Genetically Resistant Animals

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The production of high-quality animal products depends on healthy animals that thrive and produce. Animals need to be protected from infection by pathogens (disease-producing organisms) or from their effects. This is usually done by eradication of the pathogen, by vaccination to induce protective antibodies, or by chemotherapy.

Since animals can inherit the ability to resist disease and to improve response to the usual methods of control, recent developments in genetics research have exciting implications for breeding more disease-resistant animals.

Genes can influence resistance at many levels in the cycle of infection, immune response, and disease development.

An animal can passively resist infection if the pathogen cannot enter the body, organ, or cell, or is inactivated by some body fluid that is present earlier. Alternatively, an animal can respond actively, often through its immune system, to develop resistance to the pathogen and eliminate it.

Therefore, genetic resistance, even to a single disease, is usually a complex trait controlled by many genes. However, single genes have been found that block infection or a single step in the origin and development of a disease. Such genes, however, often prevent only a specific disease.

Over the years, animal breeders have selected animals for breeding if the animals' relatives survived well under farm conditions.

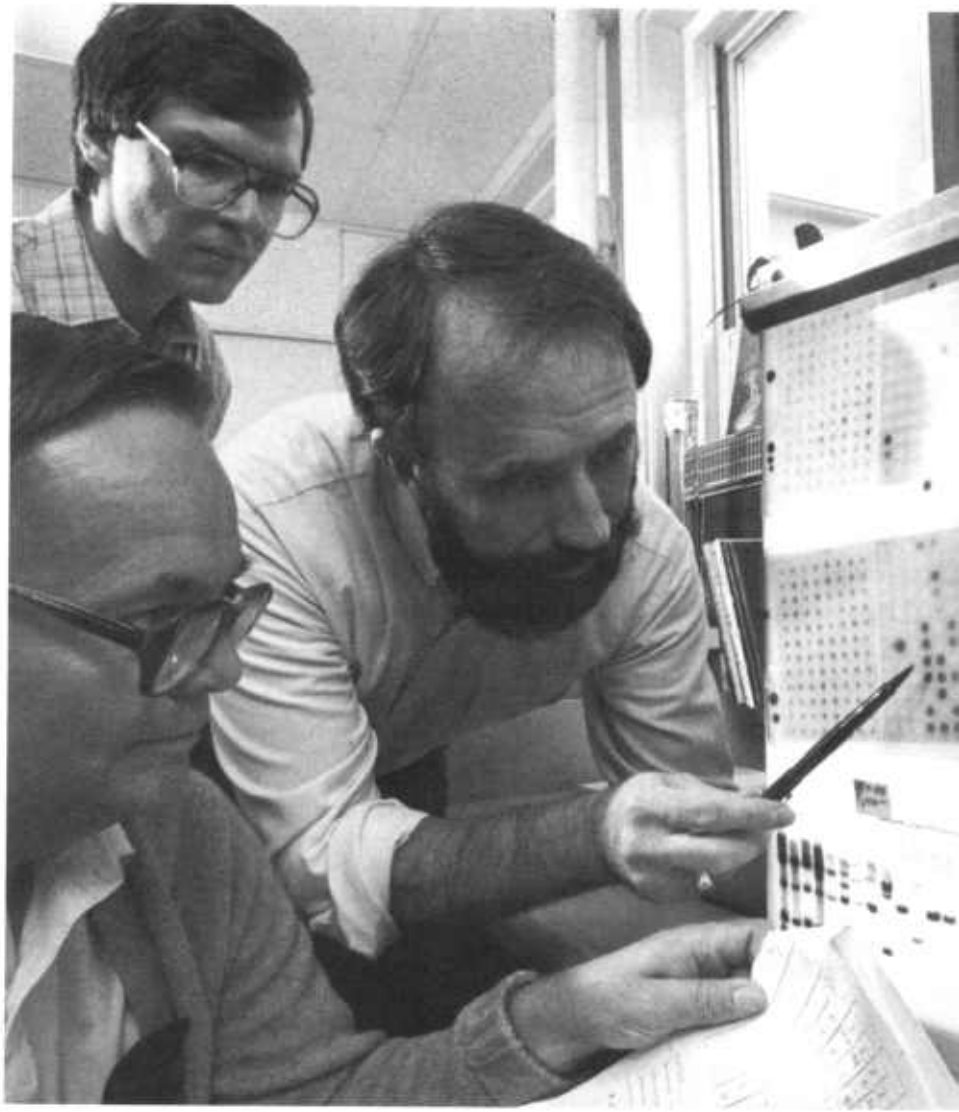
Some animals, particularly in poultry, are selected for breeding based on the ability of their relatives to survive after artificial exposure to a specific pathogen. This selection is usually made only when an epidemic is causing severe economic loss and there is no alternative method of control. This is because selection for resistance to a specific disease reduces the ability of the breeder to select for other traits of economic importance, such as growth rate or egg production.

