
futures
MICHIGAN AGRICULTURAL EXPERIMENT STATION
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BIOMEDICAL RESEARCH FOR ANIMAL AND HUMAN HEALTH

looking into futures

Biomedical Research for Animal and Human Health

Asthma, cystic fibrosis, Lyme disease, premature birth, campylobacteriosis and diseases caused by West Nile virus, *E. coli* and bovine viral diarrhea viruses afflict hundreds of thousands of people and animals each year, many times with devastating effects.

Keeping people and animals healthy is a large and important part of the MAES mission; many times animal health research and human health research are intertwined. For example, Susan Ewart, acting associate dean for research for the College of Veterinary Medicine and director of the MSU Molecular Respiratory and Equine Genetics Laboratory, started studying pulmonary diseases in horses that keep the animals from reaching their peak performance. Today, one of her research projects is searching for the genes responsible for human asthma. Her long-term goal is identifying people with genetic susceptibility to the disease and then offering them counseling about their environment, diet and exercise tailored to their specific needs.

In this issue of *Futures*, we feature the research of a number of scientists that is focused on finding treatments and ways to prevent illness in humans and animals.

MAES researcher Jack Harkema, university distinguished professor in the Department of Pathobiology and Diagnostic Investigation, uses mice and rats to study chronic respiratory diseases that are similar to those in humans. Research by Harkema and scientists at the University of North Carolina has shown that airway dehydration plays a major role in the lung problems that cystic fibrosis patients have. Kurt Williams, MAES veterinary pathologist, has identified a disease in cats that mimics idiopathic pulmonary fibrosis, a lethal disease in humans that has no treatment because scientists don't know what causes it. Thanks to Williams' research, scientists may soon be able to start new studies on the mechanisms of the disease.

The MSU Diagnostic Center for Population and Animal Health (DCPAH) protects the state's people and animals from disease and potential biological attacks or outbreaks. Dedicated in September 2004, the new facility allows MSU scientists to run more than 1.3 million tests per year, making it one of the top three diagnostic labs in the country and the only lab with a biosafety level III (BL-3) necropsy floor. The DCPAH is certified to work with nine agents of concern that are on the federal government's overlap list (meaning they affect both animals and humans).

Bovine tuberculosis reemerged in Michigan 11 years ago, prompting quarantines and closed markets for Michigan beef. In response, MAES-funded research has helped state agencies to create bovine TB eradication strategies and MSU Extension to educate communities. As a result, rates of bovine TB in white-tailed deer are falling and markets are starting to reopen to Michigan beef.

In honor of MSU's 150th anniversary in 2005, each issue of *Futures* this year features a special sesquicentennial article highlighting the intersection of MAES and MSU history. The MAES has supported research in veterinary science since it was created in 1888. Keeping livestock healthy and free from disease has been the focus of much research, and many times this work has benefited human health. I. Forest Huddleson, who enrolled at the Michigan Agricultural College as a graduate bacteriology student in 1915, was an early pioneer in brucellosis research, and his work made major strides in controlling the disease.

We hope you enjoy this issue of *Futures* and that it helps you understand more about the MAES and the research it funds. If you have comments about this issue or would like to subscribe (it's free!), send a note to *Futures* Editor, 109 Agriculture Hall, Michigan State University, East Lansing, MI 48824-1039, or send an e-mail to depolo@msu.edu.

For the most current information about the MAES, I invite you to subscribe to the free MAES e-mail newsletter. Sign up by visiting the MAES Web site at www.maes.msu.edu/news.htm. Scroll to the bottom of the page and complete the subscription form. You can also view this and past issue of *Futures* on the Web site as well.

