1 % for several traits. This level of progress could certainly be maintained over many generations on the basis of existing knowledge. If a substantial increase in genetic progress is to be achieved, it is necessary to mobilize: new knowledge, new technology (Everett, 1984).

The finite object for selection is in fact the gamete. However, in practice selection is made between gametes. By uniting gametes from "the best", we gradually change the gene frequency in the desired direction. However, we never find gametes carrying only "plus" genes. We have to accept a proportion of "minus" genes along with the "plus" genes.

Genetic engineering may, however, eliminate these problems to a large degree. It may be possible to transfer single genes from improved populations without them being accompanied by undesirable alleles, as

well as to achive gene transfer from one species to another.

In other words, we are talking about transgenic animals. As described in a literature review by Skjervold (1984) success has been achieved in producing transgenic. In studies carried out by Hammer et al. (1985), the gene for human growth hormone was injected into 5 thousand zygotes of rabbit, sheep and pig. The gene was expressed as mRNA and human growth hormone in rabbit and pig. However, no significant stimulation of growth was demonstrated probably because of failure of the receptor system. It may also be mentioned that a Chinese research group has succeeded in developing transgenic gold fish, and that attempts have been made to transfer genes from Merino sheep to zygotes from English meat breeds of sheep. In Norway, promising results have been obtained with regard to the transfer genes for human growth hormone to fish eggs.

In the survey below, a comparison is made between different species concerning the production of transgenic animals (Krausslich, 1986).

Table 2. Production of transgenic animals.

	Mouse	Rabbit	Pig	Sheep	Cattle
Ovulations per animal					
- without superovulation	6-10	8-12	10-15	1-3	1
- with superovulation	15-30	20-30	30-40	4-8	4-7
Visibility of nucleus	+++	+++	++	+	+
Survival rate					
(progeny/injected egg)	10-15%	8-12%	5-10%	5-7%	3-5%(?)
Integration frequency					
(transgenic/progeny)	15-25%	10-15%	8-12%	2-5%	?

Three methods of transfer have been pursued: 1) direct, physical injection on the male pronucleus, 2) retroviral-aided introduction, and 3) a two step procedure based on the incorporation of the chosen gene into a population of embryo stem cells, the selection of cells that express the gene, and the subsequent incorporation of such cells into the blastocyst (Fig.3). Most studies have been conducted with the laboratory mouse by direct injection. The rate of incorporation in domestic livestock species has been lower than in mice (Land & Wilmut, 1987).

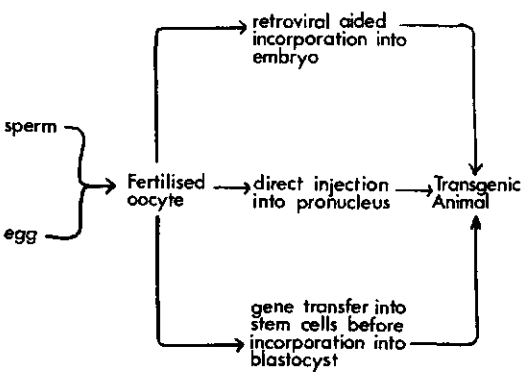

Fig. 3. Three routes for the production of transgenic animals. (Land & Wilmut, 1987).

It seems reasonable to believe that gene technology/gene transfer will

be most appropriate for traits depending on one or a few genes. There are now several examples of single genes which increase litter size in sheep. The best documented is the Booroola gene (Piper & Bindon, 1985), though others have been reported in Icelandic sheep (Jonmundsson & Adalsteinsson,1985), and the Cambridge breed of sheep (Hanrahan & Owen,1985). Whether these are allelic or possibly even the same allele is not known. The only other examples of single genes affecting normally polygenic traits are the "halothane" and double muscling genes of pigs and cattle, respectively, which increase the yield of lean meat. Not only are there few examples, it is also very relevant to note that these genes exert both beneficial and adverse effects, the latter limiting their application. The double muscling gene increases calving difficulties, while the "halothane gene", though increasing the lean meat yield, leads to increased mortality due to stress as well as a greater incidence of PSE (pale, soft, exudative) meat. Present evidence seems to indicate that the molecular biologist is unlikely to find single genes with purely favourable effects for transgenesis.

If, however, we try to predict more precisely the relevant fields of application for gene transfer in animal breeding, the following likely candidates appear:

- Gene therapy. A large number of hereditary defects in domestic animals have been discovered. In 1973 the World Health Organization started publication of a Bibliography on Congenital Defects in Animals, which is regulary updated. For breeding purposes, it would often be valuable to detect carriers of recessive disease genes. A homozygous condition for a dominant gene may, furthermore, not always be apparent phenotypically. Assuming the availability of a DNA probe for the gene in question, it is now theoretically possible to study DNA in a blood test from the animal and decide the status. Furthermore, research is being carried out to develop techniques for substituting the "sick" gene with a healthy one. This has already been achieved in mouse model systems like lack of immune responsiveness to certain antigens (Le Meur et al. 1985).
  Certainly, it would be desirable to increase general and specific resistance against infectious and production diseases.
- Increase in the production capacity of animals by transferring genes coding for "key substances" (e.g. hormones). Palmiter et al. (1982) transferred a gene for growth rate from rat to mouse. They concluded that there is a correlation to the number of copies of DNA for growth rate, and that the transferred gene is adopted.
- Increase in the number of the copies of genes coding for a particular protein in order to increase its rate of synthesis(genes coding for milk-protein, egg-protein, muscle-protein, wool-protein, and so on) (Ward et al., 1986).

According to Land & Wilmut (1987) a gene transfer must improve an economic trait by at least 10 percent to be justifiable, without any negative consequences for the other traits. The same authors emphasized that 200 cows are necessary to identify one of five useful gene constructions for a dairy trait.

Land & Wilmut (1987) also pointed out that it will be important to define both the beneficial and the deleterious effects of the gene, as well as to compare the benefit gained with that achievable by conventional genetic selection. As gene expression depends upon the site of incorporation and of copies of the gene, this assessment will be required for each transgenic line.

Closely related to the applications already mentioned is tissue typing. Tissue typing antigens are gene products showing great variation, and a relationship with disease resistance. This has been mainly studied in human beeing and mouse, but seems also to be the case in domestic animals (see e.g. Syed et.al., 1986). Some examples are given in Table 3.

Table 3. MHC-associated diseases in farm animals.

Species	Disease
Chicken	Marek`s disease
	Lymphoid leukaemia
	Rous-sarcoma-virus induced tumours
	Autoimmune thyroiditis
Cattle	Leukaemia virus infection
	Mastitis
	Resistance to various parasites (Ixodes spp.)
Horse	Sarcoid
	Sweet Itch (Summer eczema)
Swine	"Piglet-mortality"
Sheep	Scrapie?

The most common method employed to carry out tissue typing involves the use of specific antiserum. Antisera produced in the traditional way include polyclonal antibodies. As mentioned earlier it is possible to-day to produce monoclonal antibodies using cell fusion technique. The new techniques developed within the field of biotechnology allow tissue typing studies to be done more directly i.e. they allow the comparison of the base sequence in DNA in different animals. A simpler method to clarify genetic variation at the DNA level is the application of RFLP-technique (RFLP - Restriction Fragment Length Polymorphism) (see e.g. Syed et al., 1986). This technique is currently being used in Norway in cattle, pig, goat, horse and fish.

"Key words" for some Norwegian biotechnology/gene technology research projects in animals

Embryo transplantation and embryo sexing in cattle.
- Topics: Embryo; transplantation; sexing; freezing.

Study of DNA in bacteria with respect to virulent factors.
- Topics: Plasmid profile; gene probe; antibiotic resistance; ecology.

DNA finger-printing.
- Topics: Identification; gene mapping.

Immune response in fish, methods and inheritance.
- Topics: Immune mechanisms; immunogenetics; infection resistance; fish.

Increased feed efficiency in fish using recombinant DNA technology
- Topics: Feed efficiency; insuline; fraction of carbohydrate; salmon; trout.

Recombinant DNA technology to diagnose inheritable defects in animals.

- Topics: PHI-gene; Hal-gene; DNA probe; meat quality; pig.

Hereditary regulation of disease resistance in animals.
- Topics: Tissue typing: lysozyme activity; DNA probes; c-DNA library, genomic library.

Monoclonal antibodies and transfection technology.
- Topics: Biotechnology; monoclonal antibodies; gene-transfection; disease control.

In vitro fertilization of eggs in cattle.
- Topics: In vitro fertilization; biotechnology; reproduction; cattle.

Ethical aspects

The ethical aspects related to the use of biotechnological methods in human medicine has been, and will continue to be, a topic for careful examination and debate, both nationally and internationally. Similar concerns arise in animal breeding and veterinary medicine, although not to the same extent. The ethical aspects in the animal field are essentially related to animal welfare. A more detailed discussion is given by e.g. Fossum (1986).

The prospects for gene technology

It is difficult to predict exactly how important a role gene technology will play in different areas of animal science. Skjervold (1986) made an inquiry among American scientists, the results of which are given in Table 4.

Table 4. The influence of gene technology in 1990, 1995 and 2000 according to 150 American scientists. Higher value means greater influence (Skjervold, 1986).

Application	Influence		
	1990	1995	2000
Disease resistance, diagnosis of diseases	1.55	2.28	2.73
Medicines (hormones, vaccines, antibiotics, and so on)	1.74	2.46	2.91
Nutrition (growth hormones, rumen bacteria, and so on)	1.23	1.97	2.37
Genetic progress (yield/ productivity)	0.97	1.39	2.09
Gene mapping	1.35	2.09	2.50

As can be noted from the table, the expectations are greatest with regard to "disease resistance" and medicines.

Economic resources in biotechnological research.

Research funds channeled into biotechnological research in the Nordic countries amount to about 2.5 billion (USA) Norwegian kr. per year. Expressing this figure in another way input is about 5000 "research years", the percentage of funds from government (public sector) and industrial sources being almost the same (Nordisk Industrifond, 1987). As can be seen from Table 5, Sweden tops the list in Scandinavia. In Norway, it is planned to spend about 250 million Norwegian kr. on research in biotechnology during the period 1986-88, about 25 percent of this being within the field of veterinary medicine, and plant and animal breeding.

Table 5. Number of "research years" within biotechnology-related areas (Nordisk Industrifond, 1987).

	Government		Industry	
Country	Number of "research years" Total	Gene techn.	Number of concerns undertaking research	Number of "research years"
Denmark	650	approx. 215	30	1250
Norway	450	approx. 90	23	240
Iceland	40	approx. 5	6	> 10
Finland	380	approx. 75	23	>200
Sweden	770	approx. 300	60	1100
Total	2290	approx. 685	142	2800

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INTERACTION BETWEEN MOLECULAR AND QUANTITATIVE GENETICS

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Summary

Animal breeding programmes are currently based on quantitative genetic principles, but the advent of molecular genetic techniques such as insertional mutagenesis and insertion of specific constructs as transgenes opens new possibilities. Molecular techniques for induction of insertional mutations in mammals are reviewed. The rate of production of quantitative genetic variation by induced mutation compared to the spontaneous rate and likely increases in response are assessed. Insertional mutagenesis is also a potential tool for molecular analysis of quantitative variation. Insertion of specific transgenes must, to be effective, give rates of progress competitive with those currently achieved, or add to existing schemes. The major problem is the identification of suitable genes for insertion to improve quantitative traits, which stems from the present lack of under standing of quantitative characters at the biochemical level. The implications of imprinting (inactivation of maternally or paternally derived genes) for quantitative traits are reviewed.
Key words: quantitative genetics, molecular genetics, animal breeding, mutations, transgenes, imprinting.

Introduction

Current breeding programmes in animals are based mainly on quantitative genetic principles. Essentially we design the programme and select each generation on the premise that many genes influence each trait and that we can describe their inheritance in terms of genetic and environmental components of variation and covariation. Sometimes we have information on individual genes, for example halothane susceptibility and its relation to lean meat content of pigs. In such cases we can and do use the information in both the design and execution of a programme, for example in crossbreeding or progeny testing. The number of such identified genes is few, however, and so their application is limited. In view of the fact that current breeding programmes achieve rates of progress in excess of 1% of the mean per year, up to 4% in poultry for meat (Smith, 1984), it seems likely that molecular based programmes, whatever they might be, are going to be an addition to, not a replacement of, conventional selection. Three specific applications of molecular methods, at least with present technology, can be identified:

(i)Marker assisted selection using restriction fragment length polymorphisms (RFLPs). The increasing availability of many molecular markers for man and the similarity of mammalian genetic maps (Womack & Moll, 1986), makes it likely that the same probes can be used in animals. This opens up several possibilities: (a) Identification of genes or short regions of DNA which have a large effect on the quantitative trait using within or between population variability. Subsequently, identified or cloned genes

can be transferred by conventional crossing or transgenic methods. (b) Transfer of known genes between populations by repeated backcrossing but with transfer of little associated chromosome. (c) Incorporation of RFLP markers in selection indices. As it is very unlikely that the RFLP variant identifies the actual base change or insert associated with the trait, use has to be made of linkage disequilibrium between the marker and trait loci either in the population as a whole or within families, for example by selecting young bulls on the basis of segregation within the half-sib family (Soller & Beckman, 1982). The use of RFLPs is undoubtedly interesting and important, but is to be discussed elsewhere in this volume.

(ii) Insertional mutagenesis. Rates of response to selection are dependent on the genetic variation in the population. Molecular methods offer the possibility of increasing variability by mutagenesis, even though individual genes are not identified. Various methods have potential for inducing mutations by insertion of foreign DNA and disrupting the genome of the host. We shall consider the theoretical background to the maintenance of genetic variation, factors which influence it, potential methods and the possible role of insertional mutagenesis. As this area has not received much attention in the literature, we focus on it.

(iii) Transgene insertion. Specific genes can be inserted which, if suitably expressed, can lead to large phenotypic changes. We consider the possibilities of what can be regarded as directed mutation and in particular how transgenic and quantitative genetic methods interact. Although undoubtedly important and exciting, there have been many reviews of this area, so our contribution will be relatively brief.

Quantitative geneticists know little about the genes that determine traits of interest, neither their effects on the trait nor their mode of action, neither their number nor their interactions. Molecular methods offer possibilities for elucidating the genetics of quantitative traits, important both scientifically and for eventual application in improvement programmes. Furthermore, molecular studies have provided new information about modes of inheritance, and in particular the ideas of "imprinting", which may have an impact on our quantitative genetic assumptions. Some of these aspects, not directly related to improvement, are also discussed.

Mutation and long-term selection responses

Substantial rates of change are currently being achieved in well organised conventional selection programmes, and it is unlikely that new methods will replace these successful schemes. Let us review the factors that maintain genetic variability and selection responses in natural and domestic populations.

Theoretical analysis shows that if gene effects are additive andmutants are neutral with respect to fitness, then the steady state variance in a population of effective size N is equal to $2NV_M$, where V_M is the new variation produced by mutation each generation (Hill, 1982; Hill & Keightley, 1988). Somewhat surprisingly, it can be shown that this value also pertains with directional selection providing mutants are equally likely to increase or decrease the trait. As the proportion of favourable mutation declines, so the variance declines roughly pro rata. Evidence from Drosophila, reviewed later, shows that if mutations are neutral with respect to fitness, their rate of occurrence is sufficient to maintain the variation we observe in most populations. Natural selection will,

however, probably reduce variation. If stabilizing selection applies (i.e. individuals are less fit if their phenotype is extreme for the trait in question), it can be shown that the genetic variance is proportional to the total number of mutants affecting the trait per generation, and can be much less than if they are neutral (Turelli, 1984). If, alternatively, mutants influencing important metric traits are unfit through their direct effects on viability or fertility, variation is again reduced, the extent depending on the joint distribution of effects of mutants on the trait and on fitness.

It is clear from such analyses that long term responses to selection depend greatly on rates of mutation, and it seems likely that the continued response in poultry populations derive at least in part from mutations arising since modern breeding programmes were started. In the long term, therefore, changes in mutation rate are likely to have substantial effects on variation maintained and utilizable by selection unless all mutants produce unfit individuals or are poorer for the traits under selection than existing variants. Presently we have very little information on distributions of mutant effects on which to base calculations. The relation between the level of the trait and the proportion of favourable mutants is particularly critical. Molecular methods give us the opportunity both to induce mutations and to study the effects of the mutants on traits of interest, and thus to bridge some of the gap between molecular and quantitative genetics.

Rates of generation of quantitative variation by mutation

There is no information currently available on the mutational variance spontaneously arising per generation in quantitative traits of commercial species. We therefore have to rely for our predictions on estimates from laboratory species. The two basic methods of estimation of new mutational variation are by selecting from an inbred base or by analysis of variance among inbred sublines. Lynch (1988) has reviewed methods of estimation and published estimates of the ratio of mutational to environmental variance, V_M/V_E, arising from spontaneous mutations. The most extensive data are for various Drosophila bristle traits, for which $V_M/V_E = 0.001$ is typical, and there is a fair degree of agreement among estimates (Hill, 1982). Thus the increase in variation from spontaneous mutation is small. However, because the steady state variance is proportional to NV_M, its eventual contribution to variance and response is large.

Interestingly, however, some of the highest estimates of mutational variance (as V_M/V_E) come from subline divergence of various morphology traits in mice (Bailey, 1959; Festing, 1973), which, although very variable, tend to be an order of magnitude greater than for Drosophila bristle traits. It is not surprising that rates differ among species because such factors as number of cell divisions in the germ line per generation and generation interval vary between species. There are also likely to be substantial differences between characters in the frequency distribution of the effects of new mutant alleles, i.e. in the relative number of mutations with small and large effects.

'Conventional' artificial mutagenesis

Artificial mutagenesis has been of little use in generating new variation in commercial traits in animal species and its success in plants has been limited and disappointing. Experimentally, the most extensive quantitative genetic studies are of X-ray mutagenesis of various Drosophila melanogaster bristle traits.

Classically, X-ray mutation rates are measured by a sex-linked lethal test. Early studies showed a linear relationship between the rate of sex-linked lethal mutations and X-ray dose (reviewed by Auerbach, 1976, Ch. 5). One kR of X-irradiation induces a frequency of about 0.03 sex-linked lethals in Drosophila spermatozoa. As the average spontaneous rate to sex-linked lethals from a range of natural and laboratory stocks is about 0.0026 (reviewed by Crow and Temin, 1964), 1kR of X-rays increases the rate of sex-linked mutations about tenfold.

To compare these rates with rates of generation of variation in Drosophila bristle traits by X-rays, the experiments of Kitagawa (1967) and Hollingdale and Barker (1971) are most relevant. They provide data on response to selection of abdominal bristles from inbreds subject to X-rays each generation. Such data can be used to estimate V_M/V_E by employing theory for predicting selection responses from new mutations (Hill, 1982). The large experiment of Clayton and Robertson (1964) cannot be used for this purpose because the X-irradiation was done during the 150 generations prior to artificial selection, so most new variation would have been lost by drift and natural selection. Hill (1982) derived an approximate expression for the cumulative response (C_t, in units of environmental standard deviation) to generation t from new mutations of small additive effects on the trait,

$$C_t = 2Ni(V_M/V_E)[t-2N(1-\exp(-t/2N))]. \qquad (1)$$

This can be rearranged to give V_M/V_E in terms of C_t, N and selection intensity (i). The population parameters, responses and estimates of V_M/V_E from Kitagawa's (1967) and Hollingdale and Barker's (1971) experiments are given in Table 1. Responses in the non irradiated controls were small, but give values of V_M/V_E close to the value of 0.001 mentioned earlier. If a value of V_M/V_E = 0.001 for spontaneous mutations of abdominal bristles is assumed, then 1kR of X-irradiation increases the rate at which new mutational variation is generated by a factor of about 6. It should be noted, however, that equation (1) assumes an 'infinitesimal' model with mutants of small selective value (Ns). The true distribution of effects of new mutants is not known, but the presence of large effects will lead (1) to over-estimate V_M/V_E.

Table 1. Selection responses in bristle number of D. melanogaster in inbreds and estimates of V_M/V_E.

Reference	N_e	i	t	C_t	X-irradiation	V_M/V_E	(V_M/V_E)/kR
Kitagawa (1967)	8.4	1.4	17.5	3.36	1.5kR	0.0100	0.0067
	8.4	1.4	17.5	0.19	-	0.0006	-
Hollingdale &	140	0.8	20	1.04	1.0kR	0.0058	0.0058
Barker (1971)	140	0.8	20	0.16	-	0.0006	-

X-ray induced V_M/V_E estimated from cumulative response to selection averaged over lines using eq. (1). Effective population size (N_e) was assumed to be 70% of actual size (Falconer, 1981, p.66).

In view of the relatively small responses obtained in these experiments and the number of generations required, it is perhaps not surprising that there has been little success using radiation to induce variation in

vertebrates. Small improvements were, however, detected in an irradiated mouse line at an apparent body weight selection limit (Roberts, 1967).

Mutagenesis by transposable elements

The classical work on maize showed the existence of mutator loci, and similar phenomena were later discovered in Drosophila. These elevated mutation rates were later shown to be caused by the movement of transposable elements, the best characterised system being the P-M system of D. melanogaster (see Engels, 1988, for a review). Some strains carry P elements, some do not, and in crosses between them a number of unusual features collectively termed "hybrid dysgenesis", are noted. In particular, mutations occur as a consequence of movement of these elements into and out of many sites in the DNA.

Recently, the movement of P elements following such crosses has been shown to induce large amounts of genetic variation in bristle traits (Mackay, 1985, 1987) and in fitness (Yukohiro et al., 1985; Mackay, 1986; Fitzpatrick and Sved, 1986). Mackay's (1987) estimate of V_M/V_E per generation for abdominal bristles was of the order of 0.1, i.e. approaching twenty times greater than that induced by 1kR of X-rays (Table 2). The rate of production of sex-linked lethals by P-element transposition in "dysgenic" crosses was estimated to be 0.03 by Simmons et al. (1980). As discussed by Engels (1988), this rate may include mutations arising from excision as well as insertion. The rate of mutation from insertion alone was estimated to be 0.008 (Simmons et al., 1985).

Table 2. Comparison of spontaneous mutation rates with those from X-rays and P-element transposition in D. melanogaster

	Spontaneous	1kR X-rays	1 generation of P-element transposition
Recessive lethal rate	0.0026	0.03	0.03 (c)
V_M/V_E for abdominal bristles	0.001	0.0062 (a)	0.11 (b)

a) Average of Kitagawa's (1967) and Hollingdale & Barker's (1971) results.
b) Average for reciprocal crosses of Mackay (1987).
c) Presumed to include excision and rearrangements.

Thus, Mackay's results show a difference between the mutagenic effects of X-rays and P-elements on genes causing recessive lethal mutations and those affecting variability in bristle number. One kR of X-rays and one generation of P-element transposition induced by a dysgenic cross both increase the rate of recessive lethal mutations to ten times the spontaneous rate. However 1kR of X-rays leads to a sixfold increase in the rate of production of variability in bristle number whereas one generation of transposition leads to a hundredfold increase. Several hypotheses are possible to explain the apparent discrepancy.

(i) The frequency distribution of mutant effects on abdominal bristles induced by X-rays and P-element transposition is extremely leptokurtic and a few mutants of very large effect happened to be obtained by chance with P-elements, but not X-rays. This explanation, however, seems

unlikely in view of the apparent consistency of the results of independent experiments (Mackay 1985, 1986, 1987).

(ii) There were "hot spots" of P-element activity in Mackay's lines which for some reason caused proportionally more variation in abdominal bristles and fitness traits than X-linked lethal mutations. This is probably part of the explanation for the difference in mutation rates because there is considerable variation between loci in rates of P-element insertion (Engels, 1988). The same or similar mutation was probably obtained as independent events in the abdominal bristle lines (Mackay, 1985), some of which may have been caused by excision rather than insertion. Intriguingly, in Drosophila ananassae a class of mutations, Om, which produce pleiotropic eye morphology defects has been shown to be caused by insertion of tom transposable elements at 20 different loci (Shrimpton et al., 1986).

(iii) The types of mutations caused by the insertion/excision of P-elements may be different from those caused by X-rays, and as such have more effect on quantitative traits. There is evidence that P elements insert preferentially in the 'control' region upstream from amino acid coding sequences (reviewed by Engels, 1988). T.F.C. Mackay (personal communication) has argued that such insertions cause changes in the 'regulation' of genes which gives the necessary range of subtle effects to cause genetic variation in quantitative traits.

Possibilities in vertebrates

The finding that large amounts of quantitative variation can be generated by insertional mutagenesis is surprising and, as discussed above, the explanation is not clear. Presumably, mutagenesis by transposition is powerful because it is highly specific, in contrast to X-irradiation which causes non-specific damage so that doses cannot be raised sufficiently to produce much useful variation. Although transposable elements of the type found in Drosophila are not known in vertebrate species, there are other methods currently available for introducing insertional variation:

(i) DNA micro-injection.

This method applies to mammals, and has been successful with large farm animals (Hammer et al., 1985). A foreign DNA species (the particular sequence used is of little relevance for these purposes) is injected in multiple copies into the pronucleus of the fertilised egg, which can be re-introduced into a foster mother. DNA inserts apparently randomly, usually at a single site as a large tandem repeat (Palmiter & Brinster, 1986). In the mouse, the insertion of foreign DNA into the germ line to make transgenics by such methods has also been shown to induce mutations. In a survey, Palmiter and Brinster (1986) concluded that 9 visible or lethal mutations occurred in 110 transgenic mouse strains produced by DNA micro-injection.

(ii) Use of Electric Fields.

DNA enters cells subjected to a strong electric field which causes temporary holes in the membrane (electroporation) with similar results to micro-injection (e.g. Chu et al., 1987). With iontophoresis foreign DNA is again introduced into the pronucleus using a micro pipette. Instead of

using pressure to expel the contents as with micro-injection, however, an electrical potential difference is set up between the pipette contents and the cell medium. DNA enters the pronucleus in a manner analogous to electrophoresis and inserts into the genome either as tandem repeats or as multiple single copies (Lo, 1983; C.W. Lo, personal communication).

(iii) Retroviral Infection.

There are several routes to obtain proviral inserts in the germ line which have been developed in the mouse (reviewed by Gridley et al., 1987). The germ line can be infected with retrovirus from the 4-cell stage of the embryo to the midgestation embryo stage. Alternatively, embryonic stem (ES) cells (Evans and Kaufman, 1981) can be infected and these subsequently introduced into chimaeras (Bradley et al., 1984). Proviruses insert into the genome apparently independently and at a large number of possible sites, the number of sites of insertion depending on the number of cycles of infection. Using ES cells, the number of inserts can be large, with tens of sites possible per cell (Robertson et al., 1986). A similar frequency of mutation as for DNA micro-injection also occurred for mutagenesis by insertion of proviruses after retroviral infection of embryos, albeit with a smaller sample (Gridley et al., 1987). The retroviruses used in these experiments are usually defective, i.e. depend on externally supplied helper functions. Such methods could, in principle, be extended to other mammals or birds.

Nothing is presently known about quantitative variation generated by insertional mutagenesis in mammals. The use of proviruses has currently the greatest potential because, like Drosophila transposable elements, they are likely to insert near the 5' end of genes (Vijaya et al., 1986; Rohdewohld et al., 1987), and multiple sites of insertion can be generated.

Potential contributions of mutations to response

The time scale required and possible benefit of increased mutation in a quantitative trait can be evaluated by simplifying eq. (1) assuming $t/2N$ is small:

$$c_t = t^2 i (V_M/V_E)/2. \qquad (2)$$

The response from mutation increases approximately quadratically with generation number. Predicted responses for a range of values of V_M/V_E and two initial heritabilities assuming the "infinitesimal" model and ignoring changes in genotypic variance from disequilibrium and mutation are shown in Table 3. If large quantities of useful variation could be generated, as occurred in Mackay's Drospohila lines, selection responses can be substantially increased. It should be noted, however, that this model has several limitations, the most severe of which are: an equal frequency of beneficial and deleterious new mutations is assumed, although most mutations for traits connected with fitness are likely to be harmful; the infinitesimal model is assumed so eq. (2) underestimates the possible response (Hill, 1982).

Table 3. Predicted selection responses from existing and new mutational variation in units of $i\sigma_P$ from existing variation.

	$h^2 = 0.1$		$h^2 = 0.5$	
V_M/V_E	t=5	t=10	t=5	t=10
0	0.50	1.00	2.50	5.00
0.001	0.51	1.05	2.51	5.05
0.01	0.62	1.50	2.62	5.50
0.1	1.75	6.00	3.75	10.00

There is assumed to be negligible change in phenotypic variance due to selection on existing variation or from recurrent mutation. An infinitesimal model of many mutants of small effect is assumed.

Isolation of genes by insertional mutagenesis

The availability of insertional mutagenesis opens up a further possible use in quantitative genetics. Rather than attempting to induce quantitative variation with a view to fixing beneficial alleles as in the previous discussion, insertional mutagenesis can also be used to dissect the 'genetic architecture' of a quantitative character. The effects of insertion on traits of interest are likely to be large because genes may be disrupted or changed in activity or expression. Such mutations could, in principle, be identified byfixing mutant alleles in selection lines or associating specific inserts with an effect on the trait by statistical means. The particular benefit of the method is that the insert acts as a 'tag' for subsequent molecular cloning and it has been used in Drosophila to isolate smooth, an allele with major effect on bristle score (A.J. Leigh Brown, T.F.C. Mackay and A.E. Shrimpton, in preparation). Such approaches are extendable, in principle, to vertebrate species. A likely problem, however, is that many alleles of large effect are recessive (Kacser & Burns, 1981) and their presence may be difficult to determine in an experimental population. Schemes involving subdivision and 'local' inbreeding are likely to improve the chance of expression and subsequent fixation of beneficial recessive alleles.

Insertion of specific transgenes

In the previous discussion we have considered the random insertion of constructs as potential mutagens, simply with a view to disrupting the structure or expression of the genes at or near the site of DNA insertion. In contrast new genes can be constructed and inserted to produce genes foreign to the species, or in many copies at novel site(s) or with different promotors so expression is under different control. This can be regarded as directed mutagenesis, to produce new variants with effects far outwith the normal range. The practical possibilities were demonstrated by Palmiter et al. (1982) with their "giant" mice, but progress to productive change in farm animals has come relatively slowly. This aspect of "genetic engineering" has received extensive reviews and speculation by both molecular and quantitative geneticists (e.g. Wagner, 1985; Robertson, 1986; Smith et al., 1987), so we know more about possibilities than actualities.

A major difficulty in the use of "genetic engineering" is to identify

candidate genes and obtain their expression as transgenes. In view of the rates of response feasible by standard quantitative genetic procedures and the cost of implementing the new technology, it is obvious that the effects of any transgenic constructs must be large to be worthwhile (e.g. Smith et al., 1987). These may be hard to find because large changes in specific components of the animal's metabolism are likely to produce only small changes in output traits such as growth. For example, if it was desired to increase the flux through any enzyme pathway, altering the gene for any one enzyme in the pathway would have only a small effect because most fluxes respond little to changes in individual enzyme activities; there are not "rate-limiting" steps (Kacser & Burns, 1979). Indeed it would seem easier to produce large changes by inhibiting rather than increasing the production of a relevant metabolite.

Two distinct routes can be identified for finding genes for insertion, either by locating genes which are responsible for some of the variation observed within or between populations, or by locating genes through their physiological role, such as structural genes for hormones or their releasing factors or receptors, without there necessarily being any existing variability observed. The metallothione-growth hormone construct of Palmiter et al. (1982) is an example of the latter.

Whilst the cases of single genes with large effects on economic traits on animals are well documented, there are few of them. When selected lines of Drosophila are investigated in detail, however, many genes of large effect on bristle number are found (Shrimpton & Robertson, 1988). It may be possible to identify many more genes of large effect by statistical analyses of populations, particularly using techniques developed most highly for man, but as yet these have not been exploited adequately in farm animals (Hill & Knott, 1988). A further promising route has been suggested and is being developed by Bulfield (1985), namely to use two dimensional gel electrophoresis to identify proteins which differ in structure or degree of expression in one or more tissues between replicated selected lines of, for example, mice or poultry. In principle it is then feasible to ultimately identify these proteins and clone their structural genes from a DNA library. Having identified a putative transgene, its usefulness depends on the biochemical effects of the new allele, but there are several potential problems.

There would be no value in changing copy number by transgenic methods within the species if the gene is "null" for some product or receptor. Transfer of copies of such a gene to other species would be pointless, although attempts to construct and introduce the anti-sense gene might not be. If the mutant is due to over-expression, returns from extra gene copies may show rapidly diminishing returns.

The other major problem of using genes identified through their phenotype, for example the double-muscling gene of cattle, is to locate the relevant piece of DNA when the gene product is completely unknown. The difficulties of this should not be underemphasised. Initial linkage studies may be feasible in mice for which there is a well developed map and in pigs for halothane where linked markers are known; but where do we look for others? It is likely that much information is likely to come from the study of man in view of the close correspondence of the short range linkage map of different mammals (Womack & Moll, 1986).

It seems to us that the more promising route for finding candidate transgenes is not by searching for variation in populations, but by improving our understanding of the biochemical and physiological basis of quantitative genetic characters. Through a proper understanding of how genes operate within the complex systems of organisms we are more likely to be able to change their mode of action usefully.

Other important points have been made by Smith et al., (1987). Most notably, each transgene of the same construct creates a new and unique line of animals, so resources both for insertion, which presently leads to low rates of recovery of transgenes, and testing are enormous. In view of the rates of progress achievable by conventional means, Smith et al. suggest that effects of 5-10% of the mean or more are likely to be necessary for a transgene to be of potential value. They also point out the importance of working with stock at the top of the breeding pyramid and suggest the introduction of transgenes into such open nucleus stocks together with selection. Whilst such a policy of adding in the constructs and using selection to determine their fate, just as they were random rather than direct mutants, might seem logical and appealing to quantitative geneticists, it would seem more likely that marketing considerations would lead to attempts to fix and exploit any useful construct quickly.

Imprinting

New information deriving partly from molecular genetics should be included in quantitative genetic models. We consider such a case.

The expression of classical Mendelian autosomal genes is determined solely by the genotype of the offspring; an Aa heterozygote has the same phenotype whether the allele A comes from its mother or its father. But there are complications. In the embryo of a female eutherian mammal, most of the maternally or paternally derived X chromosome is randomly inactivated, although in extra embryonic tissue and in marsupials the paternal X is inactivated. The system has no "memory" through the germ line, however; the inactivation is not inherited. Diploid parthenogens possessing two maternal genomes are inviable, and by substitution of pronuclei in mouse embryos it can be shown that both maternally and paternally derived genomes are required for normal development. The maternal genome is relatively more important for early embryo development, while the paternal genome is necessary for extra embryonic tissue development (Surani et al., 1984). The process whereby the source of the genome affects its expression in the next generation is termed "imprinting". The mechanism for the process of imprinting, like that of X chromosome inactivation, is thought to be DNA methylation (addition of methyl groups to a subset of the cytosine residues in the DNA) which interferes with transcription; but the mechanism whereby it is reversed in germ cells in unknown (see Surani et al., 1988, for a review).

Not all the genome is involved with these parental effects. Mice with either maternal or paternal disomy of certain chromosomes survive normally, whereas other chromosomes must be of paternal and others of maternal origin for normal development. More detailed analysis shows that maternal or paternal duplication/deficiency of specific regions of chromosomes influence characters such as size and shape of mice (Cattanach & Kirk, 1985). These studies indicate that about one quarter of the genome is imprinted, although this refers to regions of the genome and it may not apply at the level of individual genes.

More specific analyses have been carried out by use of transgenes, which act as molecular markers and their passage followed through the maternal and paternal lines (Reik et al., 1987; Sapienza et al., 1987). The majority of transgenes so studied show imprinting, i.e. methylation and perhaps expression dependent on the sex of the parent transmitting the transgene regardless of the construct used, suggesting that its site in the chromosome was relevant. In most of these cases, the imprinting could be reversed by transmission through the opposite sex, i.e. was "remembered" for only one generation.

Let us consider the quantitative genetic implications of imprinting. A quote on the subject from an editorial in the farming press may help to set the scene: "... the inheritance of some characteristics can come through more strongly from one parent than the other... Observant breeders have been saying that for years. They have maintained all along that some characteristics from male - and particularly female -lines come through more strongly than others. Geneticists would have none of it ..." (The Farmers Weekly, 6th May, 1988). This is because geneticts' experience is that, like Mendelism, our current quantitative genetic theories do a good job of predicting responses to selection and there are not, as a rule, widely different correlations of offspring with their two parents. Nevertheless, let us quantify predictions for a simple model.

Assume a proportion m of the genetic variance is from genes in which only the male parent's copy is expressed, similarly f from the female parent, and 1-m-f from regular Mendelian inheritance. Because only one gene is expressed, questions of dominance do not arise for the imprinted genes, but let us assume those not imprinted are additive and the total variance is V_A. The covariance of offspring (male or female) and sire is the standard $(1-m-f)V_A/2$ for non-imprinted genes; the covariance is $mV_A/2$ from male derived imprinted genes because the gene the father passes to his offspring is always expressed, but there is only an evens chance it was expressed in the father; the covariance is 0 for female derived imprinted genes; and so the total is $(1-f)V_A/2$. Results are summarised in Table 4. Note in particular that m and f contribute differently to offspring-parent and sib correlations, so estimation of variance due to maternal genetic effects in the sense of Willham (1963) or Falconer (1965) are affected. Unlike cytoplasmic or mitochondrially inherited variation, correlations decline with decreased relationship. All these factors, namely maternal, cytoplasmic and imprinting effects can also induce differences between reciprocal crosses, and powerful experiments to distinguish them will be difficult to design.

Table 4. Influences of imprinting on covariances among relatives, where m and f are the proportion of variance in which the male derived and the female derived genes, respectively, are expressed, and n is generation, where n = 2 is grandparent.

Relationship	Covariance x V_A
Offspring and sire	$(1-m-f)/2 + m/2 = (1-f)/2$
Offspring and dam	$(1-m)/2$
Offspring and father's ancestor	$(1-f)/2^n$
Offspring and mother's ancestor	$(1-m)/2^n$
Paternal half sibs	$(1-m-f)/4 + m/2 = (1+m-f)/4$
Maternal half sibs	$(1-m+f)/4$
Full sibs	1/2

A frequent observation in dairy cattle is that heritability estimates are higher from daughter-dam regression than from paternal half-sib correlation, typically 30% and 25% respectively. There are several explanations of this, but let us just consider the novel possibility of imprinting. From Table 4 the ratio of their expectations is $(1-m)/(1+m-f)$. A ratio of 1.2 could be obtained with m = 0, f = 0.17 which would not be out of line with estimates if up to 25% of the genome is imprinted. It

would not, however, accord with the results of Reik et al. (1987) from a limited number of transgenes that a higher proportion of paternal than maternal genes are unmethylated, implying i.e. m > f, so imprinting does not seem a very plausible explanation here. Nevertheless it is important for quantitative geneticists to watch how the subject develops.

Concluding remarks

Animal improvement relies on exploiting the variation we have available and the new variation we can produce. Molecular methods have a potential input in utilizing the available variation, through marker assisted selection, introgression and, for example, identification of heterozygotes, and in generating new variation, whether by random insertional mutagenesis or by directed mutation through transgenes. We are not likely to see a replacement of our existing or developing quantitative genetic technology, such as use of BLUP to compare individuals, but rather an integration of the new technology in order to maintain or increase rates of response. The particular potential of transgenic methods would seem to us to be in making stepwise increases into new areas, where relevant variation is lacking. The ideas of producing lactose-free milk (Mercier, 1986) or pharmacological products (Lathe et al., 1986) are such examples.