Conventional, nongenetic, methods of control have been effective for many acute infectious diseases that have troubled livestock in the past. But as such diseases come under control, genetic resistance will become more important for the control of chronic diseases. An important research goal is to find ways to select for genes that impart general resistance to a variety of diseases so that the breeder will need to select for only a few additional traits to improve resistance.

Gene Identification for Disease Resistance

The classic method of gene identification is to look for differences in a trait or characteristic, mate animals that have different characteristics, and describe the variation observed among the progeny for the next few generations. By such observations the geneticist can determine whether a few or many genes control the trait. This approach depends on the identification of genetically controlled variation in an observed trait or in a chemically defined gene product.

With the advent of molecular cloning technology, a single gene can be isolated from an animal, spliced into a microbial vector (carrier), and then replicated in large amounts in this new form of DNA (deoxyribonucleic



Researchers evaluate autoradiograms of chicken blood in research aimed at identifying chickens with avian leukosis virus genes.

acid). Thesc manipulations enable the gene's coding sequences to be read—even though chemical variation in the product is not recognized. Once thc isolated DNA has been characterized, gcnetic variation can be sought at the DNA level and used by the breeder. The use of molecular cloning methods has greatly increased understanding of four multigene families which regulate the immune systems of mice, humans, and farm animals.

Wings of day-old chicks show short feathers on males and long feathers on females.

These families are:

1) the major compatibility complex that controls both tissue transplant rejection and the level of immune response to a variety of antigens (substances that stimulate production of antibodies);

2) the genes that control the production of specific antibodies;

3) the T-cell receptor genes that regulate the responses of specific cells of the immune system; and

4) genes for soluble factors that are released by certain cells having immune functions.

As these and other genes are cloned in several livestock species, they will become raw material for selection, and gene transfer to other animals. They also will be sources of DNA that can be used as molecular probes, for identifying a related gene in an animal as a way to search for genetic variation in their own and other species. Some of these genes may be valuable as regulators—in a general way—of the immune response in an animal. Some particular problems may be solved by an understanding of genes at the DNA level.

Hatcheries selling day-old egg-producing chicks discard male chicks which are identified as such by experts who charge about 3 cents per chick. To cut these costs, some breeders have introduced a gene for slow feathering in male chicks so that even unskilled hatchery workers can easily identify and discard the males. Half the egg-producing chickens in the United States are feather-sexed. Male chicks have short wing feathers and females long wing feathers.

Many breeders who have introduced this gene, however, have noticed some flocks that do not lay the expected number of eggs. Also, such flocks have unacceptable rates of mortality with lymphoid leukosis, a virus-induced lymphoid tumor, as well as other diseases. This called for further investigation. Further experiments showed that the slow-feathering gene was located near another

gene on the sex chromosome which increases a chicken's susceptibility to attack from the leukosis virus. Actually, these endogenous leukosis virus genes interfere with the development of antibodies to the invading, disease-causing virus, crippling the chicken's ability to fight back. Now, using similar methods, breeders can look for new sex-linked slow-feathering genes that are not associated with the leukosis virus gene.

So new developments in molecular genetics can help animal breeders identify and characterize general classes of genes for disease resistance as well as help solve particular disease problems.

Gene Manipulation

Since the domestication of animals, their genetic traits have been manipulated to select animals with desirable characteristics for reproduction. In the last few years, it has become almost routine to manipulate genes artificially by inserting cloned genes into the genetic material of mice to achieve changes in their characteristics rapidly. We are just learning to transfer genes in farm animals.