::: Jamie DePolo

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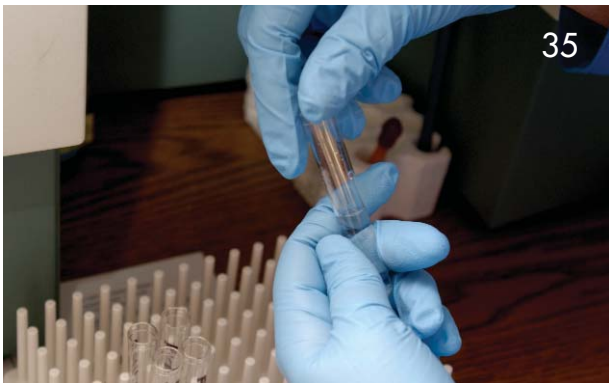

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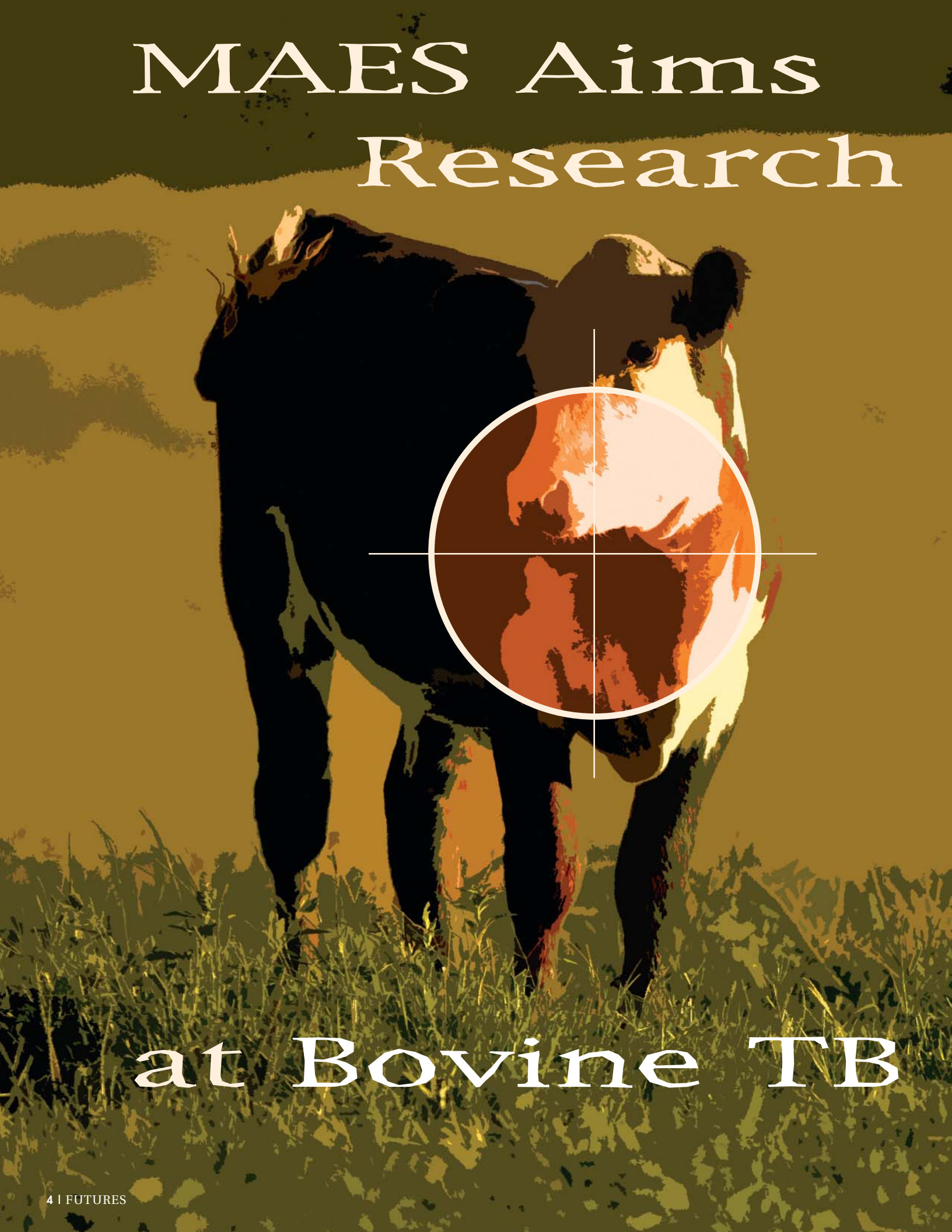
MAES Aims Research at Bovine TB



From a clash between hunters and farmers to an unprecedented epidemiological puzzle, bovine tuberculosis (TB) has posed many challenges to Michigan since the disease reappeared in the state in 1994. Yet behind the headlines about the decade-long fight against bovine TB has been a stream of MAES-supported research aimed at squelching the disease.