There is also a need to integrate the approaches of exogenous administration of hormones, for example, with their endogenous expression from transgenes. The former may be less convenient and in the long term relatively expensive, but is much cheaper in the short term and the ability to control the system is retained. In both scenarios quantitative geneticists need to consider the interactions between these treatments and genotype. Although it appears that BST has similar effects in all populations of cows, however selected, this scenario might not apply elsewhere. For example, immunisation against somatostatin increased growth rate of slow but not of fast growing breeds of sheep (Spencer, 1986).

A very important aspect is the acceptability of the product for human consumption. In view of increasing public concern with health and welfare, it is by no means certain that any "genetically engineered" animals will be allowed in the food chains. Some possibilities are less emotive than others. Low down the list for acceptability must be viral inserts, of whatever form. Genes for, say growth hormone, are likely to be less acceptable than others for their releasing factors.

At this stage of development it is important that we should view molecular approaches and particularly transgenic techniques as an important research tool in helping to learn how animals regulate their growth, lactation and other productive functions. The spin-off into animal improvement may well be indirect.

Our discussion has largely addressed what impact molecular methods are likely to have our quantitative genetic methods and thinking, but the molecular geneticists can also learn from us. There is currently a lot of variation in most production traits, so limits are not a problem. The traits which show least genetic variation, fitness traits such as embryo survival rate, are not obviously accessible to molecular manipulation. There is evidence that many genes affect the important traits, and their production is the consequence of a complex interactive pathway. Therefore it will not be easy to change the output by changing individual parts. Further, any change in one trait is likely to be associated with changes in others: pleiotropy of gene action and genetic correlations among traits are not readily avoided by molecular manipulation. Molecular geneticists must bear in mind that testing of stocks is expensive and

slow, particularly in large species with long generation intervals which are least easily improved by conventional means. Finally, quantitative approaches such as selection and random mutagenesis may lead to identification of genes for molecular manipulation. We can anticipate a closing rather than widening of the molecular-quantitative gap.

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IDENTIFICATION OF SUPERIOR ANIMALS AND THEIR USE IN IMPROVEMENT PROGRAMMES

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Summary

A discussion is given as to what exactly a superior animal is. Depending on the use it can mean an animal with a high average phenotypic expression, a high genotypic value or a high breeding value. Since in the foreseeable future one might not be able to replicate identified superior genotypes, the main emphasis is still on breeding values. There the role of genotype - environment interactions is disussed and the advantages of progeny testing under these conditions are stressed. The accuracy needed for predicting the breeding values and the available statistical techniques are shortly reviewed. The problem of predicting components of breeding values (identified loci, linkage groups or intermediate physiological traits) is considered and some reservations are expressed. Since in a long term breeding scheme not only the additive genetic variance available at the beginning of the breeding work is exploited but also genetic variation occurring during the selection process, ways are mentioned to increase genetic variability (transgenics, induced mutations, etc.) and ways of utilizing best the newly arisen variability. From selection experiments it is concluded that chemical mutagens are potential means to increase genetic variability but that without continuous selection most of the variability will be lost due to drift and natural selection. The limitations on the use of identified superior animals are mentioned.
Keywords: breeding value, genotypic value, genotype - environment interaction, correlated traits, induced mutation, fitness.

Introduction

At nearly all times animal breeders have tried to identify the best animals and to use them as much as possible. They have also tried to mate the best females to the best males, something we now call assortative mating. Thus the theme of this lecture is a very old one!

One of the main differences between the more traditional breeding of the past and the scientifically influenced breeding in the major livestock species as is carried out today is understanding what is best. Whereas in the past it was mainly the intuition (or worse still the fashion or prejudice) of the breeder which determined which type of animal should be aimed at, today the breeding organisations try to determine the best animal from the economic point of view by deriving marginal profits, etc.. There is no question that this is a real advance. However, with state interference marginal profit of today may no longer be valid tomorrow.

Another difference is the identification of the "superior animal". It may be safe to claim, that in the past the main emphasis was on the phenotypic expression of the animal itself and perhaps even stronger on the performance of the ancestors. The potentially very precise method of

progeny testing was hardly used in a systematic way. Also the combination of different pieces of information was done in a more intuitive way. Today sophisticated statistical procedures are employed whose use is made possible due to the availability of high speed computers.

In this essay the question of which animal is superior, how it can be identified and what use can be made, will be discussed. It is assumed, that from the economic aspect we know what kind of animal we aim for.

What is a superior animal?

For the following discussion we first assume an environment without systematic differences. If an animal performs only once we have the phenotypic value (P). If the trait can be expressed several times, we partition the phenotype into two components, a permanent component and one which changes from one expression to the next. The permanent component can be further partioned into the genetically influenced part and the remainder and finally we partition the genetically influenced part into the breeding value (additive genetic value) and the remainder. Thus we arrive at the following description:

$$y_{ij} = P_{ij} = \mu + A_i + (G_i - A_i) + (P_i - \mu - G_i) + (P_{ij} - P_i)$$
$$= \mu + A_i + (D_i + E_i) + E_{pi} + E_{tij}$$

where

$y_{ij}=P_{ij}$ is the phenotypic expression of animal i at the realisation j
μ is the general mean
A_i is the breeding value of animal i
G_i is the genotypic value of animal i
P_i is the average of the phenotypic expression of animal i
D_i is the dominance deviation of animal i
E_i is the epistatic deviation of animal i
E_{pi} is the permanent environmental effect of animal i
E_{tij} is the temporal environmental effect of animal i at realisation j

All effects (except μ, P_i and P_{ij}) are expressed as deviations.

If we want to select a "superior" animal in order to have another expression of the same trait from the same animal we have to predict P_i. If we want another animal of the same genotype (monozygotic twin or sibling, clone) we have to predict G_i and if we want to use it for conventional breeding A_i has to be predicted. Thus depending on the goal different animals may turn out to be the most superior.

As breeding value we use the simple definition of twice the true deviation of the offspring when mated at random to animals of the population. Here again we have to define what population we are dealing with since a superior animal for one population may not be good for another population, something which gives rise to selection programmes like the reciprocal recurrent selection. There we assume that the breeding value for the own population is not a good predictor for the breeding value for the population to be crossed with.

There is still another aspect which makes the definition of the superior animal difficult, namely genotype - environment interaction. In a thesis, supervised by Prof. dr. Politiek, Merks (1988) deals with these interactions and there is quite convincing evidence in pig production that these interactions are substantial. As Dickerson (1962) pointed out there are two options in this situation, either developing special strains for each environment or selecting for a good overall performance in all relevant environments. In many situations only the second option

is possible e.g. if environments are equivalent to (small) herds.

We consider the following situation, which is motivated by the structure of the pig industry. There are I_1 herds, on each herd being a number of sows which are mated with AI-boars, the offspring being fattened on the same herd. If there are genotype - herd interactions each animal has conceptually a different breeding value for each herd. So the breeding value of male j can be characterised by the vector $\underline{A}_j$. The length of $\underline{A}_j$ is equal to I_1. In each herd the additive genetic variance can be different (σ^2_{Ai}) and the covariance between breeding values for herds i and i' is $\sigma_{Aii'}$.

Thus $E\underline{A}_j \approx 0$ $\quad$ $\mathrm{Var}(\underline{A}_j) = \underline{V}_A$

The only condition on $\underline{V}_A$ is that the matrix is positive-(semi)-definite and that we have $\sigma^2_{Ai} < \sigma^2_{Pi}$, where σ^2_{Pi} is the phenotypic variance for herd i (h^2 must be smaller than unity).
The linear model for an observation would be:

$$y_{ijke} = h_i + [s_j + (hs)_{ij}] + d_{(ij)k} + e_{(ijk)e}$$

where:

h_i	effect of herd i
$sh_{ji} = s_j+(hs)_{ij}$	effect of sire j in herd i e.g. $A_j[i]/2$
$d_{(ij)k}$	effect of the dam
$e_{(ijk)e}$	residual effects.

If we assume that $\sigma^2_{Ai} \neq \sigma^2_{Ai'}$ then it is quite obvious that σ^2_{di} and σ^2_{ei} also vary from herd to herd since they all contain a fraction of σ^2_{Ai}.
What we now use as breeding value is a question of <u>definition</u>. If the herds are all of equal size then $A_j = \underline{1}'\underline{A}_j/I_1$ would be appropriate, otherwise a weighted average could be used $A_j = \underline{N}'\underline{A}_j/\underline{N}'\underline{1}$ where $\underline{N}$ indicates the size of the herds. In the following the simpler definition is used.
Then we have:

$$E\underline{A}_j = 0 \qquad \mathrm{Var}(\underline{A}_j) = \underline{1}'\underline{V}_A\underline{1}/I_1^2$$

In general the matrix $\underline{V}_A$ has to be determined, and it may not be possible to assume a simple structure, since variances might vary from farm to farm (e.g. depending on the mean - scale effects) and some farms may be very similar thus $r_{AiAi'}$ may be near unity whereas other farms are such that this correlation is very low. In order to simplify and to get <u>qualitative</u> statements we make two assumptions:
i) the correlation is the same between any two herds and
ii) the genetic and phenotypic variances (σ^2_A, σ^2_d, σ^2_e, σ^2_P) are the same for all herds.
In this case we have $\underline{V}_A = [(1-r)I+rJ]\sigma^2_A$. It should be stressed, that this is a highly symmetric situation and care should be taken to justify these extremely simplified assumptions. Using these assumptions we get the following results:
Regression of offspring on parent, both in the same herd

$$\beta_{O|P} = 0.5\sigma^2_A/\sigma^2_P$$

Regression of offspring on parent, animals in different herds

$\beta_{O|P} = 0.5r\sigma^2_A/\sigma^2_P$

Thus: $h^2_{\text{different herds}} \approx r \cdot h^2_{\text{same herd}}$

Variance of A_j

$$\text{Var}(\underline{1}'\underline{A}_j/I_1) = [1+(I_1-1)r]\sigma^2_A/I_1$$

$$\approx r\sigma^2_A \qquad \text{if } I_1 \to \infty$$

Covariance between two linear combinations of $\underline{A}_j$

$\text{Cov}(\underline{k}_1'\underline{A}_j, \underline{A}_j'\underline{k}_2) = \underline{k}_1'\underline{V}_A\underline{k}_2$

special cases

i) between A_{ij} and A_j ($\underline{k}_1' = [1\ 0\ 0\ \ldots\ 0]$; $\underline{k}_2' = \underline{1}'/I_1$)

$$\text{Cov}(A_{ij},A_j) = [1+(I_1-1)r]\sigma^2_A/I_1$$

$$r_{Aij,Aj} = \sqrt{[1+(I_1-1)r]/I_1}$$

$$= \sqrt{r} \qquad \text{if } I_1 \to \infty$$

ii) between the average of breeding values in I_2 herds and A_j
($\underline{k}_1' = [1\ 1\ \ldots\ 1\ \ 0\ \ldots\ 0]/I_2$; $\underline{k}_2' = 1'/I_1$)

$$\text{Cov}(\underline{k}_1'\underline{A}_j,\underline{A}_j'\underline{k}_2) = [1+(I_1-1)r]\sigma^2_A/I_1$$

$$r_{AjAj} = \sqrt{\frac{[1+(I_1-1)r]/I_1}{[1+(I_2-1)r]/I_2}}$$

iii) between the average of breeding values in the first I_2 herds and the average over the next I_3 herds
$\underline{k}_1' = [1\ 1\ldots1\ 0\ 0..]/I_2$; $\underline{k}_2' = [0\ 0\ldots0\ 1\ 1\ldots1\ 0\ 0\ldots]/I_3$

$$\text{Cov}(\underline{k}_1'\underline{A}_j,\underline{A}_j'\underline{k}_2) = r\sigma^2_A$$

$$r_{k1'Aj,k2'Aj} = \sqrt{\frac{r}{([1+(I_2-1)r][1+(I_3-1)r]/I_2I_3)}}$$

$$\approx 1 \qquad \text{if } I_2,\ I_3 \to \infty$$

If the phenopypic relations are considered one arrives at:

$$\text{Cov}(P_{ij},A_{ij}) = \sigma^2_A$$

$$\text{Cov}(P_{ij},A_j) = [1+(I_1-1)r]\ \sigma^2_A/I_1$$

$$r_{PijAj} = \sqrt{[1+(I_1-1)r]\sigma^2_A/\sigma^2_PI_1}$$

$$\approx r\sigma^2_A/\sigma^2_p \qquad \text{if } I_1 \to \infty$$

If we are interested in the breeding value of a sire having K offspring (no full sibs)

i) all offspring in one herd

$$\text{Cov}(P_j,A_j) = [1+(I_1-1)r]\ \sigma^2_A/2I_1$$

$$\approx 0.5\ r\ \sigma^2_A \qquad \text{if } I_1 \to \infty$$
$$\quad rk$$

$r_{Pj,Aj} = \sqrt{\frac{}{k+\tau}}$ if $I_1 \dashrightarrow \infty$

where

$$\tau = (\sigma^2_p - \sigma^2_A/4)/(\sigma^2_A/4)$$

Selection gain in that path (for A_j and $I_1 \dashrightarrow \infty$)

$$\delta G = ir_{PjAj}\sigma_{Aj} = i\sqrt{(\frac{rK}{K+\tau})}\sqrt{(r\sigma^2_A)} = ir\sigma_A\sqrt{(\frac{K}{K+\tau})}$$

ii) offspring in K herds

$$Cov(P_j,A_j) = [1+(I_1-1)r]\sigma^2_A/2I_1$$

$$\approx 0.5r\sigma^2_A \quad \text{if } I_1 \dashrightarrow \infty$$

$$r_{Pj\,Aj} = \sqrt{(\frac{rK}{1+\tau+(K-1)r})}$$

$$\approx \sqrt{\frac{rK}{rK+\tau}} \quad \text{for K large}$$

Selection gain in that path

$$\delta G = ir_{PjAj}\sigma_{Aj} = i\sqrt{(\frac{rK}{rK+\tau})}\sqrt{(r\sigma^2_A)} = ir\sigma_A\sqrt{(\frac{K}{rK+\tau})}$$

The ratio of $\delta G_{\text{one herd}}/\delta G_{\text{several herds}}$ for $\tau = 15$ is given in Table 1.

Table 1. Ratio of $\delta G_{\text{one herd}}/\delta G_{\text{several herds}}$ for $\tau = 15$.

r \ K	1	5	20	50	$\dashrightarrow\infty$
0.5	1	0.95	0.85	0.79	0.71
0.7	1	0.97	0.91	0.88	0.84
0.8	1	0.98	0.94	0.92	0.89
0.9	1	0.99	0.97	0.96	0.95
1.0	1	1	1	1	1

In the presence of genotype - environment interactions the heritability estimated within herd by daughter-dam regression is expected to be larger than the estimate obtained by daughter-dam regression where daughters and dams are in different herds. If paternal half sibs are used, then the sire component approaches $r\sigma^2_A/4$ as the half sibs are distributed over many herds. Unfortunately a large difference between the heritability estimates obtained by daughter-dam regression and by half sib analysis is not conclusive for a genotype - environment interaction since other factors such as incomplete elimination of herd effects or maternal inheritance can also be responsable for that difference.

The main conclusion to be drawn is that by testing animals over many herds we automatically determine and select on that variable which is the real target variable in breeding projects dealing with a large population where the animals are distributed over many herds and thus environments. Table 1 indicates what can be lost otherwise even in such a simplified situtation. A loss of efficiency of 10 % can easily occur.

If as a consequence we have to test an animal (a genotype) over many environments then this is at present only possible by progeny testing. There we not only test the genotype but much more important we test the

breeding value as it is relevant for the whole population.

This causes other problems since by testing in many herds some traits can hardly be measured at all (e.g. physiological traits such as hormone level or feed consumption, etc.). For these traits a centralized testing scheme would almost be necessary. Also in connection with Moet a centralized testing scheme is often discussed.

If there are genotype - environment interaction between such a specialized, centralized testing station and the ordinary production herds then the advantages may seriously be questioned. To make things worse for some traits it may in practice be nearly impossible to carry out a reasonable experiment to test the hypothesis of no interaction. However, a certain kind of compromise is possible. If we think of dairy cattle breeding, in most breeding programmes the daughters of test bulls are distributed over nearly all herds under milk recording. In this case milk recording must by necessity be a compromise between what is needed for breeding and what is needed for the management of the farm. If the testing were concentrated on a number of large commercial farms (where nearly all the offspring were then sired by test bulls) then we might be able to measure complex traits and still have a very high correlation with the breeding value with respect to all herds.

To close this section we may summarise that we have to clearly define for what purpose the animal should be superior (superior for the production of the animal itself or superior with respect to the production of the offspring). If it is the production of the offspring then it has to be considered from what population the other parent is taken from and in which environment the offspring have to perform. Not being sure of the absence of genotype - environment interaction it is advisable to test the offspring in the range of environments they have to produce.

How precisely do we have to identify superior animals.

In breeding schemes our main interest should not be focused on individual superior animals but on a high genetic progress per unit of time. Genetic progress per unit of time can be expressed as (two paths model)

$$\frac{\delta G}{\delta t} = \frac{(i_f r_f + i_m r_m)}{\delta t_f + \delta t_m} \sigma_A$$

(i_f, i_m intensity of selection in females and males respectively; r_f, r_m correlation between estimated and true breeding value; δt_f, δt_m generation interval)

For a fixed testing capacity selection intensity and correlation (and sometimes generation interval) are inversely related (Robertson, 1959) and quite often it is better to identify the animals only with a low accuracy. If, for example, in a progeny testing scheme we have a testing capacity of 720 offspring, we arrive at the results given in Table 2 given that we select 4 males and that $h^2 = 0.25$.

It is obvious that the number of bulls tested depends on many factors. Thus the number (48) optimal according to this calculation would hardly be chosen, one reason being that in testing fewer bulls the parents can be selected more intensely and as a consequence the mean of all testbulls will be higher. In addition the finiteness of the sample is not taken into account. However, even if we consider all these factors we will get a similar situation, namely that there are two equally good suboptimal designs as e.g. in the above calculation with 29 and 81 testbulls. From a scientific point of view the question is of interest whether the two

option really lead to the same result? If the phenotypic and breeding value follow a bivariate normal distribution then that is the case. However I have not seen a critical experiment where with real traits that question was tested. From a practical point of view farmers are often unwilling to use bulls which are not accurately tested. The latter point makes it difficult to operate a young sire program where information is only provided by either half sibs or by the dam performance.

Table 2. Characteristics of the selection process given a testing capacity of 720 offspring and 4 bulls selected (h^2=0.25).

Number of bulls tested	ir	r	n
5	0.333	0.95	144
8	0.739	0.93	90
10	0.879	0.91	72
19	1.160	0.85	38
29	1.261	0.79	25
36	1.289	0.76	20
48	1.301	0.71	15
63	1.289	0.66	11
81	1.261	0.61	9
137	1.161	0.51	5
720	0.715	0.25	1

Methods to predict total breeding value

In the past two decades great advances have been made in the application of elaborate statistical methodology to predict breeding values (Henderson, 1972). The more or less different methods like selection index, BLUP, Nonlinear methods can all be looked upon in a unified way within the framework of the Bayes - methodology (Dempfle, 1977). In the Bayesian way of approaching statistical problems all parameters in the classical sense are regarded as random variables for which a prior distribution is specified. The data from our experiments add new information and thus modify our prior "opinion" leading formally to the a posteriori distribution. All inferences should then be based only on the a posteriori distribution. There is no doubt that this framework is very elegant. However, there are two problems. First, by going from the a posteriori distribution to a decision (e.g. point estimate) we have to apply a loss function. In animal breeding this loss function should be inversely related to genetic gain achievable. In practice it is not always clear as to whether people try to determine such a loss function, often a certain loss function is chosen purely for mathematical convenience (squared error loss function?) or is dictated by the complexity of the problem (e.g. taking the mean or the mode of the a posteriori distribution supposes two different loss functions). Also if there are several parameters to estimate should that be done with the joint or with the marginal a posteriori distribution?

The second problem concerns the a priori distribution. The Bayes procedure is only optimal if the a priori distribution is really the correct one reflecting the true state of nature. If that is not the case a Bayes estimator can easily be worse than another non-Bayesian es-

timator.

In improving the applied statistical methodology it would sometimes be useful to know how much improvement is altogether still possible. The latter would be most desirable for nonlinear methodology. In certain settings a lower bound for the error variance of point estimators can be given (e.g. Cramér-Rao inequality). If we had such a lower bound it would be easier to judge whether a further search for an improved methodology would still be worthwhile.

As long as we deal with linear models it is now often possible to take into account most of the existing relationships between the observations and the breeding values. The now very topical animal model (Quaas & Pollak, 1980) takes into account all the relationships between the additive genetic values, though relationships caused by dominance or epistatic deviations are still mostly neglected.

Methods to predict components of the breeding value

If by some test we can identify a component of the breeding value directly then the precision of predicting the breeding value will be increased (Soller, 1978). Let P and A be as before the phenotypic and the breeding value with the corresponding variances σ^2_P and σ^2_A. We use the partition $A = A_1 + A_2$ with σ^2_{A1} and σ^2_{A2} where A_1 can be determined directly and where A_2 is independent of A_1. With selection based on phenotype the correlation ρ_{IH} is $\sqrt{h^2}$ and if in addition we determine A_1 directly and select on an index based on A1 and P we arrive at the following correlation

$$\rho_{IH} = \sqrt{\frac{h^2 - 2\tau h^2 + \tau}{1 - \tau h^2}} \quad \text{where } \tau = \sigma^2_{A1}/\sigma^2_A$$

If $\tau \to 0$ we get $\rho_{IH} \to h$ and if $\tau \to 1$ then $\rho_{IH} \to 1$. Other values are given in Table 3. If we have progeny testing, we obtain the results of Table 4.

As can be seen from Table 3 determining a component of the breeding value increases precision quite drastically if the heritability is very low. As soon as the heritability is high (greater than 0.4) then σ^2_{A1}/σ^2_A must be quite large in order that the procedure be of real value. In dairy cattle breeding with σ_A=300Kg and σ_P=600Kg in order to obtain σ^2_{A1}/σ^2_A=0.3 we need under the best circumstances (no dominance, two alleles with equal frequencies, loci of equal effects) the differences between the homozygotes given in Table 5.

Table 3. Correlation between estimated and true breeding values. Selection is based on A1 and P.

h^2	σ^2_{A1}/σ^2_A							
	0	0.001	0.01	0.1	0.3	0.5	0.7	0.9
0.01	0.1	0.105	0.141	0.329	0.552	0.709	0.837	0.949
0.05	0.224	0.226	0.243	0.375	0.570	0.716	0.839	0.949
0.10	0.316	0.318	0.329	0.426	0.592	0.725	0.842	0.949
0.20	0.447	0.448	0.454	0.515	0.636	0.745	0.849	0.950
0.50	0.707	0.707	0.709	0.725	0.767	0.816	0.877	0.953
0.75	0.866	0.866	0.866	0.870	0.880	0.894	0.918	0.961
0.90	0.949	0.949	0.949	0.949	0.951	0.953	0.959	0.973

Table 4. Correlation between estimated and true breeding values. Selection is based on A_1 and 50 offspring.

h^2	σ^2_{A1}/σ^2_A			
	0	0.1	0.3	0.5
0.01	0.334	0.437	0.597	0.728
0.10	0.750	0.763	0.794	0.834
0.25	0.877	0.880	0.889	0.901

Table 5. Differences needed at any one locus between the two homozygotes in order that σ^2_{A1}/σ^2_A is greater than 0.3

number of loci	difference in Kg
1	465
2	329
3	268
5	207
10	147
50	66

As can be seen from Table 4 with progeny testing the additional gain is very low unless the heritability is near zero. If the heritability is 0.1, σ^2_{A1}/σ^2_A=0.3 and there are 50 daughters the genetic progress is increased by 5.9%. If in that situation the determination of A_1 is very inexpensive, we could use it in a two stage selection scheme. In the first stage selection would be based on A_1 (and ancestor information) and in the second stage selection would mainly work on A_2. The usefulness would mainly depend on the cost of measuring A_1. If there is an inexpensive method it could be used in large screening programmes.

Possibilities to predict a component of the breeding value

Identification of the alleles of a major locus

With the help of blood typing and especially since the introduction of starch gel electrophoresis and related methods quite a number of loci could be identified and its relation to economic important traits studied. I think it is a fair statement that at least in cattle none of the loci studied is really used for improving a quantitative trait in an applied breeding scheme. The reason for this disappointing result is that most of the time the superiority of one allele over the other was not clear enough or large enough to really exploit it. Due to new techniques (Restriction fragment length polymorphism and two dimensional gel electrophoresis) we can expect a lot of additional detectable polymorphism and thus new prospect to identify loci of importance. However, it will still be an enormous task to determine also the indirect effects on other traits (like fitness). If a locus with a clear cut large effect is found it always raises the question why that locus has not been influenced by traditional breeding. Perhaps the net effect of the allele

on overall fitness under the economic environment is really not so great.

Identification of linkage groups

Linkage groups are of course less useful than directly identified loci, otherwise the effect of them is similar. The reduced usefulness depends on the strength of the linkage and the amount of linkage disequilibrium. In this case one can easily obtain different results from one population to the next since the allele desired can be linked to different alleles of the marker locus. Even more complicated becomes the use of linkage if there is no general linkage disequilibrium. Then essentially the linkage relationship has to be determined for each individual, resulting in a two stage procedure. This could be carried out in progeny testing schemes in cattle, where the daughters from the testing phase could be used to determine the linkage relation, and only sons with the advantageous linkage relation then being progeny tested.

Identification and use of correlated traits

A large amount of work is carried out to elucidate the physiological basis of economically important traits like milk yield in cattle or lean growth rate in pigs. If such traits are available they might be useful if they can be measured early in life (as screening procedure or to decrease generation interval) and/or can be measured in both sexes. That selection with such traits can work was clearly shown for the activity of NADPH generating enzymes (Müller, 1986), though even in this very informative experiment direct selection on backfat thickness was more effective. In cattle research is focused on growth hormone, IGF, insulin, glucose level and related hormones and substrats. If these combined efforts of several research teams are successful there are still some aspects which could decrease the usefulness of these traits for breeding.

- Selection is based on a correlated trait, the efficiency thus being reduced. However, in the short term only genetic progress per unit of time in the main trait is of importance and this may still be increased.
- If selection is based on both the correlated trait and the main trait (e.g. correlated trait in male, main trait in female) it can be expected that the correlation between the two becomes more and more unfavourable, making the correlated trait progressively less useful.
- Artificial selection often have undesirable side effects. From a theoretical point of view we can expect that in a population which is in an equilibrium selection for any trait, except fitness itself, will decrease fitness. To a certain extent these consequences are unavoidable. However, it may be reasonable to assume a large tolerance region i.e. if we change the mean of a quantitative trait by not too large an amount the fitness is little affected. In models this is often expressed as quadratic or exponential fitness function. Assuming that fitness is affected once we move the mean of the population way out of the current range of expression, then one has the following situation:

$$\delta G_M^* = \delta G_M/\sigma_{AM} \; ; \quad \delta G_C^* = \delta G_C/\sigma_{AC}$$

$$\delta G_M^* = r \; \delta G_C^*$$

where:
δG_M selection gain in the main trait
δG_C selection gain in the correlated trait

σ^2_{AM} additive genetic variance in the main trait
σ^2_{AC} additive genetic variance in the correlated trait
r genetic correlation between main and correlated trait

If fitness is decreased markedly once $\delta G^* > k$, then using a correlated trait the population decreases in fitness even when for the main trait we still have $\delta G_M^* < k$.

In a large experiment with Drosophila melanogaster (Murrmann-Kahl, 1984) we tried to verify these suppositions. There we had a trait which consisted of two subtraits. If the main trait was used, not only was the long term genetic progress higher but also, as far as measurable, the fitness was less affected and in addition after relaxation of selection the regression to the original mean was much less than in the lines where selection was based on the subtraits. In the lines where the selection was based on the main traits the changes in the subtraits were as expected less.

If we think of physiological traits such as activity or level of growth hormone or thyroxine there are detrimental effects when we have too much or too little activity, so changing them directly in order to change indirectly a trait like milk yield seems to me to be somewhat dangerous.

Creating genetic variation

The usual attitude in quantitative genetic was that there is a population with a given genetic variation and that the task of the breeder was to exploit that given genetic variation in the best way.

More recently it was realized that not only the given genetic variation is utilized but also genetic variation which either occurs spontaneously or is created in a more systematic way.

Systematic ways to create genetic variation:

- Transgenics; the genetic information of one allele of a specific gene usually linked to an appropriate promotor is introduced in the fertilized egg. Since this technology is covered by other papers it will not be discussed further apart from mentioning that the specificity of this method with regard to the gene is very high. The success rate may be sufficient, but up to now there are extremely few genes known to be useful for the quantitative traits of interest.
- Transformation; Pandey & Patchell (1982) and Bumstead et al. (1987) irradiated poultry semen with very high doses in such a way that the sperms were still motile but the DNA must have been pulverised. Hens were inseminated with that semen and one day later with untreated semen. There was conclusive evidence that the resulting offspring derived from the untreated sperms but that they also had genes from the treated sperms and these genes were expressed.
  In this experiment there was gene transfer within a species but it should be possible to transfer genes between such species where cross-fertilisation does occur (e.g. between male sheep and female goat). The specificity of this method is essentially zero but from the genes transferred and functioning there may be a few useful ones for the quantitative trait.
- Use of mobile elements; In some species there occur mobile elements whose movement can be triggered by making certain crosses. By random (?) insertion at new places genes may be turned off or on such creating genetic variation. MacKay (1986) showed that genetic progress can be increased by this mechanism. The specificity of this method is zero but many genes can be involved.

- Spontaneous and induced mutation; Frankham (1980) and Hill (1982) pointed out that from experimental observations and from theoretical considerations spontaneously occurring mutations should contribute quite a sizeable amount to the long term selection response. A forteriori that should be true if we increase mutation rate by some means.

In a large experiment using essentially isogenic lines we tested this hypothesis on the contribution of mutations. The details will be given elsewhere but the following conclusions can be stated:

i) Spontaneous mutation is indeed powerful enough to account for a sizable fraction of the long term response
ii) induced mutation by γ-rays was hardly effective in increasing the long term results
iii) induced mutation by the chemical mutagen EMS (Ethyl methanesulphonate) increased long term response dramatically.

For the breeder it is of utmost importance to identify the animals which carry newly created advantageous alleles. In this respect one point should be observed. In sophisticated approaches for prediction of breeding values we use the full numerator relationship matrix. This matrix is proportional to the probability of identity by descent, i.e. also identity by state. However, if a mutation has occurred, that calculated probability is no longer true, thus we are not using the best approach, since the individual performance should be given somewhat more weight.

Another interesting and perhaps significant point concerning the utilisation of useful mutants was observed in our EMS-lines.

After some random number of generations the lines responded to selection and some changed bristle number dramatically. After eventually reaching a plateau some of the heavily responding lines kept that plateau after relaxation of selection which can be interpreted that the favourable allele(s) are either neutral and/or fixed in the lines.

In order to throw some light onto this question and also to investigate whether we can induce mutation, accumulate them by simply propagating the line over several generations and then exploiting the accumulated mutations by selection, a small experiment with 16 lines lasting 6 and 11 generations was carried out.

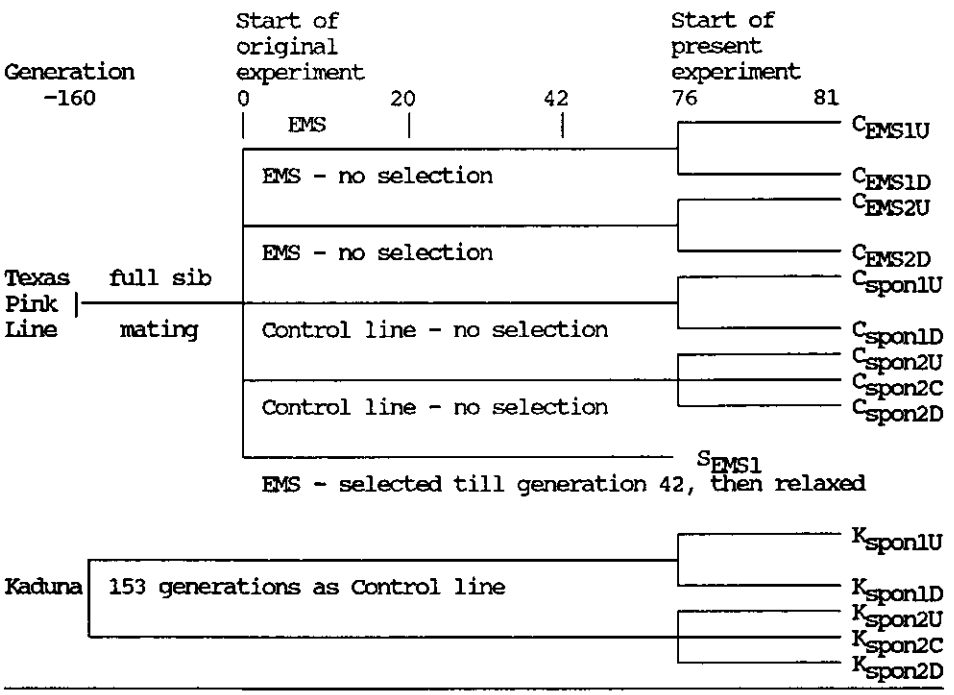
In that experiment the first 9 lines were marked with a recessive mutation (texas pink) and were all derived from one line which was kept for at least 160 generations by full sib mating before sublines were taken.

Line C_{EMS1} was used in the original experiment as a control line with a size of 10 males and 10 females. During the first 20 generations the line was treated with EMS. At generation 76 subline C_{EMS1U} was selected upwards and C_{EMS1D} downwards for 5 selection cycles. Line C_{EMS2} was a different control line otherwise identical to C_{EMS1}. Again two sublines were selected in opposite directions. Line C_{spon1} was used as an untreated control line in the original experiment. Otherwise it had the same history and size as C_{EMS1}. Also two sublines were selected in opposite directions. Line C_{spon2} was a different control line but otherwise identical to C_{spon1}. In addition to the two sublines selected a control line was also kept.

Line S_{EMS1} was treated the first 20 generations with EMS and it was selected from the start of the experiment till generation 42. From generation 42 to 76 there was no selection. The size of the line was identical to the above mentioned lines and the fraction selected was 10 out of 50 for each sex.

The other lines were derived from the Kaduna population. Line K_{spon1} was used as a control line (10 males and 10 females) and was kept of that size for 153 generations prior to this experiment. Two sublines were selected in opposite directions. Line K_{spon2} was a different control line, but otherwise similar to K_{spon1}. In addition to the two sublines selected a control line was also kept.

Table 6. History of the lines used in the experiments.



Theoretical considerations.

Part of the additive genetic variance is lost each generation by drift and another part is added by mutation (σ^2_M). We can write (Clayton & Robertson, 1955)

$$\sigma^2_{At+1} = \sigma^2_{At}(1-1/2N_e) + \sigma^2_M$$

If N_e stays constant then we will get an equilibrium value of
$\sigma^2_A = 2N_e\sigma^2_M$
We assume that with full sib mating N_e=2.61 and with random mating of 10 males and 10 females $N_e \approx 12$, the environmental (including non-additive) variance is 2.4, the additive genetic variance of the Kaduna is 1.6, and σ^2_M is 0.0045 under spontaneous mutation and 0.022 under EMS induced mutation. The values for σ^2_M were derived from the original experiment. Using these assumptions and the above equations we can calculate the heritabilities of the various lines and can compare them with the realized heritabilities estimated with the present experiment. The details are given in Table 7.

Table 7. Expected genetic variances and heritabilities and estimated realized h^2

Line	expected $\sigma^2 A$ at start of present exp.	expected h^2 at start of present exp.	estimated realized h^2 and s.e.	estimated realized h^2 pooled
C_{EMS1U}	0.127	0.050	-0.01±0.04	
C_{EMS1D}	0.127	0.050	0.03 0.05	
C_{EMS2U}	0.127	0.050	-0.01 0.04	0.01±0.02
C_{EMS2D}	0.127	0.050	0.04 0.04	
C_{spon1U}	0.105	0.042	0.06 0.04	
C_{spon1D}	0.105	0.042	0.09 0.04	
C_{spon2U}	0.105	0.042	0.04 0.05	0.06±0.02
C_{spon2D}	0.105	0.042	0.06 0.04	
C_{spon2C}	0.105	0.042	- -	
K_{spon1U}	0.110	0.044	0.27 0.06	
K_{spon1D}	0.110	0.044	0.17 0.09	
K_{spon2U}	0.110	0.044	0.07 0.04	0.13±0.03
K_{spon2D}	0.110	0.044	0.03 0.04	
K_{spon2C}	0.110	0.044	- -	

There are large discrepancies between the heritability expected at the start of the experiment and the one estimated by the selection response. The EMS treated lines responded only to a very slight extent, thus the strategy to induce mutation, accumulate them over several generations and then exploit them by selection was not effective in this experiments. Different results with Tribolium were, however, obtained by Enfield (1986). The results of this strategy is in sharp contrast to the strategy to induced mutations and to try to exploit them immediately by selection. The difference is even more startling as the EMS-treated line did not regress towards the original mean after relaxation of selection indicating that fitness might not be involved, although a different explanation might be that a major locus is involved and the favourable allele is fixed. To elucidate this the EMS-selected line was crossed with a control line. The EMS line had a bristle number of around 31 in the generation 41 to 73. The control line had a score of 20-21, the average of the reciprocal F1 had 23.6 and the backcross to the EMS line had 26.8. From that backcross two lines were formed, which were reproduced over 9 generations without any selection. The results are given in Table 8.

From the results in Table 8 it is quite clear that the lines derived from the crosses are regressing, thus indicating that the stability of the EMS line is due to fixation and not due to neutrality with regard to fitness. If that is the case it can also explain at least partly the result obtained by the C_{EMS} lines. If we induce mutation and try to accumulate them, natural selection is selecting against them and eliminates the alleles favorable for the trait but detrimental for fitness. Only if we have continuous selection pressure can we keep such alleles in the population and increase their frequencies. The formula for the evolution of variance is not valid in this case because additive genetic variance is not only lost because of drift but also because of natural selection.

Table 8. Mean values of the lines, the F_1, the backcross and the lines derived from the backcross.

			Generation								
			1	2	3	4	5	6	7	8	9
Pure Line	F1	Back-cross	Lines derived from backcross								
Cont. ≈21			26.63	24.81	24.04	23.31	23.09	23.64	22.43	22.93	23.77
	23.6	26.8									
EMS ≈31			25.77	24.92	24.60	24.33	24.19	23.29	22.37	22.35	22.61
Mean			26.20	24.87	24.32	23.82	23.64	23.47	22.40	22.64	23.19
corresponding			20.40	20.32	20.37	20.46	20.61	20.50	20.95	19.98	21.15
control lines			19.20	19.38	19.84	19.96	19.67	19.93	20.10	18.94	20.82
Mean			19.80	19.85	20.11	20.21	20.14	20.22	20.53	19.46	20.99
Difference			6.40	5.02	4.21	3.61	3.50	3.25	1.87	3.18	2.20

Apart from the direct effect natural selection may also reduce N_e thus even further decreasing genetic variance.

How do we use superior animals

Here we must distinguish as to whether superior refers to the average of the phenotypic expression, to the genotypic value or to the breeding value.

