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GENETICS OF DISEASE RESISTANCE AND THE POTENTIAL OF GENOME MAPPING

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Evidence for genetic variation in resistance to disease has been accumulating for many years but it is only recently that much direct use is being made in commercial animal production. Although there has been evidence of local breeds being more resistant than imported breeds to a variety of pathogens little use has been made of this. It is perhaps because of the immense success over the past 100 years of bacteriology and parasitology, coupled with advances in therapy and vaccine development, that there has been reduced interest in genetic resistance.

There are many economically important diseases for which there is no cost effective vaccine. Trypanosomiasis, African swine fever, *Theileria sergenti* infection are three. With some of these there is no treatment either, but even where there is a therapy, drug resistance becomes a problem. Development of drug resistance to many parasites, ticks and intestinal nematodes is widespread and increasing. It is a serious problem in many countries and as resistance develops the new acaricide or anthelminthic to overcome this resistance will be more expensive than the one it replaces. With tropical theileriosis where a new drug, Butalex, has been only recently marketed, there has not yet been time for resistance to develop. But develop it almost certainly will and as there are no other drugs in the pipeline at the moment this route for protecting against the disease will only have a finite life.

In Zimbabwe for instance there had been, preindependence, very intensive acaricide application, enforced by laws. During the independence struggle one of the ways to fight against the government was not to obey those laws and dips were filled in and dipping stopped. East Coast fever in particular killed thousands of cattle during this time as the cattle included many European breeds, highly susceptible to East Coast fever. If they had had more indigenous breeds then the effect would have been less marked and some in Zimbabwe advised against returning to a blanket dipping regime in the future.

An alternative means of control is by genetic means. Genetic resistance to disease is the sustainable control measure par excellence. Because once established it does not require high management inputs to maintain it. Look for instance at the situation with myxomatosis in rabbits. It was introduced to the rabbit population here and in Australia. Initially it was highly lethal but gradually resistant animals developed and now the disease is a non event. But one cannot generally expose agricultural animals to disease as happened with rabbits.

Poultry provide an example of a species where genetic resistance has been used and is used commercially. It was shown many years ago that there were genetic components to resistance against a variety of protozoal, bacterial, fungal and viral diseases. It was shown that one could breed chickens resistant to Marek's disease by exposing birds to the virus. But then a vaccine was developed and most of the industry forgot about genetic resistance. It was then found that some animals were not well protected by the vaccine and succumbed to disease before commercial slaughter age. Genetic resistance was revisited and it was found that the vaccine worked better in genetically resistant animals. Now both vaccines and genetic resistance play a part in the poultry industry.

Although there has been suggestive evidence for many years that there are breed differences in disease resistance in cattle, there has been too little use of this fact in the improvement of animals for the tropics. It is only relatively recently that genetic resistance to trypanosomiasis has been considered seriously. Although the Belgians were using trypanosomiasis resistant N'Damas in commercial cattle production in the Congo, many animal breeders were advising Africa to import European breeds as the best means of improving their cattle productivity. Tropical theileriosis has become more important as European cattle breeds have been exported to the tropics. Similarly *T. sergenti* infection was not a problem in local cattle breeds in China but is now reported to be killing cattle in pure Holstein farms. With *Theileria annulata* there is a highly effective vaccine, with *T. sergenti* there is not but with both if it were possible to identify resistant genes these would have great value. With tropical theileriosis in Morocco there is clear evidence that the disease is most pathogenic in pure Holsteins, less in crossbreds and does not cause clinical disease in local cattle. Results obtained in Morocco are shown in Table 1 (adapted from Oudich *et al.* 1993).

Serious efforts are underway to identify the genes that control resistance. There are now around 1,000 highly polymorphic markers distributed over the genomes of the major animal species. Thus maps of the bovine, pig and chicken genomes are now at a stage when one can at least search for the area of the genome controlling resistance. One can also paint animal chromosomes with coloured probes specific for individual human chromosomes and find which human chromosome each part of the animal chromosome corresponds to. As so much more is known about the human genome it can then be used as a model.

Experiments are now underway to identify the genes responsible for the trypanosomiasis resistance in N'Damas. In ILRI Alan Teale is crossing N'Dama with susceptible Boran cattle, producing F I and F2 backcross animals and now searching for the genes that segregate with resistance. It is clear from the results so far that resistance is segregating in the F2 population so that gene identification should be possible. At the same time as running the cattle experiment Teale and Kemp have carried out an experiment in mice, crossing trypanosomiasis resistant strains and producing F1, F2 and now up to F6 progeny to search for genes controlling resistance in this species. It is interesting that the major effect found lies in the same region as the MHC. Whether it is a classical MHC gene, or another gene in the region, such as TNF, is currently being studied.

Resistance genes are being sought in cattle for tick resistance in Australia. They are concentrating on what seems to be a single gene resistance to ticks in Taurus cattle and by a multi genic resistance in Zebu cattle.

In poultry, resistance to Salmonellosis and Coccidiosis has been shown to vary between lines. Now genes are being sought that control this resistance. It is interesting in this regard that in the 1970s a gene was identified in mice that controls resistance to salmonella, tubercle and leishmania. This gene has now been identified. It has been named Nramp. But it controls resistance to a low virulence BCG challenge which is overridden by more pathogenic strains of tubercle. The work so far in Poultry indicates that there are

TABLE 1

Occurrence of tropical theileriosis in different cattle breeds in Morocco

	Holstein	Crossbreed	Local
% farms using acaricide	100	60	6
% carriers	22	40	52
% clinical cases	23	34	–
% of clinically ill that died	24	–	–

other genes more important than Nramp in the control of salmonellosis in chickens. Moreover, before the development of the gene map it was found that an MHC gene B^{21} was associated with resistance and this finding has been and is being used by commercial breeeders to select resistant animals. Now genes are being sought and already genes with greater effects are being identified.

Tropical theilerlosis has a highly effective vaccine which, if used, controls the disease. But as shown above, local breeds in Morocco can survive even without the vaccine and therapy. When one looks at the Holstein cattle imported into Morocco, only about 40% of those that are exposed to the disease in a disease season go down with clinical disease and need treatment. Those that do not become ill are immune to further challenge. Are there therefore genes within the Black and White cattle population which affect their susceptibility to challenge? If there are, and they could be identified, then one would be able to use these genes to select which animals to export to challenge environments. Setting up an experiment to identify these genes would be possible and I hope that before too long it will be possible to set it up.

Identifying resistance genes is expensive and will involve very substantial resources, however the value, particularly in the tropics is immense and I hope that those working with disease control in these areas will consider genetic control very seriously. In the long run it will be cheaper and sustainable.

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