Recent data released by the Michigan Department of Natural Resources (MDNR) suggests that this research is hitting the target.

Rates of bovine TB in the white-tailed deer population, which has acted as a reservoir for the disease, continue to fall. And a year after the U.S. Department of Agriculture (USDA) relaxed guidelines for some of the state's cattle producers, markets are gradually opening again to Michigan beef.

"The success is a classic case of how a land-grant university serves its state," said Scott Winterstein, MAES fisheries and wildlife researcher, who studied how deer behave when fed by hunters as well as how the animals range and migrate through the environment. "MAES researchers generated information that helped state agencies to craft TB eradication strategies and MSU Extension to educate communities."

The news wasn't always so good. In the mid-1990s, the disease started showing up in deer harvested in northern Michigan. Scientists were stumped — the general consensus at the time was that bovine TB, a contagious lung disease usually spread between cattle packed together in close quarters, couldn't sustain itself within free-ranging deer populations.

In 1998, a cow in an Alpena County beef herd tested positive for the disease. Things spiraled downhill from there, and in 2000, the USDA revoked Michigan's TB-free status. The decision restricted movement of cattle and reduced out-of-state demand for Michigan beef and dairy products. ▼

MAES fisheries and wildlife researcher Scott Winterstein studied how deer behaved differently when fed by hunters — important information for state agencies crafting TB eradication strategies and MSU Extension's work educating communities. "The success [in addressing bovine TB] is a classic case of how a land-grant university serves its state," Winterstein says.

DON'T FEED THE ANIMALS

One element of the state's disease-control strategy was to restrict deer feeding, which causes deer to congregate around feed piles. Private hunt clubs and other landowners increasingly had been feeding deer culled vegetables and grains during the winter. The goal was to boost the deer population that would be waiting when the hunters arrived the next fall.

The supplemental feeding restrictions, which went into effect in 1998, sparked controversy. Hunters, many of whom believed that cattle operations were the source of the disease, worried that one harsh winter would cause mass starvation of deer. Farmers fired back, saying that their livelihood was at stake.

MAES research informed the state's regulatory decisions, helping to ensure that science-based policies prevailed despite the charged atmosphere. MAES epidemiologist and veterinarian John Kaneene was part of a team of scientists who analyzed the connection between supplemental feeding and bovine TB in deer.

The team surveyed more than 200 residents in the core infection area about their deer feeding and baiting habits from 1995 to 1997. Then the researchers looked at the prevalence of bovine TB in the same geographic area during the same time period.

Increases in the number of feed sites in a given area, number of deer fed per year, and amount of fruit and vegetables or grain dumped in feed piles all were associated with higher rates of bovine TB in the deer population.

"The outbreak of bovine TB in Michigan and the role of supplemental feeding in support of the outbreak should serve as a cautionary example of an unintended effect of a human intervention in the ecology of wildlife species," Kaneene and his co-authors wrote in a 2003 *Journal of Wildlife Diseases* article that described the research results.

Through much of the 1990s, private hunt clubs and other landowners would feed deer culled vegetables and grains during the winter. The practice boosted deer populations and also created crowding conditions that facilitated the animal-to-animal spread of TB.

Today, seven years after it went into effect, the supplemental feeding ban remains in place throughout the Lower Peninsula, and calls by hunters for it to be lifted have mostly subsided.

DISEASE TRACKERS: ACROSS MICHIGAN AND ACROSS TIME

The role of supplemental feeding wasn't the only question about the disease. Scientists and regulators also had little idea how bovine TB was transmitted and maintained in the deer population — important information in shaping Michigan's wildlife disease surveillance program.