With regard to the average phenotypic expression it should be noted that this is relevant in dairy cattle. Having the first (part) lactation we predict the average phenotypic expression and cull the animals with the lowest prediction. Even if we increase the correlation between true and predicted value by a sizeable amount the selection intensity is rather low otherwise a lot of replacement heifers must be raised, the cost offsetting some of the advantages. Thus the effect of identification and use of animals with respect to superior average phenotypic expression is of lesser importance especially since there are no cumulative effects.

With regard to the genotypic value the genotype has to be replicated in order to exploit it. One possibility to replicate a genotype would be cloning though there are also other means. Cloning in farm animals is not yet possible and some experts express doubts as to whether it will ever be possible to clone an adult mammal. Given that the biological difficulties can be overcome what advantages would we have? It should not be forgotten that animal breeders can already almost replicate genotypes by the time consuming method of developing inbred strains. Animals of a highly inbred line have apart from mutations all the same genotype and the same is true for crosses between two inbred lines. Also monozygotic sibs have the same genotype. The essential point is to prevent either segregation (cloning) or make it without effects (inbreds).

In order to replicate superior genotypes, genotypes have to be tested, the best selected and then replicated. This implies that the animal has to express the phenotype and only then (as adult) should it be replicated. If embryos are split, we simply replicate random genotypes resulting in several copies from each genotype but fewer genotypes among which

to select. There is an analogy to progeny testing. There we can test many animals for their breeding values each with few offspring or few animals each with many offspring. I cannot see much potential for having multiple copies of random genotypes and the non-use of identical twins in dairy cattle breeding might gives some support to this opinion.

Even if we can replicate from adult animals we are still in a very static situation. Superior production animals can be produced but then there is no progress. In order to find a better genotype we have to allow segregation with ensuing selection of a better genotype. That is again similar to working with inbred lines. There once we have achieved the goal of replicating a superior genotype we are essentially deadlocked. To improve further we have to start all over again with crossing, developing new inbred lines and selecting the best. This kind of breeding scheme though used in the past is hardly applied today.

With regard to breeding values the use of superior animals is quite clear. Just about the only limitation to making as heavy use as possible of the most superior animals comes from considerations of inbreeding and reduction of additive genetic variance. The best balance depends on the balance between short and long term responses. If we utilize only the few very best animals with highest breeding values short term response will be high but due to the low effective population size used genetic variance is reduced and the intermediate and long term response are lower (Robertson 1960). Ways to find good compromises are pointed out by James (1972) and Dempfle (1973).

Conclusions

For the forseeable future the animal breeder will still depend on the breeding values, since the average phenotypic values are of only minor importance and techniques to replicate identified superior genotypes are not yet available. With regard to the breeding values care has to be taken to specify precisely the economic goals, the population the animal is mated to and the environment in which the animals have to perform. Especially if there are genotype - environment interactions it is most useful to test the breeding values in a range of environments, something which is easiest with progeny testing, since there we nearly automatically predict the breeding value as it applies to the whole population. Otherwise only a correlated response is realized.

The accuracy of the identification of superior breeding values is not so important since the real goal is to achieve a high genetic progress per unit of time and that is better achieved by testing many animals with a subsequentially lower accuracy. The accuracy can be improved by appropriate statistial procedures, whose widespread and sophisticated use has been made possible by high speed computers.

The identification of components of breeding values (single loci, linkage groups or physiological traits) is especially useful in multistage selection where these components are used for screening purposes and where they may help to decrease generation interval. The heavy use of physiological traits is regarded with some scepticism, since the physiological trait might be changed quite drastically having a detrimental effect on fitness whereas for the main trait only the correlated response is realized.

In long term breeding schemes one has not only to consider the genetic variation present at the beginning but one has also to consider the genetic variation occurring during the lifetime of the breeding program. In the future perhaps more emphasis will be placed on increasing the useful genetic variability by various means (induced mutation, trans-

genics), but one has also to consider how mutations are identified and utilized best. The use of identified animals with superior breeding values should be as extensive as possible constrained only by the consideration of inbreeding and associated reduction of genetic variance resulting in decreased long term response.

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BREEDING PROGRAMS IN DAIRY CATTLE - CURRENT AND FUTURE CONSIDERATIONS

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Summary

Methods of evaluating dairy cattle using mixed models with Best Linear Unbiased Prediction properties have progressed from the sire model to the animal model. Definitions of effects in models need refinement, particularly for contemporary groups. Pedigree selection and progeny testing is the standard for producing sires used in artificial insemination, but multiple ovulation and embryo transfer schemes are being tried. Efficient production is necessary under conditions of surplus. Efficiency can be achieved by higher production per cow and reducing costs by improved reproduction, increased herd life, reduced health costs, and reduced dystocia. Preferential treatment is a major problem. New biotechnological developments such as bovine somatotropin, mitochondrial genetics, sexing semen, embryo transfers, cloning, transgenic animals, and markers are considered as potential new technologies that may be useful for dairy cattle improvement.
Keywords: Dairy cattle evaluation, models, secondary traits, biotechnological developments.

Introduction

"A cow's milk should amount each year to five times her own weight. Do not be content with less. Count no cow hansom that does not daily produce at least a one-pound print". So said Jacob Biggle (1897).

Production of milk has increased since the turn of the century. The increase has been dramatic in the developed world over the last two decades. This has led to surplus production in many countries, while others have been less fortunate and are suffering from famine. Surplus production has led to quotas on production in some countries and price reductions in others.

Cunningham (1983) compared the structure of dairy cattle breeding in western Europe and North America in the last two decades. In general, production per cow has increased sharply in the United States and increased in the European Economic Community (EEC), but at a slightly slower rate. Dairy cow numbers have dropped substantially in the United States, but only slight in the EEC. Over 80% of the beef in western Europe originates from the dairy herd, whereas over 80% of the beef in the United States comes from beef cattle.

What should be the breeding policy under surplus production? Cunningham (1987) surveyed 16 countries. The most common change in selection objectives in 14 countries with quotas was to put negative weight on carrier, with increased emphasis on fat and protein yields.

Breeders in some countries discussed placing greater emphasis on soundness, mastitis, fertility, and longevity. In Canada, Denmark, Norway, and The Netherlands, studies concluded that increased output

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per cow with increased emphasis on fat and protein percentage was needed. Efficiency of production should be emphasized when production is in excess. This can be accomplished by increasing production per cow and reducing the costs of production. The breeder's input to increasing production per cow is obvious. More emphasis on efficient evaluation and breeding programs, increasing herd life, reducing health costs, and use of new genetic techniques can also increase efficiency.

This paper will briefly review evaluation of breeding animals, models, selection programs, and potential problems and opportunities that are currently available. In addition, possibilities of using new techniques that may become available are briefly discussed. Space does not permit detailed discussion of any of these.

Current Technology - Cow and Sire Evaluation

Identifying elite cows and superior sires to be propagated through the use of artificial insemination (AI) is central to making genetic progress in dairy cattle for any breeding objective. Developments in sire and cow evaluation will be reviewed briefly since Van Vleck and Pollak (1984) gave a comprehensive discussion of this topic.

Best Linear Unbiased Prediction (BLUP) of genetic values using the mixed-model equations developed by C.R. Henderson (1963, 1972) is now used throughout the world and has become the standard for sire and cow evaluation. Applications of BLUP started with a single trait and included only first lactations. Reasons for using only first lactations are to reduce selection bias and to reduce preferential treatment effects if the basis of applying such treatment was first-lactation performance. The mixed-model equations account for competition by adjusting for differences in herdmates of the daughter of the sires being evaluated. Including a cow effect in the model allows the use of multiple lactations to predict cow breeding value and real producing ability along with sire transmitting ability.

The U.S. Department of Agriculture (USDA) Animal Improvement Programs Laboratory and agencies in many other countries developed and used contemporary comparisons. They were initially effective, but as the genetic assumptions for use of herdmate comparisons became increasingly violated, their usefulness declined. The primary assumptions were that sires, dams, and herdmates were a random sample from a homogeneous population with no genetic trend. The USDA Predicted Difference (PD)-74 and PD-82 were major improvements and ranked sires similarly to single-trait BLUP evaluations. As models improved with BLUP properties the rankings diverged more. The USDA plans to evaluate sires and dams using an animal model in 1989. The animal model includes all relationships among animals being evaluated and has BLUP properties.

Henderson (1963) showed that the numerator relationship matrix could be incorporated into what have become known as mixed-model equations with BLUP properties. Use of this relationship matrix was limited because it rapidly became too large to invert. Henderson (1976) made another discovery that allowed major advances when he described how the inverse of the relationship matrix, A^{-1}, could be formed without inverting the original matrix by following a simple set of rules relating to an animal and its parents. This discovery allowed use of extensive pedigree data with minimal costs. Use of A^{-1} reduces prediction error variance by utilizing relative information to evaluate an individual. Often, individuals with little or no data can be evaluated quite accurately through their relatives' performance. Early applications of A^{-1} used the sires and maternal grandsires of the sires being evaluated. Use of a more

extensive A^{-1} has been included in recent evaluations.

Further developments built on the mixed-model equations and A^{-1} that allowed estimation of transmitting abilities with BLUP properties. The next improvement applied in practice was the maternal grandsire model. This model was suggested by Henderson (1972) and was implemented in the northeastern United States (Everett et al., 1979). The maternal grandsire model was used in an attempt to adjust for genetic merit of the mates of different sires. This adjustment is through the sire of the mates and assumes that the mates are a random sample of his daughters.

With BLUP in place and use of a maternal grandsire model, what is the next level of knowledge that can be applied to sire and cow evaluation? Few breeding goals are for a single trait. Milk, fat, protein, and perhaps content of the latter two will have economic importance in many cases. Measures of herdlife and type conformation, and in some countries, disease incidences are included in sire and cow evaluation. For multiple-trait selection, mixed-model multiple-trait analyses are appropriate because they use the correlated structure among traits to simultaneously estimate transmitting abilities for all traits. Covariances among traits allow increase in accuracy; the increase depends on the magnitude of the correlations. The correlation structure is well known among milk and its components, but is less well known among yields and non-yield traits. Inaccurately estimated correlations could result in less accurate evaluations than single-trait analyses. The Northeastern AI Sire Comparison is a multiple-trait analysis that uses milk, fat, and protein yields and their correlated structure, and additionally fits stayability which is uncorrelated with the production traits. Stayability is used to monitor herdlife of daughters of sires. Only first lactations are used for sire evaluations. Single trait cow evaluations using all lactations are computed separately from their own and relative's records and from external sire evaluations. Multiple trait analyses with all lactations are theoretically possible, but to date have not been applied.

When multiple lactations are used in analyses, selection bias becomes a consideration. Henderson (1975) has shown that for estimates of transmitting ability to be unbiased all records upon which selection was practiced must be included in the data. Additionally, there are other assumptions required for unbiased estimates from selected data that are not likely to be met for practical sire and cow evaluation.

Use of the animal model (Henderson and Quass, 1976) is the most advanced procedure for evaluating sires and cows. It is demanding computationally because it requires solving equations of order larger than the number of records. The reduced animal model (RAM) developed by Quass and Pollak (1980) gives identical solutions to the animal model and is less demanding computationally. The RAM separates parents from nonparents and, by absorbing equations for nonparents into parents, allows solving larger equations when supercomputers are not available. The primary advantage of the animal model applied to dairy cattle evaluation is that A^{-1} includes the relationships of all animals being evaluated. In addition to sires with progeny distributed across herds, A^{-1} includes relationships of daughters to female relatives in all herds. Merit of potential bull dams is more accurately estimated in the animal model. Use of all relationships in the animal model can improve bull dam evaluations because some cows have several sons by embryo transfers (ET) and their daughters are potential bull dams. The animal model, with the addition of a permanent environment effect, can include multiple lactations for evaluating a single trait. This is the application of the animal model that the USDA Animal Improvement Programs Laboratory plans to implement in 1989 (Wiggans et al., 1988).

Schaeffer (1984) gives equations for a multiple trait animal model with cow effects included. If the data are large, computer memory may be limiting. He states that, "Although these equations are simple to write symbolically, the actual construction and solution phases can be cumbersome and costly". Computer capacities have increased and costs per operation have consistently decreased in recent years. Also, more efficient computer algorithms are being discovered. So, it may be expected that, in the future, larger problems may successfully and economically be solved and allow more precise animal evaluations.

Models

The development of appropriate models for sire and cow evaluation has perhaps lagged research on evaluation procedures. The issue is how environmental differences can be eliminated for comparisons among cows and sires without also eliminating genetic differences.

Van Vleck (1987) wrote a symposium paper discussing contemporary groups for genetic evaluations. He expresses the true model for a vector of records as y = f (genotype, environment, people). Choices of appropriate models to evaluate genetic differences must consider not only random environmental effects, but also how people manage cattle. Ideally, this function needs to be considered in defining contemporary groups. Choice of a model is a compromise between what is known biologically about the species and its management and what can be reasonably accommodated in a model that is computationally feasible.

The well known mixed linear model $y = X\beta + Zu + e$, with properties given by Henderson (1972), has flexibility to handle different definitions of contemporary groups as the application may require. BLUP equations are derived by minimizing prediction error variance (PEV) subject to unbiasedness (Schaeffer, 1983). Van Vleck (1987) points out that consideration of mean square error ($MSE = (BIAS)^2 + PEV$) may be appropriate because the linear model is, in practice, a compromise between bias and PEV. Inclusion of unnecessary fixed factors in β will result in increased PEV, whereas exclusion of important fixed effect will result in bias. These considerations should be taken into account, when choosing contemporary groups.

Contemporary groups should be chosen to group animals that have been exposed to similar management practices. Enough animals should be in a contemporary group to reasonably estimate the true contemporary group effect. Heidhues et al., (1961) derived a method of estimating the true contemporary group average from the mean of a conditional bivariate normal distribution. If the ratio of the variance of random to fixed effects is about unity, 10 records in a contemporary group estimates the true contemporary average with about 90% accuracy. With a ratio of five, 10 records has an expected accuracy of 67%.

Another consideration in choice of contemporary groups is the effective number of daughters per sire. The latter is the diagonal element of the mixed-model equations for a sire after absorption of fixed effects. As effective number of daughters increase, PEV decreases. The effective number of daughters depends on the balance between the number of a sires progeny and number of contemporaries. Van Vleck (1987) showed how effective number changes with the balance of daughters and contemporaries for both fixed or random contemporary group effects. For fixed herd-year-seasons the effective number is $(nm/n + m)$ for n daughters of the sire evaluated and m daughters of other sires. For random herd-year seasons the effective number is $n(m+\tau)(n+m+\tau)$, where $\tau = \sigma_e^2/\sigma_h^2$. Decreasing PEV increases accuracy and thus increases genetic gain. When herd-year-

seasons are fixed, the expectations of the random variables are not biased, but this is not the case for random herd-year-seasons.

Traditionally herd-year-seasons, being variously defined, have been used as contemporary groups both in the United States and other countries. Where herds sizes have been small, broader definitions have been used. Wiggans et al., (1988) suggested defining contemporary groups by herd-year-month (2 month seasons), first and later parities, and registry versus grade status. They suggested expanding to greater than 2 months when necessary to have at least five lactations in a contemporary group.

Expansion of milk recording to include data relative to how cows are managed within herds could be useful. Examples are assignment to "strings" that differ in feed offered, use of "magnet feeders", etc. More concise assignment to contemporary groups might be possible if such data were available.

Other considerations relative to the choice of models relates to whether the assumptions of the model are fulfilled, or at least, realistic. One such assumption is homogeneous variance among herds. This assumption is violated when herds differ in production levels. If sires' progeny are unequally distributed across herd levels, their progeny tests will be biased. Cow evaluations will also be biased when cows produce in herds of different levels. Of primary concern are bull dams that have high production in high-level herds. There is little doubt that differences in variance within herds exist and cause bias in genetic evaluations. This has been demonstrated by many researchers as referenced by Vinson (1987). Recent work by Welper and Freeman (1987) showed that USDA PD's for milk and fat were biased by both herd level of production and mates of sires. R.E. Pearson (personal communication, Virginia Polytechnic Univ., 1988) found the phenotypic correlation between mean and variance for milk by herds to be .49. K.G. Boldman (personal communication, Iowa State University, 1988) found this phenotypic correlation by herds to be .34 and, by herd size, to be .15. Boldman also found an increase across production levels for genetic, permanent environmental, and error variance when data were divided into three levels by herd means. The correlation between sires with progeny test across the data divided into three levels did not differ from expected, indicating no sire by herd level interaction. A transformation, $\log_e$, is used in the Northeastern Multiple Trait Sire Comparison in an attempt to stabilize variances across herds. After transformation the genetic variance decreases.

Vinson (1987) considered potential bias in genetic evaluations from differences in variation within herds. He demonstrated that the proportion of animals selected from different herds is a function of the herd variance. Further, the response to selection depends on the extent of the greater variability and whether it is genetic or environmental. Hill (1984) discussed methods of correcting for heterogeneous variance where selection is on individual performance among groups with the same genetic mean, and environmental effects on mean performance are removed by selection within groups. He states that these results apply if genetic differences in means exist, but are known and corrections can be made. The example given was with dairy cattle where sires are accurately progeny tested and no genotype x environmental interactions exists. In extreme cases, over 90% of selected individuals came from the more variable groups. Vinson (1987) showed that biases are smallest when heritability is largest in more variable environments and biases are largest when heterogeneity is caused by nongenetic components.

Boldman (personal communication, Iowa State University, 1988) has shown that a transformation, $\log_e$, essentially stabilized the genetic variance of milk yield when data were divided into three production levels. With

the animal model and after stabilizing the genetic variance, unequal permanent environmental and error variances estimated from different production levels can be accounted for in the mixed-model equations. This approach is a possible solution to the unequal within a herd variance problem.

Other problems with inadequate models could be discussed. Some are selection bias, use of parameters (ratios of variances) in the linear model estimated from selected populations, and inaccurate variance components estimates (BLUP assumes the variances are known). Detailed discussion of these are beyond the scope of this paper.

Selection Programs

Pedigree selection and progeny testing is the standard method of producing sires used in artificial breeding over the world. In countries where the same cattle population supplies both milk and beef, pedigree selection is followed by testing of bull calves for beef characteristics and the best of these are progeny tested. Cunningham (1983) compared sire selection in European, North American, and New Zealand populations. He compared the number of bulls tested per million first inseminations per year per lifetime in AI. He found most European populations test more bulls in relation to population size than do American populations; however, American populations have greater usage rates per sire. He concludes the effective selection differential is similar in these populations and that the New Zealand population has the highest calculated selection differentials because of exceptionally high usage rates. A major difference in breeding structure in North America and Europe is the large importation of Holstein genes into European populations. Progeny testing and exchange of germ plasm is well in place and will likely continue for some time.

Multiple Ovulation and Embryo Transfer (MOET) Schemes

Nicholas (1979) and Nicholas and Smith (1983) introduced the refreshing idea of MOET schemes as an alternative to progeny testing. Expected results compared with progeny testing are reviewed by Ruane and Smith (1987). The basic idea is that full and halfsib progeny are produced by embryo transplants and these relative groups are used for selection. Parents are chosen at earlier ages than in progeny testing. Compared with progeny testing, accuracy is reduced, but generation intervals are also reduced resulting in expected increased genetic gains compared with progeny testing. In a nucleus herd, depending upon the number of donors and number of progeny per donor and whether a juvenile or adult scheme is used expected gain is accelerated from 71% to 14% vs. progeny testing, respectively. In the juvenile scheme, animals are selected at 15 months and in the adult scheme after first lactations, giving generation intervals of 2.08 and 3.83 years. If a variation of the juvenile scheme is used that increases genetic intervals to 2.5 years, returns are 46% greater than the progeny scheme and 17% greater than when used to produce progeny tested young bulls. When bulls proven outside the nucleus are used in the nucleus herd, gains vs. progeny testing are about equal or less.

An advantage is that selection could be practiced for increased feed efficiency and, perhaps, fewer health problems in a nucleus herd. This would need to be demonstrated, probably by an independent test, to convince producers of gains made.

Other considerations such as split embryos and indicator traits can

theoretically be introduced into a MOET scheme that could increase progress. Increased inbreeding reduces gains, but decreases are relatively small.

There are other considerations of MOET schemes that have not been published. Will expected gains be realized? When predicting progeny tests from sires and maternal grandsires of the bull being progeny tested, expected gains have been essentially realized; however, gains predicted from dams have been much lower than expected, particularly for milk production (Jeon, 1986). A highly probable reason for lack of predictability is preferential treatment of dams. Differences in mitochondrial effects, however, that are transmitted from a dam to her progeny but not from a son to his progeny could explain part of this lack of predictability (see later section). Another potential cause for gains to not be as large as expected in MOET schemes is failure to realize as many offspring per donor as expected. This potential problem has been considered in some applications and does not change the basic results. Modifications of the nucleus herd MOET scheme to operate in commercial herds can also be considered. The concept of the MOET scheme is being put to tests in at least three countries. The results are awaited with great interest.

Other Considerations of Quantitatively Inherited Traits

Use of quantitative theory has produced consistent genetic gains in production in dairy cattle, and such gains can be expected to continue.

In thremmatology, little has been done to genetically improve reproduction in animals. Dairy cattle must be kept economically fit in all traits related to production of milk and its components, or less than maximum net returns will result. As populations are selected farther and farther from their original mean, some traits such as reproduction are likely to become limiting. The negative genetic correlation between production of milk and its percentage components are well known examples. Another example is a genetic antagonism between production and reproduction that is in the formative stages in dairy cattle.

Production and Reproduction

Freeman (1986) reviewed the physiological and genetic literature and summarized work of he and his colleagues. Heritabilities of milk, fat, and protein production are of the order of .20 to .25 and, for percentages of the latter two, are about .5. Heritabilities of measures of reproduction from paternal half-sibs are < .10 and more recently estimates are < .05. In general, there is good evidence of antagonism between production and reproduction.

Dairy cows partition nutrients between production and reproduction. Production seems favored over reproduction, at least early in lactation. R.O. Harrison (personal communication, Iowa State University, 1988) compared the reproductive performance of high and low milking cows separated by selection and found that progeny of high sires have as many reproduction cycles as progeny of average sires, but the high producing cows do not express visible estrus nearly as early. Van Raden and Freeman (1987) using restricted maximum likelihood analyses found antagonistic genetic correlations of the order of .4 between mature- equivalent milk and fat (adjusted and not adjusted for days open) in first lactation and three measures of reproductive performance. Genetic correlations between virgin heifer reproduction and first parity production were slightly complementary. This conclusion was reached earlier in studies using

independent data from California and the northeastern United States which were reviewed by Freeman (1986). Hanson et al., (1983) showed that, with current economic conditions, gains from direct selection for improved reproductive performance would be offset by more losses in production. Holding reproductive change to zero while selecting for production might be a reasonable goal. At least, daughter fertility should be monitored in AI, and some selection for improved fertility in bull mothers should be considered. Many young sires in the United States are produced by ET, and it is difficult to measure fertility in the dams of these young sires.

If new developments in reproductive physiology allow cows to be successfully bred regardless of production level, then selection for reproduction would not be needed.

Production and Herdlife

Body conformation is selected for in most practical breeding programs. Use of linear scoring (ranges vary from 1 to 9 up to 1 to 50) of conformation data allows conformation to be related to production and herdlife where all traits are scored on a continuous basis. The primary usefulness of conformation data should be using body conformation as an aid to predicting herdlife. Some linearly scored traits are related significantly to production and herdlife (Foster et al., 1986; Sieber et al., 1988). Production can be measured directly. Herdlife has obvious economic significance. Foster et al., (1986), showed that stature, udder depth, rump width, and milk out had intermediate optima when associated with herdlife while dairyness, rear legs side-view, and disposition were linearly associated with herdlife. After adjusting for herd differences R^2 values were generally low. There had not been enough time elapsed, however, in the study of Foster et al., (1986) to allow all cows to express herdlife. They also related conformation to production traits but used only first lactations. Relationships among conformation and production may change with advanced lactations, so these are preliminary results. This work will be repeated with more data. Linearly scored conformation traits may allow the data to determine which conformation traits have economic importance for production of milk, rather than using preconceived ideas of their importance.

Health Problems Associated With Production

Increased production puts additional stress on cows. For example, it can be computed that a cow producing 9072 kg of milk with a fat content of 3.6% recycles 36,287 kg of ATP to ADP, and this does not account for maintenance or other body functions.

Complete health records of progeny of AI sires selected for only high and average milk production have been kept since 1968 in a selection experiment at Iowa State University. Bertrand et al. (1985) summarized the results and reviewed other work. In general, progeny of high sires have more health problems in all body systems (mammary, reproduction, locomotive, digestive, and skin and skeletal) than progeny of average sires. The greatest difference is in the mammary system. In recent years, reproductive problems are greater in progeny of high sires. This conclusion has been repeated in several other experimental herds in the North Central Regional Dairy Breeding Project in the United States. Although health costs are greater, profitability is much greater in progeny of high sires.

The industry needs to monitor such costs and apply better management to keep cows economically fit. Improvements can be due to management or

selection against health costs using data collected in the field. This has been shown to be possible (Solbu, 1982; Lyons, 1987). In the latter study, heritability estimates were largest for mammary, digestive and locomotive traits. More extensive work is needed, not only on health traits, but also on their association with production and other traits of economic significance. Ideally, mixed-model multiple-trait evaluations should be done, but this requires much better estimates of variance components than currently available.

Another approach to this problem is to determine whether there are tests for general immune functions, either humeral or cellular, that can be used to detect general immune deficiencies. An attempt will be made at Iowa State University to determine whether daughters of high sires in our research herd have depressed immune function compared with daughters of average sires. An ultimate objective could be to prescreen young bulls in AI for health of their daughters.

Calving Ease

The economic loss to the dairy industry in the United States because of increased days open, losses in milk and fat, and death losses in calves from dystocia has been estimated to be $14.66 per cow per lactation (Djemali et al., 1987a). Additional losses because of cow culling and occasional deaths of cows gives estimated total losses of $35.00 per cow per lactation.

Advances in methods of analyzing ordered categorical traits have been developed that allow more precise estimates of transmitting abilities with desirable properties. The ordered categorical analysis uses the observed scores to estimate underlying causal effects of dystocia on a continuous scale. This model more nearly reflects the biology of the trait, allows for thresholds, and allows predictions of direct effects for calving ease of sires as an output form the analysis. Djemali et al., (1987b) discussed the literature and applied this procedure to data in the United States. They used a model including fixed sex and parity effects and random herd-year-seasons and sires. This methodology will be used for the National Association of Animal Breeders Calving Ease Evaluation in 1988. After selection for production, it is recommended that virgin heifers be bred to sires with the least expected dystocia in their offspring.

Preferential Treatment

An implicit assumption in evaluating cows is that all animals within a contemporary group have equal opportunity. This obviously is not the case in commercial herds. Dairy producers cannot be faulted if some cows will respond to increased feed allocated and, thus, increase profit compared with other cows that will not respond. Cows divided into different "strings" and fed according to production as well as cows that are fed more than others by "magnet feeders" are not, to the authors knowledge, identified in recording production data. These practices can produce biases in sire evaluation. Biases can be larger in cow evaluations.

Additional biases that have even more consequence are produced when some daughters, or cows, are purposefully treated differently than herdmates. Daughters of elite cows may be treated differentially during growth and subsequent production. These biases accumulate over generations and are particularly important in selecting bull dams. Methods of detecting such bases have not been developed. Preferential treatment may be the largest single source of bias in genetic evaluations.

New and Potentially Useful Technology

In the next few decades, technology at the molecular or cellular level has the potential of producing new tools for the animal breeder. Control of all genes that influence quantitatively inherited traits is unlikely in the near future. It is reasonable to believe, however, that some new biological techniques will be developed that can be used along with statistical methods now used and/or to be developed in the future to improve dairy cattle. This means that methods will be needed to integrate new knowledge from the molecular or cellular level with quantitative methodology for evaluation and selection programs. This could be viewed as a very large multiple-trait evaluation with both known genes effects or markers combined with quantitative methods for evaluation of sires and dams.

Development of basic knowledge from research on humans and other species is at a rapid rate. Adapting this to livestock and using new developments in livestock *per se* is a challenge that will allow better understanding of the biology of domestic livestock. Understanding the biology of dairy cattle should allow more efficient production of food.

Some discussion of new and existing technology will be considered. The number of potential new developments is too large to attempt to discuss all of them and to discuss any in detail. Selected topics will be addressed.

Bovine Somatotropin (BST)

A recent symposium (Natl. Invitational Workshop on Bovine Somatotropin, 1987) discussed mechanisms of action, production of BST, administration, responses to administration, and socioeconomic aspects of BST. BST is a naturally occurring hormone produced in the pituitary gland of all cattle. It is produced commercially by using recombinant DNA technology. The gene responsible for coding BST has been isolated from cattle and transferred to E. coli. The E. coli are then increased in number by fermentation, and the BST is purified for injection into dairy cows (Animal Health Institute, 1987). Supplemental administration of BST, usually after peak lactation, extends peak lactation, resulting in an estimated 10 to 25% increase in production. Additional feed is required for increased production, but feed efficiency is increased 5 to 15%. No change in milk content is expected. It is highly probable that BST will be used commercially though use may be rejected for socioeconomic reasons in some countries.

If sires are progeny tested from daughters where the administration of BST has not been equally distributed across their progeny, large potential biases could result. Even larger biases could be expected in cow evaluation with and without BST administration.

Burnside (1987) considered the impact of BST and other biochemical products on sire summaries and cow indexes. Methods of genetic evaluation could be developed if the cows receiving BST and possibly the levels of administration are known in field data. This would require recording procedures to be in place. Genetic evaluations could be performed using records before and after administration on the same cows to determine if sires and cows rank the same, provided that administration is during the lactation and not for the complete lactation. Contract herds could be established by AI organizations to record BST administration and obtain accurate data to get either before- and-after administration evaluations or genetic evaluations on split daughter groups of bulls some of which have been administered and not administered BST. As with all new develop-

ments, research is needed to answer new problems. Currently "magnet feeders" are common in many countries where some cows within a contemporary group receive more grain than others. This is not accounted for in genetic evaluations. Will BST bias data more than this practice?

Cytoplasmic Inheritance

There is growing evidence that cytoplasmic inheritance controls a part of the variation in production in dairy cattle. Bell et al., (1985) have shown that 2% of the variation in milk production and 3.5% of the variation in fat% are explained by cytoplasmic effects. Huizinga et al., (1986) attributed 10% of the variation in kg milk fat and protein production and 13% of the variation in economic returns from milk to cytoplasmic components. Further, they showed that 8 to 10% of the variation in reproductive performance was controlled by cytoplasmic effects. Tess et al., (1987) concluded that cytoplasmic effects on lactation were large enough to influence calf preweaning body weight in Herefords. McAllister (1986) reported consistent differences between reciprocal crosses. F_1 females with Ayrshire dams produced significantly ($P < .05$) more milk and fat then did F_1 females with Holstein dams. The differences were 585 kg milk and 29 kg fat. Many other references show evidence of cytoplasmic effects.

Some evidence from simulated and field data suggest that cytoplasmic effects are not important. Kennedy (1986) simulated data of about the same size as those of Bell et al., (1985) and concluded that the variation attributable to cytoplasmic inheritance in their study could be the result of residual additive genetic effects not accounted for by the model used. Reed and Van Vleck (1987) analyzed a large number of daughters, dams, and granddams from field data and found no evidence of cytoplasmic effects; these data, however, were inadequately corrected for environmental effects (corrected only for herd-year-season of daughters), and the authors analyzed the residuals from the model.

Unpublished evidence for cytoplasmic inheritance and polymorphic difference in mitochondrial DNA (mtDNA) will be presented from research at Iowa State. Data for a phenotypic analysis are from 669 holstein cows with 1595 records from 53 maternal linages in the Iowa State Breeding Research herd. The lineages were traced to the beginning of the Holstein Herdbook and averaged 21 generations, with an average of 12.6 cows per line. Each cow's record was preadjusted for age effects and preadjusted for sire and maternal grandsire effects by subtracting 1/2 the sire's transmitting ability and 1/4 of the maternal grandsire's transmitting ability. A model was fit to each record containing the effects of mean, year-season of calving, parity, age linear and quadratic, maternal lines and cows within maternal lines. The remaining 1/4 of the additive effects should have been accounted for by cows within maternal lines. The maternal line variance accounted for the following percentages of the total variance; mature equivalent (ME) milk, 5.2%; ME fat, 4.1%; percent fat, 10.5%; and percent solids-not-fat, 10.0%. Expressed as a percentage of the residual variance, these values were essentially doubled.

In addition, mtDNA has been isolated from white blood cells and cloned at Iowa State. About 400 base-pairs have been sequenced from the displacement loop (D-loop) from all lines. Seventeen base-pair substitutions and four polymorphisms have been found by restriction fragment polymorphism (RFLP) analyses. This is clear evidence that there is a molecular basis for cytoplasmic inheritance. We plan to sequence the entire D-loop for all lines and do more exhaustive RFLP analyses. We expect to find more polymorphisms in mtDNA. The intent is to determine whether mtDNA

markers can be associated with traits of economic importance primarily production, health, and feed efficiency. Possible applications of this work are: adjustment of dams' records for mitochondrial effects that are not transmitted through their sons' to granddaughters, choice of females donors for embryo transplants, choice of cows from which to choose herd replacements, determining parentage, and choice of embryos from superior maternal lines from which to replace the nuclei with superior nuclear material. The preponderance of evidence is for a cytoplasmic effect that is large enough to be important in dairy cattle.

Sexed Semen and Embryo Transfer

The technologies of sexing semen and embryo transfer combined with AI have promise of being useful separately and in combination for improving dairy cattle. Embryo transfers are now routine. Sexing of semen has not produced repeatable results but may be available in the future. Van Vleck (1981) considered genetic gain using these technologies. This discussion follows his work.

Table 1. Expected gain by utilizing sexed semen and embryo transfer (Van Vleck, 1981).

	Genetic gain per year (kg)	Net present value
Regular AI	100	$ 14
Sexed semen	115	$ 63
AI with embryo transfer	134	$126
Embryo transfer - few bulls	158	$126
Embryo transfer - sexed semen - few bulls	166	$148

The net present value was computed with an interest rate of 10%, discounted over 15 years and assumed net returns of $.023/kg of milk.

The increased gain due to sexing semen is 15 kg of milk and $49 net present value. Van Vleck (1981) concluded that without loss of semen and with perfect sexing, the cost of sexing semen would have to be less than $19 to be profitable. Little gain from sexed semen for the paths of sires to breed sons or daughters is expected. If substantial semen is lost in the sexing process, additional sires would be needed, probably selected with decreased intensity, and the potential gains could be negated.

Use of AI with ET could produce about 34 kg more annual genetic gain and $112 more net present value compared with regular AI. Most of the gain with AI and ET comes from producing replacements from the best cows in the herd. These values assume an accuracy of dam selection of .64 and producing all replacements from the best 10% of the cows. The cost of ET would have to be reduced substantially for this to be economically feasible. For an individual dairy producer, the alternative to using ET is to use semen from a sire with a transmitting ability as large as the expected gain by AI combined with ET, which is much less costly. AI and ET can be extremely useful when introducing new sources of germ plasm into a population.

The use of fewer sires to produce both sons and daughters should produce 24 kg more genetic gain per year, but not more expected net returns. The final comparison in Table 1 produces the most gain per year,

66 kg more genetic gain per year and $134 more net present value, compared to regular AI. The largest incremental genetic gain was due to increased intensity of sire selection. All these alternatives are attractive enough that, if they are technically feasible and cost effective, they should be considered for improving the cow population. As they become available, system analyses should be used to consider these adaptations.

Cloning

Production and use of clones is an intriguing idea, but as with much potential technology, true cloning still has technical problems being applied successfully in cattle. The idea is that, for example, nuclei from a 16-cell embryo could be transplanted one at a time into single-cell embryos from which the nucleus had been removed. The 16 embryos then would be transferred to donor cows. Ideally, this would produce a clone of 16 identical individuals. Problems, techniques and promise in genome transfer are discussed by Lovell-Badge and Mann (1986). Sidel and Elsden (1988) estimated that with the current level of technology, two embryos would survive from transfers from a 16-cell embryo. Van Vleck (1981) estimated that 6000 pounds of milk superiority at $.023/kg would be needed to balance a $300 embryo transfer cost. Cloning probably is not possible from mature tissue.

Clones from truly superior cows would be useful. For a cow with 13,608 kg superiority above her contemporary group, her genetic superiority would be expected to be 3,402 kg. Van Vleck (1981) pointed out that projection of genetic gains may be inaccurate because normal theory may not hold for such extreme records. Accuracy of cow evaluation would increase, but not dramatically.

If large numbers of clones could be produced from a truly superiority cow, their initial superiority could be used. Selection among clones from different cows could be practiced either in a MOET scheme or in commercial herds, but increased inbreeding could be a problem.

A possible use of embryo splitting is to progeny test a sire and keep one frozen embryo. If the progeny test is high enough, the identical twin from the frozen embryo could also be used without progeny testing. This is not, however, a very likely scenario. If the selection differential is one out of eight progeny tested bulls entering AI, then the frozen embryo would have a one out of eight chance of being used. Ideally all embryos should be split, but costs could be prohibitive and many frozen embryos would not survive. The thawed embryo competes with bulls born in the years the embryos were produced and as future bulls are entering AI, the useful lifetime of the embryo would be limited.

Transgenic Animals

Transgenic animals result from introduction, by embryo injection or by a viral vector, of a cloned gene into a single cell embryo. Multiple copies of the cloned gene are introduced. If some of the injected DNA is incorporated into the animals genome, it will be present in all cells, and to be most useful, should be transmitted to its offspring. Using recombinant DNA technology transgenic mice have been produced with a nonhomologous growth hormone gene and grew to about twice the size of litter mates that were not transgenic.

Gannon (1986) gives six steps to obtain transgenic animals: 1) select gene of interest, 2) prepare a DNA construction which should allow expression of that gene in animal cells, 3) collect freshly fertilized

one-cell embryos, 4) micro-inject the DNA into the pro-nucleus, 5) reimplant the micro-injected eggs in pseudopregnant females, and 6) analyze offspring. All steps must be successful to obtain the transgenic animal. In dairy cattle, the obvious choice of genes would be those which are only expressed in the mammary gland; namely, the α and β -caseins and α and β -lactoglobulins. If multiple copies could be a permanent part of the genome, protein production might be increased.

For traits where many genes are involved in their expression, a primary problem is likely to be in isolating this segment of the DNA, not to mention finding a construct that will allow expression of the DNA. It does not seem likely that all the genes involved in production or reproduction are likely to be controlled by molecular biology techniques in the foreseeable future, so a mix of using new biological techniques with quantitative techniques can be expected.

Isolation and use of genes with major effects may, in general, be the best prospects for gene insertion. Examples could be genes such as the borrolla gene in sheep. The growth hormone gene could be another. It seems likely that if major genes are involved in milk production conventional selection would be increasing the frequency of such genes.

Marker Genes

Molecular genetics has the possibility of locating genes, or segments of DNA, that are linked to other genes that influence productive traits. Linkage can be complete when the marker (RFLP, sequenced DNA) is within the coding sequence of the DNA that directly affects a quantitative trait. It is more likely that the association of the marker and gene(s) that affect production is through linkage. Selection within halfsib groups with relatively large numbers of halfsibs and no recombination is an appropriate genetic situation for use of markers. One of the more likely applications is as an aid to selection of young bulls for progeny testing. Stam (1986) computes an upper limit for the gain in selection due to marker assisted selection within halfsib families is 40%. This assumes that 50% of the variation among young bulls is explained by the predictor and that very large numbers of daughters are measured for the predictor. This projection was from use of a single locus. Stam (1986) estimated (he used "guess") what proportion of the variation between paternal gametes could possibly be "explained" by a large number of markers. His estimate was approximately 20% under the following assumptions: 1) that marker genes were present at an average cross-over distance of 40 centimorgans, 2) that the polygenes for the trait of interest were more or less distributed uniformly over the genome, and 3) that the recombination frequency is .15 between a marker and its nearest gene that influences a trait. If there are about 3 billion base-pairs, which has been given as an estimate for humans, this approximation of 20% is discouraging, even considering that there are many repeats of DNA sequences in the genome. There are so many assumptions in these estimates and so much yet unknown biology that such estimates could be considered as only an educated guess.