Gene transfer provides new sources of genes because genes can be transferred between any species even though natural mating between the species is impossible. In addition, a beneficial gene can be introduced into a highly productive strain of animals without introducing other harmful genes.

To achieve permanent change in a strain of animals, the genes inserted must be stably inherited through succeeding generations. They must be in the right configuration and location so that the characteristic governed by the gene is expressed in the appropriate tissue at the correct stage of development.

Extensive research in the mouse is under way, using gene transfer, to understand the factors that are important in gene regulation. Such experimental work in mice and other laboratory animals will pave the way for successful application to farm animals.

The first gene-insertion studies in the mouse were discouraging because the inserted genes, although stably inherited, were expressed in unexpected organs and sometimes at the improper stage of development. More recently, single-cloned genes from some of the multigene families that regulate immune response have been inserted and have been expressed properly.

For example, a class-I gene from the major histocompatibility (state of mutual tolerance that allows some tissues to be grafted effectively to others) complex of swine has been introduced into an inbred strain of mice that ordinarily accepts skin grafts from other members of the same strain. Skin from mice carrying the gene from swine was rejected by unmanipulated mice from the same strain. This showed that the new gene was expressed as a histocompatibility antigen.

These exciting results not only indicate that it will be relatively easy to introduce active genes that can alter the immune response, but also show that transferring a single-cloned member of a complex gene family can lead to proper expression in the absence of other genes of that family.

Some viruses insert an antigen into the membrane of the infected cell, and this antigen interferes with further infection by the same or related viruses. If one could introduce the viral gene for the interfering antigen into the genetic material of the host and it were expressed in the host cell membrane, then it should act as a gene for resistance to the virus.

Since only the gene for the interfering antigen would be introduced, the infectious virus could not be pro-

duced by the host.

Also, one might introduce a gene for the immunizing portion of a disease-causing agent or vaccine into the chromosomes of the host in such a way that it is expressed at the time that vaccination would ordinarily take place. Such a gene would then become an inherited vaccine—each animal, in a sense, would have its own built-in vaccination shot—eliminating the need to vaccinate every animal.

Prospects for Application

These are exciting prospects. But the animal breeder must consider how to integrate these new methods into a breeding program aimed at improving the whole animal and not just a specific trait controlled by a single-cloned gene.

Probably the first applications will be to introduce genes that will control specific diseases that cause severe economic loss. Theoretically, this can be done without altering the other important genes carried by a highly productive strain of animals. The breeder, however, must test carefully the altered strain of animals to determine if some undesirable side effect has been introduced, as was done by introducing sex-linked slow feathering into egg-production crosses of chickens by conventional breeding methods.

Animal breeders in collaboration with molecular geneticists will conduct basic studies on gene identification and cloning, on gene regulation after transfer, and on the effect of transferred genes on productivity. These studies will provide the basis for using these new methods to augment conventional breeding programs aimed at providing healthier and more productive animals.

A Revolution in Immunology—Monoclonal Antibodies

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The construction of antibody-secreting cell lines—hybridomas—by fusing antibody-secreting lymphocytes with appropriate tumor cell lines—myelomas—has forever changed immunology. Indeed, the monoclonal revolution has spread far beyond the shores of its mother discipline and now laps the coasts of biochemistry, neurobiology, developmental biology, agriculture, medicine and toxicology.

This article will describe the technology of hybridoma production. A companion piece by David Snyder tells how monoclonal antibodies are used to solve many problems.

Hybridoma technology, like recombinant DNA technology, is rooted in basic biology and is the capstone of years of basic research in cell fusion. It is a procedure in which two different kinds of cells are artificially caused to fuse to form a single hybrid cell. Such hybrids are particularly interesting because they incorporate the genetic potential of both parent cells. This technique has made it possible to construct and study the properties of cell hybrids made from such combinations as normal cells with cancer cells, mouse cells with human cells, and even human cells with those of mosquitoes.

Early Research

In 1973, Jerold Schwaber and Ed Cohen, working at the University of