How Mice Can Help Cattle

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More remarkable discoveries have been made in science during my adult lifetime than in all of recorded history. When the atom was split (at the time of World War II), those of us who were in our 20's thought that it was excitement enough for one lifetime. But discovery after discovery has occurred, utilizing new instrumentation, radioactive-labeled substances and remarkable new techniques. Molecular biology was born and blossomed. And now we're beginning to really appreciate the flowers that are blossoming all around us. Rivaling the splitting of the atom and its many beneficial consequences is what has come to be called genetic engineering and related technology. Terms like gene-splitting and recombinant DNA are becoming almost household words. In our laboratories (and many others), we are utilizing many of the new techniques involving monoclonal antibodies and hybridomas which are somewhat less than household words. There is renewed excitement about the prospects of remarkable advances to be made in the future. By splicing genetic material and reshuffling hereditary material, we are at the threshhold of using bacteria to manufacture many life-saving substances for people and animals.

I hasten to add, however, that genetic manipulation is not new to animal and plant agriculture, nor to the biomedical sciences. Animal and plant breeders have, during my lifetime of 60 plus years, been manipulating genes, but it has been a slow, tedious and expensive procedure. The green revolution, for example, is a product of classical genetic techniques. Cells have been swapping genes since life began, but now molecular biologists, by a tremendous amount of very tedious, careful and exacting basic research, have discovered ways to transplant specific genes into cells that direct them to produce very specific products. It seems that almost every Monday morning a new breakthrough is announced. Specially manipulated bacteria are producing insulin for diabetics and interferon, a possible anticancer agent. Other exciting agents, similarly produced, include previously expensive human growth hormones for stunted children and beta-endorphins, a natural pain-killer recently discovered in people.

In the area of animal disease, we are excited about a new vaccine for foot-and-mouth disease, one of the world's most serious cattle diseases. After almost three decades of study at USDA's Plum Islan Animal Disease Center (off Long Island, New York, scientist there and at a genetic engineering firm (Genentech) used recombinant DNA techniques to obtain a real breakthrough. They produced a safe, effective, relatively inexpensive vaccine which could save billions of dollars. In Wisconsin, USDA and the University of Wisconsin scientists have developed a technique for moving genes from one kind of plant to another. They have successfully transferred, for example, a gene for storage protein from a French bean seed to a sunflower seed. (So don't be surprised if someday someone shows you a Sunbean plant.) In Beltsville, Agriculture Research Scientists have discovered a viroid in a potato disease, utilizing the techniques just described; a commercial method can now be developed that could help eliminate these infected seed tubers. The successful application of these techniques serves to introduce us to a new era of plant and animal genetics involving disease resistant strains and plants that fix nitrogen from air. These developments are coming none too soon as we look at the problem of world hunger in the immediate future.

Before we start thinking about producing hamburger on ears of corn or safflower oil in milk from dairy cows, a word of caution is in order. The dramatic breakthroughs just described are comparatively simple to produce; however, when considering transplanting genes between plants or between animals things are a little more complex, especially with animals. We've been talking about transplanting single genes into bacteria or yeasts and then growing them in large vats. Tailoring crops, plants or animals to withstand disease or other untoward conditions, however, involves very complex technology involving more than one gene. In the absence of such complex technology, veterinary scientists at WSU are using another approach which was alluded to

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above, i.e., monoclonal antibodies and hybridomas. For a long time, in fact since early in the century when antibodies were first used to diagnose disease, scientists have sought a ready source of antibodies that would detect single antigens that identify individual types of disease-causing organisms. Through a series of fortunate events, scientists have found a way to capture and grow the cells that produce the antibodies of interest—that is, single antibodies. The ways they did this was to vaccinate a normal mouse and remove the spleen from this mouse and fuse spleen cells (i.e., antibody-producing cells that ordinarily won't grow outside the body) in a tube with tissue culture adapted cancer cells derived from another mouse that had malignant myeloma. The fused cells, called hybridomas, continue to grow in culture as did their parent myeloma cells and, in addition, produce the antibody of the normal cell. Critical to this production is the fact that these myeloma cells no longer make their own type of antibody. When fused to form a hybridoma, they only produce the antibody made by the normal cell partner.