Genetic Evaluation of Animals With New Reproductive Technology

Before selection is practiced choices of parents must be made. Methods of evaluating animals need to be developed as new technologies become useful. Kennedy and Schaeffer (1988) considered animal evaluation for several potentially useful reproductive techniques. Their work indicates that, if the biology is known, evaluations can generally be made by

modifying mixed-model procedures. Much work will be needed on such evaluations.

Optimum mating plans for using new technologies and for combinations of new and existing knowledge have not been considered to the authors knowledge.

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FUTURE BREEDING PROGRAMMES IN PIGS

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Summary

An overview is given of current pig breeding programmes, with emphasis on the methodologies applied in order to simultaneously improve production and reproduction traits. Several restrictions on selection intensity presently prevent fully efficient breeding schemes. Some of the challenges and questions for the future are discussed. Changes in breeding objectives, in selection criteria, in methods of evaluation, together with reproductive rate manipulation and use of exotic (e.g. Chinese) germplasm are already perceptible evolutions. The pig genome is presently rather poorly understood and knowledge gained in that domain is expected to have beneficial effects on future breeding programmes.
Keywords: pig, selection, production, reproduction, gene map, marker gene, molecular genetics.

Introduction

An early example of breeding programme for pigs is the lecture given to the Royal Danish Agricultural Society in Copenhagen, on February 5, 1896, by Peter August Moerkeberg. His plan, described by Jonsson (1965), aimed at developing a new breed, the Danish Landrace, to be crossed with imported Yorkshire boars for bacon production. Breeding centers were then established and official performance recording for carcass traits started in 1907 with the creation of the first progeny-testing station. Since then, progressively refined techniques have been devised and the task of developing efficient breeding programmes has become more and more complex (see Harris et al., 1984).

Various organisational and methodological aspects of past and current pig breeding programmes have been recently reviewed by Sellier & Rothshild (1988). The general context of pig breeding is now dominated by crossbreeding systems calling for specialised sire and dam lines and the development of a stratified supply system. In this review, emphasis will be put on the principles underlying current pig breeding programmes, and some of the challenges and questions for the future will be discussed.

General principles of breeding programme evaluation

The first objective of a breeding programme is to produce 'most improvement per unit of time', as stated by Dickerson & Hazel (1944). They show that selection response depends on 3 parameters, selection accuracy (ρ), selection intensity (i) and generation interval (t). The annual response R_a (in genetic standard deviation units) is:

$$R_a=(i_1\rho_1+i_2\rho_2)/(t_1+t_2) \quad (1)$$

where the indices refer to dams and sires respectively. Thus R_a is a function of genetic (ρ) as well as demographic (i,t) parameters. In general, those parameters are not under the breeders control and reproductive rate sets an upper limit on the response possible in each

species. The limit corresponds to optimal replacement policies for breeding females and males (Ollivier, 1974 and 1988).

A second aspect concerns dissemination of the genetic progress obtained in the nucleus down to the producer. This process generates genetic lags (Bichard, 1971) which depend both on the structure of the breeding pyramid and on the genetic level of the individuals migrating from one tier to the next. The gene flow technique (Elsen & Mocquot, 1974; Hill, 1974) allows to define truncation points of the migrating individuals which minimise genetic lags. This has been done, for instance, in the study of a rabbit breeding scheme by Yadav & Dempfle (1988).

Cost/benefit considerations are a third important aspect, and the situation then becomes more complex. For a given dissemination structure, discounted profits at all levels may be evaluated and taken as a criterion of overall efficiency of the system. This approach has been used by Elsen & Sellier (1978) to determine an optimal selection policy in dam lines. Alternatively, for a given selection policy in the nuclues, the same approach may serve to optimise the dissemination system.

Finally, chance plays an important role in breeding programmes. Stochastic models bring useful additional information on the variability to be expected. They also allow taking into account more complex genetic situations, including such parameters as dominance, epistasis, linkages and number of loci. This approach has recently been applied to the study of pig breeding schemes in small closed population by De Roo (1988).

Breeding for production traits

Complete testing

Production traits in pigs are either measurable on both sexes before breeding age (growth rate, feed efficiency, backfat thickness) or measurable after slaughter (lean content, meat quality). Individual and family (sib) information may be used in selection. For individual selection, the annual response given by (1) is maximised when $i/t=(i_1+i_2)/(t_1+t_2)$ is maximum. It can be shown that the maximum response is approximately linear in the logarithms of 2 reproduction parameters, c and $a\lambda$ defined as follows: c is the degree of polygyny (or mating ratio), a the age at first offspring and λ the dam annual fecundity or number of candidates of one sex (sex ratio assumed to be 1/2) successfully bred. The following empirical expression applies (assuming $\rho_1=\rho_2=1$):

$$\max R_a = (2 + \log c + 3 \log a\lambda)/4a \qquad (2)$$

in which, however, a should be corrected for discontinuity of birth process (see Ollivier, 1974), giving the corrected value a=0.75, instead of the actual value a=1 for pigs. Table 1 gives the exact maximum of i/t for various combinations of λ and c. The selection procedure implied here, which assumes uniform culling ages within each sex, may be slightly improved by sequential selection. However, the 2-3% extra gain may not be sufficient to compensate for the operational difficulties of the scheme (Hagenbuch & Hill, 1978).

When sib information is used, the expression of i/t has to be adapted to the reduction in the number of candidates available. Fecundity and polygyny then depend on the number m of individuals slaughtered per litter and the resulting sex ratio α among the remaining candidates (Ollivier, 1988), so that:

$$\lambda^*=2(\lambda-m)(1-\alpha) \qquad c^*=c\alpha/(1-\alpha) \qquad (3)$$

Table 1. Maximum value of i/t in individual selection.

λ	c		
	5	15	25
1	0.74	0.91	0.99
2	1.04	1.23	1.32
4	1.36	1.56	1.65
6	1.54	1.75	1.84
8	1.68	1.88	1.97
10	1.78	1.98	2.07

c = degree op polygyny (mating ratio)
λ = annual fecundity (number of selection candidates/litter)
Age at first litter (a): 1 yr.

Thus, the optimum replacement rates for sib (or combined) testing may be obtained in the same framework as for individual selection. The loss in i/t incurred in any combined testing scheme can than be set against the increased accuracy of selection. This loss decreases with increasing λ and it is, for instance, of the order of only 8% for combined testing (individual and 2 sibs of different sexes) when λ =10.

Incomplete testing

When facilities for testing are reduced, the biological limit set by reproductive rate is lowered, and, as shown by (2), the expected response tends to increase linearly with the logarithm of the number tested. Similar increases with logarithms have also been noted previously, in other selection contexts, by Robertson (1957) and Smith (1969). When testing facilities are limited, allociation of testing places between males and females affects overall selection intensity (Smith, 1969). If annual response is considred instead of selection intensity, it can be shown that a critical value of testing capacity exists, below which only males should be tested (Ollivier, 1989). For pigs, this value is around 0.25 (table 2). As testing capacity decreases, the maximum annual response obtained from testing only males implies that their generation interval be progressively increased, while maintaining female generation interval at its minimum.

In practice, various surveys indicate that testing is presently far from being complete, in national breeding schemes as well as in breeding companies. Realised values of i/t rarely exceed 1 (Bichard et al., 1986; Christensen et al., 1986; Groeneveld & Werhahn, 1986; Steane, 1986). This partly results from culling for reasons other than performance.

Table 2. Critical value of testing capacity (k) below which only males should be tested (individual selection).

	c	
	15	100
$R_a(1)$	1.75	2.08
k	0.22	0.25
$R_a(k)/R_a(1)$	0.59	0.67
t_1	1.0	1.0
t_2	1.4	1.2

c : degree of polygygny
$R_a(1)$: maximum of i/t with complete testing
$R_a(k)$: maximum of i/t with testing capacity k
t_1 : female generation interval for R_a (k)
t_2 : male generation interval for R_a (k)
c, a (here 1) and λ (here 6) defined in table 1.

Restrictions on selection intensity

Selection intensities in expressions (1) usually assume that comparisons are made among a large number of independent observations. In practice, however, this assumption is not fulfilled, particularly in on-farm testing with continuous farrowing. Comparisons than bear on a limited number of full-sib groups. For normal distributions, one can use approximations given by Bulmer (1985, p. 147) and Hill (1976) to define an 'effective' proportion selected (p_e), for any actual proportion (p) selected among s groups of n individuals with an intra-class correlation t. For low values of p, for instance, the following expression holds approximately:

$$p_e=p(1+1/2k) \text{ with } k = nsp(1-t+t/n) \quad (4)$$

Selection intensities in formula (1) may be corrected accordingly and the annual response then depends on "effective" fecundity and polygyny defined as:

$$\lambda_e=\lambda/(1+1/2k_1) \text{ and } c_e=c(1+1/2k_1)/(1+1/2k_2) \quad (5)$$

where k_1 and k_2 are the k values defined in (4) for females and males respectively. If replacements are taken within L gilt litters, one has $k_1=L[1-t(1-2/\lambda)]$ as $n=\lambda/2$ and $k_2=k_1/c$ if $L>c$ or k_1/L if $L\leq c$. Consider individual selection with complete testing for $c=15$, $\lambda=6$ and $t=0.2$, in a herd producing 100 gilt litters per year, distributed uniformly over 17 periods of 3 weeks. Then $L=6$, $=5.47$, $c_e=4.2$ and the reduction of response is expected to be 15% compared to the value 1.75 in table 1.

Breeding for reproduction traits

Whereas for production traits a broad agreement exists between estimated and realised genetic parameters (with the possible exception of feed efficiency), the situation is less clear for reproduction traits. Theoretical predictions, such as those given in table 3, indicate that conventional methods of selection for litter size in pigs should be sucessful, with an annual gain of at least 0.2 piglet at brith, even

within herds of limited size (Toro et al., 1988).

Table 3. Predicted annual selection responses for litter size.

	References				
	Ollivier (1973)	Ollivier (1974)	Avalos & Smith (1987)	Toro et al. (1988)	
R_a	0.25	0.30	0.47	0.34	0.20
σ_a	2.70	2.70	2.85	2.85	2.85
c	10	15	10	10	10
i/t	1.43	1.47	1.43	1.40	1.40
I	D2	D4	DF2	DF2	DF2
N	large	large	large	100 dams	100 dams
F	ignored	ignored	ignored	ignored	-0.2 per 0.10

R_a : annual response in litter size
σ_a : phenotypic standard deviation
c : degree of polygyny
i/t: selection intensity/generation interval
I : selection criterion (D: dam; F:family; 2=2 litters ..)
F : inbreeding depression for litter size
Selection across sires. 1 sire selected per litter. Heritability 0.10, repeatability 0.15.

To this, the lack of experimental evidence in pigs has often been opposed (see, for instance, the recent review of Eisen, 1986), contrary to the situation in mice. However, recently, evidence has accumulated showing that selection for litter size might well be as efficient in pigs as it is in mice. A significant genetic gain for litter size at birth of 1.7 piglet has indeed been obtained in the last 6 generations of the French selection experiment (Bolet et al., 1987). In another experiment, with extremely intense selection on dam performance, realised heritability for litter size at birth is 0.14 (Le Roy et al., 1987). A gain of 0.7 in litter size at birth has also been reported in the last 4 generations of the Nebraska experiment on ovulation rate (Johnson et al., 1984. An unresolved question remains the possible interaction response x parity found in several selection experiments. However, a lower response in gilts should be expected when selection is based on several dam parities, because the selection criterion is then more highly correlated to genetic merit for medium parities than for the first one.

Breeding for production and reproduction traits

The question for the future may not be how to improve prolificacy, but rather how to simultaneously improve litter size and production traits. The point has been investigated theoretically, with various methods. The index approach of Smith (1964) for specialised lines appears to be the simplest (see Ollivier, 1983 Avalos & Smith, 1987 and Webb & Bampton, 1987). More elaborate methods consider economic returns of entire selection-crossbreeding schemes (Elsen, & Sellier, 1978) or life-cycle economic efficiency (Smith et al., 1983). Whatever the method used, the general conclusion is that moderate gains may be obtained from including litter size in the selection objectives. Table 4 shows that the predicted gains increase with the importance of litter size in the breeding goal, with the accuracy of the selection criterion used for litter size and

with increasingly unfavourable genetic correlations between litter size and production traits. On the latter point, however, most studies indicate that litter size is phenotypically and genetically uncorrelated with growth and carcass traits (see the review of Brien, 1986). Table 4 also indicates that the intra-class correlation of the selection index increases with its expected efficiency. This may partially offset its advantage in a situation of limited herd size.

Table 4. Efficiency of index selection for production and reproduction traits in specialised dam lines.

r	a					
	1		2		3	
	ρ	ρ'	ρ	ρ'	ρ	ρ'
	103	106	107	115	112	125
0.2	0.11	0.16	0.13	0.19	0.14	0.20
	(0.28)	(0.37)	(0.38)	(0.52)	(0.46)	(0.63)
	102	105	108	117	117	134
0.0	0.04	0.09	0.07	0.15	0.10	0.17
	(0.27)	(0.33)	(0.41)	(0.56)	(0.55)	(0.72)
	102	104	110	121	128	151
-0.2	-0.03	0.01	0.03	0.11	0.08	0.17
	(0.25)	(0.29)	(0.47)	(0.62)	(0.74)	(0.85)

a : economic value of 1 standard deviation of litter size at weaning relatively to 1 standard deviation of production traits.
r : genetic correlation between litter size at weaning and production traits.
ρ(ρ') : accuracy of genetic evaluation for litter size at weaning 0.13 (0.19).
1st line : overall selection response in percent of that obtained from selection for production traits in a general purpose line.
2nd line : expected annual response for litter size at weaning (i/t=1.75).
In brackets : intra-class (full-sib) correlation of index (adapted from Ollivier (1983)).

Some prospects and questions for future breeding programmes

Objectives

Appreciable genetic gains have quite convincingly been demonstrated for growth and carcass traits in recent years. They are of the order of 0.5 to 1.5% of the mean per year (Sellier & Rothschild, 1988). Less evidence exists for genetic trends in meat quality traits, but most available results point towards unfavourable trends, as expected from the negative genetic correlations existing between lean growth and meat quality. This general picture is exemplified in the figure below, for a sow population which has been genetically monitored over 25 years.

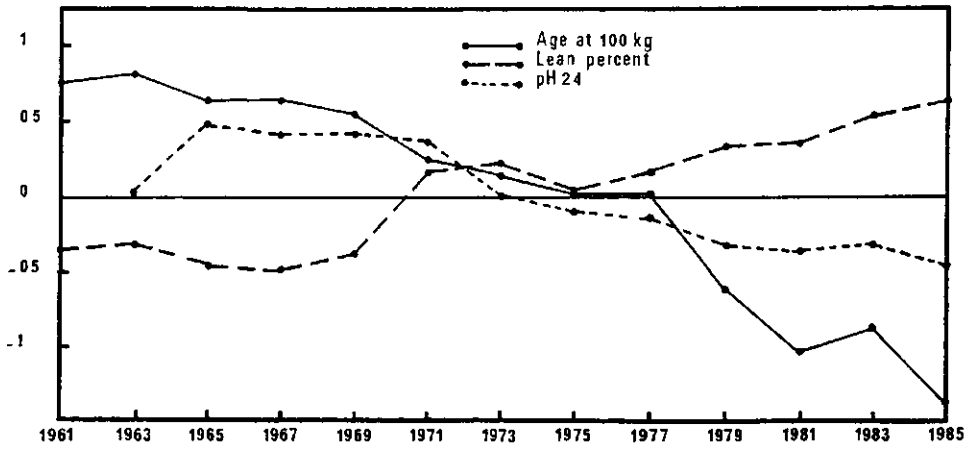

Fig. 1. 25-year genetic trends in a French Large White sow population (Ollivier, 1986). The traits are expressed in phenotypic standard-deviation units, i.e. 16 days for age at 100 kg, 2.9 for lean percent (predicted) and 0.21 for pH24.

One can predict tha meat quality will become an increasingly important objective in pig breeding. It is not certain, however, that this will bring a reduction of emphasis on lean content in the coming years. Is lean content approaching its optimum (Webb & Bampton, 1987), or may it be considered as still far from a biological maximum set at 75% by De Roo (1988)?

In contrast to production traits, no phenotypic change of appreciable magnitude has occurred for litter size at birth, and in some cases negative genetic trends have even been obtained (Johansson, 1981). This was to be expected from the low selection pressure so far applied to litter size. It is also a strong argument in favour of negligible genetic associations between production and reproduction traits, as apparently no indirect response to selection for the former has been experienced. A growing awareness of the possibilities of selection for litter size is already noted, and future breeding plans will increasingly incorporate litter size in their objectives. The economic gain form selection on litter size may be expected to increase if less emphasis is put on lean growth, or if genetic antagonisms of litter size with lean growth develop. This is shown by the effects of the variations of a and r in table 4. But, on the other hand, it is also well known that the economic importance of litter size should decrease as its mean increases (Moav & Hill, 1966).

Evaluation

Accurate breeding value estimation will remain an essential pre-requisite for future improvement schemes. Application of selection index theory in animals has begun with pigs (Hazel, 1943) and it has been continuously pursued in many countries for several decades (Rönningen, 1978; Lindhé et al., 1980). Recently, more refined applications of the theory are being developed through the use of mixed model methodology, providing best linear unbiased predictions (BLUP) of breeding values, as in the programme introduced in Canada in 1985 (Hudson & Kenndy, 1985).

For production traits, moderately heritable, accuracy of evaluation should not be greatly enhanced, in the case of within-farm (or station) selection. The advantage of BLUP in better exploited in across-farms (or stations) evaluation, as shown by Mabry et al. (1987) on actual data from boar testing stations and by Soerensen (1987) on simulated populations. Selection accuracy for reproduction traits is markedly improved by using family information, and here BLUP offers the possibility of including it with great flexibility. However, BLUP has also shortcomings arising from the heavy computations involved. This limits its applicability to species like pig, where selection decisions have to be taken rapidly and repeatedly and where multi-trait informaton is essential.

Selection criteria

Indirect information on live pigs is presently the basis of selection. Technical developments in the estimation of body composition may have important consequences for breeding programmes, as stressed by Kanis (1986). If the predictive value of live measurements is raised from a present genetic correlation value of 0.6 to 0.85, a value expected from ultrasound scanning, the gain from combined selection over individual selection (for $h^2=0.4$) is reduced from 23 to 9% and from 37 to 14%, for the case of 1 or 2 sibs respectively. Then globally, combined selection would lose its advantage over purely individual selection in most cases.

As to meat quality, present and prospective methods of selection have been recently discussed by Sellier (1988), in an extensive review of genetic aspects of meat quality in pigs. Several European countries include meat quality in their selection criteria and selection indices with constraints find here an interesting practical application. Such indices should avoid any decline in meat quality, at the expense of only a moderate reduction in overall efficiency of selection, in spite of the antagonism between meat quality and other production traits. However, this is only true when sib (or progeny) information is used, and the method fails in individual selection when no predictor of meat quality is available (Guéblez & Ollivier, 1986). This justifies research efforts presently devoted to finding valuable in vivo tests, outside the halothane gene context, which would greatly facilitate the maintaining of an acceptable meat quality in the future.

Selection environment

The existence of genotype x environment interactions is well documented since the late 1970's (see the recent review of Merks, 1988). This raises the question of choosing the best environment(s) for selection. Of particular concern is the importance of selection regime x production system interactions, as discussed by Webb & Curran (1986). A thorough investigation of similar problems in the Dutch herdbook breeding programme has been recently carried on by Merks (1988). His results show the importance of genotype x herd interactions, both in on-farm test and in commercial conditions, especially for daily gain. He concludes that environmental differences between herds, in addition to selection regime differences, could contribute to reduce selection efficiency. Consequently, the value of sib (or even progeny) testing relatively to performance testing should increase. However, the organisational requirements of programmes combining central and on-farm performance test with sib or progeny test under commercial conditions (number of testing places, electronic identification, extensive use of artificial insemination (AI) are to consider (see Merks, 1988, p. 124-127).

Reproductive rate manipulation

Compared to other mammalian farm species, pig may be considered as highly efficient in terms of multiplicative power. Vauban, a celebrated French military engineer, had already calculated in the 17th century that from a single female about 6 millions offspring could be obtained in 10 years. As shown by formula (2), selection efficiency may be expected to increase to variable degrees, through (i) use of AI (which increases c), (ii) improved prolificacy or use of embryo transfer (which increase λ), (iii) earlier breeding age (which lowers a).

Though AI in pigs does not allow raising the mating ratio to values comparable to those possible in cattle, it remains a powerful mean of increasing the efficiency of breeding schemes. For example, comparison of tables 1 and 2 shows that testing only 3 males/dam annually with AI (c=100 k=0.25 in table 2) gives about the same expected response as testing 3 males and 3 females with natural mating (c=15 λ=3 in table 1).

AI offers other advantages in breeding programmes. For instance, high merit boars can serve the various levels of the breeding pyramid, and thus reduce genetic lags. AI may also be used to connect several herds, thus increasing actual nucleus size while keeping individual herd sizes moderate (Webb & Bampton, 1987).

The potential of embryo transfer (ET) for pig breeding programmes has so far received little attention (see Smith, 1981, for an example). Because of the high reproductive rate of pigs under normal conditions, the extra gains to be expected from ET should be modest. The result will of course depend on various technical parameters, such as number of transferable embryos (after superovulatory treatment), conception rate and embryo survival, which will determine the ultimate number born per donor from one (or several) recipient sow(s). Recent data of Nieman (1987) indicate that this number is below normal litter size. Repeated transfers from the same donor are, however, feasible and a considerable increase in λ can thus be obtained, even with a low litter size. Table 5 shows the expected increase in response to individual selection for various values of λ. The results show that not much can be gained by increasing litter size above normal values of 6-8. The expected gain is then of the order of 20-30%, with about 5 transfers per donor, i.e. a recipient herd about 5 times the donor herd size. However, ET appears to be potentially more attractive if it can be coupled with early breeding. Table 5 shows that the expected gain might exceed 50% if transfers could begin at about 5 months of age, and one less transfer per donor would then be necessary compared to later breeding. Prospects for obtaining earlier puberty through various means have been reviewed by Dyck (1988).

Table 5. Potential of embryo transfer for individual selection.

λ	c = 5		c = 15		c = 25	
	a	a'	a	a'	a	a'
24	116	148	112	143	111	142
	6.1	5.0	5.7	4.6	5.5	4.5
36	127	161	120	154	118	152
	5.3	4.4	5.0	4.1	4.9	3.9
48	132	169	125	161	123	160
	4.9	4.0	4.6	3.7	4.5	3.6
60	136	176	129	167	127	165
	4.6	3.1	4.4	2.9	4.2	2.8

c and λ : defined in table 1.
a(a') : age of donor at birth of 1st transferred embryos 1yr (0.75 yr).
1st line : selection response in percent of that in a standard situation (a=1, λ=6).
2nd line : Optimal number of transfers per donor, assuming one month interval between transfers.

Use of Chinese breeds

The evaluation of the Chinese breeds imported in France in 1979 has led to conclusive evidence regarding their genetic merit for reproduction traits under modern husbandry conditions (Sellier & Legault, 1986; Bidanel, 1988). In addition to litter size, 3 other characteristics deserve attention: early puberty, teat number and low preweaning mortality. However, their disadvantage in growth and carcass performance rules out their use in any crossbreeding system under present economic conditions in most countries (Guéblez et al., 1987). From the parameters estimated by Bidanel (1988) in a Large White x Meishan (LWxMS) crossbreeding experiment, the LW-MS lag for production traits may be about 8 standard deviations, compared to an advantage of about 1 standard deviation for litter size at weaning (table 6). However, in a crossbreeding system using a LWxMS dam line, the production lag would ultimately be divided by 4 and thus not too far from being compensated by the gain in dam line reproductive performance. On the other hand, selection for production traits in a LWxMS composite line could be 1.5 times as efficient as in a European-type line (Bidanel, 1988), because of early puberty. In theory then, the time necessary for a LWxMS line to overtake present conventional dam lines should not exceed 2 or 3 years of intensive selection for production traits.

Table 6. Meishan (MS) - Large White (LW) comparisons for production and reproduction traits (from Bidanel, 1988).

Trait	Genotype		
	MS	F1(MSxLW)	F2(MSxLW)
Average daily gain (g)	-206	0	-51
Feed conversion ratio	0.9	(0.45)	(0.45)
Lean tissue weight (kg)	- 16	-8	- 8
Litter size at weaning	2.9	4.2	2.7

Values derived from LW x MS crossbreeding parameters (except for feed conversion ratio) and expressed as deviations from LW.

A more realistic approach is to consider the overall return of crossbreeding systems implying Chinese stocks, as done by Bidanel (1988) for systems using MSxEuropean composites as grand maternal line. He shows that the best of such sytems reach the break-even point in comparison to a standard LWxLandrace dam line within a time horizon of about 5 years.

This type of strategy should, however, also take into account the constantly increasing production lag of the Chinese breeds, if they undergo no selection, and the time necessary to break down linkage disequilibria involving production and reproduction genes in the composite stock. An unresolved question so far is to know whether prolificacy genes in Chinese stock have any adverse pleiotropic effects on production traits. Careful monitoring of litter size is therefore essential in such selection schemes.

The use of highly prolific breeds as recipient line in ET programmes also deserves consideration. However, succesfull ET might be more dependent on embryo quality than on recipient uterine capacity, as reciprocal transfers between LW and MS tend to indicate (P. Rombauts, personal communication). More information on this point is needed before ET based on Chinese prolific breeds (or possibly better on F_1 Chinese x European crosses) can be envisaged.

Prospects from a better knowledge of the pig genome

Gene identification and localisation

The number of genes identified in the pig is still limited. It has been estimated to be about a hundred (Ollivier & Sellier, 1982). Since 1985, the existence of a new class of genetic variation, expressed at the DNA level, such as restriction fragment length polymorphism (RFLP), has been established in farm animal species including pig (see the review of Beckman & Soller, 1987). The first syntenies, i.e. location of several genes on the same chromosome, and assignments of genes to particular chromosomes were reported in the early 1980's. By 1986, 10 syntenies and 17 gene assignments were reported (Ruddle & Fries, 1986). Pig gene mapping is still in its infancy, particularly when compared to the explosive development of human gene mapping, which presently covers more than 5000 genes. Potential applications in human medicine are a powerful incentive, for which there is no equivalent in the economic conditions of livestock production. Gene mapping in animals will, however, benefit from the knowledge gained in man, because of the expected homologies of DNA sequences across species. Human DNA probes have indeed been used for gene mapping in pig (Geffrotin et al., 1984). Undoubtedly, such transfer of

information will increasingly contribute to the pig map, together with the use of specific porcine probes (Fries et al., 1988).

Correct assignment implies accurate identification of chromosomes, and so necessarily requires reliable cytogenetic techniques. In that respect, chromosomal markers resulting from various structural rearrangements are useful tools in pig gene mapping. An ever-increasing number (presently 22) of reciprocal translocations are being reported. In addition to the drastic reduction they inflict on litter size, their interest for gene mapping is worth considering. Variations of size brought about by some translocations may be exploited in chromosomal sorting techniques and so facilitate the establishment of chromosome-specific gene banks, subsequently used for chromosome exploration (Popescu & Legault, 1988).

Use of indentified genes in breeding programmes

Pig offers a good example of this approach in farm animals, with the exploitation of the halothane gene (Hal). This area of research, initiated by the basic paper of Eikelenboom & Minkema (1974), has received enormous attention in recent years. We are here in an exceptionally favourable genetic situation, because of well established large effects of Hal on lean content and meat quality and because of its tight linkage with easily identifiable biochemical markers. The discovery of the halothane gene has shed a new light on pig breeding as a whole. It is tempting to look and to hope for similar targets for use in future programmes. The next candidate might be the set of genes of the major histocompatibility complex (MHC). The central role played by MHC in immune functions and disease resistance has been reviewed by Warner et al. (1987), who stress that pig is the best studied mammalian domestic species in that respect. They also summarise the association found so far between MHC and various production and reproduction traits. In the field of disease resistance, the linkage mentioned by Gibbons et al. (1977) between transferrin and a gene for resistance to colibacillosis, which has been confirmed by Duval-Iflah et al. (1987), would also deserve some consideration. Whether similar conditions will prevail for other genes of interest, as those hypothesised by Sellier (1987) for meat quality and by Sellier & Legault (1986) for litter size, remains to be seen.

Contribution of molecular genetics

The new generation of DNA polymorphism recently discovered (such as RFLP, hypervariable regions, oligonucleotide polymorphism) is expected to contribute to animal improvement in the coming years. Briefly, molecular markers may be used for early identification of particular genotypes, or, perhaps more ambitiously, as a general mean of analysing polygenic quantitative variation. A good example of the first approach is Hal identification, as discussed by Archibald (1987). Other genes, such as those mentioned in the preceding paragraph, might in the future be similarly manipulated. The analysis of polygenic quantitative variation and its eventual conversion into individually defined Mendelian entities (Beckman & Soller, 1987) is a more distant prospect. Such analyses require adequate coverage of the genome, which is still far from being achieved in farm species. The effort required for quantitative characterisation (about 2000 individuals for establishing RFLP - quantitative traits relationships in a cross between 2 breeds) as well as for genetic characteristics (molecular analyses) needs also evaluation. Recent results obtained in plants, particularly maize well adapted to the application of such methods (Helentjaris, 1987), show their effectiveness

in identifying factors implied in quantitative variation. However, as pointed out by Edwards et al. (1987), inferences may be limited to the particular genetic background and environment of each experiment.

Potential applications of gene transfer in farm animals presently attract considerable attention. The two main techniques available for introducing foreign genes have been show to work in pigs, i.e. micro-injection by Hammer et al. (1985) and infection with retrovirus vectors by Petters et al. (1987). More details on methods of transfer, control of transgene expression and present barriers to applicatoin on domestic animals are given in the review of Renard & Babinet (1987). Implications for livestock improvement have also been discussed by Smith et al. (1987). The difficulty of finding useful genetic material for transfer has often been emphasised. In some cases, it would be more useful to be able to "turn off" an existing gene than to introduce a new one. This would be the case for genes coding for receptors to specific pathogens, as the K88 E. Coli receptor in pig. However, molecular investigations on 2 important genes in pig, Hal and MHC, might open up some exciting possiblities, as indicated by Archibald (1987) and Warner et al. (1987). In both cases the possibility of obtaining stable heterozygosity is envisaged, either by obtaining pigs homozygous for the 2 Hal alleles which would then breed true, or by increasing MHC heterozygosity to produce good responders to several different pathogens. Progress in that direction would open a new route for exploiting heterosis, outside conventional crossbreeding schemes.

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FUTURE BREEDING PROGRAMS IN POULTRY

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Summary

Of domestic animals, poultry are among the most efficient converters of plant to animal protein. Success in poultry breeding results mainly from development of specialized sire and dam lines which are crossed in various combinations to produce a commercial product with potential for either rapid growth or high egg production. Development of specialized lines and crosses involves application of quantitative genetic procedures, large populations, and intense artificial selection. Breeding programs for poultry meat and eggs are based on efficient use of additive and nonadditive genetic variation with differences in heritabilities for growth and reproductive traits determining breeding strategies.

Involvement in breeding programs of major loci such as sex-linked dwarfism, dominant white, sex-linked feathering and the major histocompatability complex requires repeated backcrossing and knowledge of how alleles at these loci interact with various background genomes. This form of gene transfer is not only costly in time and money, but success has been varied. Just as the computer facilitated obtaining, summarizing and analyzing voluminous data in a rapid efficient manner, advances in biotechnology hold much promise for future progress. The fruits will probably come both directly and indirectly. In the case of the latter, enhancing disease resistance allows for more intense selection while the former holds promise for insertion of major genes into known genetic backgrounds and mapping for identification of quantitative trait loci. Future breeding programs in poultry will orchestrate a symbiotic relationship whereby molecular techniques become a part of existing quantitative procedures.

Keywords: poultry breeding, growth, reproduction, chickens.

Introduction

Breeding of poultry for meat and/or eggs as a source of food dates back several thousand years. Industrial production to provide meat and eggs to a non-agricultural human population is, however, a phenomenon of this century (Lerner & Donald, 1966; Gordy, 1974; Smith & Daniel, 1975).

Less than a score of large organizations, which employ highly trained staffs and utilize large populations with intensive selection, conduct most commercial poultry breeding. Although breeding programs are based on sound genetic principles and utilize computer technology, the use of biotechnology in a molecular biology context is limited.

Negative genetic and phenotypic relationships between growth and reproduction have resulted in development of specific breeding programs for meat and for egg production. Realization of the incompatability of the two was seminal because it meant that chicken meat production would no longer be a by-product of the egg industry. Annual production of the poultry meat industry is in excess of 10 billion animals and rivals beef and pork as a source of animal protein in many countries. Breeding

programs for poultry meat production are designed to meet these markets without complications of attempting to develop dual purpose stocks.

This paper will adress the recent history of breeding for poultry meat and eggs. Certain aspects of this paper rely on recent evaluations of industrial breeding programs for egg-type chicken (Arthur, 1986), meat-type chickens and turkeys (Cahaner & Siegel, 1986), and waterfowl (Pingel, 1986).

Recent history

Knowledge of the past aids in understanding the present and viewing the future. Technological advances have contributed to efficiency in poultry breeding. These include invention of the trap-nest, the force-draft incubator and use of artificial insemination. The trap-nest, which has been replaced in many cases by individual cages, allows for obtaining pedigree data essential to the estimation of heritabilities, genetic correlations and breeding values. The force-draft incubator allows production of large populations at predetermined intervals. Artificial insemination enables not only testing of many males, but eliminating sexual behaviour as a factor in measuring fertility, particularly in turkeys.

A prime decision that influenced poultry breeding was that specific stocks be developed for meat production and for egg production. A second was the realization that the purebred was not sacred and that poultry breeders could capitalize on the use of hybrid vigor, particularly for reproductive traits. Changes in poultry breeding occurred rapidly as breeding became a science rather than an art. The two decades after the end of World War II saw many breeders disappear from the scene as hybrid egg-layers and white-feathered meat chickens and turkeys were demanded by producers and processors. Poultry breeding became more of a science than an art, forcing breeders to employ geneticists who used quantitative and qualitative procedures with intense within-line selection, plus hybridization to produce a commercial product. Those breeders who resisted change lost their competitiveness and attrition was great. As Cahaner & Siegel (1986) pointed out, the survivors used sound genetic principles, had a willingness to gamble, and had considerable luck. In many cases, they became subsidiaries of multinational corporations. Egg breeders adopted systems designed to maximize both general and specific combining ability (Arthur, 1986). The same is true for poultry meat breeders (Cahaner & Siegel, 1986).

Poultry breeding programs utilize independent culling to varying degrees (more for broilers, waterfowl and turkeys than for egg production), the index procedures of Lush (1947) and Osborne (1957) to combine family and individual selection, and the concept of developing specific sire and dam lines (e.g. Moav, 1966; Moav & Hill, 1966). These procedures and techniques will continue because they have survived the test of time. As we look to the future, the question is how to integrate new procedures with those that have brought poultry breeding to its present level.

Disease resistance

Historically, poultry geneticists and poultry veterinarians have worked in concert to develop programs for effective control of infectious diseases and parasites. Primary tools have been eradication, vaccination and isolation programs. Although genetic variation for resistance has been demonstrated for many diseases and parasites (e.g., see reviews by Gavora & Spencer, 1983; Hartmann, 1985), breeders rarely select for

resistance to specific diseases. This reluctance is understandable because breeding for resistance to infectious agents frequently requires exposure of animals to pathogens. Not only may such exposure mask expression of other traits, but there are complications of host-pathogen dynamics and costs associated with adding another trait to a selection program. Also, selection efforts can be quickly negated by development of an effective vaccination program for controlling the disease. Such was the case with Marek's disease.

The poultry industry has been fairly successful in developing vaccination programs for breeder females to produce maternal antibodies which are passed through the egg and in eradication of egg transmitted pathogens. Eradication programs require strict sanitation and immunological testing, procedures that are routine for poultry breeders. Examples of successful eradication programs include Salamonella pullorum, Mycoplasm synoviae and Mycoplasm gallisepticum. Recent advances in immunology such as development of monoclonal antibodies and ELISA testing are becoming cost-effective tools for breeders.

Poultry breeders are quick to respond to new information on disease control and prophylactic procedures. In seminal studies, Spencer et al. (1979) and Gavora et al.(1980) demonstrated that presence of leukosis shedders in breeder flocks reduced effectiveness of selection. Today chickens are routinely tested and shedders are eliminated from flocks. In an attempt to develop packages for enhancing immunoresponsiveness breeders may screen for response to general antigens such as sheep erythrocytes and/or alleles for various blood allosystems, particularly the major histocompatability complex (Van der Zijpp, 1983; Arthur, 1986; Cahaner & Siegel, 1986). An excellent review of the relationship between diseases and the major histocompatability complex has been provided by Bacon (1987). Developments in molecular biology suggest that chromosomal regions associated with immunoresponsiveness (as well as other traits) will be identified and that desirable "genes" involved can be cloned. When this becomes reality, the next step will be to insert these genes into the genome of other populations. The procedures, while still in the experimental stage, show promise (e.g., Soller & Beckman, 1987a; 1987b; Crittenden & Salter, 1988).

Egg poultry

Breeding for egg production is usually discussed in the context of brown and white-egg layers. Breeding systems include reciprocal recurrent selection or some modification of that system to utilize nonadditive genetic variation (Arthur, 1986). He points out that white-egg stocks are usually strain crosses and brown egg stocks are generally breed crosses. As with meat stocks, phenotypic changes over time are due to genetic and nongenetic factors. Lasley (1983) states that in the U.S.A., annual egg production increased from 209 to 242 eggs per hen and feed per dozen eggs declined from 2.4 to 1.9 kg. Current production values in our state (Ruszler, personal communication) are approximately 255 eggs and 1.5 kg feed per dozen eggs. The general sense in the recent past was that egg production had plateaued and selection was essential in maintaining existing levels (e.g. Clayton, 1968; 1972). Research regarding the effect of leukosis shedders on estimating breeding values (Gavora et al., 1980) enabled breeders to more accurately assess response, and genetic progress reoccurred.

Although a number of selection experiments for egg production appear in the literature, those addressing long-term effects are dated. The void is understandable because of the long generation interval and cost of such

research. Instructive and important reading for those interested in commercial multi-trait selection experiments is the series on Kimber Farms (Bennett et al., 1981; Kashyap et al., 1981; Dickerson et al., 1983) and the Canadian selection experiment (Gowe & Fairfull, 1985). These papers show a steady, yet slow improvement in egg production, concomitant to improvements in other traits. The shift from floor to cage environments for egg layers had implications in the context of genotype-environment interactions (Lowry & Abplanalp, 1970). A situation that may have contributed to reductions in response during the transition period.