Kaneene and Winterstein joined colleagues at MSU, the MDNR, the Michigan Department of Community Health (MDCH) and the USDA to look for an answer.

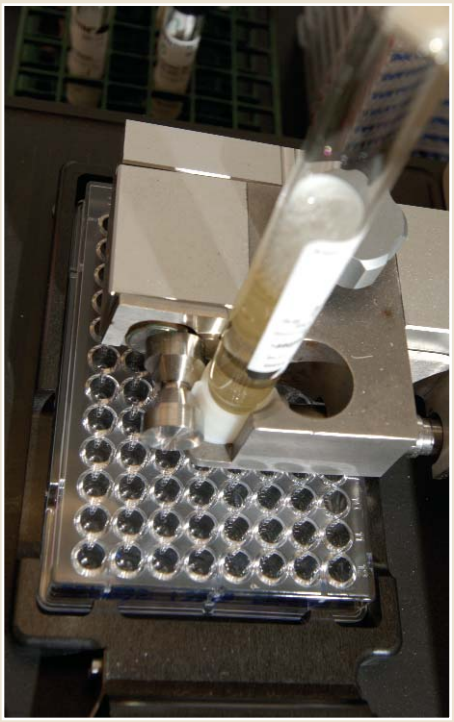
Dan O'Brien, an MDNR veterinarian, led efforts to compile data from post-mortem examinations of more than 60,000 deer. The animals came from all 83 Michigan counties and represented a fraction of the deer harvest from 1995 to 2000. This Herculean and macabre task — it involved taking tissue samples from deer heads delivered by the truckload — was performed by MDNR and MSU staff members, many of whom today work in the new Diagnostic Center for Population and Animal Health (DCPAH) on MSU's south campus.

"This was very much a combined effort, with MDNR collecting the deer heads, establishing a database, and making preliminary exams to determine sex and age of animals; while all the gross lesion evaluation, histopathology and sample collection for necessary TB culture were performed by MSU personnel, many of whom are supported in part by the MAES," said Scott D. Fitzgerald, an MSU veterinarian and pathologist, who also worked on the postmortem examinations. "Without the enormous efforts of these people, there would be no data on deer TB prevalence, geographic distribution and so on, which was critical to the MDNR and to all the researchers involved."

Some of the most wrenching stories have been of farmers who've been forced to destroy their herds more than once.

Researchers analyzing data from these surveillance efforts found that bovine TB prevalence varied widely by geographic area. Deer from the core infection area were almost 150 times as likely to be TB-positive as deer from other areas.

Over the years, MDNR and MSU staff members have tested well over 100,000 deer from around the state for bovine TB.



Over the years, Michigan Department of Natural Resources and MSU staff members have tested more than 100,000 deer from around the state for bovine tuberculosis.

But O'Brien's results, published in a 2002 article in *Preventive Veterinary Medicine*, suggested the merits of more targeted testing.

Today, with the prevalence of bovine TB dwindling, the MDNR is concentrating its surveillance activities in the core infection area, saving money and applying its limited resources more efficiently.

As a side benefit, the study's results also may have helped to limit any remaining ill will between cattle producers and hunters.

During the outbreak, cattle producers

MAES epidemiologist and veterinarian John Kaneene is studying the root of false positives — animals that react to the TB skin test but subsequently turn out to be free of the disease. It's important work because false positives lead to "unnecessary culling of cattle, increased time costs associated with handling of cattle, increased cost of follow-up testing, and psychological stress to producers and veterinarians," wrote Kaneene and several collaborators in a 2005 research article.

How the Medieval Monarchs Dealt With TB

Lifelong Midwesterners might recall seeing farm kids with scrofula — swellings of the lymph nodes of the neck, usually resulting from a bovine TB infection.

During the Middle Ages, TB of the lymph glands of the neck was very common and was known variously as scrofula, struma and the "King's Evil." For centuries it was believed that the "royal touch" could cure this disease, and many English and French monarchs were in the habit of touching their afflicted subjects during major religious holidays.