So what are the applications of this technique? Many diseases have overlapping signs, so it is difficult to identify the specific cause. Of particular interest to cattlemen, my associates, Drs. Bill Davis, Travis McGuire, Lance Perryman and coworkers, believe monoclonal antibodies will aid in the identification of genes that can be used to selectively for desirable genetic traits in food-producing animals. They are optimistic that the approach they are using will lead to the identification of genes controlling resistance to disease (such as mastitis), fertility, muscle mass, milk production, twinning and weight gain. The reason little progress has been made so far is that so few genetic markers are known that can be applied to identifying useful genetic traits. The monoclonal antibody technology offers an expeditious approach to identifying the needed genetic markers.

The current work of Dr. Davis and associates importantly includes the study of inherited resistance to cattle diseases. In people and other animals, there is a cluster of genes called the Major Histocompatibility Complex (MHC) that offspring inherit from their parents. MHC seems to influence susceptibility and immunity to disease. Dr. Davis and his associates are attempting to zero in on the specific genes that are responsible for inherited resistance to diseases in cattle.

Before I proceed, I would like to review for you how Dr. Davis and associates came on to this discovery. Dr. Bill Davis was trained in Immunology at Stanford. He became very interested in tissue and organ transplants and the acceptance and rejection of these grafts, which he knew had a genetic basis. The genes responsible for this came to be called tissue histocompatibility genes. The existence of this histocompatibility complex has been known since the late 30's when these gene complexes were discovered in mice, an animal that has been Dr. Davis' major experimental animal. Other studies have revealed the gene complex has a very important role in regulating the immune response not only to foreign tissue grafts, but also to disease-causing organisms. These basic studies in mice by Dr. Davis and others have now led him to look at diseases in cattle. The gene complex described above for mice is called Bovine Lymphocytic Antigens (BoLA) in cattle.

There's a good deal of optimism that somethings will come of this as a result of exciting results on several fronts relative to an association between the occurence of certain histocompatibility antigens and certain diseases, both in people and animals. It has been observed, for example, that 95% of the people with ankylosing spondylitis (an arthritic disease of the spine) have a very specific histocompatibility gene antigen called the HLA B27 antigen. Because of this, persons at risk in the population can be identified and followed more closely to allow for early diagnosis and treatment. In chickens, it has been observed that resistance to Marek's disease, an economically very important disease, is associated with the inheritance of certain histocompatibility genes. It is helpful to have genes that are not readily identifiable associated with an identifiable trait.

It is now generally believed that one set of genes involved in a key role in disease resistance is located either within, or close to, the histocompatibility gene complex. With this knowledge, Dr. Davis and associates have developed a strategy to define these disease-controlling genes by locating the histocompatibility antigens associated with the occurrence of the disease and, using such antigens as markers, to follow the inheritance of disease-controlling genes.

Heretofore, appropriate antiserums for typing animal characteristics were attainable only by immunizing cattle. The problem encountered in using this approach to obtain typing these antisera usually contained antibodies to many antigens; so extensive laboratory work was necessary to make them monospecific, i.e., specific for one antigen. By using hybridomas, we can produce a group of monospecific antibodies in a matter of months instead of many years. These antibodies can identify specific immune response genes. Thus, through the use of monoclonal antibodies, we should be able to pinpoint animals that have a particular resistance to disease. When identified, such animals can be used as primary breeding stock for the rapid production of animals. Artificial insemination and embryo transfer offer mechanisms for accelerating the process. (In our work, we are cooperating with Drs. Clyde Stormont and Domenico Bernoco at the University of California-Davis where they have assembled a great deal of typing data in cattle herds.)

It appears that the sky's the limit as we excitely look to the remarkable possibilities that can revolutionize agriculture. There are chiefly two limitations—our imagination and research money to support basic and applied research. The latter will be the unfortunate stumbling block at a time of diminishing resources. The tragedy of this is that a small investment now will pay off handsomely in the future.