One may speculate that recent improvements in egg production resulted not from rate of lay per se, a trait with low heritability (Kinney, 1969), but rather to reductions in body weight and age at sexual maturity, traits with moderate to high heritabilities (Kinney, 1969). Reductions in body weight would, in turn, improve feed conversion efficiency. Caution must be exercised in reduction of body weight not only because of its relationship with egg weight, but because minimum body weights as well as carcass composition influence age at onset of lay (Siegel & Dunnington, 1987). This conundrum suggests that further improvements in egg production and feed conversion efficiency through reductions in body weight will be minimal.

On the surface the use of synthetic compounds to stimulate ovulation rates is appealing. These procedures, however, offer little promise because the single oviduct is a limiting factor in allowing for production of more than one egg per day. Moreover, ova number is only one factor in production of an egg. Albumen production and shell are important components. Millions of generations of natural selection have resulted in a yolk to albumen ratio which is essential to hatchability. Concomitantly, time for the egg to transverse the oviduct shows little variation which, in turn, results in a constant laying down of shell. Whether adequate shell quality can be maintained with continued increases in egg production is problematic.

Presently breeders are emphasizing livability, production and associated traits during the first cycle of production. My sense is that potential for future improvements will result from increased livability, particularly during the second cycle of egg production. Although the assumption is made that those females which are best producers during the first cycle are also superior during the second cycle, literature on this point is wanting. Selection for a second egg production cycle increases the generation interval. In the world of poultry breeding, breeders do not have the luxury of extending the generation interval and remaining competitive in the long run. Ironically, such studies are not realistic at research institutes or universities. Thus, in the short term, the future of egg-type breeding will be more of the same, which has been successful, plus capitalization on disease control programs discussed in the previous section of this paper.

Meat poultry

Poultry meat breeding includes chickens, turkeys and waterfowl. In the case of waterfowl, feather production is an important component, as is egg production particularly in Southeast Asia (Pingel, 1986) and liver production for specialty markets. Although the histories of the broiler, turkey and waterfowl industries differ, breeding programs have similarities in that they address needs of rapid growth, high processing yields and superior food conversion efficiency. Broiler breeding will serve as the model for the discussion.

Broilers are produced from strain cross dams, a practice that will

continue because it utilizes heterosis for reproductive traits and provides more protection of genetic material for the primary breeder. Changes in production values are a function of genetic and nongenetic factors. In 1935 about 95 days and 5.6 kg of feed were required to produce a 1.3 kg broiler. By 1960 it was 67 days, 3.8 kg of feed and a 1.5 kg broiler (Lasley, 1983). In the U.S.A. today, a 1.8 kg broiler is produced in less than 45 days from 3.6 kg of feed. Thus, demand has changed so that while market weight is considerably larger, broilers reach this weight in half the time on a third less feed (Cahaner & Siegel, 1986). Today's broiler may be characterized as a fast growing, lethargic, compulsive overeater with generally low immunoresponsiveness and a tendency for obesity.

A typical generation interval for broiler breeding is one year. A considerable portion of changes observed in production values over the past 50 years is genetic (e.g., Marks, 1979; Chambers, et al., 1981). Moreover, there is little evidence to suggest a plateau for broilers reaching market weight about one day earlier each generation. Heritability estimates for body weight continue to be of moderate magnitude and responses to selection suggest that alleles contributing to broiler weight are not near fixation. Frankham (1979) and Hill (1982) provide a case for new mutations as an explanation for continued variation in selected populations, and additive genetic variation still exists for the selected trait in a long-term single trait selection experiment for body weight (see review by Siegel & Dunnington, 1987). Thus, there is little evidence to suggest plateauing of response for the primary trait, market weight, from depletion of additive genetic variation. Broilers eat near gut capacity (Nir et al., 1978) and selection for increased body weight alters satiety centers (Burkhardt et al. 1983; Denbow, 1985), suggesting that these may be limiting factors in selection response rather than growth potential *per se*. Research to determine if these are potential factors and how to circumvent such barriers is limited (e.g. Sorensen, 1985; Katanbaf et al., 1988).

A time barrier for response to selection will develop because reaching a fixed market weight one day earlier per year cannot continue indefinitely. This limit, however, will be delayed if the present trend to market broilers at heavier weights continues. It is expected that this trend for heavier weights will accelerate, particularly in those nations where further processed poultry is replacing the whole bird in the market place. Coupled with the change to a heavier broiler at marketing will be increased problems with leg weakness, "sudden death syndrome" and various maladies associated with directing resources from general homeostasis to growth.

At the phenotypic level, food conversion efficiency, until the present decade, improved concomitantly with selection for body weight because broilers were marketed at earlier ages. The correlated response of increased feed consumption was also viewed in a positive manner because it resulted in faster growth. Potential problems from excessive body weight and obesity in breeder flocks were addressed by development and application of various feed restriction programs. These nongenetic programs, coupled with heterosis in breeder females, alleviated many reproductive problems. Also use of the sex-linked dwarf allele has gained popularity in some quarters. Mating of normal males to dwarf females results in nondwarf broiler progeny. The effect of the dwarf allele varies with the background genome (see review by Merat, 1982) and incorporation of it in egg stocks has had limited success. Although genetic and nongenetic procedures have been relatively successful, reproduction of meat stocks is still considerably inferior to that of egg

stocks. Progeny testing is needed to reduce erratic ovulation and defective egg syndrome, incidence of chromosomal aberrations (see review by Siegel & Dunnington, 1985) and a lack of persistency of lay. Thus, progeny testing for reproductive traits will gain increasing favor in poultry meat breeding.

Rapid changes in consumer demands continue to be a challenge for poultry meat breeders. Alleles for dominant white and early-late feathering were introduced to meet requirements of processors for a white feathered bird and for uniformity. Although these alleles have been implicated for their adverse effects (e.g., Harris et al., 1984) little is known about pleiotrophic effects of alleles at these loci in various genetic backgrounds. The advent of further processing increased demands for breast meat and higher processing yield of broilers. Experience with turkeys shows that emphasis on these traits, while meeting a marketing demand, results in mechanical barriers to mating that are correctable by artificial insemination. This procedure is very labor intensive and may not be feasible for broiler production. Other challenges caused by changing consumer demands include development of measurement criteria, complication of selection indices, and the need for sib testing if individuals have to be killed. These challenges occur simultaneously when meat breeders emphasize measurement of food conversion efficiency. As stated earlier, rapid growth meant earlier market age and hence superior food conversion efficiency. This relationship did not, however, mean genetic improvement for this trait. When it became evident that differences in food conversion efficiency existed among commercial stocks at a common body weight, breeders had to address the situation. Unfortunately, there was a dearth of information not only on modes of inheritance of food conversion efficiency but also on measurement criteria (Cahaner & Siegel, 1986). At this time, it is still unclear as to what procedures are most realistic in a breeding program that includes feed conversion efficiency as a trait.

From the above it is evident that poultry meat breeding is in a dynamic state. Much of the success has come from judicious use of genetic theory, a solid base in poultry science and breeding, and a primary trait (body weight) where genetic variation has not been depleted. Availability of capital and computer technology allowed the use of large populations and intense selection. Modern transportation and a general lack of genotype-environment interactions facilitated development of major central facilities with satellite operations. Responses to future challenges will be more difficult. Although genetic variation exists for the primary trait, a finite age at marketing will become a reality. The public research base has become smaller, requiring more emphasis within breeding organizations on research rather than development. Lastly, proprietory interests in biotechnology will reduce availability of information to breeders in general.

General comments

Breeders must continuously assign emphasis on various traits for their selection programs. Poultry meat breeders have had considerable basic information on economic traits available for use in determining selection criteria and mating systems. As a result, they have been primarily users of science rather than producers of new knowledge and success of their development programs is evident. Future development, however, will in many cases require expanding their research programs. This situation is particularly true for advances in molecular genetics and biotechnology, especially since some of the general research community in this area are

entrepreneurs. Breeders that are part of multinational groups with biotech subsidiaries should have access to such expertise. Others will have to form liaisons with biotech firms. Lacking will be a general access to patentable items. The arena will be quite different from that seen with use of quantitative genetic research, computer technology and disease eradication programs.

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SEXING OF BOVINE PREIMPLANTATION EMBRYOS

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Summary

Highly specific monoclonal antibodies against the H-Y antigen have been prepared for use in an indirect immunofluorescence assay to identify the sex of preimplantation bovine embryos. Under differentconditions the accuracy of the assay varied from 73 to 77 %. With conditions that reduced non-specific binding of the antibodies to the embryonic cells, no false positive (fluorescent) embryos were scored,indicating that the assay is male-specific. Although the assay has to be optimized, it is clearly shown that bovine embryos can be sexed by means of monoclonal antibodies against the H-Y antigen. Finally, some remarks have been made about the impact of a sexing technique on breeding programs.
Keywords: sex ratio, embryos, H-Y antigen, immunofluorescence.

Introduction

The development of several invasive as well as non-invasive techniques for sexing bovine embryos have been reported.Invasive techniques include cytological methods (King, 1984) and chromosome hybridization of Y-chromosome specific labeled c-DNA (Leonard et al., 1987). Invasive techniques have several disadvantages, such as possible reduced embryo viability due to damaging of embryonic cells. Furthermore, embryos cannot be cleaved after such treatment. Therefore, non-invasive methods for sexing embryos are preferable. Quantification of differences in metabolic activity of X-linked enzymes in male and female embryos has been proposed as a non-invasive method (Rieger, 1984). Data from experiments designed to test this hypothesis in the mouse have, however, not been encouraging (Williams, 1986). On the other hand, immunological detection of a male-specific protein, referred to as either the H-Y antigen or serologically detectable male antigen, has shown to be a relatively successful non-invasive method of identifying the sex of embryos (for reviews, see Booman, 1986 and Anderson, 1987). In our laboratory monoclonal antibodies against the H-Y antigen have been produced for use in an indirect immunofluorescence assay to sex bovine embryos.

Materials and methods

Anti-H-Y antigen monoclonal antibodies

Monoclonal antibodies against the H-Y antigen were produced using spleen cells from female C57BL/6 mice hyperimmunized with cells from syngeneic males as described by Booman et al., (1988a). Positive anti-H-Y antigen clones were detected by enzyme immunoassays. Supernatant fluids from Daudi cell cultures and testicular cell preparations taken from normal and sterile mice, rabbits, or calves served as presumptive sources of H-Y antigen. Male specificity was ascertained by the fact that the antibodies could be absorbed with spleen cells from male but not from

female mice. Binding of the antibodies to H-Y antigen on the cell surface of male and female cells, obtained from a number of tissues and species, was confirmed by an indirect immunofluorescence assay. Several monoclonal antibodies appeared to be positive in all assays tested, sug- gesting that the molecule conferring the H-Y antigenicity lacks species- specificity and appears to be identical for both soluble and mem- brane-bound H-Y antigen.

Indirect immunofluorescence assay

Based on the binding of the monoclonal antibodies in the screening assays described, several highly specific antibodies have been selected to be used in an indirect fluorescence assay (Booman et al., 1988b). In brief, bovine embryos were recovered from the uteri of superovulated donor cows at 6 - 7 days after estrous. Non-transferable embryos according to the embryo qualification system of Lindner and Wright (1983) were excluded. The embryos were transferred to a petridish containing anti-H-Y antibody and incubated for 90 min. After washing, the embryos were incubated for another 60 min. with a fluorescein isothiocyanate labeled secondary antibody. After washing again, fluorescence was evaluated by use of an inverted phase contrast microscope. Embryos were classified as either fluorescent (H-Y positive) or non-fluorescent (H-Y negative). After classification all embryos were karyotyped. Only 100 % readable karyograms were taken into account.

Results and discussion

Immunofluorescence assay

A total of 112 embryos were evaluated for expression of H-Y antigen; of these, 63 (56 %) were classified fluorescent and 49 (44 %) non-fluorescent. From 30 embryos a readable karyogram was obtained. 23 Embryos (77 %) were assigned correctly: 10 out of 16 (63 %) as H-Y positive classified embryos and 13 out of 14 (93 %) as H-Y negative classified embryos. Detailed results are given in Table 1 from which it can be concluded that all misclassifications are in the relatively large intermediate group of embryos. The overall larger number of fluorescent than non-fluorescent embryos seems to be a consequence of the false H-Y positives in this intermediate group of embryos.

The false positives may be mainly caused by non-specific binding of the monoclonal antibodies which might overshadow low intensity specific fluorescence. After having worked out several possible conditions to increase the ratio of specific to non-specific binding, sexing under 'improved' conditions resulted in a shift from too many positives to only false negatives (Table 1). In the improved assay a total of 96 embryos were evaluated for expression of H-Y antigen; of these, 40 (42 %) were classified fluorescent, 53 (55 %) non-fluorescent and 3 (3 %) not-sexable because of non-specific fluorescence of the zona. From 22 embryos a readable karyogram was obtained. 16 Embryos (73 %) were assigned correctly: 6 out of 6 (100 %) as H-Y positive classified embryos and 10 out of 16 (63 %) as H-Y negative classified embryos. Detailed results are given in Table 1 from which it can be concluded that nearly all misclassifications are in the category of H-Y negative embryos. In this category, 5 out of 14 embryos appeared to be false negative. All fluorescent embryos were males. The intermediate group of embryos was relatively small when compared with sexing under standard conditions.

No false positives mean that the fluorescence assay is male-specific.

Table 1. Numbers of embryos and accuracy of sex determination in each category of (non-)fluorescent bovine embryos under standard and improved conditions.

	no. of embryos observed			no. of embryos sexed correctly		
	fluorescent	non-fluorescent	no. of karyotypes	fluorescent	non-fluorescent	total
standard conditions						
H-Y positive embryos	39(35%)	-	10	10/10(100%)	-	10/10(100%)
H-Y negative embryos	-	44(39%)	12	-	12/12(100%)	12/12(100%)
intermediate embryos*	24(21%)	5(4%)	8	0/6 (0%)	1/2 (50%)	1/8 (13%)
total	63(56%)	49(44%)	30(27%)	10/16(63%)	13/14(93%)	23/30(77%)
improved conditions						
H-Y positive embryos	35(36%)	-	5	5/5 (100%)	-	5/5 (100%)
H-Y negative embryos	-	45(47%)	14	-	9/14(64%)	9/14(64%)
intermediate embryos*	5(5%)	8(8%)	3	1/1 (100%)	1/2 (50%)	2/3 (67%)
total	40(42%)	53(55%)	22(23%)	6/6 (100%)	10/16(63%)	16/22(73%)

* embryos with less clear staining characteristics; depending on intensity of fluorescence and size of fluorescent part of cellmass classified as fluorescent (H-Y positive) or non-fluorescent (H-Y negative)

The false negative embryos might be caused by a weak expression of the H-Y antigen and/or a low affinity of the monoclonal antibodies for bovine H-Y antigen combined with a not fully magnified signal in the assay. In fact, the detection system is not sensitive enough to pick up the positive signal. Current research is going on in order to optimize the assay by preparing high affinity monoclonal antibodies and by magnification of the positive fluorescence signal.

Impact of sexing on breeding programs

After optimalization, the described immunofluorescence assay can be applied on the farm within the normal embryo transfer procedure, the technique sets no limit to the number of embryos to be sexed, takes about 3 hrs (probably to be reduced to 2 hrs), and experiments with mouse embryos (Booman et al, 1988b) indicate that the viability of embryos is not affected by the manipulations. In addition, after sexing the embryos can still be split or frozen and using this non-invasive technique no problems will arise with disease control. Commercial price of sexing will be in the order of $ 40 - $ 50 per embryo. One striking feature of sexing programs is that fewer embryos will be transferred per donor. This could result in higher fees per pregnancy over and above sexing costs. As discussed by Seidel & Elsden (1985), splitting embryos and the wider application of multiple ovulation and embryo transfer (MOET) will probably keep embryotransfer costs down.

It is likely that a successful technique for sexing embryos will be used widely in dairy cattle breeding. From the top few per cent of the population the male offspring would be more valuable in the breeding program of A.I. organizations than the females. For the individual breeders the guaranteed female embryos from these proven donors are most valuable. From the second-best cows in most cases female offspring would be wanted. With sexing, cattle breeders will be able to obtain nearly as many heifers as without sexing but with only half of the recipient resources. Theoretically, economic benefits from MOET applied to the dam of the cow are highly dependent on reducing the costs of a successful transfer (Van Vleck, 1986). Sexing may help to reduce the costs to economic feasibility. The largest impact of sexing for these cattle breeders, however, will be on expansion of the embryo market. Male embryos are less required and the supply of suitable recipients poses a real practical problem in many markets.

Embryo sexing can also contribute to extension of the use of MOET at the commercial level. Sexing would hasten the trend that the genetically superior cows of the herd provide female embryos for replacements, increasing the selection intensity for dams of replacement females. Part of the genetically less valuable cows are superovulated and inseminated with sperm of beef type bulls and only male embryos are implanted in the rest of the herd for fattening. As an alternative purebred male beef embryos are implanted. Specialization in respectively milk and beef production can be practised in the same breeding plan. Already at this moment, there is a brisk trade in beef embryos. In general, according to Gibson & Smith (1986), with embryo sexing and commercial embryo transfer, separate maternal and paternal breeds would be selected for different objectives. Such a system has been described by Oldenbroek & Van der Schans (1988) in order to develop an economic feasible dual purpose breeding and production system. A different beef production system has been suggested by Taylor et al. (1985). They have shown that a system consisting almost entirely of females which are slaughtered after weaning their first (and female) progeny could be 50 % more efficient than

current systems of lean beef production. An important selection objective in such a system would be for early reproduction with ease of calving.

Finally, embryo sexing is a prerequisite in the application of new technologies as in vitro fertilization and cloning where the production of many embryos demands the selection on sex in order to reduce the recipient resources.

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EXPERIMENTAL APPROACHES TO STUDY BOLA, THE MAJOR HISTOCOMPATIBILITY COMPLEX OF CATTLE.

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Summary

The important role of the major histocompatibility complex (MHC) in the regulation of immune responses and the documentation of disease associations, especially in man, have been an important impulse to study the MHC of farm animals. Here an overview on the strucure of MHC molecules and the current knowledge of the MHC of cattle, BoLA, is presented. Experimental approaches to study BoLA are described and the cloning of BoLA class II genes from a genomic library is reported.
Keywords: MHC, BoLA, gene cloning, disease associations.

Introduction

The primary task of the immune system is the induction and regulation of protective immune responses against disease causing pathogens such as bacteria, viruses and other microorganisms. The major histocompatibility complex (MHC) plays a central role in the immune system: the cells of the immune system recognize foreign antigens together with or in the context of self MHC molecules. The essence of this phenomenon, known as MHC restriction, is, that an immune response can only be induced and regulated through simultaneous recognition of self MHC molecules and (foreign) antigen (Klein, 1986; Schwarz, 1985; Zinkernagel & Doherty, 1979). Since the MHC molecules are important recognition- and interaction molecules for the cells of the immune system, they have been investigated in detail using serological, biochemical and recombinant-DNA techniques.

As a consequence of the involvement of the MHC with the regulation of the immune responses, many disease associations with particular MHC antigens were documented (for a review for humans see Tiwari and Terasaki 1985). As the MHC of man (and mouse) is the best studied this will be taken as the point of reference. In this paper the structure of the MHC molecules will be discussed and the current knowledge of the MHC in cattle,the BoLA complex, will be reviewed shortly. Finally, an experimental approach to study BoLA will de described.

Structure of the MHC molecules

Systematic analysis of MHC specific antisera, using serological assays, resulted in the description of an unparalleled polymorphic genetic system. Classical genetic analyses documented that many allelic antigenic series belong to the MHC. The human MHC, named HLA (human leucocyte antigens), consists of the HLA-A, -B, -C, -DP, -DQ and -DR antigenic series and comprises a set of closely linked genes, located on one chromosome (chromosome 6). For the mouse (and essentially all other mammalian species investigated) similar complexity has been observed.

The MHC complex contains the genetic information for two types of gene products, the class I and class II molecules, which can be distinguished based on their characteristics. Both types of MHC molecules are integral cell membrane glycoproteins, which consists of two polypeptide chains. The class I molecules have a wide tissue distribution, they are present on virtually all types of nucleated cells. The class II molecules have a limited tissue distribution, they are present on subsets of cells of the immune system (B cells, macrophage lineage cells and activated T cells).

The class I molecules consist of a glycosylated heavy or alpha polypeptide chain of 44.000 daltons associated with beta-2-microglobulin (beta-2-m), a polypeptide of 12.000 dalton. The highly polymorphic heavy chains are encoded by multiple alleles per locus, in man the HLA-A, -B and -C loci have been defined. The beta-2-m chain is invariable.

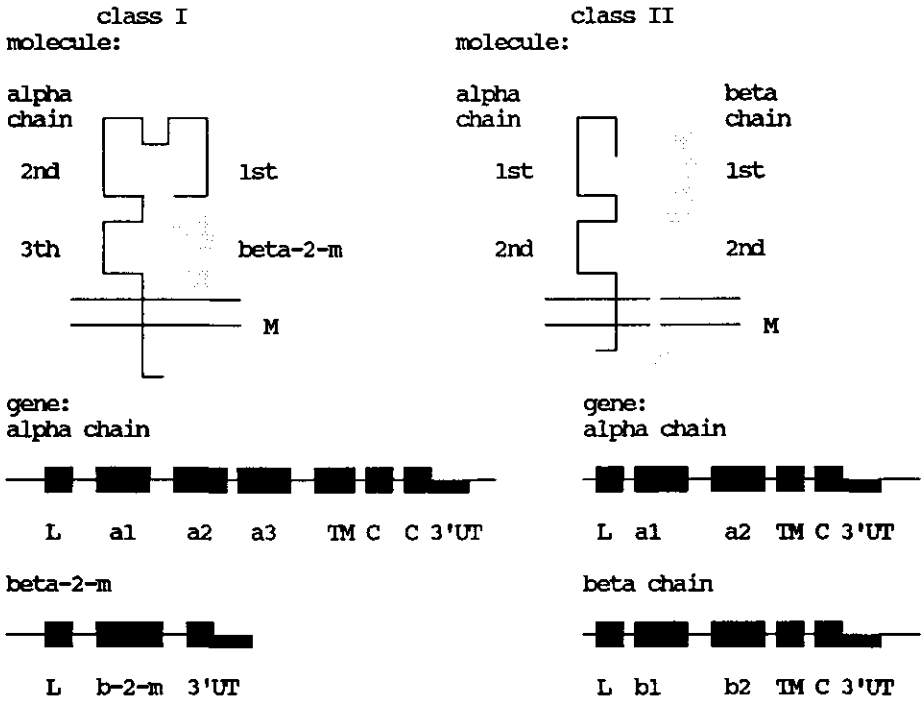

Figure 1. A schematic diagram of the exon-intron organisation of the class I and II genes and the domain structure of the MHC gene products. The introns are represented as solid lines (——). Exons are shown as boxes (▬) and labeled L (leader sequence), a1, a2, a3, b1, b2 and b2-m
for alpha or beta chain domains of the class I or II genes respectively, TM (transmembrane sequence), C (cytoplasmatic sequence). The box indicated with the symbol (▬) represent 3'untranslated sequences. The exons are transcribed into messenger RNA, which are translated into the final gene product. M denotes the cellmembrane.

Biochemical analysis indicated that the heavy chains can be divided into three extracellular domains named alpha 1, alpha 2 and alpha 3, a transmembrane and an intracellular region, the associated beta-2-m

molecule is present as a fourth domain (Figure 1). Recently confirmation of the structural features has come from analysis of crystals of class I molecules (Bjorkman et al., 1987). The domains are approximately 90 amino acid residues long. Variability between MHC molecules of one allelic serie is primarily located in the alpha 1 and alpha 2 domains. The alpha 3 domain is relatively constant, most likely to ensure that the non-covalent association with beta-2-m takes place, which is a prerequisite for the expression of class I molecules at the cell surface.

Using molecular biological techniques several class I genes have been isolated and their structure has been analyzed. The class I genes were found to consist of in total 7 coding regions (exons) interspersed with non-coding intervening sequences (introns). The organisation of the class I genes in exons and introns is directly reflected in the molecular structure. Thus the exons 2, 3 and 4 correspond with the alpha 1, 2 and 3 domains of the functional gene products, i.e. the class I molecule. In man, the HLA-A, -B and -C regions probably contain single class I genes at the respective loci (see figure 2). In addition several other class I genes have been identified, for most of which no gene product has been defined sofar. These may represent for instance pseudo-genes i.e. non-functional genes

The class II molecules consist of two glycosylated polypeptide chains ; an alpha or heavy chain of 32.000 to 36.000 daltons associated with a beta or light chain of 27.000 to 29.000 daltons. Both the alpha and the beta chains are encoded by multiple allelic series, in man the HLA-DP,-DQ and -DR series.

The DR alpha chains appeared to be invariant whereas the beta chains are polymorphic and therefore responsible for allelic polymorphism. In contrast, for the DQ and DP series both the alpha and the beta chains are polymorphic. Both polypeptide chains of the class II molecules are glycosylated and have two extracellular domains, alpha 1, alpha 2, beta 1 and beta 2, respectively for the alpha and beta chains, a transmembrane and an intracellular region (figure 1). Within one allelic series the variability of the alpha 1 and beta 1 domains is much greater than that of the alpha 2 and beta 2 domains. The restricted variability of the second domains, which are closest to the membrane, is probably of functional significance, as for the class I molecules to ensure proper association of alpha and beta chains. The molecular genetic analysis indicated that the class II genes consist of 5 exons (coding regions) interspersed by introns. The exons 2 and 3 correspond with the first and second domains of the functional gene products. The overall structure of the class I and class II molecules is very similar as well at the level of the gene product as the organisation of the genes (figure 1).

Many of the class II genes have been isolated and characterized. The HLA-DR region is reported to contain one alpha and three beta chain genes named DRA, DRB1, DRB2 and DRB3, respectively. The DRB2 gene appeared to be a pseudogene. The HLA-DQ region contains two alpha chain genes, named DQA and DXA, and two beta chain genes, named DQB and DXB. Although the DX genes have the characteristics of potentially functional genes, no expression of DX molecules has been detected as yet. The HLA-DP region also contains two alpha chain genes, SXA and DPA, and two beta chain genes, SXB and DPB. The SX genes appeared to be pseudogenes. Furthermore two additional genes, namely DZA and DOB, have been mapped in the HLA-D region. The genetic organisation of the HLA-D region, which contains in total 14 alpha and beta chain genes, is shown in figure 2. In summary only 7 of the 14 alpha and beta chain genes have proven to be functional :DRA, DRB1, DRB3, DQA, DQB, DPA and DPB.

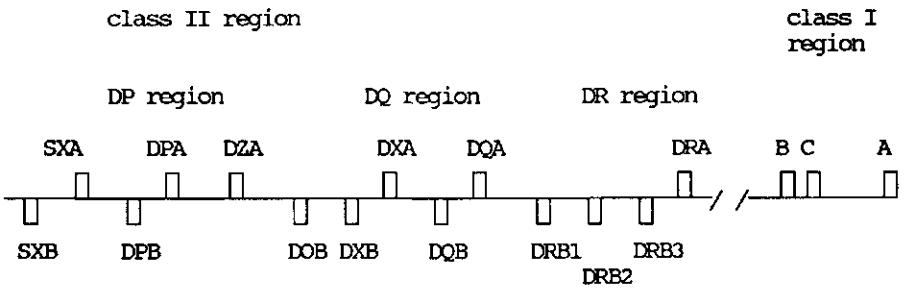

Figure 2: Molecular map of the HLA region.

The symbol ⊓⊔ denotes individual class I or class II alpha or beta chain genes.

Current knowledge of the MHC of cattle

The BoLA (Bovine Leucocyte Antigen) is the MHC of cattle. As compared with the MHC of man much less is known about the polymorphism and genetic organisation of BoLA. Within the BoLA complex, the BoLA-A and the BoLA-D regions can be distinguished, encoding respectively the class I and class II genes. Sofar only one class I locus, the BoLA-A locus, has been defined using serological techniques. Some 17 alleles can be distinguished and are defined as internationaly recognized workshop specificities (Amorena & Stone, 1978; Caldwell, 1979; Spooner, 1978). The existence of the BoLA-D region was established in studies on the genetic control of the mixed leucocyte culture (MLC) response. The presence of two loci controlling the MLC response has been postulated (Usinger et al., 1977). As yet no standardized serological reagents are available to study the polymorphism of the BoLA-D region encoded MHC molecules.

The biochemical characteristics of the bovine class I and class II molecules are similar to those of man and mouse (Hoang-Xuan et al., 1982). Recently the analysis of bovine class I and II antigens using the one-dimensional isoelectric focusing technique has been reported. At the moment this technique probably gives the most accurate description of the polymorphism especially of the BoLA-D antigens and possibly also of the BoLA-A antigens (Joosten et al., 1988a,b). The polymorphism and genetic organisation of the BoLA class II genes are being studied using human class II specific DNA probes. These studies show that the the BoLA class II genes are highly polymorphic and indicate the presence of 1 DRA gene, 3 DRB genes, 1 to 2 DQA and DQB genes, 1 DOB and 1 DZA gene as well as two other class II genes named DYA and DYB (Andersson et al., 1988a; Andersson & Rask, 1988b).

In analogy to the disease association studies in man, studies concerning the role of BoLA in relation to disease have been performed. Such studies indicated the presence of associations with BoLA for several diseases : mastitis, bovine leucosis, parasite infections (worms, ticks) (Lewin & Bernoco, 1986; Solbu et al., 1987; Stear, 1986). Also in trypanosomiasis and Theileria parva infections a BoLA dependent modulation of the immune response seems indicated. Most of the disease association studies give only indications for association with BoLA. Probably this type of study is hampered by the fact that no complete BoLA typing

for class I and class II antigens is momentarily feasible. More detailed knowledge of the polymorphism of the BoLA complex is needed to test BoLA as a genetic marker for disease resistance or susceptibility.

Approaches to study BoLA.

Our own research is directed to the characterization of the BoLA gene complex using serological and molecular biological techniques.

Serological techniques for class I and class II BoLA typing are being set up as well as the production of BoLA-A and BoLA-D specific antisera using different immunisation schemes. The obtained antisera will be tested on a reference panel and selected families for segregation analysis. Comparison of serological analysis with results obtained in the analysis of the BoLA antigens using one-dimensional iso-electric focusing is expected to be of great value since especially for BoLA-D no typing sera are available.

The second line of research aims at the molecular genetic characterization of the BoLA gene complex. Firstly, to study the polymorphism of the BoLA genes and secondly to inventarize the genetic organization and to obtain structural information of the BoLA genes. The BoLA gene complex has sofar been studied using Southern blot analyses with heterologous i.e. human MHC specific DNA probes (Andersson et al., 1988a). In Southern blot analysis (Southern 1975) genomic DNA isolated from nucleated cells is digested with restriction endonucleases (restriction enzymes), which cut the DNA at specific sites (restriction sites). Such restriction sites have an enzyme specific sequence comprising mostly 4 to 6 nucleotides. After size separation, the DNA fragments are made single stranded by denaturation and immobilized onto nitrocellulose or nylon filters. Subsequently assay conditions are used where denatured radiolabeled probe DNA can reassemble with the denatured immobilized genomic DNA fragments (hybridization), when the homology between probe and genomic DNA is sufficiently high. After washing procedures to remove non hybridized probe DNA, detection of hybridization occurs by exposure to X-ray films. The polymorphism thus visualized is based upon the probe that has been used and the presence or absence of restriction sites in the genomic DNA. This will lead to variation in the length of the restriction fragments and therefore this type of analysis is referred to as restriction fragment length polymorphism (RFLP). Although the study of the bovine MHC using heterologous MHC class II probes has been succesfull, RFLP analyses are probably most sensitively performed with homologous BoLA specific DNA probes. To obtain bovine specific probes for RFLP studies and to investigate the genetic organization of the BoLA-D region in more detail we have constructed a bovine genomic library to isolate BoLA class II genes.

A genomic library has been constructed as follows. After partial digestion with a restriction enzyme of bovine genomic DNA, the DNA fragments are size separated to obtain fragments of about 20,000 base-pairs (bp) in length (20,000bp is indicated as 20kb). The 20kb random genomic DNA fragments are then inserted into a bacteriophage lambda vector. The resulting recombinant phage lambda vectors, containing random genomic DNA fragments, can be further propagated in bacteria like E.Coli as host cells. The resulting recombinant lambda phages, at least representing several times the complete bovine genome, are subsequently screened with radiolabeled probe DNA to isolate individual genes present in separate lambda phages. The bovine genome size is 3.10^6 kb. To obtain a representative library containing at least one time the haploid genome 3.10^6 : 20 (total genome size : insert size) = $1.5\ 10^5$ independent

recombinant lambda phages are needed. Using the bacteriophage lambda vector EMBL 3, a genomic library was constructed containing a total of 1.5 10^6 independent phages, thus representing about 10 times the bovine genome. This library was screened with DNA probes specific for the human HLA class II genes; DR alpha, DR beta, DQ alpha and DQ beta. In the initial screening 80 positively hybridizing phage clones were selected. In subsequent screening procedures 12 lambda clones could be identified as specific for DQ beta, 5 for DQ alpha, 6 for DR alpha and 6 for DR beta. The number of clones isolated for the DR and DQ class II genes are in accordance with the number expected.

The lambda clones containing the bovine analogues of the DQA, DQB, DRA and DRB genes were further characterized by restriction mapping i.e. determination of the presence of specific restriction sites and spacing of these sites relative to each other. An example of a restriction map of lambda clone containing a DRB gene is shown in figure 3. After digestion of DNA of this lambda clone positively hybridizing DNA fragments were identified in Southern blotting analysis using human subprobes specific for the exons encoding the first and second domains of the DRB gene.

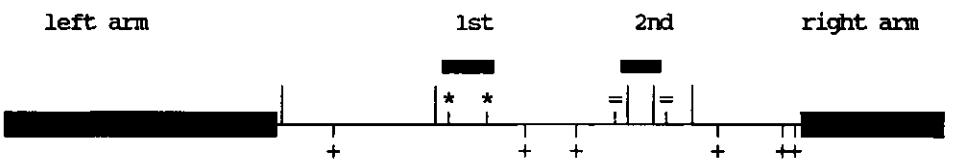

Figure 3. Restriction map of a lambda clone containing a bovine DRB gene.

The symbols * , = , | and + indicate the presence of recognition sites for the restriction enzymes Hind III, Sal 1, Bam H1 and Eco R1, respectively. A Sal 1 fragment contains the exon for the first domain and a Hind III fragment contains the exon for the second domain of a DR beta gene, as indicated.

Similar maps have been made for all the lambda clones isolated and selected from the genomic library. Several overlapping clones were identified for the different genes such that in principle the bovine analogues of the HLA DR alpha, DR beta, DQ alpha and DQ beta class II genes have been obtained. The presence and location of the first and second domain encoding exons in the clones has also been investigated (see figure 3). The preliminary results indicate that the organisation of the BoLA class II alpha and beta genes is similar to those in man: the intron length between the exons encoding the first and second domain is relatively small in the the DR and DQ alpha genes (0.5 to 1.0 kb) and relatively large for the DR and DQ beta genes. Several restriction fragments containing individual exons have been subcloned into plasmids and are being used as bovine MHC specific probes in RFLP studies. Further characterization especially nucleotide sequencing of the bovine class II genes is being performed. It is our expectation that a complete description of the genetic variation of the BoLA system can be made using bovine specific MHC probes for RFLP studies. An adequate and complete description of the BoLA system is a prerequisite to evaluate BoLA as a genetic marker in disease association studies. Combination of serologi-

cal, isoelectric focusing and RFLP analyses will, probably, be most succesful to meet this goal.

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ADVANCES IN GENETIC DISEASE RESISTANCE IN POULTRY.

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Summary

Resistance to infectious diseases is influenced by environmental factors as well as genetic constitution. Qualitative and quantitative inheritance of resistance is known for a variety of poultry diseases. However, genes directly responsible for resistance or susceptibility have not yet been identified. In this paper the strategy to identify the genes responsible for antibody production to sheep red blood cells (SRBCs) and the effect of these genes on resistance to Marek's disease is described.

After seven generations of selection for antibody production to SRBCs we have obtained high (H) and low (L) antibody titer producing lines of ISA Warren origin. Differences in antibody production (titer 7.1 versus 4.3 for H and L lines in the seventh generation) became significant ($P<.05$) from the first selection onwards. Upon contact exposure to Marek's disease virus the H line showed 20-30% less mortality than the L line ($P<.001$) .

The divergence in H and L lines demonstrates that genetic variation in immune responsiveness and disease resistance exists and exemplifies genetic differences between breeds and crosses in poultry production. As has previously been demonstrated in the mouse, genes contributing to these immunological and pathological differences between H and L lines may belong to polymorphic immunoglobulin (Ig) loci and/or loci of the major histocompatibility complex (MHC). To establish the role of these loci in the chicken, F_1 and F_2 generations will be obtained by crossing the H and L lines. In the F_1 and F_2 hybrids background genes of H and L lines will be randomly distributed. With the application of serological techniques for identifying Ig-allotypes and MHC-alleles it will then become possible to determine the effects of the individual alleles on SRBC antibody production and resistance to Marek's disease.

Identification of the different loci, genes, alleles and their correlation with resistance has to be established. Subsequent cloning and sequencing of genes, and ultimate transfection are desirable tools to avoid many generations of crossbreeding and selection for both resistance and productivity. Chicken Ig- and MHC-probes have been isolated, which can be used in Southern blot analyses. Restriction fragment length polymorphism (RFLP) obtained from Southern blots may refine the serologically defined variation and further clarify the role of Ig- and MHC-genes in SRBC antibody production and resistance to Marek's disease. The polymerase chain reaction (PCR) may then be applied, using allele specific oligonucleotides (ASOs), to define the genetic variability at the nucleotide level. Resistance and/or immune response genes can then be isolated and used in the generation of transgenic chickens, either by microinjection or by a retrovirus vector. Follow-up studies will involve the identification of transfected gene products, production of homozygous animals and the determination of the mode of inheritance and effect on

productivity.
Keywords: Major histocompatibility complex, Marek's disease, poultry breeding, restriction fragment length polymorphism.

Introduction

Principal methods to control infectious diseases include hygienic measures, effective management of housing, climate and nutrition, preventive medication, vaccination, eradication and breeding for genetic resistance. Breeding for resistance may be preferred, because it diminishes the need for continuous or repeated preventive measures and it is conferred to following generations.

A detailed treatise on genetic variation in immune responsiveness and disease resistance was presented by Hartmann (1982) and Van der Zijpp (1983). Recent studies emphasize the interactions of the immune system in the defense against disease (Powell, 1987). Resistance is the result of a complex reaction composed of innate and acquired immunity. Molecules of the chicken major histocompatibility complex (B-complex) play a central role in the immune defense. In a detailed review Bacon (1987) has indicated that chickens can be typed for disease resistance traits on the basis of their polymorphic B-haplotypes.

In many situations genetic resistance in combination with several preventive methods leads to the best results. Gavora & Spencer (1983) studied the effect of combined vaccination and selection on Marek's disease resistance. Maximum resistance to Marek's disease, expressed in percentage mortality, was found in vaccinated chickens of the most resistant strain; for maximum productivity, however, vaccination had to be applied in a strain selected for production. This implies that breeders have to consider the pathogenic environment and the opportunities for effective vaccination to define their breeding goals with respect to diseases. For some diseases, such as Marek's disease and coccidiosis, the present interest in genetic resistance is based on availability of vaccination or medication procedures and their effectiveness in diverse geographical locations and a variety of stocks.

Breeding for disease resistance is based on pathological and immunological traits and on genetically linked markers. These traits and markers have to show genetic variation, have to be relevant for disease resistance or susceptibility and have to be determined easily in routine testing on large numbers of animals. Examples of useful traits are specific mortality rate after challenge with Marek's disease virus (Gavora & Spencer, 1979) and the hemagglutination-inhibition titer after vaccination with inactivated Newcastle disease vaccine (Van der Zijpp, 1984).

In this study we present results obtained from the selection of chicken lines for high (H) and low (L) in antibody production to SRBCs, demonstrating a significant effect differences on resistance to Marek's disease. Using immunological and biotechnological techniques in association studies, the effects of particular loci and genes on antibody production and Marek's disease mortality can be established. Theoretically, once such genes have been isolated, lines or breeds with disease problems can then be transfected with genes affecting resistance.

Characterization of high and low antibody producing lines

Selection for antibody production to complex antigens to which animals have not previously been exposed, may provide a tool to breed for disease resistance. In mice, lines have been selected for antibody production to complex antigens and tested extensively for immunological and patholo-

gical differences (Biozzi et al., 1979). Selection for high antibody production resulted in diminished microbicidal activity of macrophages, while cell-mediated immunity remained unaffected. Pathological differences became obvious through effective resistance of lines to a variety of diseases.

In 1980 we started a selection experiment using hybrid ISA Warren chickens. Chicks were intramuscularly injected at 37 days of age with SRBCs, and total hemagglutinating antibody titers were determined five days post immunization. Results of selection for high and low antibody production, as well as for a randombred control (C) line after seven generations are shown in Table 1 and Figure 1.

Table 1. Titers of SRBC-agglutinating antibodies in generation seven of control (C) and selected high (H) and low (L) line chickens.

	Line		
Sex	C	H	L
Male	4.59 (n = 176)	6.79 (n = 123)	1.88 (n = 188)
Female	5.23 (n = 172)	7.37 (n = 125)	2.39 (n = 189)

In the base population, a heritability of hemagglutinating antibody titers for half sibs was estimated at .57 $\pm$ .21. Realised heritabilities (h2) were calculated after four generations of selection by regression of cumulative response on cumulative selection differential (Table 2). In the L line, realised heritabilities agree with the half sib estimate in the base population, especially in females.

Table 2. Realised heritabilities for haemagglutinating SRBC antibody titers based on four generations of selection of high (H) and low (L) lines.

Line	Males	Females
H	.217	.191
L	.482	.566

The frequency distribution of chicks is shown in Figure 2. In each generation the overlap between the H, L and C line decreases, signifying the response to selection.

The immunological characterization of the differences between the lines (Van der Zijpp & Nieuwland, 1986) has produced significant differences in the humoral response against diverse antigens (H > L) between lines. Tests for cell-mediated immunity revealed no differences between lines. So far, differences in phagocytosis efficiency were small. With prolonged

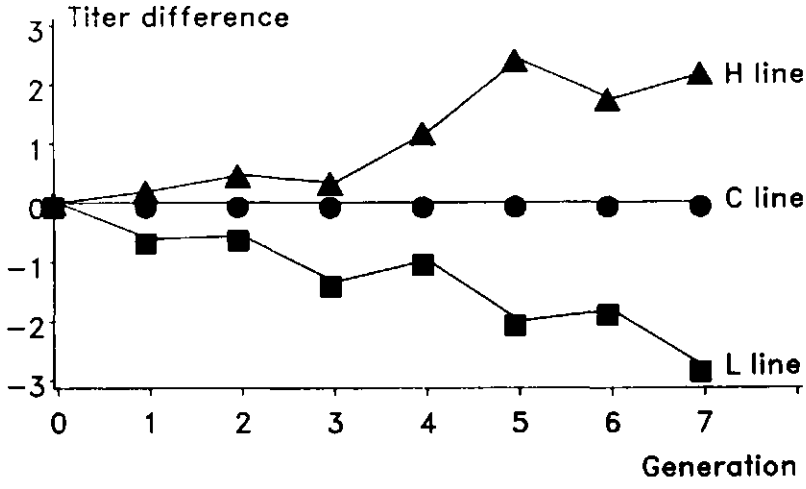

Figure 1. Selection response in H and L lines for SRBC antibody titers relative to a random control (C) line.

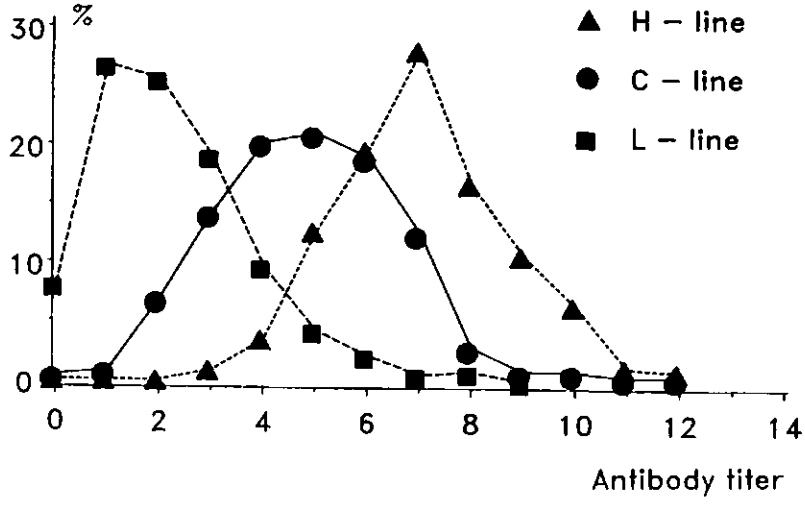

Figure 2. Frequency distribution of H, L and C lines after seven generations of selection.

selection for high and low SRBC responsiveness the contribution of phagocytosis to the overall difference can be established more precisely.

Differences in productivity between the lines have not yet been observed. A distinct negative genetic correlation was found in the base-population : $r_g = -.57$ for bodyweight at 57 days of age and primary titer where as r_p was -.06. In all following generations the body weight of the H line chickens at that age was significantly reduced compared to the L line chickens. In contrast, the H line chickens have a higher relative spleen weight before and after immunization.

Disease resistance has been determined in a contact challenge experiment for Marek's disease. The percentage mortality for H and L line birds is shown in Table 3.

Table 3. Percentage mortality measured 15 weeks after exposure of Marek's disease virus to high (H) and low (L) lines.

Line	number		Marek's disease mortality	
	males	females	males	females
H	100	92	13	28
L	125	130	33	59

Differences between sexes and lines were significant ($P<.001$). Preliminary results have indicated significant differences in the frequency of B-complex alleles between the lines.

Although data of the characteristics of H and L lines are accumulating slowly, they apparently show many similarities with the selection lines of Siegel and Gross at Virginia Polytechnic Institute and State University (Siegel & Gross, 1980; Siegel et al., 1982; Dunnington et al., 1986). Despite different breeds (White Leghorn versus ISA Warren), effects on immune responsiveness, Marek's disease resistance and body weight were similar.

Loci and genes involved in antibody production and Marek's disease resistance

Biozzi et al., (1979) estimated that about ten independent loci controlled the antibody response to SRBCs in mice. The inter-line difference could be explained only in part by two defined loci. Positive associations were demonstrated with an allotypic marker of the Ig heavy chain and with certain alleles of the mouse MHC (H-2). The Ig locus explained 10% and the H-2 complex explained 20% of the difference in agglutinin synthesis. Association studies were extended after the discovery of large, or even absolute differences in frequency of Ig allotypes and H-2 alleles between the H and L lines. F_1 and F_2 hybrids, as well as backcrosses between F_1 hybrids and H or L parental lines were produced. The normal immunization procedure was carried out and hemagglutination titers to SRBCs determined. Maximum differences in agglutinin titer between Ig allotypes and H-2-haplotypes were 10 and 20% respectively. The inter-line divergence may be determined directly by these loci or by closely linked loci.

In chickens extensive polymorphism has been described for IgG C_H and IgM C_H allotypes (Benedict & Berestecky, 1987). Fourteen allotypic speci-

ficities have been described for IgG C_H and five for I_gM C_H, which belong to the G-1 and M-1 loci respectively.

The B-complex encompasses three tightly linked loci which code for B-F (class I), B-L (class II) and B-G (class IV) molecules. The B-G molecules are highly polymorphic products of genes closely linked to the class I and II genes. Polymorphism of B-G molecules can easily be defined using typing sera in a direct hemagglutination test. For example, the thus defined B-G21 allele is associated with resistance to Marek's disease. However, resistance is rather influenced by the B-F21 or B-L21 locus than by the B-G21 locus (Briles et al., 1983; Crone & Simonsen, 1987).

Based on preliminary results, we expect to find distinct differences of the B-haplotype distribution between the H and L chicken lines. However, a complicating factor, when compared to the mouse experiments, is that three or four haplotypes may be present in both the H and L line. We will therefore proceed to evaluate these haplotypes, confounded with background genes, in our H and L lines followed by the production of F_1 and F_2 generations.

Identification of genes responsible for antibody production and Marek's disease resistance

Identification of MHC genes at the DNA level by restriction fragment length polymorphism (RFLP) has been described in human, mice, cattle, pigs, as well as in chickens. Because parts of MHC genes are highly conserved in evolution, heterologous human and mouse probes can be used in Southern blot analyses of other species (Andersson et al., 1986ab, 1987; Tilanus et al., 1988; Vaiman et al., 1986). Whereas human and cattle MHC genes are very homologous, the chicken B-complex displays only limited homology with their human counterparts. Therefore chicken derived class I and class II probes should be used. By genomic and cDNA cloning techniques, probes have become available for the B-L (Bourlet et al., 1988) and B-G (Goto et al., 1988) genes. Moreover, genomic libraries will give insight in the gene organization of the B-complex. Similar studies for the Ig gene family have been performed with V and C chain probes (Reynaud et al. 1985, 1987). Probes used in Southern blot analysis reveal RFLP which, once correlated with either disease susceptibility or resistance, may, directly or via known serologically defined disease association, identify the gene(s) involved. A refined characterization of the gene(s) at the nucleotide level can be determined by sequencing the genes, e.g. by using the polymerase chain reaction (PCR) method. Moreover, to come to gene transfer, not only the gene has to be identified, but also regulatory sequences that allow its transcription. Once gene transfer has been established, expression of introduced genes can be tested by "convential" methods and their influence on resistance to disease.

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EFFICIENCY OF ESTIMATING GENOTYPE PROBABILITIES OF SIRES AT INDIVIDUAL LOCI FOR A SEX LIMITED TRAIT

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Summary

The accuracy of estimating genotype probabilities of sires for a single locus trait with two alleles has been determined for different modes of inheritance and population allele frequencies. Data were simulated for a female sex limited trait over a 10 year period with random mating during which sires produced either 3, 6 or 12 female offspring.

The accuracy of estimation was markedly higher for a trait with additive gene action than for a trait with complete dominance and 80% penetrance. With additive gene action the lowest accuracy was found at a population frequency of 0.5 while with dominance the accuracy decreased with an increasing population frequency of the dominant allele. The influence of the different sources of information on the accuracy of estimation depended on the number of offspring per sire and the mode of inheritance.

Keywords: individual loci, estimation, accuracy, genotype probabilities.

Introduction

The potential for use of single genes in livestock improvement programmes is increasing. Some economically important traits in livestock are influenced by single genes having major effect, like the halothane gene in pigs (Webb & Simpson, 1986) and the Booroola gene in sheep (Piper & Bindon, 1982). Genetic polymorphism at loci affecting a quantitative trait and with markers linked to them can be used in livestock improvement (Soller & Beckmann, 1982; Smith & Simpson, 1986). An increase is expected in the number of genes of large effect on commercial traits that can be identified. Identification of animals with the highest probability of having the desired genotype could improve the efficiency of selection programmes making use of these genes.

Milk casein variants in dairy cattle and goats are sex limited single locus traits which can be measured in the milk (Schaar et al., 1985; Grosclaude et al., 1987). These variants have been shown to affect cheese yield and are therefore of economic importance. Information on the number of daughters needed to determine the sire's genotype is lacking.

Van Arendonk (1988) described a method to estimate genotype probabilities of animals for a single locus trait with a known mode of inheritance and known allele frequencies. The method uses phenotypes of the individual, relatives, collateral relatives and mates and it allows for missing observations and data over several generations. Some basic ideas were taken from studies in human genetics by Elston & Stewart (1971) and

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Heuch & Li (1972). In this paper, the effectiveness of this method and the influence of different sources of information will be determined for a female sex limited trait with various modes of inheritance and numbers of offspring per sire.

Method

Estimation of genotype probabilities

The method to estimate genotype probabilities for a single locus trait uses information on the individual, its parents, offspring and their relatives and collateral relatives (Van Arendonk, 1988). It is assumed that the mode of inheritance and the allele frequencies are known. The method allows for animals with unobserved phenotypes. For this study an autosomal locus with two alleles will be considered.

The probability of individual i having genotype u_i, $prob_i(u_i)$, can be calculated from the following equation:

$$prob_i(u_i) = prior_i(u_i)\ g(f_i|u_i)\ post_i(u_i) / \left(\sum_{v=1}^{k} prior_i(v)\ g(f_i|v)\ post_i(v) \right) \quad (1)$$

where

$prior_i(u_i)$ = the prior probability of individual i having genotype u_i,
$g(f_i|u_i)$ = conditional probability given genotype u_i of individual i having phenotype f_i,
$post_i(u_i)$ = posterior probability of individual i having genotype u_i,
k = number of possible genotypes.

The probability g(f|u) describes the relation between phenotypes and genotypes which accounts for dominance, penetrance and probabilities of misclassification. Table 1 gives the probabilities g(f|u) for two situations used in this study, I: no dominance and complete penetrance; and II: complete dominance of A allele and 80% penetrance of the recessive aa genotype. The first reflects the mode of inheritance of casein variants while the second situation reflects that of the halothane gene in pigs (Southwood, 1988). In case of a missing observation of the phenotype g(f|u) is set equal to one for all u.

The prior probabilities combine the information on the parents and their relatives and mates but it does not include the phenotype of the individual being assessed or that of any of its descendants. The prior probability of i having genotype u_i, $prior_i(u_i)$, can be calculated from equation (2):

Table 1. Conditional probability given genotype u of observing phenotype f, g(f|u), for I: no dominance and complete penetrance; II: complete dominance and 80% penetrance of recessive genotype.

	I			II	
	f= AA	Aa	aa	f= A-	aa
u=AA	1	0	0	1	0
Aa	0	1	0	1	0
aa	0	0	1	0.2	0.8

Table 2: The conditional probability of the individual having genotype u_i given its parents genotype u_s and u_d, $pt(u_i|u_s,u_d)$.

	u_s=AA			u_s=Aa			u_s=aa		
u_i=	AA	Aa	aa	AA	Aa	aa	AA	Aa	aa
u_d=AA	1	0	0	.5	.5	0	0	1	0
Aa	.5	.5	0	.25	.5	.25	0	.5	.5
aa	0	1	0	0	.5	.5	0	0	1

$$prior_i(u_i) = \sum_{u_s=1}^{k} prob_s(u_s,i) \sum_{u_d=1}^{k} prob_d(u_d,i)\ pt(u_i|u_s,u_d) \qquad (2)$$

where $prob_s(u_s,i)$ is the probability of the sire having genotype u_s when the information from i is not used, similarly $prob_d(u_d,i)$ gives the probabilities for the dam and $pt(u_i|u_s,u_d)$, is the conditional probability of i having genotype u_i given its parents genotypes are u_s and u_d (table 2). In case of an unknown sire or dam, $prob_s(u_s,i)$ or $prob_d(u_d,i)$ respectively, is set equal to the proportion of individuals in the population having genotype u, $\tau(u)$.

The information from the progeny of individual i is combined in the posterior probabilities, which can be calculated as,

$$post_i(u_i) = \pi \left(\sum_{u_m=1}^{k} prob_m(u_m,p) \sum_{u_p=1}^{k} g(f_p|u_p)\ post_p(u_p)\ po(u_i|u_m,u_p) \right)_{p=1}^{n_i} \qquad (3)$$

where

n_i = number of offspring of individual i,
$prob_m(u_m,p)$ = probability of mate producing offspring j having genotype u_m when information of j is not used,
$g(f_p|u_p)$ = conditional probability given u_p-th genotype that phenotype f_p should be observed,
$post_p(u_p)$ = posterior probability of offspring p having genotype u_p,
$po(u_i|u_m,u_p)$ = conditional probability of individual i having genotype u_i given genotype of mate and offspring (table 3).

Table 3. The conditional probability of the individual having genotype u_i given the genotype of mate (u_m) and progeny (u_p), $po(u_i|u_m,u_p)$.

	u_m=AA			u_m=Aa			u_m=aa		
u_i=	AA	Aa	aa	AA	Aa	aa	AA	Aa	aa
u_p=AA	·67	·33	0	·67	·33	0	0	0	0
Aa	0	·33	·67	·33	·33	·33	·67	·33	0
aa	0	0	0	0	·33	·67	0	·33	·67

For a more detailed description of the method and for a description of the iterative algorithm to estimate the genotype probabilities, see Van Arendonk (1988).

The probable frequency of the A allele in sire i, p(A), is estimated from its genotype probabilities as: $p(A) = prob_i(AA) + 0.5\ prob_i(Aa)$.

Simulation

To determine the effectiveness of estimating genotype probabilities, a simulation program was written to generate data for a single locus female sex limited trait. To generate a pedigree structure, data were simulated for a 10 year period with random mating. All dams in the base population were unrelated and had known phenotypes. Every year one-third of the dams were replaced by animals which originated from dams in the population and the sires used. At two years of age, when the females had their first offspring, the phenotype for the single locus trait was measured.

Twenty sires, originating from 5 sires which had 4 sons each but no female offspring, were used simultaneously. A dam was allowed to produce only one son and, to avoid inbreeding, these dams were unrelated to other animals in the population. The phenotype of the dam of the sire was recorded. Sires were used for two consecutive years during which they all produced either 3, 6 and 12 female progeny with known phenotype.

A single autosomal locus model with two alleles (A, a) was used for the inheritance of the trait. Data were simulated for frequencies of the A allele of 0.2, 0.5 and 0.8. A population in Hardy-Weinberg equilibrium and equal viability of all genotypes was assumed. Two alternatives for dominance and penetrance were considered, I: no dominance and complete penetrance; and II: complete dominance and 80% penetrance of the aa genotype (table 1).

Alternative methods

Genotype probabilities of the sires in the simulated data were, unless stated otherwise, estimated using equation (1). This will be referred to as method 1. To determine the influence of different sources of information on the effectiveness of that method four alternative methods, derived from equation (1), were used. In method 2 no relations between sires were used. Method 3 did not use the relations between dams, which implies that no information was available on mates of a sire. In method 4 phenotypes of the dams of the sires were not utilized. Only phenotypes of the offspring of a sire were used in method 5. Hardy-Weinberg genotype probabilities were used for the parents and the mates in that alternative.

For all methods of estimation, the gene frequency and the relation between genotype and phenotype assumed were taken to be equal to those used in the simulation of data. Iterations were stopped when the sum of absolute differences between genotype probabilities of sires in the last and previous round was less than 0.01.

To determine the efficiency of the different estimation methods the relative selection differential (S) when 10% of the sires are selected on the estimated allele frequency was used. This was calculated as:
$S = \{(est - pop)/(true - pop)\} * 100$ where est and true are the average frequency of the A allele of 10% of sires with highest estimated and the true frequency of A allele, respectively and pop is the average population frequency of the A allele.

Results for each alternative were based on 20 replicates.

Results and discussion

No dominance and complete penetrance

Table 4 gives the distribution of genotype probabilities of sires estimated by method 1 for different true genotypes and number of offspring for situation I with complete penetrance and frequency of A allele of 0.5. As an example 65% of the heterozygous sires had a estimated probability of 90% or higher of having the Aa genotype.

With a few offspring per sire there was a marked difference in the distribution of the estimated genotype probabilities between homozygous and heterozygous sires (table 4). With 3 offspring per sire the estimates for the homozygote sires were centered around a value of 80%. From the heterozygous sires, however, 65% had a estimated genotype probability of 100% but a relatively large proportion of sires had an estimate smaller than 40%. As soon as a sire has one offspring with genotype AA and one with genotype aa it is certain that the sire is heterozygous. Tracing all combinations of offspring of a Aa sire having 3 offspring, it can be shown theoretically that the estimated genotype probability(%) using only information from its offspring (method 5) can take values of 20, 33, 50 and 100, the expected frequency(%) of each being 3, 19, 50 and 29, respectively. In method 1 more information is used which causes a greater variation in the estimated values and increases the proportion of sires with an estimate of 100%.

The distribution of the estimated genotype probabilities changed markedly when number of offspring increased from 3 to 12 (table 4).

For prediction of changes in frequency of genotypes due to selection, the average estimated allele frequencies of the selected sires as well as of the selected dams are needed. For selection purposes it is therefore important to estimate the frequency of the A allele in each sire. This frequency was calculated from the estimated probabilities of a sire having genotype AA and Aa.

Table 4. Distribution of estimated probability (%) of a sire being correctly genotyped for different true genotypes and number of offspring (method 1:all information, population freq.=0.5, mode I: no dominance and complete penetrance).

No. off.	True Genotype	Estimated probability(%) 0-25	25-40	40-60	60-75	75-90	90-100
3	AA	0	4	8	18	44	26
	Aa	10	9	11	4	1	65*
	aa	1	1	11	20	39	28
6	AA	0	0	1	2	19	78
	Aa	5	2	1	0	0	92
	aa	0	0	1	3	19	77
12	AA	0	0	0	0	0	100
	Aa	1	0	0	0	0	99
	aa	0	0	0	0	0	100

* 65% of sires with genotype Aa had an estimated probability 90-100% of having genotype Aa

Table 5. Distribution(%) of estimated frequency of the A allele of a sire for different true genotypes and number of offspring without dominance (method 1:all information, population freq.=0.5).

No off	True genotype	Estimated frequency of A allele (%)								
		0-5	5-15	15-30	30-45	45-55	55-70	70-85	85-95	95-100
3	AA	0	0	0	0	0	5	20	49	26
	Aa	1	5	8	3	65	3	9	5	1
	aa	28	46	24	2	0	0	0	0	0
6	AA	0	0	0	0	0	0	2	20	78
	Aa	1	2	2	0	92	0	1	1	1
	aa	77	19	4	0	0	0	0	0	0
12	AA	0	0	0	0	0	0	0	0	100
	Aa	0	0	0	0	99	0	0	0	0
	aa	100	0	0	0	0	0	0	0	0

Table 5 gives the distribution of the estimated frequency of the A allele in sires for different true genotypes and number of offspring for additive gene action (I) and a population frequency of 0.5. With 3 offspring, 65% of the Aa sires had an estimated frequency of the A allele between 45 and 55%. This is in agreement with results in table 4. The heterozygous sires showed greater variation in estimated frequency than the homozygous sires. The variation decreased markedly with increasing number of offspring. There was close to complete agreement between estimated and true values when sires had 12 offspring.

Dominance and 80% penetrance

The distribution of estimated allele frequencies of heterozygous and homozygous recessive sires showed considerable overlap in the case of complete dominance and 80% penetrance and a population frequency of A of 0.5 (table 6). The estimates of Aa and aa sires showed much larger variation than those of AA sires. The combination of dominance with incomplete penetrance resulted in a lower accuracy of estimation compared to the situation with additive gene action (table 5). More offspring were needed to distinguish between homozygous recessive and heterozygous sires. This also holds, to a lesser extent, for the distinction between homozygous dominant and heterozygous sires.

Population frequency

The influence of population frequency of the A allele on the distribution of estimated allele frequency in sires having 6 offspring is given in table 7. With additive gene action (I) the estimates of the homozygous sires are affected by the population frequency. The proportion(%) of AA sires with an estimated frequency(%) of A between 95 and 100 was 97, 78 and 70 when the population frequency of A was 0.8, 0.5 and 0.2, respectively (table 7 and 5). The population frequency had a very limited effect on the estimates of the heterozygous sires in the case of additive gene action.

Table 6. Distribution(%) of estimated frequency of the A allele in a sire for different true genotypes and number of offspring in a situation with dominance and 80% penetrance (method 1, population freq.=0.5).

No. off.	True genotype	Estimated frequency of A allele (%)								
		0-5	5-15	15-30	30-45	45-55	55-70	70-85	85-95	95-100
3	AA	0	0	0	0	1	13	57	29	0
	Aa	0	2	12	39	10	11	22	4	0
	aa	3	18	31	34	4	4	6	0	0
6	AA	0	0	0	0	0	2	17	65	16
	Aa	1	2	8	33	36	2	7	10	1
	aa	13	20	28	30	6	1	1	1	0
12	AA	0	0	0	0	0	0	1	12	87
	Aa	0	2	4	19	69	0	1	1	4
	aa	27	23	22	20	8	0	0	0	0

With dominance and 80% penetrance the population frequency had a big influence on the distribution of estimates of all genotypes (table 6 and 7). With an increase in the population frequency of the dominant A allele the distinction between genotypes based on estimated allele frequency reduced. This is clearly shown by the reduction in relative selection differential which reflects the average true allele frequency of the 10% of sires with the highest estimated frequency (Table 8). The relative selection differentials(%) with six offspring per sire were 99, 82 and 69 for population frequencies of 0.2, 0.5 and 0.8, respectively.

Table 7. Influence of mode of inheritance and population frequency of A allele on distribution(%) of estimated frequency of the A allele in a sire having 6 offspring for different true genotypes(G) (method 1).

Pop.freq.	G	Estimated frequency A allele (%)								
		0-5	5-15	15-30	30-45	45-55	55-70	70-85	85-95	95-100
		I: no dominance and complete penetrance								
0.8	AA	0	0	0	0	0	0	0	3	97
	Aa	0	1	1	0	95	0	0	1	2
	aa	70	15	14	1	0	0	0	0	0
0.2	AA	0	0	0	0	0	1	14	15	70
	Aa	2	1	0	0	95	0	1	1	0
	aa	97	3	0	0	0	0	0	0	0
		II: dominance and 80% penetrance								
0.8	AA	0	0	0	0	0	1	7	74	17
	Aa	0	0	0	18	24	2	11	40	5
	aa	0	0	6	40	26	5	9	14	0
0.2	AA	0	0	0	0	2	2	19	64	13
	Aa	3	6	15	30	38	2	3	3	0
	aa	62	20	12	5	1	0	0	0	0

Method of estimation

Relative selection differential when 10% of sires were selected on allele frequency estimated by different methods are in table 8. As expected method 1, using all information, was superior to the other methods while method 5, which used information only on offspring, showed poorest results. The differences between the methods depended on the population frequency of A allele, mode of inheritance and the number of offspring. Smallest differences for a given mode of inheritance were found at a low population frequency (0.2). In that case on average 4% of the sires had the AA genotype and most of these sires were also included in the top 10% on estimated frequency from methods with a lower accuracy of estimation. This shows that the differences between methods depended on the proportion of sires selected.

With additive gene action the relative selection differential was lowest at a population frequency of 0.5 while the relative selection differential decreased with increasing population frequency in the case of dominance and 80% penetrance. In the latter case the relative selection differentials(%) with 12 offspring per sire were 88 and 58 for method 1 and 5, respectively. This shows that in a situation with dominance even at a higher number of offspring a substantial improvement in accuracy can be made by including all information on related animals in estimating genotype or allele frequencies of individual animals.

General discussion

In this study data were generated for a sex limited trait with a known mode of inheritance and known allele frequencies in a random mating population. Effectiveness of estimation is expected to decrease when only poor estimates of population parameters are available. Population allele

Table 8. Relative selection differential when 10% of sires are selected on allele frequency estimated using different methods for different population frequencies of A allele, number of offspring and modes of inheritance.

Pop. freq.	.2	.2	.2	.5	.5	.5	.8	.8	.8
No. off.	3	6	12	3	6	12	3	6	12
	I: no dominance and complete penetrance								
method*1	99	100	100	93	99	99	97	100	100
2	99	100	100	82	96	99	88	100	100
3	96	100	100	87	97	99	97	100	100
4	95	100	100	86	97	99	93	98	100
5	85	100	100	74	92	99	78	98	98
	II:complete dominance and 80% penetrance								
method 1	83	99	100	75	82	97	50	69	88
2	84	99	99	65	76	93	40	68	78
3	84	99	99	67	79	94	44	62	73
4	79	98	99	65	79	93	45	61	86
5	55	95	99	29	54	86	31	28	58

* 1: all information, 2: no relations between sires, 3: no relations between dams, 4: no information on dams of sires, 5: only information on offspring.

frequencies mainly affect the prior probabilities of a animal. The influence of the population allele frequencies is expected to be smaller when information on phenotypes of parents can be used in estimating the prior probabilities. The possibilities to use the developed methodology in estimating population frequencies and the mode of inheritance should be investigated further.

The effect of non-random mating of individuals based on their phenotypes is expected to be accounted for when the information on the parents is used in estimating the genotype probabilities. Non-random mating is therefore expected to affect the significance of the different sources of information. This, however, remains to be shown.

The method of estimating genotype probabilities is expected to contribute to a better identification of animals with a desired genotype.

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THE PUBLIC'S CONCERN ABOUT ANIMAL MANIPULATION

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Man has been ruining its environment for already a considerable time. Misuse of land and careless disposition of waste products are some of the major points of concern related to agriculture. Concern brought about by genetic and cellular manipulation of micro-organisms, plants and animals, is not far from new either, (The Biology Bomb (R. Taylor) is from 1964, Silent Spring was published a few years earlier only). Nevertheless, the scientific work discussed in this symposium has only recently attracted attention of the public at large. It is, however, not so much the issue of environmental effects that raised concern about unconventional animal breeding, but certainly, waves of protests against these experiments originate from this general trend. As one spoke in the past of the chemists for being responsible for disturbance of ecosystems, now one more and more blames the biologists for interfering with natural evolution. The physicists were, of course, the first to be accused, when having liberated the nuclear force for military application. It is against this general background that a whole anti-technology syndrome has developed. But the tide is changing again. It is felt nowadays that new technologies are also very much the basis of our welfare and civilization.

Opposition to animal experiments comes in different grades. Most people do not deny the human benefit and allow experimentation to some extent, but not if an unnecessary constraint is put on the animals. In general the researchers share that view and consequently consider animal care as part of good laboratory practice. It leaves, however, still open a large field of discussion as to what is necessary and unnecessary, particularly with respect to specific goals. Is a pain strain allowed for medical applications and not for development of new cosmetics? In which category does fall the use of animals for agricultural purposes?

Some people reject any type of use of animals in experimenting, or even in breeding; those are for example the vegetarians, who believe that Man can feed himself adequately enough on plants. It is pretty questionable, whether these people are always consistent in their behaviour, and reject for themselves also the application of modern medicine, which could not have been developed without extensive animal experiments.

When we focus our attention now on the main points of concern, then three different aspects require our attention:

a: By gene transfer across the species barrier, a new gene combination, not yet occurring in nature, might be established in a creature dangerous to Man or one which disturbs existing ecosystems.
This is the main concern of environmentalists. At first sight this only would involve the microbiologists, who might liberate a new infectious agent, either of higher virulence than naturally occurring, or with wider host ranges. It should be noted however, that - by purely classical crosses - so far also animals have been produced

with unpleasant qualities, e.g. insects and dogs with increased aggressiveness (a certain bee in S.America, certain unfavourable strains of the pittbull terrier).

b: The production of hybrids or chimera as such. Here we find as opponents those who believe that we should not interfere with natural evolution at all.

c: Experimenting with animals to establish chimera, which might be a constraint to these laboratory animals. Considering this last aspect we are faced with the members of animal protection leagues.

I want to avoid already from the beginning that in this audience of animal experimenters an irritation is raised, which might keep you from listening to argumentation or even make you leave the conference room. Therefore, I had better firstly outline my general attitude towards the three aspects, which is quite moderate, I assure you. I hope you will not be irritated by the statement that I believe we should take opposition, if any, with respect to the three concerns mentioned very seriously. If we behave as responsible scientists, we must take note of and even appreciate criticism on our approach of certain subjects.

But I also want to state at the beginning that in my opinion most of the opponents are usually exaggerating possible dangers as well as the quantitative stress put on animals in captivity. But let us be honest, some experiments are quite unpleasant. What, from our scientific view, makes the behaviour of some opponents illogical, is the underrating of comparative risks and strains in naturally occurring phenomena. Therefore, I first want to analyze the origin of that attitude.

Humans, particularly children, are accustomed to attributing to (higher) animals, similar feelings as Homo sapiens experiences. This is induced by the behaviour of domesticated animals, living in our social system, in which we enforce on them also our social ethics. Examples in literature are the famous Winnie the Pooh and the rabbits in Watership Down. One of the most important strives of humans is for freedom. We do not accept slavery and captivity. How this is with animals, we do not know. For sure, humans are prepared to give up their absolute freedom, to do what they want, if in exchange some form of security is obtained. Therefore, we live in societies. So do many species in wildlife, when living in social groups, in which a certain degree of discipline restricts the freedom of the individual. Man and animals certainly have many instincts in common and it is not surprising that many people believe animals to feel about freedom as we do. We can only argue that, if we domesticate animals, we offer them in exchange also protection from persecution by their natural predators (including infectious diseases).

The underlying reason for concern about the suffering of laboratory animals is an over-assessment of their suffering in captivity, the under-assessment of their suffering, when they are at the mercy of the harsh conditions in the wild, where the expression "the survival of the fittest" applies. We know for sure that wildlife is pretty rough. All carnivorous animals have little consideration with their prey. In wildlife almost all animals have their particular predator, who eats them alive without anaesthesia. If not swallowed, wildlife animals end their lives without any med-care, usually by starvation or thirst when aging prevents them from finding their food. The picture we can give of our animals in captivity, even of the laboratory animals we "torture", is very different and certainly more comfortable. Food always available; pain suppressed by pharmaceutics; death seldom so cruel as in wildlife. I

would even go so far as to say that the average laboratory animal that is subjected to the worst, even most aggravating, experiment in the laboratory is better off than its mates in the idealized wildlife.

The opposition against the production of transgenic animals, the mixing of gene pools, which does not occur frequently in wildlife, is in my opinion largely due to an over-assessment of the definition of a species. We consider two individuals to belong to different species, if a male representative of one, when crossed with a female of an other, does not give rise to fertile offspring. We should keep in mind that this definition is quite arbitrary. The inability of a certain gene pool to mix with another gene pool, is the result of just a few out of a thousand (or probably million) differences between those gene pools. Moreover, also within a species there is a tremendous amount of variation (if not inbred) and differences among individuals of the same species can be even greater than among the individuals of two different, but related species. The concept of a species is to a certain extent a man-made arti-fact, based on cross-incompatibility. Now that we have new means to make genes cross the species barrier, we should, in my opinion, reconsider also the species-concept. And I foresee that in the near future our systematic biologists will come up with proposals to reduce considerably the number of species we distinguish. In microbiology we have gone through that process already in the nineteen-fifties.

Why is it that the people at large, and also the scientists, have such a high esteem of a species? That is, of course, because of the fact that natural evolution, seen within a life-time, is so slow. A single generation has the impression that natural evolution is almost at a standstill. Which is not true. What indeed is slow, is the rate at which by variation and selection, results (new species) are observed, but the process itself always goes on with a tremendous intensity. Why should we allow new species to arise only by variation and selection, followed by isolation? (possibly the main cause of induced cross-incompatibility). The opposing argument is rather similar to that against animal experiments in general. One sees only the monsters being produced and takes it for granted that during embryonic growth the hybrid animals suffer considerably, because of fundamental incompatibility of their gene pools.

Again we must state that such "suffering" also occurs, even when two individuals of the same species are crossed. It is estimated that in humans, approximately 70% of fertilized eggs have no real chance to survive, because of incompatibility of the (haploid) gene pools involved, and thus are subject to early abortion. In that case we should, however, state, that "suffering" of the embryo is not the right term to use. We can speak of suffering only, when the first neurons are produced, in humans approx. three weeks after fertilization. Therefore, when we produce hybrid animals, our care for them obliges us to give special attention to that specific period of their life-cycle, when the nervous system is developing.

Again it is tempting to compare suffering, if any, of animals in the wild and of those in the laboratory.Indeed, the spontaneous formation of chimera as such occurs very seldom, the mule being one of the exceptions. But within species gene pools also do change continuously and most of the time not for the better. I mentioned already the frequent incompatibility of human gene pools. We all know that in wildlife a small fraction of the offspring survives to maturity; the major fraction, which does not win the war of the survival of the fittest, die without medicare.

When considering hybrids, we should distinguish between real chimera in which two haploid gene pools are mixed, and those transgenic animals in which a single or a few heterologous genes are transferred.I focus the attention on the latter, because scientific prospects to produce true chimera are still scanty. I need not explain this in this scientific conference. Meanwhile over a thousand different transgenic species have been produced in the laboratory. Unfortunately, only a few "monsters", that have been produced, attracted the attention of journalists. It is in fact surprising how easily healthy transgenic animals are produced, at a high frequency if one masters the introduction of isolated DNA in fertilized eggs. The bottle-neck is only of this technical nature. In TNO we produce several transgenic mice a week, at a success rate of 25-50%. It is very obvious that no real harm is done to the majority of animals when subjected to transgenic manipulation. Opposition can only be based on the philosophy that Man should not manipulate the origin of species at all, and as I mentioned that philosophy is based on a general overall overassessment of the artefact species as such.

A similar conflict of philosophy can be recognized in the fear that by gene transfer a gene combination might be established that consequently disturbs existing ecosystems (my first aspect mentioned in the introduction). The risks here are extensively over-assessed by the public at large, because it does not understand how experimental breeding is quantitatively related to natural evolution. The latter process has been going on, variation and natural selection, for billions of years, with the result of four million species, which have optimized their gene condition for their continuous struggle in the wild. By means of classical crosses, Man has domesticated a few hundred species, improved for human benefit. Not for the benefit of the species themselves, though they are no longer involved in the struggle for life in the wild. As far as I know, all the domesticated races will vanish from earth or will run wild again, if we would not protect them, and only in a very few cases has accidentically a strain been produced that might upset an ecosystem.

The actual question now is, is the risk that such a dangerous species would arise greater, when we cross the species barrier, than if we only perform classical crosses? In my opinion the risks with transgenic species are lower instead of higher for the following reason: As I said, nature itself has optimized the survival of its wildlife species to a very great extent. By using these already optimized gene pools in classical crosses, we mix two of those optimized pools, and certainly there is a small risk of producing an even more optimized gene pool for life in the wild. But as we noted, the risk is almost negligible. What do we expect if we combine two different gene pools that we know are not an optimum combination? A lot of evidence has been compiled from somatic cell hybridization of different species as to their incompatibility. Also a lot of evidence on transgenic micro-organisms has been gathered over the last fifteen years and never has a harmful organism been produced so far that would survive better in the wild.

We would not expect that to happen, just because of the fact that it is apparently very difficult to compete in the laboratory with billions of years of variation and selection by nature itself. Nevertheless, unrest in society continues and strangely enough other hazards when Man is manipulating ecosystems as such, are almost totally neglected. One of these hazards is world travel. We all know there is a hazard in mixing

ecosystems. When species are transported from their natural habitat to a foreign ecosystem, they might well destruct that ecosystem if it is lacking in its natural enemies. But whether these natural enemies are there or not, the destruction may take place anyhow. The spread of AIDS is a good example. If there was not such a high intensive world travel, AIDS may well have been contained in its original African or Haitian habitat. An example of less dangerous species are microorganisms invading the gut. Tourists coming from foreign countries may "import" infectious diseases against which we have no resistance. Still, only a few people think of taking precautions when travelling, or even restrict world travel, while the danger to disturb ecosystems is far more direct and potentially hazardous, than any transgenic experiment we can think of.

Summarizing, we must conclude that the three aspects I mentioned of opposition against genetic engineering, have in fact basically in common a philosophy of nature, which I consider in need of reconsideration. That philosophy must be characterized as:
(1) an over-assessment of the species-concept;
(2) an idealization of wildlife, which is not justified;
(3) an appreciation of natural evolution as being untouchable by Man.

When I had a first draft of this presentation circulated among three members of our TNO PR-department, I received the messages: your presentation is provoking rather than convincing with respect to evolution, the species concept, etc. and I tend to agree with these specialists as to communications with the public at large. The views I have expressed are still beyond proof, indeed. But the picture I have given you of, for example, the species, is nevertheless my view. I comfort myself with the idea that it is always difficult to get one's view across, even in the scientific world, particularly as to biology. For instance, it took more than 10 years before DNA was really accepted as the carrier of genetic information.

By the way, I was not asked to prove whether the benefits, dangers or ethical conflicts that arise, represent the background of people's concern as regards animal manipulation and experimenting. I added some personal views why I think that the people at large exaggerate their concern, by their unwillingness to see the effects of laboratory experiments in proportion as to unpleasant, naturally occurring phenomena.

COMPARISON OF FRIESIAN CATTLE FROM DIFFERENT ORIGINS

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Summary

A comparison of milk production traits of Friesian cattle from different origins was made. In the basic herd, originated as random sample from two Dutch Friesian subpopulations, a contrast of 11% in milkproduction was demonstrated. The herd of this farm was divided in three equal parts and since 1971 per year five top proven bulls on yield from the Dutch Friesian (DF), the Holstein Friesian (HF) and the British Friesian (BF) subpopulation were used over a period of twelve years. The basis of selection was fat + protein yield.
The estimated genetic differences over four generations between HF and DF was +1227 kg milk, -0.31% fat and -0.12% protein. The BF heifers were intermediair between HF and DF.
Keywords: milk production, comparison, selection, Friesian.

Introduction

The aim of cattle breeding is to select the most profitable cow that excels genetically in a balanced combination of dairy and beef traits. The Friesian cattle population is spread over many countries. Genetic differences between subpopulations of the same breed can be expected when the selection goal is different or also when the selection strategies are different. A comparison was carried out of genetic differences between Friesian cattle from different origins in the same herd environment on an experimental farm of the Agricultural University. The basic herd was formed by Dutch Friesians randomly sampled within two breeding districts and two levels in The Netherlands (Politiek,1974). The second purpose of this experiment was to estimate genetic differences between progeny of DF, HF and BF proven bulls and to estimate genetic and phenotypic parameters of traits recorded in a herd with no artificial selection for production characteristics.

Material and methods

The basic herd was founded with the purchase of two batches of 120 calves drawn at random from the breeding districts Friesland and North Holland in The Netherlands. The data analyses and the used model for the basic herd are described by Politiek et al.(1982). Each year since 1971, five newly top proven bulls from the Dutch Friesian (DF), Holstein Friesian (HF) and British Friesian (BF) subpopulations have been selected on fat + protein yield and randomly mated to a part of the basic herd (randomly divided into three equal groups). Matings have been taken place within subgroups over 3 - 4 generations. Milk production traits were analyzed with a mixed model containing fixed effects for season of calving, calving interval, interactions between generation and breeding group and between year and age of calving. Also the random effect of sire was included in the model.

Results and discussion

In the same environment with no culling on production cows from North-Holland produced 10 - 11% more milk compared with cows orignating from Friesland (Table 1).

Table 1. Mean and contrast between North Holland and Friesland for milk production of the basic population.

Lactation	First lactation				Second lactation			
	n	milk	fat%	protein%	n	milk	fat%	protein%
Mean	204	4392	4.22	3.41	166	4756	4.28	3.56
Contrast NH - Fr		+468	-.06	-.04		+456	-.08	-.04

In North Holland young bulls were selected more on milk production than in Friesland. The degree of repeatability in milk yield between the first and second lactations was high (0.60).

Within each generation the Holstein Friesian had the highest milk yield and the Dutch Friesian the lowest (Table 2). The estimated difference was 1227 kg. The difference between British Friesian and Dutch Friesian was 224 kg. The Dutch Friesian had the highest levels for fat and protein content. The difference between the subpopulations decreased with the increase of the generation number.

Table 2. Estimated breed differences between HF - DF and BF - DF.

	kg milk	kg fat	kg protein	fat %	protein %
HF - DF	1227	34.2	33.1	-0.31	-0.12
BF - DF	224	1.1	6.5	-0.16	-0.01

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PERFORMANCE TEST RESULTS OF YOUNG BULLS IN RELATION TO FEED INTAKE AND EFFICIENCY OF FEMALE PROGENY

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Summary

A selection experiment is going on for two generations in five years (five batches). Young performance tested bulls were selected on roughage intake. The weighted standardized selection differential applied was 2.54 in sires and dams were random. Data of progenies were recorded on young growing, pregnant and lactating heifers for intake, growth and milk yield. Data were available on one generation and included 202 growing heifers. Genetic parameters were estimated by paternal half-sib analyses. Feed intake characteristics had a heritability of about 0.50. Residual energy intake, energy intake adjusted for growth and metabolic weight, had a heritability of 0.25.
Keywords: feed intake, performance test, heritability, selection.

Introduction

Feed to dairy cattle constitutes a major part of the total cost of milk yield. The literature indicates a clear genetic component for gross feed efficiency. Freeman (1975) concluded that selection for higher milk yield automatically improves feed efficiency. This conclusion was based on literature sources which showed a range for the genetic correlation between feed efficiency and milk yield between 0.88 and 0.95. Experimental procedures may have inflated the values of these correlations. These correlations were calculated by feeding concentrate or grain according to milk yield, thus forcing a high correlation. Besides feed efficiency, feed intake is an important trait, especially in the first part of lactation. The intake of nutrients does not meet requirements of the high yielding dairy cow. Results of Gravert (1985) suggested that selection on milk yield would not automatically increase feed intake of dairy cows in the first part of lactation.

Performance testing of young AI-bulls gives a possibility for selection on feed intake in a breeding program. In 1982/1983 a selection experiment on feed intake started with the following objectives:

- To estimate the relationship between young performance tested potential AI-bulls and female progeny during growth and lactation for traits feed intake, residual feed intake and efficiency on an ad libitum feeding system without feeding concentrates according to production.
- To study relationship between feed intake and efficiency traits of young (growing), pregnant and lactating heifers.

This selection experiment will be carried out during two generations. Preliminary results of young heifers were described by Korver et al. (1987) and these will be summarized in this contribution.

Material and methods

Sires were chosen for this selection experiment on basis of their feed intake performance. 38 performance tested bulls were selected in two

groups, one each with a high or a low feed intake. Contrasts for roughage dry matter intake between the sire groups varied between a proportion of 25 and 40 of the average of all the sires. Sires were used in more than one year to eliminate year effects. The three available batches of 202 young heifers for the analysis originated from 24 sires. The phenotypic selection differential applied between 12 sires with a high feed intake and 12 sires with a low feed intake was 2.76 phenotypic standard deviation units (S/σ_p) dry matter roughage intake. Sire variance components were estimated by an univariate REML algorithm and relationships among sires were included. Feed intake and efficiency traits were analyzed. Residual feed intake reflects differences between animals in using metabolizable energy for maintenance and growth.

Results and discussion

Heritability of feed intake of young heifers at an age of 44-60 weeks was 0.55 from half-sib analysis (table 1). Adjustment of roughage intake for differences in metabolic weight changed heritability of dry matter intake from 0.55 to 0.17. Residual energy intake, ME intake adjusted for growth and metabolic weight, had a heritability of 0.25. This reflects genetic differences between animals in efficiency of using metabolizable energy for growth and maintenance. The standardized phenotypic selection response (R/σ_p) was 0.28 units phenotypic standard deviation, compared with the standardized weighted selection differential of 2.54 in the sires while the dams of the young heifers were random. This computes to a heritability of 0.22, assuming that roughage intake of the young heifer and the young potential A.I.bull are the same trait. This assumption is questionable because of differences such as age of measuring of animals, sex and feeding regime.

Table 1. Overall mean, contrasts between selection group (Low - High), standardized selection response (R/σ_p) and heritability (h^2).

	Mean	Contrast	R/σ_p	h^2
Roughage intake (kg dm.day)	6.42	-0.17	-0.28	0.55
Roughage intake (g dm/day.$W^{3/4}$)	88.9	-1.7	-0.24	0.17
Energy intake (ME kJ/day)	62030	-1678	-0.28	0.58
Daily gain (g/day)	638	-53	-0.63	0.31
Feed conversion (ME kJ/g)	101.0	+6.7	+0.40	0.43
Residual intake (ME kJ/day)	62030	-331	-0.07	0.25

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GENETIC ASPECTS OF INDIVIDUAL FEED INTAKE OF GROWING PIGS, HOUSED INDIVIDUALLY OR IN GROUPS

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Summary

An automatic device for registration of individual feed intake in group housed growing pigs is developed: the IVOG-station. The IVOG-station makes it possible to use group housing for performance testing of boars and gilts, while competition among pigs for the feed is similar to commercial conditions.

Experiments are under way with pens used for group housing and pens for individual housing, each pen equipped with an IVOG-station. The differences in feed intake pattern between pigs housed in groups and pigs housed individually will be determined. These data will be used to test genotype x housing system interaction and to estimate heritability of feed intake pattern and relationships between feed intake pattern and production traits.
Keywords: IVOG-station, group housing, feed intake pattern, genotype x housing system interaction.

Introduction

In order to be able to measure the individual feed intake, performance testing at central test stations is usually done by housing pigs individually. However, under commercial conditions pigs are housed in groups. In group housing, social dominance plays an important role. Dominance can influence feed intake pattern and growth rate (Beilharz & Cox, 1967; Kir'aly & Wittmann, 1982; Mc Bride & James, 1964; Wittmann, 1983) and consequently cause genotype x housing system interaction.

The IVOG-station is an automatic device developed for registration of the individual ad libitum feed intake for group housed pigs. The station is designed in such a way that competition among pigs for the food is possible, similar to group housing in a commercial situation. The station registers the time at the beginning and the end of a meal, the starting and final weight of the food and combines it with the automatic identification of the pigs.

The advantages of using group housing with an IVOG-station for selection purposes are:

1. testing is done under the same system as used for fattening pigs (to prevent genotype x housing system interaction)
2. larger test capacity within the same building, which enables a more intense selection
3. recording of feed intake pattern.

The objective of this research is first to determine the difference of feed intake pattern between pigs housed individually and in groups and to investigate genotype x housing system interaction for several production traits. Secondly, the heritability of the feed intake pattern and correlations with production traits will be determined for pigs housed in groups.

Material and method

Initially, 10 pairs of littermates per batch from 3 - 5 sires will be separated over 10 individual pens and 10 group pens with 7 other pigs. During the test, the feed intake pattern is recorded with the IVOG-station. Further, growth rate, ultrasonic backfat thickness, meat percentage and feed intake of all the pigs will be determined. These results will be used to determine the significance of genotype x housing system interaction for several traits.

After the batches with individual and group housing, 20 pens will be equipped with an IVOG-station and will be used for group housing. From these results and the data of group housed pigs in the earlier batches, the phenotypic correlations between feed intake pattern and production traits will be estimated. After more than 8 batches, genetic correlations and the heritability of feed intake pattern will be estimated.

Results

Data of two pig breeding companies were used to test genotype x housing system interaction. The genetic correlations between progeny in the two housing systems varied from: 0.63 - 1.00 for ultrasonic backfat thickness, 0.96 - 1.09 for daily gain during life and 0.62 - 0.71 for daily gain during the fattening period. These results are hampered by confounding of housing system and sex of the pigs.

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CONSEQUENCES OF SELECTION FOR FEED CONVERSION IN BROILER CHICKENS

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Summary

Selection for feed conversion in broiler sire stock improves feed conversion, apparent digestibility of fat and protein and utilization of protein for body weight gain.
Keywords: broiler chickens, feed conversion, selection, digestibility.

Introduction

In broiler stock selection for feed conversion has two advantageous effects: the chickens are more efficient and they are leaner than chickens selected for body weight (Pym, 1985; Leenstra, 1988). However, selection for feed conversion is laborious and requires special accomodation (individual cages).

It is not known, what the exact causes of genetic differences in feed efficiency are, nor how much differences in body composition and other physiological characteristics contribute to the differences in feedconversion. This synopsis describes differences in metabolizability of energy, digestibility of fat and protein and utilization of feed for body weight gain between chickens of a line selected for feed conver- sion and of a line selected for body weight.

Material and methods

From a broiler sire population two lines were selected: the FC lineby mass selection on feed conversion (feed consumed/weight gained) be- tween three and six weeks of age and the GL line by mass selection for six week body weight.

In the seventh generation the lines were compared while feeding them three isoenergetic diets differing in protein content (Table 1). Metabolizability of energy (ME) and digestibility of fat and protein were determined with cage housed chickens between 17 and 19 days of age by quantitative collection of droppings (12 chickens/cage; 3 cages/ line/-sex/diet). Utilization of energy, protein and fat were studied in a slaughter trial: feed consumption and body composition were determined for group housed chickens at about equal body weight (10 chickens/group; 2 groups/line/sex/diet). Target weight for the comparison was the weight of the heaviest group at 42 days of age.

Results and discussion

Table 1 gives the characteristics of the diets and the results of the digestibility trial. For digestibility the average of males and females is given, as sex nor interactions with sex had any influence on ME or digestibility. The lines differed significantly for ME and digestibility of fat and protein for all three diets examined. The effect of selection line on ME of the diet appeared to be mainly dependent on differences in fat digestibility between the lines.

Table 1. Characteristics of the experimental diets and apparent metabolizability of energy and digestibility of fat and protein for chickens of two selection lines (average of males and females).

Diet	1		2		3	
Combustion value (MJ/kg)	17.8		18.0		18.2	
Crude protein (%)	19.8		25.8		31.8	
Crude fat (%)	10.1		9.3		8.5	
Line	GL	FC	GL	FC	GL	FC
ME (MJ/kg)	13.01	13.53	13.55	13.70	13.71	13.87
Dig.protein (%)	83.24	84.30	86.27	87.15	88.13	89.22
Dig.fat (%)	72.23	78.53	80.67	83.58	83.78	86.15

SED for ME: .08MJ; for dig.protein: .38%; for dig.fat: 1.05%

In Table 2 body weight and certain measures of efficiency determined in the slaughter trial are presented. GL chickens contained more fat and less protein and water than FC chickens. The differences between the lines in body composition were of a greater magnitude than the differences between males and females within line.

Table 2. Body weight at slaughter for male and female chickens and different measures of efficiency for chickens of two selection lines.

Diet	19.8% protein		25.8% protein		31.8% protein	
Line	GL	FC	GL	FC	GL	FC
Body weight males (g)	2271	2080	2346	2277	2333	2287
Body weight females (g)	1978	1944	1991	1932	1943	1993
Feed efficiency	.52	.54	.55	.59	.53	.59
Energy efficiency	.29	.27	.30	.28	.28	.27
Protein efficiency	.47	.51	.41	.46	.32	.37

SED for feed efficiency: .007; for energy efficiency: .006; for protein efficiency: .005.

FC chickens were more efficient feed converters than GL chickens. However, due to the differences in body composition, GL chickens being fatter than FC chickens, GL chickens were more efficient if energy conversion is considered. Major differences between the lines were present in protein efficiency. Relatively, the differences in protein efficiency were of a greater magnitude than the differences in gross feed efficiency. This is surprising, as selection was for gross feed efficiency and not for protein efficiency only.

Differences between the lines were still present if utilization of digested nutrients was considered. This implies that, besides digestibility, also protein and fat metabolism are genetically controlled.

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SELECTION EXPERIMENT ON RESIDUAL FEED CONSUMPTION IN LAYING HENS

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Summary

A selection experiment has been designed to study the trait 'residual feed consumption' and its genetic component in laying hens.
Keywords: efficiency, residual feed consumption, selection, laying hens.

Introduction

Feed costs are circa 68% of total costs per kg of eggs in laying sector. At this moment stabilization of production is much more important than enlargement of production, so lowering of feed costs is necessary to improve net income.

In 1982 the Dutch Agricultural Economical Institute presented a factor analysis showing that ca. 13% of the differences in net income between egg producers was caused by differences in feed costs (between producers): ca. 6% resulting from differences in feed prices (especially differences in contracts) and the remaining ca. 7% from differences in feed consumption (especially differences in brands of hens). As data were corrected for differences in egg production, these 7% differences in feed consumption are also 7% differences in feed efficiency. In this study, This difference could reach a level of Dfl. 1.30 per laying hen per year.

Therefore our department started a research project on differences in feed efficiency between laying hens independent of egg production.

Material and methods

In 1982 a synthetic population had been created after three generations of crossing four different WL populations. From 1982 to 1985, this population was bred randomly. In 1985 there were 704 hens and 168 cocks; each FS family of this population was divided in two; one half was fed a normal laying diet (11.7 kJ ME/g), the other half a low energy laying diet (10.0 kJ ME/g). In this base population we have done the following experiments:

- Comparison of total energy balance of laying hens extremely different for residual feed consumption.
- Estimation of repeatability of residual feed consumption, also for a second laying period.
- Estimation of heritabilities and phenotypic and genetic correlations of/between residual feed consumption and production traits.
- Estimation of heritability of feathering and the correlations with residual feed consumption.
- Estimation of the phenotypic correlation between yolk percentage and residual feed consumption in a small sample.
- Measurements of activity of young animals in respiration chambers.
- Measurement of differences in complete energy balance between the two feed groups.
- Estimation of genotype * diet interaction of residual feed consumption.

In each feed group, a similar divergent selection experiment was started. The selection criterion is residual feed consumption (in g/day)

from 20 to 44 weeks of age using a selection index with information from female relatives, both for hens and for cocks. Next to the four selection lines, one unselected control line is kept. Each line consist of 141 hens and 33 cocks;. A computer simulation program was designed to find the optimal numbers of animals to be selected in any selection experiment (Luiting, 1986b); based on this program, and using the population parameters from the base population ca. 35 hens and ca. 22 cocks were selected for each selection line; for the control line, ca. 140 hens and about 70 cocks.

Results

A part of the results from experiment (1) has been published by Luiting (1986a). All the other experiments are in the computing or writing stage.

Literature

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GENETIC CORRELATIONS BETWEEN PRODUCTION TRAITS AND EXTERIOR IN BOARS

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Summary

A linear scoring system for exterior traits in pigs has been applied on several boar test stations in the Netherlands. Heritability estimates for exterior traits ranged from 0.1 to 0.3. Only a few genetic correlations between exterior traits and production differed more than 0.4 from zero. Fast growing coincides genetically with weak pastern, steep rear legs and more liquid in the stifle joint.
Keywords: exterior, production, pig, genetic parameters

Introduction

The animal's exterior has traditionally played an important role in pig breeding. Nowadays selection on exterior is mainly aimed on improvement of constitution. Constitution can be defined as the animal's ability to challenge its internal and external environment. An important part of forced cullings in pigs is caused by anomalies of attitude and gait and difficulties to rise and mount. This syndrome is called leg weakness and is thought to be correlated mainly with the condition of legs and claws. Selection on those exterior traits can have a considerable effect on genetic improvement of production traits, depending on genetic (co)-variances. Numerous estimates of genetic and phenotypic parameters of performance traits in pigs have been reported in literature. Only few heritability estimates of leg weakness are known, which range from 0.10 to 0.45. No genetic correlations between leg weakness or exterior traits and performance were found in literature. The purpose of this study was to estimate genetic variances and covariances of linear scored exterior traits and genetic covariances between performance and exterior traits.

Material and method

Data were obtained from central test station boars of the herdbook and from three breeding companies. Inspectors of respective organizations judged boars at the end of the test only on their own test station. The exterior traits considered are described in Table 1. A detailed description of scored exterior traits and method of scoring is given by Van Steenbergen (1988). Performance traits considered are average daily gain on test (ADG), ultrasonic backfat thickness (UB) and feed conversion (FC) measured as kg feed per kg body weight gain. All boars were fed ad libitum. After screening 2093 boars, offspring of 443 sires, were used for final analysis. Sires were completely nested within test station.

(Co)variances were estimated with multi-variate equal design Restricted Maximum Likelihood (REML) procedures based on a sire model as described by Meyer (1985, 1987).

Results and discussion

Heritability estimates of linear scored exterior traits (Table 1) range from 0.10 to 0.30, which is in agreement with estimates in dairy data. Most genetic correlations do not differ clearly from zero. Side view pastern front legs, side view stifle joint rear legs and dryness are genetically correlated with ADG. Boars which have weak pastern, steep rear legs and much liquid in the stifle joint, have the highest genetic potential to grow fast. Animals with a dry stifle joint are likely to have a worse FC. Therefore selection on exterior traits, to reduce the leg weakness syndrome, can have impact on the genetic improvement of average daily gain. Correlations of exterior traits with leg weakness are object of further studies.

Table 1. Descriptions and heritability estimates (h^2) of exterior traits and genetic correlations (r_g) with average daily gain (ADG), backfat thickness (UB) and feed conversion (FC).

Trait	Scale[1]			h^2	r_g		
	0	4.5	9		ADG	UB	FC
Front legs.							
Side view	sickled		buckled	0.10	0.05	0.12	0.05
Side view pastern	steep angle		low angle	0.28	**0.42**	0.28	-.20
Rear legs.							
Side view legs	straight		bow leg	0.22	0.04	-.07	-.15
Side view stifle	steep	sickle	hocked	0.24	-.49	-.26	0.11
Side view pastern	steep angle		low angle	0.30	-.16	0.06	0.01
Dryness stifle joint	wet		dry	0.10	-.59	0.17	**0.46**
Claws.							
Evenness of toe;ratio size inner/outer claw	$\leq$ 1/2	3/4	$\geq$ 1	0.14	0.05	-.11	-.21
Toe size	small		large	0.17	0.08	-.21	-.09
Gait pattern; movements	slow		easy	0.20	-.31	0.22	0.26

[1] 19 classes.

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MEAT QUALITY IN PIG BREEDING PROGRAMS

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Summary

Some problems concerning meat quality in pigs are shortly summarized. From literature studies it appeared that an important problem is toughness that is related with PSE or DFD meat and intramuscular fat percentage. Some parameters are related with sensoric properties, e.g. pH, meat colour and drip loss. A study is carried out to define meat quality in pigs and to use meat quality traits in breeding programs, including an economic optimization of the breeding program. A short plan for this study is outlined in this synopsis.

Introduction

The meat production segment is an important part of the Dutch economy. This can be illustrated by the number of people working in this segment (about 115,000 in 1986). The pig meat production segment took account of about 30% of the total Dutch livestock export value that raised to Dfl. 17,430 million in 1986 (LEI & CBS, 1988).
In currently used pig breeding programs, emphasis is put on efficiency of meat production. This includes a strong selection for growth, feed efficiency and fertility. In addition, selection for backfat thickness, ham and cutlet percentage or meat percentage resulted in improvement of the efficiency and in improvement of carcass quality which is reflected in a higher meat to fat ratio in the carcass.

Selection for meat quality

The only effective example of selecting for meat quality is the selection on halothane susceptibility. In Swiss this resulted in a decrease of halothane positive pigs in the field of 17.7% in 1978 to 1.1% in 1983 and a decrease of herdbook pigs giving PSE meat of 32.7% in 1978 to 8.8% in 1987 (Schwörer, 1988). In The Netherlands selection against halothane susceptibility resulted in a decrease of 36% halothane positive pigs (1977) to 8% in 1984 (Eikelenboom, 1985).

Meat quality traits

Several difficulties in selection for meat quality exist:
* there is no clear definition of "meat quality";
* there is great diversity in wishes of the consumers, not only in The Netherlands but also on export markets, e.g. Italy, France and Western Germany;
* there is hardly good equipement available for objective measuring the several components of meat quality; for some traits only subjective measuring methods are available, e.g. taste, for other traits available methods are expensive or hardly useable in the slaughter line.

While a good flavour is of course essential, the main problem with eating

quality in pork seems to be toughness (Barton-Gade & Bejerholm, 1985). Furthermore Barton-Gade & Bejerholm (1985) showed that two meat quality characteristics are of particular importance for the tenderness of pork. First, PSE and DFD meat appeared to have a minor eating quality. Although, DFD pork appeared to be extremely tender but the tenderness was compensated by a poorer flavour score resulting in a lower overall acceptability than pork with a normal quality.
Secondly intramuscular fat appeared to have an effect on eating quality. Several studies made clear that a certain amount of intramuscular fat (about 2%) is necessary. However, high amounts of intramuscular fat ($\geq$ 3%) do not lead to any further improvement of sensory pork quality (Barton-Gade & Bejerholm, 1985; Bejerholm & Barton-Gade, 1986; Fjelkner-Modig & Persson, 1986).

Schwörer (1985) found that selecting for leaner pigs and for better feed efficiency, results in lower intramuscular fat percentage. Furthermore he found intramuscular fat percentages ranging from 0.77% to 1.26% in the M. Longissimus dorsi of Landrace and Yorkshire pigs, respectively.

Steenkamp & Van Trijp (1988) found a lower acceptability of pork by the consumers in comparison with beef, poultry and fish, mainly due to health concern and lower sensory quality of pork. It appeared in their study that consumers associate pork with fatter meat and the use of colouring matters. Furthermore, Steenkamp & Van Trijp (1988) found significant relations between sensory properties and pH_{24} hours, meat colour (Japanese scale), drip loss, cooking loss and rate of marbling.

Plan of the study

The possibilities to incorporate meat quality in pig breeding programs are studied. The aims of this study are:
1. to define "meat quality" and to find methods to quantify meat quality;
2. to estimate genetic parameters for meat quality and for other traits already used in breeding programs;
3. to calculate economic values for meat quality parameters;
4. to economically optimize breeding programs including meat quality.

A pilot study is carried out using records of 408 pigs of four breeds to estimate correlations between five meat quality traits. These traits are intramuscular fat percentage, pH_{24} hours, drip loss and colour (Japanese scale) of the caudal side of the M. Longissimus dorsi and pH_{24} hours of the M. Adductor. The results of this pilot study will be used to adjust the plans for the study in the next three years.

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PARAMETERS OF THE CENTRAL TESTING OF DUTCH WARMBLOOD STALLIONS

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Summary

In the framework of a study on genetic parameters of the Dutch Warmblood horse, observations on stallions during a central testing period will be analyzed. Parameters of the traits scored for four successive judgements during the test period will be presented. Genetic correlations between performances of stallions in a central test and that of their offspring in competition will also be shown.
Keywords: performance, central test, genetic correlation, stallion, horse.

Introduction

When the breeding goal is restricted to performance traits, abilities for dressage and jumping in competition are most important. In the breeding program the performance testing of stallions before entering mating service playes a predominant role (Ström & Philipsson, 1978; Philipsson et al., 1987; Arnason et al., 1986). Bruns et al. (1985) analyzed German central test data of stallions; heritability estimates for their fourteen scored traits averaged 0.46. Bade et al. (1975) observed a low phenotypic correlation between performance of stallions at station and that of their paternal halfsibs in competition.

Since 1978 the stallions in The Netherlands are centrally tested under uniform circumstances for 100 days. Each year 30-40 stallions are tested, from which about 50 % is selected. The objectives of this study are:

1. To estimate heritability and the phenotypic and genetic correlations of ten subjectively scored traits.
2. To estimate phenotypic and genetic relationships between four judgements of the traits.
3. To estimate genetic correlations between the performance of stallions in a central test and that of their offspring in competition.

Material and methods

During the 100 days of testing, four separate judgements can be distinquished. The first is completed after about 25 days, the second after 50 days, the third after 80 days in test and the fourth at 100 days. After these judgements some stallions are culled, but most are culled after the final judgement. The first judgement considers only four traits (walk, trot, canter, free jumping). The other judgements are extended by adding scores for riding ability, jumping ability, cross country, character, stable behaviour and training report (in total 10 traits).

Competition data on the offspring of about 225 stallions are available. Characteristics of the competition data are presented by Huizinga & van der Meij (1988).

To analyze the central test data of the stallions, an Individual Animal Model will be used. The competition data of the offspring of the stallions will be approached using a Sire Model.

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ESTIMATION OF GENETIC PARAMETERS FOR MILK PRODUCTION TRAITS IN A CROSSBRED POPULATION

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Summary

Estimates for genetic parameters and for genetic effects from additive and non-additive mixed models were compared in a crossbred population. Small heterotic effects resulted in an overestimation of breed differences when additive models with sire groups were used. Additive models with progeny groups slightly overestimated genetic variances and heritabilities.
Keywords: crossbred populations, genetic parameters, non-additive effects, mixed models.

Introduction

Appropriate strategies are needed to estimate breed effects and additive genetic variances in populations that have imported semen. Statistical models should account for breed differences in sires and dams and for possible non-additive effects of heterosis and recombination, unequal variances between breeds and effects of selection. In this study, different mixed models for paternal half-sib analysis of milk production records from a crossbred population were compared. Models differed in strategy to account for fixed genetic differences between parents and effects of heterosis and recombination.

Material and methods

First lactation records (305-days milk production) from Dutch Friesian (FH) x Holstein Friesian (HF) cows calving between September 1983 and September 1986 were used. The data set contained 92,333 records from 675 young bulls and 307,050 records from 202 proven sires (Van der Werf & de Boer, 1988).

Data were analysed using mixed models that accounted for fixed effects of environment; fixed effects of genetic groups and random effects of sires. In additive models, groups were defined according to breed composition of the cow (model A1), breed composition of the sire and the dam (model A2), linear regression on the percentage of HF genes of the cow (model A3), and breed composition of the sire (model A4). Nine genetic groups were defined at intervals of 12.5% HF. A non-additive model (NA) included a linear regression on coefficients for HF%, for heterozygosity and for recombination in the genome of the progeny. Variance components were estimated using a restricted maximum likelihood procedure (Meyer, 1986), treating effects of proven sires as fixed.

Results and discussion

Despite low non-additive effects, differences between additive and non-additive models (Table 1) were significant. Estimates for heterosis varied from 2.3% for milk yield to 0% for protein percentage. Recombination effects varied from -1.9% (kg milk) to 0.1 % (fat percentage). Additive models with progeny groups (A1) tended to overestimate genetic variance, whereas models with sire groups (A2 and A4) overestimated group effects and breeding values of sires from different groups.

Table 1. Estimates of genetic parameters and genetic effects for first lactation milk yield (kg) obtained with different models.

Model	σ_s^2	h^2	g_5	g_9	s_5	s_9
A1	49525	.402	298	432	326	753
A2	45586	.373	434*	904*	367	900
A3	53351	.430	154	308	368	874
A4	45647	.373	438	906	371	902
NA	46553	.380	265	530	302	680

σ_s^2= sire variance; h^2 = heritability; g_5 and g_9 = group effects for 50%HF and 100%HF; s_5 and s_9 average breeding values of sires per group.
* only estimates from sire groups are presented.

After accounting for fixed additive and non-additive genetic effects, heritabilities were higher then previous estimates for single breeds (Maijala & Hanna, 1974). Heritability for milk yield was .38; for fat percentage .80 and for protein percentage .70. Analysis of subsets of data with progeny from purebred HF and FH sires gave only high heritability estimates for the subset of progeny from imported HF sires; .44 for milk yield and 1.0 for fat percentage. Future work should account for selection based on pedigree information when ancestors can not be included in the model.

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IMPLICATIONS OF GENOTYPE X ENVIRONMENT INTERACTION FOR THE DESIGN OF PIG BREEDING PROGRAMMES

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Summary

Data of the Dutch pig herdbook were used to estimate genetic correlations between identical traits measured between (rG) and within (rg) levels of the breeding programme; nucleus with central testing, multiplication with on-farm testing and the commercial level with fattening pigs. The results showed moderate genetic correlations for backfat thickness and low genetic correlations for daily gain. The implications of these genetic correlations for the design and efficiency of pig breeding programmes were investigated. It was concluded that selection of boars based on sib or progeny information gathered on different commercial herds, is much more efficient than selection on central test results.
Keywords: genotype x environment interaction, pig breeding, genetic correlations.

Introduction

The existence of genotype x environment interaction (G x E) in pig breeding programmes, has been derived from poor genetic relationships between similar traits measured in different levels of the breeding programme (e.g. Standal, 1977; Bampton et al., 1977). However, in a breeding programme with several herds within a level and sires used across herds, G x E may be present also as a sire x herd interaction. Therefore the problem of G x E was analysed in data of the Dutch pig herdbook as (1) the genetic correlations (rG) between identical traits measured in the nucleus, multiplication and commercial fattening level and (2) the genetic correlations (rg) among identical traits measured in the various environments within each of the three levels (Merks, 1988a, 1988b, Merks & Van Kemenade, 1988). These genetic correlations were used to compare the efficiency of a breeding programme with only central testing with that of breeding programmes based on sib or progeny information gathered on different commercial herds.

Results and discussion

The genetic progress of a pig breeding programme (P1) based on central testing was compared with the genetic progress of a programme (P2) based on central testing + contemporary half sibs tested in on-farm test on different herds, and a programme (P3) based on own performance in central test (first stage) and progeny results on different fattening herds (second stage). The breeding structure of programme 2 and 3 is comparable to system 1 and 2 of Brascamp et al. (1985). The genetic parameters used were those reported by Merks (1988a, 1988b) and Merks & Van Kemenade (1988) for daily gain and ultrasonic backfat thickness.

To make a fair comparison of the three programmes, the total costs for each of the 3 programmes was kept equal. With respect to equal total costs the test capacity for both P2 and P3 was optimized. The progeny or half sibs of each sire have been spread over as many herds as possible. The relative genetic progress for P2 and P3 compared to P1 is given in Table 1. From these results it was concluded that in general central testing of boars and simultaneously their paternal half sibs in on-farm test is, depending on the trait, almost 3 times more efficient than central testing only. Also two-stage selection with progeny testing in commercial fattening appeared an efficient alternative.

Table 1. Relative genetic progress (G) of the three breeding programmes for daily gain and ultrasonic backfat thickness.

	daily gain	backfat thickness
P1: central testing	G = 100	G = 100
P2: central testing + half sibs in on-farm test	199	108
P3: central testing + progeny in commercial fattening	229	150

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USE OF STOCHASTIC AND DETERMINISTIC MODELS TO STUDY BREEDING SCHEMES

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Summary

For the optimization of breeding schemes, stochastic and deterministic models can be used to predict selection response and rate of inbreeding in alternative breeding schemes.

With a deterministic model, a lot of alternative situations can be studied. The disadvantage of a deterministic approach is that it is very difficult to derive a model that gives accurate predictions in complex situations. Especially for small populations, a lot of theoretical problems need to be solved. A stochastic approach can be useful to study the relevance of these theoretical problems in specific situations. Stochastic models can be very realistic.

Important points in the choice of the model to study breeding schemes are the factors that need to be optimized, the size of the population and the length of the period to be evaluated.

Breeding organizations prefer deterministic models that can be used for their own specific situation. Theoretically derived deterministic models need to be extended by including results from stochastic simulation studies.

Keywords: breeding schemes, selection response, rate of inbreeding, simulation models

Introduction

Breeding organizations need to decide on many factors: population size, selection intensity, test capacity, generation interval, etc.. To predict the influence of these factors on selection response, variation of response and rate of inbreeding, stochastic and deterministic models can be used.

Deterministic models

A deterministic model predicts the results of a given breeding scheme using formulas that are derived theoretically or empirically. Because of the low computational requirements, a great number of alternative breeding schemes can be evaluated. As a result, optimum designs can be derived easily and detailed sensitivity analysis is possible.

The disadvantage of a deterministic approach is that it is very difficult to derive a model that gives accurate predictions in complex situations. The model needs to account for: linkage disequilibrium, differences in accuracy of selection (e.g. because of different age classes) and deviations from normality (multistage selection). In addition, the following aspects need to be considered for small populations: reduction of genetic variance due to inbreeding, reduction of selection intensity due to small numbers (small number of selection candidates, small number of families, small sizes of families), and influence of selection on inbreeding and drift variance.

Stochastic models

Stochastic computer models can be used to simulate alternative breeding schemes. With the records and pedigree information of simulated animals, response to selection and rate of inbreeding can be estimated.

A stochastic approach can be useful to study the relevance of theoretical problems, mentioned for deterministic models, in specific situations.

Stochastic models can be very realistic. De Roo (1988) studied alternative breeding schemes in closed pig populations, using a stochastic model that included overlapping generations, continuous mating and farrowing and weekly selection of boars and sows. Effects of population size, selection intensity, mating policy, founder population size and inbreeding depression were examined for a sire line. After adaptation, the model was used to examine population size and selection intensity in a dam line (De Vries et al., 1988).

Choice of the model

The choice of the model to study breeding schemes depends on the factors that need to be optimized. For example, a simple deterministic model ($G = i*r_{TH}*\sigma_H/L$) would give wrong conclusions for the optimization of selection intensity. It overestimates response with high selection intensities, because it does not deal with reduction of genetic variance due to inbreeding and reduction of selection differential due to small numbers of families.

Size of the population and length of the period to be evaluated are also important for the choice of the model. For long-term predictions of response with small populations, inbreeding can not be ignored. Theoretical formulas that describe the interaction between selection and inbreeding do not exist.

Breeding organizations prefer deterministic models that can be used for their own specific situation. Theoretically derived deterministic models need to be extended by including results from stochastic simulation studies. Deterministic models, extended with specific results from stochastic simulation, are also specific. Therefore, a wide range of situations needs to be studied to make these models as general as possible.

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CONSEQUENCES OF IMPLEMENTATION OF NEW REPRODUCTION TECHNOLOGY FOR DAIRY CATTLE BREEDING GOALS.

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Summary

Implementation of new technology is likely to influence the definition of dairy cattle breeding goals. As an example, the economic value of birth weight within a dairy breed is studied in relation to use of embryo transfer, sperm and embryo sexing in combination with beef crossing. It is concluded, that implementation of these techniques will decrease selection emphasis on beef production traits within the dairy breed.

Introduction

Crossbreeding dairy cows to bulls of beef breeds increases beef output of dairy cow populations. Beef crossing is likely to alter selection goals in the direction of specialisation; single-purpose dairy breeds and specialised beef breeds (Cunningham, 1975). Consequences of beef crossing for dairy cattle breeding goals result from, among others, a decrease in economic values of beef production traits related to new born calves within the dairy breed (Groen, 1988b). Implementation of embryo transfer, sperm and embryo sexing will extend influences of beef crossing on beef output of dairy cow populations.

Aim of this study is to quantify influences of embryo transfer, sperm and embryo sexing on the economic values of beef production traits within the dairy breed. Following forms of beef crossing are distinguished:

1. beef crossing by use of sperm of beef bulls with dairy cows;
2. form 1. with use of sexed sperm of beef breeds;
3. form 2. with use of sexed sperm of beef and dairy breeds;
4. transfer of beef embryos in dairy cows;
5. transfer of sexed beef and dairy embryos in dairy cows.

Method

Sensitivity towards beef crossing of 'birth weight' (bw) is considered to representate sensitivity of beef production traits related to new born calves. Economic value of bw equals: change in profit of the dairy enterprise expressed per cow as a consequence of one kg change in genetic merit of bw within the dairy breed. The model described by Groen (1988a) is used to calculate economic values. The economic value of bw originates from increased selling of calves and increased energy-requirement for growing dairy replacement heifers (Groen, 1988b).

Total number of calves sold equals number of calves born alive minus number of dairy female calves needed for replacement. Use of embryo transfer, sperm and embryo sexing in combination with beef crossing determines sex and breed of calves sold. Use of sexed dairy sperm or sexed dairy embryos reduces number of cows required for dairy breeding. Without use of sexed sperm or embryos, the sex ratio equals .5. Accuracy of sexing is assumed to be 100 %.

Further assumptions are:
- basic level genetic merit bw (female calf of a first-parity dam): dairy breed 36 kg; weight advance beef breed + 4.25 kg;
- price female calf: dairy breed 7.77 Dfl/kg live weight; price advance beef breed + 4.00 Dfl/kg (male calves both breeds + 4.18 Dfl/kg);
- feed prices: roughage .051 and concentrate .058 Dfl/MJ NE_1.

(bw crossbred calf = .5*bw dairy breed + .5*bw beef breed; same counts for market price crossbred calf)

Results and conclusions

Crossbred calves express half and beef calves do not express improvement of genetic merit within the dairy breed. Hence, beef crossing decreases the economic value of bw. Use of sexed beef sperm increases the value of marginal output of crossbred calves. Use of sexed dairy sperm increases the proportion of crossbred calves on expense of dairy calves and further reduces the economic value. Application of embryo transfer gives beef calves on expense of crossbred calves. Within form 5, no crossbred or dairy calves are sold and the economic value originates only from raised feed costs of growing dairy heifers. Increasing feed prices, raises costs of growing dairy heifers. Increased price advance only influences the economic value within forms with selling of crossbred calves. Level of the weight advance has no effect on the economic values. It is concluded, that implementation of embryo transfer, sperm and embryo sexing in combination with beef crossing will decrease selection emphasis on beef production traits related to new born calves within the dairy breed.

Table 1. Economic values of birth weight in relation to form of beef crossing (Dfl/(kg*cow*year)).

Form	basis	Alternatives		
		feed prices[1]	price advance[2]	weight advance[3]
No crossing	7.69	7.35	7.69	7.69
1	6.02 (-22%)	5.68	6.12	6.02
2	6.48 (-16%)	6.14	6.58	6.48
3	4.77 (-38%)	4.44	4.97	4.77
4	3.50 (-54%)	3.16	3.50	3.50
5	- .59 (-108%)	- .92	- .59	- .59

Alternatives. [1]: roughage .071 and concentrate .072 (Dfl/MJ NE_1), [2]: + 5.00 Dfl/kg, [3]: + 5.00 kg.

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OPTIMISATION OF DAIRY CATTLE BREEDING PROGRAMS WITH THE APPLICATION OF NEW REPRODUCTIVE TECHNIQUES

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Summary

A deterministic model is build for the optimisation of breeding plans. The model describes the optimal dairy cattle breeding plan as an open nucleus plan, which allows for progeny testing of bulls. The fractions selected from each tier and age class are optimised by using truncation selection across the distributions of breeding values. The size of the nucleus relative to the base and the size of the progeny test have to be optimised by comparing alternative runs of the model. Thus it is possible to optimise a breeding plan given the reproductive rates of the animals, the age at which and the kind of information that becomes available and the phenotypic and genetic parameters of the traits.

The introduction of new reproductive techniques alters the reproductive rates of the animals and the amount of information that becomes available (e.g. full sib information). The benefits of techniques like MOET (Multiple Ovulation and Embryo Transfer), sexing of sperm, in vitro production of embryos, cloning etc. can be assessed with this model.

Introduction

The introduction of new reproductive techniques can increase the rate of gain and alter the optimal breeding scheme. This is due to increased selection intensities and more family information. New reproductive techniques are based on to recent advances in reproductive biology research, which promise increased rates of genetic gain. Many authors showed that the impact of these techniques on the genetic improvement can be large (a.o. Van Vleck, 1981; Nicholas & Smith, 1983; Christensen & Liboriussen, 1985; Foote & Millar, 1971; Mc Daniel & Casell, 1981), although the breeding plans were not optimised. Especially the conventional progeny testing scheme, which is used as reference for the plans that include new techniques, has a long suboptimal generation interval.

In this study the breeding plans, which can include new reproductive techniques, are optimised, before asserting the benefits of the technique. The generation interval is optimised, when the animals with the highest BLUP breeding value estimates are selected, irrespective their age or the accuracy of the predicted breeding value (James, 1987). Also the fractions to select from several tiers (nucleus, base, etc.) are optimised by selecting the animals with the highest estimated breeding value irrespective their origin.

It is not possible to use the gene flow technique (see e.g. Hill, 1974) for the optimisation of the generation interval and/or selection of several tiers. The gene flow technique predicts the flow of the superior genes of one selection round and doesn't predict the actual genetic level of the age classes and tiers. The genetic levels of the age classes and tiers are needed for the optimisation of the generation interval and the selection over tiers. The gene flow technique also takes no ac-

count of the reduction of the variance due to previous selections.

The aim of this study is to compare optimal breeding plans, which make use of different reproductive techniques (AI, MOET, embryo splitting, sexing of sperm, in vitro production of embryos, etc.). For the optimisation of the breeding plans a deterministic model is developed, which implicitly optimises the generation interval and the selection over several tiers and takes account of the variance reductions due to previous selections.

The model

The model describes an open nucleus breeding scheme, which allows for a progeny test of young bulls. Such a breeding scheme is optimal, provided the input parameters are optimal. It can match a conventional progeny testing scheme, a closed nucleus breeding scheme etc.. James (1977) described an open nucleus scheme as a scheme in which a nucleus provides sires for itself and for the base (where no males are reared). Female replacements are reared in both the nucleus and the base and dams are transfered from the nucleus to the base and vice versa. Because the model implicitly optimises the generation interval and the transfer rates between the nucleus and the base, the only parameters that need to be optimised by comparing alternatives are: the size of the nucleus relative to the base and the size of the progeny test.

The input parameters of this model are: the reproductive rates of the animals; the age at which information becomes available; the kind of information; the age distributions (survival rates) and the phenotypic and genetic parameters of the traits.

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APPLICATION OF SUPEROVULATION AND EMBRYO SEXING IN SPECIALIZED DAIRY AND BEEF BREEDS TO OPTIMIZE MILK AND BEEF PRODUCTION

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Summary

A cattle crossbreeding system with dairy and beef breeds is described in which superovulation and embryo transfer combined with sexing of embryos will be applied. Two specialised dairy breeds are reciprocally crossed. Only female crossbred embryos will be implanted. These crossbreds are superovulated and can be inseminated with semen of bulls from specialized beef breeds. Only male embryos of these three-way cross will be implanted and will be raised for beef production after birth. As an alternative, purebred male embryos from beef breeds will be implanted in the dairy crossbreds.
Keywords: cattle production system, embryo sexing, dairy breeds, beef breeds, crossbreeding.

Introduction

In The Netherlands cows are primarily used for milk production. Beef production consists of culled cows, beef bulls and veal calves. The calves for beef and veal production are surplus calves from the dairy herds. In breeding for milk and beef production negative genetic relationships between important characteristics (e.g. milk yield and milk constituents, milk yield and slaughter quality) impede a rapid genetic improvement for single characteristics. So far, practising crossbreeding of specialized breeds was difficult because of the low reproductive rate of female cattle and their low average herd life.

Superovulation and embryo transfer increase the number of offspring of individual cows. In the near future the sex of the embryos can be determined in the embryo transfer-process (Booman, 1988). Sexing of embryos reduces the percentage of cows in the dairy herd used for breeding replacements and increases the percentage of cows, which could produce a male calf for beef production. Besides, specialization in respectively milk and beef production can be practised in a breeding plan.

The development will be described of a cattle production system, in which the use of specialized cattle breeds, superovulation, embryo transfer and sexing of embryos is combined.

Description of the production system

First phase

Jerseys and Holstein Friesians are dairy cows specialized for milk production. In a breed comparison (De Rooy & Oldenbroek, 1988a), Jerseys showed a high fat and protein percentage in their milk, no calving problems, a low disease frequency and a high biological efficiency for milk production, especially on a roughage diet. Holstein Friesians had a high milk yield and a much higher daily gain in beef production. In many mar-

ket situations Jersey x Friesian crossbreds will give a higher net return per hectare than purebred Holstein Friesians (De Rooy & Oldenbroek, 1988b) due to the combining ability for milk production of the parent breeds. Jersey x Friesian crossbred male calves are not very suitable for beef production. Therefore, in a crossbreeding system between Jerseys and Holstein Friesians only females are desired.

Within the Jersey and Holstein Friesian population of the experimental farm "'t Gen" the cows with the highest breeding value for milk production (1/3) are used to breed purebred replacements. The other cows (2/3) are reciprocally crossed. A system is developed to prepare all cows for superovulation shortly after calving. To study the large variation in superovulatory response among cows, a longitudinal study of follicular growth and development is performed using echography and hormonal assays (Van der Schans, 1988). Embryos are collected and will be sexed and only female embryos will be implanted in purebred recipients.

Second phase

To produce calves for beef production out of Jersey x Friesian crossbred dairy cows two possibilities exist: Firstly the crossbred cows can be inseminated after superovulation with semen of sires of specialized beef breeds: Blonde d'Aquitaine, Charolais, Limousin and Pi'emontesa. Embryos will be sexed during transplantation and only male embryos will be implanted in Jersey x Friesian crossbreds. Secondly, females of the previous mentioned beef breeds can be used to produce purebred male embryos from a beef breed. Both possibilities will be studied.

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USE OF MEISHAN TO IMPROVE MATERNAL PERFORMANCE TRAITS IN PIGS

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Summary

Reproductive performance of some Chinese pig breeds is exceptional. Meishan seems to be, according to its purebred performances and in cross breeding, the most interesting breed as a component of dam lines (Bidanel, 1988). Heterosis can be exploited in cross breeding schemes, but it appears that, despite high heterosis values, the use of the Meishan breed does not lead to an increase in the efficiency of production systems. The creation and selection of a composite dam line involving Meishan might be a solution.
Keywords: Meishan, composite line, fertility, pigs.

Introduction

Efficiency of pig production can be increased by improvement of maternal performance. Litter size and weight of piglets are important traits. Meishan seems to be the best Chinese breed to improve maternal performance. Sow productivity of Meishan is very high but body composition is very inferior.

An experiment was carried out at the INRA, to estimate crossbreeding parameters between Meishan and Large White (Bidanel, 1988). Maternal heterosis was 20% for litter size (number born alive, number at weaning) and 34% for litter weight at 21 days. Direct heterosis was small for litter size at birth, higher at weaning (12%) and very important for litter weight at 21 days (17%). Direct heterosis was 23% for average daily gain. Epistatic recombination loss seems to be low.

Between breeds, additive genetic differences for fertility were mainly maternal (between 2.4 and 2.9 piglets per litter), while they are of direct origin for growth performances. Breed differences between Large White and Meishan were estimated to be about 200 g of average daily gain, -0.9 point of gain to feed ratio and between 15 and 18 % of carcass lean content.

Heterosis can be exploited in cross breeding schemes, but it appears that, despite high heterosis values, the use of the Meishan breed does not lead to an increase in the efficiency of production systems. The creation and selection of a composite dam line involving Meishan might be a solution. Good knowledge of the biology and productivity of the Meishan is needed to assess the feasibility of such a composite line. Genetic analyses of data from composite lines are needed to optimize further selection.

Experiments

Experiment 1

Cross fostering experiments are carried out to study pre- and postnatal effects on birth weight and growth of piglets. Two sows, a Meishan and a

Dutch Landrace sow, that farrowed at the same time formed one pair. Within a pair, litter halfs were exchanged. Birth weight, growth and milk consumption were recorded. Milk consumption was recorded at four successive sucklings at day 13 and 30 of lactation. Milk intake was corrected for metabolic losses, urination and defecation and expressed per piglet and per hour. Results are in Table 1.

Table 1. Effect of breed of foster sow and piglets on growth and intake.

Trait	Breed of sow / Breed of piglets	DL / DL	DL / M	M / DL	M / M
Birth weight	(g)	1356	859	1263	915
Growth from birth to day 35	($g.d^{-1}$)	212	161	181	167
Milk consumption per pig, day 13	($g.h^{-1}$)	37	31	32	30
Milk consumption per pig, day 30	($g.h^{-1}$)	46	33	34	29

Meishan sows produced 15% less milk than DL sows. Milk intake of Meishan as compared to DL piglets was on average 17% lower. Breed of sow by breed of piglets interaction was caused by a high milk intake of DL piglets nursed by DL sows. This was reflected by growth of piglets during the suckling period. The higher growth potential of DL pigs as compared to Meishan pigs could mainly be expressed by piglets nursed by a DL sow. Milk production of the sow, milk intake capacity and growth potential of the piglets appear to be balanced within breeds.

Experiment 2

An experiment is set up in cooperation with Dutch breeding organizations to develop a synthetic that consists of 50% Meishan and 50% breeds from Dutch breeding organizations. Per generation 250 first and 250 second litters will be produced. F1 and F2 generation will be produced to study:
- the existence of major genes,
- the additive genetic variance in the composite breed,
- the genetic correlation between production and reproduction traits.

Results of this and other experiments will determine how to proceed: the introgression of a major gene in Western breeds, selection based on genetic markers, DNA-technology or a quantitative genetic selection approach.

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INTROGRESSION OF THE BOOROOLA F-GENE IN A TEXEL SHEEP POPULATION

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Summary

The introgression of the Booroola F-gene in the Texel sheep aims to combine a high fecundity and a high slaughter quality in a single breed for an efficient lamb meat production. Biological and statistical tests will be applied to discriminate between carrier and non carrier males and females.
Keywords: Texel, Booroola gene, discrimination carriers.

Introduction

Reproduction rate of the dam and the growth and slaughter characteristics of the offspring determine the efficiency of a lamb meat production system. The Texel has excellent slaughter characteristics (More O'Ferrall & Timon, 1977; Wolf et al., 1980; Visscher & Bekedam, 1984). However, its reproduction rate of 1.5 lambs weaned per ewe lambing (Visscher & Bekedam, 1984) is low for an economic lamb meat production. Crossbreeding with specialised dam and sire lines has demonstrated to improve the economics of the lamb production system but is difficult to organise in the small scale Dutch sheep industry. So the combination of a high fecundity and a high slaughter quality in a single breed would be the ultimate breeding goal. The Booroola Merino has a single gene with a large effect on ovulation rate and littersize (Piper & Bindon, 1982). The introgression of the Booroola gene in the Texel sheep population combines both traits at a high level in the breed. In the process of the introgression of this F-gene it is very important to discriminate carrier and non-carrier females. The discrimination of males is only necessary in the last phase of introgression. It would be advantageous to detect carriers before the animals are used for breeding.

Bindon et al (1985) suggest that the deficiency of inhibin in the ovary could be the primary lesion caused by the F-gene. Inhibin is a gonadal peptide which selectively suppresses the secretion of FSH by the pituitary gland (De Jong, 1979; Robertson et al., 1985). To control FSH secretion inhibin must reach the pituitary via the peripheral circulation. Direct inhibin measurement in peripheral blood is not yet possible although purification of the substance (Robertson et al., 1985) is an important step towards this objective.

Prepubertal Booroola ewe lambs have higher FSH plasma levels than control Merino's (Findlay & Bindon, 1976; Bindon et al., 1985). According to Cummins et al. (1983) the feedback relationship of inhibin and FSH in Booroola and non-Booroola carriers may be different which contributes to the difference in ovulation rate. The FSH/inhibin ratio could therefore be an attractive discriminator of carriers and non carriers for both male and female lambs.

Experimental procedures

Three heterozygous Booroola * Texel rams imported from ABRO Scotland are single sire mated to Texel ewes to produce a 3/4 Texel generation. A contemporaneously generated and reared Texel control group is also established from the same Texel flock. All male progeny will be slaughtered. The heterozygous female progeny will be mated to pure bred control Texel rams for the production of the 7/8 Texel generation. Heterozygous animals of this generation are inter-mated for the production of homo- and heterozygous stock. Sires from this last generation will be tested in practice.

All lambs are bloodsampled at least twice between 28 and 42 days of age for the determination of FSH and inhibin. Up to 5 months the weight is recorded regularly. At 5 months the dimensions of the testis are scored. After slaughtering different carcass measurements are taken, the conformation is scored, the testis are weighed and the pituitaries are collected and deepfrozen for hormonal analysis.

Ewe lambs are laparotomized after synchronisation with progesteron analog impregnated sponges at an age of about 6-7 months. Carriers are defined as those animals that have an ovulation rate record of > 2. Although the present evidence indicates that the effects of the F-gene must be regarded as sex limited (Bindon & Piper, 1986) the males are involved in the investigation.

Discriminant analysis will be applied to investigate the possibility to predict ovulation rate from FSH and inhibin results. Cluster analysis and Maximum Likelihood will be applied for the selection of discrimina- ting variables and for the production of an allocation rule.

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GENETIC POLYMORPHISM OF MILK PROTEINS

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Summary

In this study, which started in spring 1988, gene fregencies of milk-proteins in Dutch Black and White and Dutch Red and White (MRIJ) cattle will be stimated. Further, relationships between milk-protein loci and milk-production traits will be subject of study.
Keywords: milk proteins, genetic polymorphism, cattle.

Introduction

For about 30 years determination of protein content is part of the Dutch milk recording program. The reason for the introduction of milk protein determination was the declining importance of milk-fat while milk-protein became more important (Politiek, 1957). In The Netherlands at the moment milk is paid for fat and protein according to a ratio of 60:40.

The major milk-protein components are α-casein, β-casein, k-casein, β-lactoglobulin and α-lactalbumin. It is known that these proteins are controlled by autosomal genes which are genetically polymorphic and that the casein loci are closely linked. Many studies examined gene frequences of the different milk proteins. However in the Netherlands research in this area is limited to the work of Schmidt (1966).

The study of Schaar et al. (1985) showed that genetic variants of k-casein and β-lactoglobulin influence manufacturing properties and yield of cheese production. Mclean et al.(1987) showed that genetic variants of these proteins also influence heat-stability of milk. Not only this qualitative aspects but also kwantitative aspects make genetic variants of milk-proteins interesting. Many studies investigated the direct effects of milk protein genes on milk production traits. Althoug results of these studies show a certain trend they are not always statistical significant (Graml, 1982). Some of the causes might be the number of animals involved, the existence of only small direct effects of milk protein loci or on the dependency of the direct effects on the genetic background (interaction of genes). Less studies have dealt with a possible marker-linked effect of milk-protein genes on milk production traits. The main reason for this might be the limited power of the statistical design to detect marker-linked effects on kwantitative traits (Soller, 1974).

The first objective of this study is to estimate gene frequencies for k-casein and β-lactoglobulin. Special attention will be paid to the influence of crossbreeding with Holstein Friesian cattle on the milk protein gene frequences. The second objective is to estimate direct effects of milk-protein genes on 305 days milk-, fat- and protein-production. Possible marker linked-effects will also be studied. A third objective is to quantify the casein content of milk. Relations between stage of lactation and milk protein genotype will be studied. Results of

this studie will be used to discus the meaning of milk-protein genotypes in a breeding program.

Material and method

Heifers of test-sires of the Dutch Black and White and the Dutch Red and White (MRIJ) breed will be fenotyped for milk proteins. To distinquish genetic variants of milk proteins the iso-electric focusing technique will be used (Seibert et al., 1985). Data on milk production traits will be obtained from the Dutch Cattle Syndicat. To correct the data for herd-year-season effects milk production records of herdmates not fenotyped will be used. Estimation of the casein content will be by infrared spectrophotometry (Karman et al., 1987) of samples taken at different parts of lactation.

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GROWTH IN TRANSGENIC (SOMATOTROPIN) MICE

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Summary

Three types of transgenic male mice (MT/hST, MT/bST and PEPCK/bST) were mated to normal female mice and growth of progeny was examined. Within each of the three groups of progeny, animals were classified as transgenic or normal on the basis of body weight distributions at 12 weeks of age. Differences in live weight between transgenic and normal animals were: MT/hST +14.0 g, MT/bST +16.8 g and PEPCK/bST +23.1 g. At 12 weeks of age, growth of transgenics was still higher than of normal animals.
Keywords: transgenics, mice, somatotropin, growth.

Introduction

Chronic administration of exogenous somatotropin promotes growth in pigs (Nieuwhof et al., 1988). Similar effects may be expected in pigs carrying one or more extra copies of genes coding for somatotropin. However, biological effects of gene transfer are not yet fully understood and may depend on the species the gene originates from and the promotor to which it is linked. Transgenic (somatotropin) mice may serve as model for transgenic pigs.

The aim of this study is to determine the effect of gene transfer on body weight in mice, the difference between human somatotropin (hST) and bovine somatotropin (bST) genes and the difference between the metallothionein (MT) and the phosphoenolpyruvate carboxikinase (PEPCK) promotor.

Experimental procedure

Six fertile transgenic male mice were obtained from the Edison Animal Biotechnology Center (Athens, Ohio). One male carried the hST gene linked to the MT promotor (MT/hST), three carried the bST gene linked to the MT promotor (MT/bST) and two carried the bST gene linked to the PEPCK promotor (PEPCK/bST). These males were mated to randomly bred NMRI females. After weaning at 21 days of age, offspring were weighed individually weekly. Progeny were classified as transgenic (T) or normal (C) on the basis of body weight at 12 weeks of age. Because body weight is also affected by sex and litter, the deviation from sex by litter average was used to discriminate between the two classes. To increase the chance for correct classifications, mice from litter-sex combinations in which the difference between the heaviest and the lightest mouse was less than 10.0 g were discarded (23 animals). A mouse was considered to be transgenic if it was heavier than its sex by litter average.

Results

No effects of gene transfer on litter size, health status or behaviour were apparent. Average weight differences between T and C animals at 12 weeks of age in the MT/hST (n=99), MT/bST (n=45) and PEPCK/bST (n=74) groups were 14.0, 16.8 and 23.1 g respectively. Deviations from average sex-litter weights at 12 weeks approximately showed a bimodal distribu-

tion for each group with, on average, 46% of the animals classified as transgenic. Overlap between distribution of T and C animals decreased with increasing age.

Growth curves, pooled over sexes, are in Figure 1. Standard deviations of body weight at each week range from 1.68 to 6.92 g and increase with body weight. At higher weights, after correction for promotor, sex and litter effects, the effect of gene transfer is highly significant ($P<.001$) for all groups. The effect of gene transfer appears to exist for faster growth, a longer period of rapid growth and subsequently a higher mature weight than in normal mice. The effect is larger in mice carrying the bST gene. The PEPCK promotor exerts a higher increase than the MT promotor, when linked to the bovine gene.

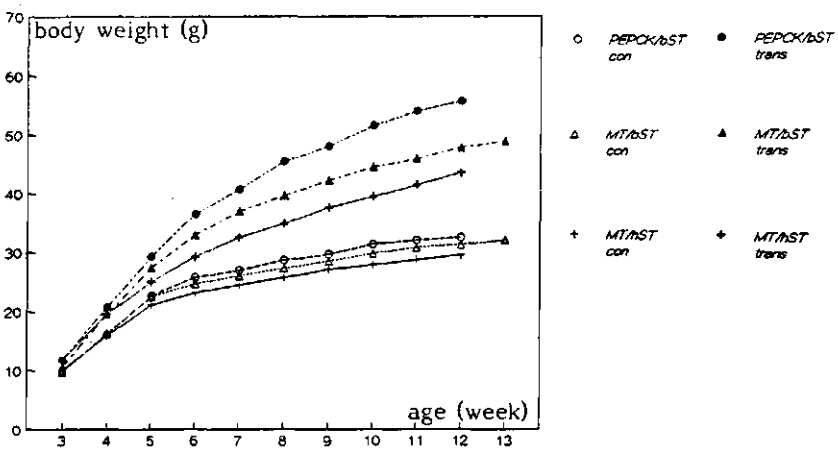

Figure 1. Body weight by age, gene source and promotor.

Discussion an conclusions

The distribution of the weights justifies the assumption that two classes exist and a Mendelian heredity is suggested. However, the procedure to discriminate between the two classes may have overestimated the class differences since litter-sex combinations with little weight variation were discarded. After the mice have reached older ages, the classification at 12 weeks can be checked and its reliability can be estimated. However, a correct discrimination can only be done with a method that establishes the presence of exogenous somatotropin in the blood or the presence of the gene in the genome.

Results show that gene transfer has an effect on growth of mice. Effects in other animals have to be studied. However, if the obtained effects on growth can only partly be extrapolated to farm animals, it is clear that the technique of gene transfer can have a tremendous impact on animal production.

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CLONING OF THE BOVINE MHC CLASS II GENES

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Summary

The possibility of using the BoLA system as a genetic marker for population and disease susceptibility/resistance studies in cattle will be studied. Several restriction fragments containing individual exons have been subcloned into plasmids and are now being used as bovine specific probes in RFLP studies and for further characterization.

Introduction

The use of molecular biology and molecular genetics in animal breeding is a potentially powerful new method. In this respect the development of specific genetic markers to screen animals at an early stage in their development is of utmost importance. The major histocompatibility complex (MHC) is often associated with the susceptibility/resistance to certain diseases. Most of the disease association studies however have been done in humans and only a few in domestic animals. There are some indications that BoLA, the MHC of cattle, is associated with diseases such as mastitis and bovine leucosis. Therefore we chose to examine the possibility of using the BoLA system as a genetic marker for population and disease susceptibility/resistance studies in cattle.

The MHC

The MHC encodes cell surface class I and class II antigens that are involved in regulation of immune responses. The human MHC, called HLA, and that of the mouse (H-2) are studied in great detail at the biochemical and molecular level (for a review see Klein 1986). Both the class I and class II antigens consist of two polypeptide chains:alpha and beta-2-microglobuline in class I molecules and alpha and beta in class II molecules. The MHC appears to be highly polymorphic. The human class I loci e.g. consist of at least 17 highly related genes including the genes coding for the classical transplantation antigens (HLA-A, B and C). The human class II region (HLA-D) is arranged into four subregions DP, DZ/DO, DQ and DR each containing at least one α and β chain pair of genes. In cattle, analogous to human, a BoLA-A and BoLA-D region is found which encode the class I and class II antigens respectively. RFLP studies using human MHC specific probes show that BoLA is also highly polymorphic. Furthermore these studies indicate the presence of 1 DRA gene, 3 DRB genes, 1 to 2 DQA and DQB genes, 1 DOB gene, 1 DZA gene and 2 other class II genes called DYA and DYB (Andersson et.al. 1988, Andersson and Rask 1988).

Bovine specific probes

To obtain bovine specific probes for RFLP studies and to investigate the genetic organization of the BoLA-D region in more detail, we isolated several class II genes from a bovine genomic library. This library has been constructed in the bacteriophage lambda vector EMBL 3. A total of approximately 1.5 x 10^6 phages were screened with human class II specific cDNA clones. This yielded 80 positively hybridising plaques, 12 of which could be identified as specific for DQB, 5 for DQA, 6 for DRA and 5 for DRB. Furthermore 8 other lambda clones also may be DRB specific.

The organization of the genes appears to be very similar to those in human. The intron between the second and third exon (encoding the first and second domain of the class II polypeptide chains) e.g. is small in the A genes (0.5-1 kb) and large in the B genes (3-5 kb). Several restriction fragments containing individual exons have been subcloned into plasmids and are now being used as bovine specific probes in RFLP studies (including disease association studies) and for further characterization (sequencing).

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ANALYSIS OF CHICKEN B-COMPLEX GENES AND GENE PRODUCTS

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Summary

Polymorphism of B-complex genes and gene products was analysed in commercially bred chickens. B-G alleles were serologically detected, B-F products were identified by 1D-IEF electrophoresis and B-L genes were characterized in Southern blots. Results indicated that recombinant haplotypes occurred in these chickens.
Keywords: major histocompatibility complex, poultry diseases, restriction fragment length polymorphism.

Introduction

The chicken major histocompatibility complex (B-complex) consists of B-G (class IV), B-F (class I) and B-L (class II) loci. Certain B-haplotypes are associated with disease resistance (Bacon, 1987). B-haplotypes have been defined by typing B-G alleles in a direct hemagglutination test using alloantisera raised against erythrocytes. In the present experiments analysis of B-G, B-F and B-L genes and gene products was performed in commercial pure chicken lines to establish the occurrence of recombinant B-haplotypes. Eventually, a better knowledge of B-G, B-F and B-L genes and gene products will be used in challenge experiments for disease association studies.

Results and discussion

Using antisera obtained from W.E. Briles (De Kalb, USA) B-G19, B-G21 and B-G34 alleles were identified in line L. Alloimmunizations performed between individuals of line L resulted in the production of monospecic typing sera for B-G19, B-G21 and B-G34, which made rapid and large scale identification of B-G alleles possible. Meanwhile, biochemical evidence for the existence of the three B-G alleles was obtained from Western blots, using SDS-PAGE and isoelectric focussing (IEF) and monoclonal antibody 18-6G2 (K. Skjødt, Copenhagen, Denmark).

Radioactively labelled B-F glycoproteins were precipitated using monoclonal antibody F21-2 (K. Skjødt), followed by one dimensional (ID) IEF. Preliminary results indicate that recombinant B-haplotypes occurred, combining different B-G an B-F alleles.

Polymorphism of B-L genes, reflected as restriction fragment length polymorphism (RFLP), was analysed in Southern blots using a human class II subprobe (DQβ-SII; Fei et al., 1986). This subprobe codes for a part of the class II gene that is conserved among different species. The hybridization patterns are shown in figure 1.

A panel of chickens was analysed for RFLP. None of the fragments correlated with the serological B-G assignment (table 1). Whether the results reflect the polymorphism that is encoded by the variable part of the gene(s) is unclear. Heterologous subprobes that code for the variable

parts of the gene only hybridize under mild conditions and results are difficult to reproduce because of high background hybridization. To obtain more detailed information on the polymorphism, probes obtained from genomic and cDNA chicken libraries are currently used in Southern blot analyses. However, the RFLP obtained with the DQβ SII subprobe may indicate a B-L polymorphism which is not in linkage with B-G.

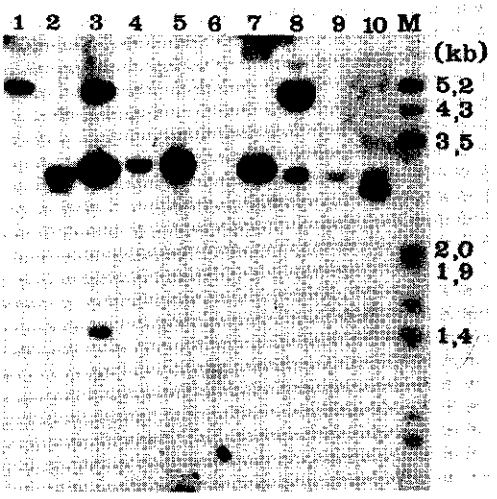

Figure 1. RFLP in ten unrelated chickens after EcoRI digestion and hybridization with DQβ-SII under stringent conditions. M represents molecular weight markers.

Table 1. Two-by-two analysis of B-G types and EcoRI restriction fragments in line L.

Fragment	/	B-G type	+/+	+/-	-/+	-/-	N	chi.sq.	R	p-value
5300	/	B19	6	11	51	55	123	0.968	0.08	0.6733
5300	/	B21	9	8	41	65	123	1.235	0.10	0.2657
5300	/	B34	2	15	14	92	123	0.027	0.02	0.8640
4700	/	B19	6	5	51	61	123	0.327	0.05	0.5747
4700	/	B21	3	8	47	65	123	0.896	0.09	0.6539
4700	/	B34	2	9	14	98	123	0.286	0.05	0.5998
3400	/	B19	4	5	53	61	123	0.014	0.01	0.9014
3400	/	B21	4	5	53	61	123	0.058	0.02	0.8051
3400	/	B34	1	8	15	99	123	0.031	0.02	0.8548
3300	/	B19	8	12	49	54	123	0.386	0.06	0.5417
3300	/	B21	10	10	40	63	123	0.865	0.08	0.6450
3300	/	B34	2	18	14	89	123	0.191	0.04	0.6665
3000	/	B19	24	24	33	42	123	0.424	0.06	0.5225
3000	/	B21	17	31	33	42	123	0.894	0.09	0.6532
3000	/	B34	7	41	8	67	123	0.419	0.06	0.5247
2700	/	B19	5	2	40	76	123	3.884	0.18	0.0461
2700	/	B21	1	6	49	67	123	2.138	0.13	0.1399
2700	/	B34	1	6	15	101	123	0.011	0.01	0.9141
2200	/	B19	4	7	53	59	123	0.484	0.06	0.5058
2200	/	B21	6	5	44	68	123	0.967	0.09	0.6732
2200	/	B34	1	10	15	97	123	0.164	0.04	0.6887

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VARIATION WITHIN AND BETWEEN SWINE BREEDS IN IMMUNOLOGICAL PARAMETERS

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Summary

Both cellular and humoral immunity of four swine breeds were studied in respect to variation. Using statistical analysis the effect of breed, litter, age, sex and testday could be determined. Variation exists between and within breeds for the mitogenic activation of T-lymphocytes, the absolute number of leukocytes and for the antibody response against two different antigens. Contrasts between breeds showed swine breeds with low responding properties for cellular reactivity (N-breed), humoral response and leukocyte population (Y-breed). On the other hand, the F-breed appeared high responding in all tests. The consequences of such a divergence between breeds for the genetic resistance remains subject of future study.

Introduction

Infectious diseases cause considerable losses in pig production. Genetic resistance to pathogenic antigens may be very important to minimize these kind of losses. In swine the knowledge of immune system and the genetics controlling the immune response is rather limited. The effect of the breed on various types of reactivity of the immune system will be described in this paper.

Materials and methods

Four different swine breeds were used: Finnish Landrace (F), Dutch Landrace (L), Norwegian Landrace (N) and Great Yorkshire (Y). These lines are bred by the cooperative breeding company COFOK BV (Oosterhout, The Netherlands). All animals were kept under similar conditions.

Mitogenic response. Lymphocytes were isolated from heparinized blood by gradient centrifugation. Cells (10^6 c/ml) were cultured with mitogen (PHA at 5,30 and 160 µg/ml; ConA at 1,5 and 10 µg/ml) during 48 hours, whereafter the proliferation was determined with a radio-active precursor. The total of leukocytes was determined using a cell counter, while differentiation of the various granulocytes and lymphocytes was possible by cellular staining (Giemsa).

ELISA. Serum samples were tested for specific antibody response against ovalbumin (OA) and tetanus toxoid (TT). Both antigens were coated on wells of microtitration plates (flat bottom). Samples of serum dilution were added and bound antibody was determined by rabbit antiswine IgG antibody, conjugated with peroxydase in combination of 5-amino salicylacid. Subsequently the extinction was determined at 450 nm.

Statistical analysis. For determination of the effects on the immunological parameters the GLM procedure of SAS (SAS Institute Inc, 1985) was used. The effect of breed, litter, age, sex, testday and interactions between these factors were determined.

Results

Experiment 1

A total of 178 pigs (four different breeds, male and female animals, 10 weeks or 5 months of age) were tested for mitogenic responsiveness as well as for composition of the leukocyte populations. Mitogenic activation caused by ConA was not influenced by breed in a significant manner. In contrast to ConA suboptimal doses of PHA (5 and 30 μg/ml) resulted in an activation significantly ($P < 0.05$) influenced by differences in breed. The effect of breed was observed too for the total number of leukocytes ($P < 0.05$), but not for lymphocytes (%) and granulocytes (%). Besides the effect of breed also a considerable influence of the litter was detected for mitogenic responsiveness ($P < 0.01 - 0.05$) caused by PHA and ConA. A similar effect was found for the absolute number of leukocytes ($P < 0.05$) and the percentage of B-lymphocytes ($P < 0.1$). These results did not reveal substantial influence of the sex and only for the B-cells (%), lymphocytes (%) and at the highest dose of PHA (160 μg/ml) the age of the animals was important ($P < 0.05$). Contrast between the tested breeds showed high responder status for the F-breed (mitogen and leukocytes) and low response for N-breed (mitogen) and Y-breed (leukocytes). Immunization with Ovalbumin and Tetanus Toxoid together with incomplete Freund adjuvance (IFA) showed a significant influence of the breed and litter ($P < 0.01$) for the production of specific IgG antibody. Futhermore the contrast between breeds indicated a high response for the F-breed, whereas the Y-breed did produce a significant lower amount of specific antibody for both antigens.

Experiment 2

The kinetics of the antibody response may be different for each swine breed. For this reason the kinetics of the antibody response to Ovalbumin (OA) and Tetanus Toxoid (TT) was studied in detail, whereas IFA was not used in order to obtain a normal course of antibody production. A total of 280 pigs (male and female animals for the 4 breeds were used at 3 to 5 months of age) were tested for antibody response against OA (4 mg) and TT (15Lf). The animals were intramusculary immunised at day 0 and blood samples were drawn at day 5-8-15-20. At the latter day the animals received a secondary immunization and blood samples were taken at day 32-34-36-39 and day 60 (after primary immunization). The specific IgG response against OA was significantly ($P < 0.05$) affected by breed at day 15 and later days. The results for TT are shown in figure 1, showing significantly breed effect at day 15, 32, and for the secondary reactivity at day 36. Besides a difference in optimum of the antibody production a remarkable variation in kinetics of the immune response between the L- and F-breed is suggested. Whereas the antibody levels of the first breed seems to reach an optimum at day 15, the latter breed seems to require a longer period. This observation seems to be confirmed by the secondary response, since hardly an increase response results after the booster (d. 29) in contrast to the increased response of the L-breed (figure 1). On the other hand the Y-breed produced a low response against both antigens, since at all times (primary and secondary response) the Y-breed was the lowest responding breed (figure 1).

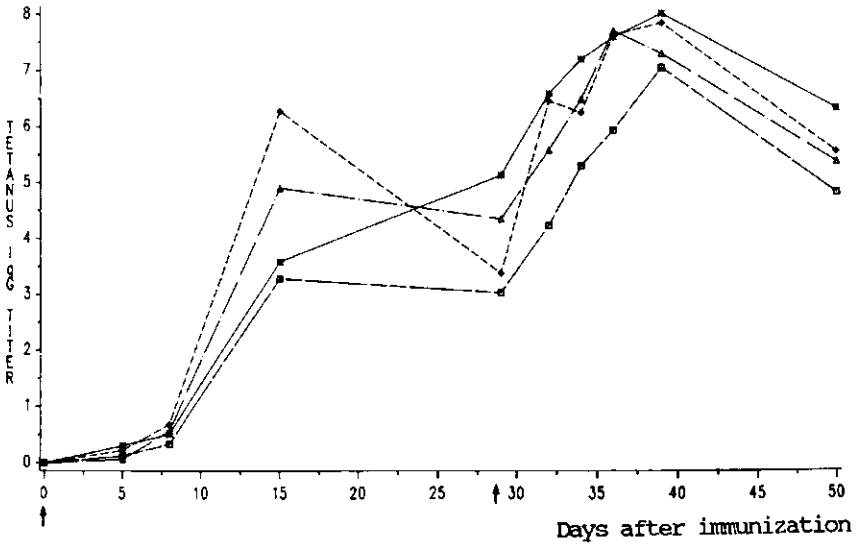

Figure 1. Specific IgG response after primary (d.0) and after secondary (d. 29) immunization with Tetanus Toxoid. Four swine breed were tested: F (*), L (●), N (Δ) and Y (□).

These results indicate that the primary response provides sufficient data to determine relevant variation between breeds on the specific antibody production, at least for these two antigens. Different kinetics of the immune response clearly shows the need to determine the specific antibody response at more than one day after immunization in order to avoid misleading results. This latter point can be illustrated in figure 1, since the results at 15 days after priming are quite different compared to the data observed 14 days later.