Andre Du Laurens, an anatomist and Paris court physician, was a firm believer in the effectiveness of the "royal touch" and reported that King Henry IV, who reigned from 1589 to 1610, often touched and healed as many as 1,500 individuals at a time.

::: Geoff Koch

MAES research informed the helping to ensure that prevailed despite the

said that the MDNR surveillance strategy was flawed because it relied on hunters to voluntarily submit their deer for testing. These farmers suggested that hunters were withholding deer with obvious signs of the disease to avoid attracting unwelcome regulatory attention to their favorite hunting haunts.

The study, which analyzed data from deer harvested by the MDNR and by hunters, found no evidence of such shenanigans. It was where the deer samples originated and not who did the harvesting that mattered most in positive TB tests, the authors reported.

UNCOVERING ON-FARM RISKS

MAES research also has focused on issues that matter most to Michigan cattle producers and dairy producers, many of whom have suffered extensive financial and emotional costs in dealing with the disease.

Some of the most wrenching stories have been of farmers who've been forced to destroy their herds more than once.

Mike and Kathy Warner used to own and operate an Alpena County farm with Black Angus cattle. In 1998, they destroyed their herd when their farm became the first one in Michigan where bovine TB was found. The Warners bought another herd, but in 2002, workers at an out-of-state slaughterhouse found a lesion on an animal from their farm. They were forced to destroy their entire herd again.

"We won't bring cattle on this farm again," Mike Warner told the Associated Press, which reported in August 2002 that the Warners had decided to sell their farm.

False positives add significant cost to the state's testing efforts. In a normal herd, 5 percent of the animals will have false-positive results.

The Warners' tragedy was an example of another gap in knowledge about the disease — no one knew what environmental and farm management conditions were associated with bovine TB showing up or reappearing on northeastern Michigan cattle farms.

To close the gap, MAES epidemiologist Kaneene, along with colleagues from MSU, the MDA and North Carolina State University, collected data from 17 infected farms and 51 control farms. Through in-person interviews, questionnaires, state wildlife disease surveillance records and satellite imagery, the researchers came up with a short list of risk factors.

Predictably, risk increased as rates of bovine TB rose in nearby cattle operations and local deer populations. Larger cattle herds (it's a crowding disease) and ponds or creeks in cattle housing areas (TB can survive for extended periods in moist, wet conditions) also were associated with greater risk.

By contrast, risks decreased as there was more open space around the cattle operation, probably because deer prefer landscapes that afford some cover and protection. Risk also decreased as producers restricted deer access to cattle by housing cattle in barns, barnyards or feedlots, and by using electrified wire or barbed wire for livestock fencing.

The highlight of the study, published in September 2002 in the *Journal of the American Veterinary Medical Association (JAVMA)*, wasn't identifying the risks in the first place. Everyone knew that keeping potentially infected deer away was a good idea. Rather, the real accomplishment was to begin measuring the relative benefits of changing farm management practices to cope with the disease.

Kaneene has extended his cost-benefit work since the paper was published. He's

state's regulatory decisions, science-based policies charged atmosphere.

working with MAES agricultural economist Chris Wolf on a software program that considers both the epidemiology of the disease and the economics of life on the farm.

Is it worth it to put up woven wire — a more effective but more expensive alternative to barbed wire? With the software program, an MSU Extension agent could visit a farm with a laptop, spend a few hours walking around collecting data and, with a tap of the "Enter" key, answer the question.

Kaneene hopes the software program will be completed and in use by 2006.

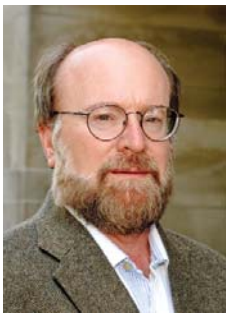
FINDING THE ROOT OF FALSE POSITIVES

The MAES also has supported research to improve the testing of the state's cattle for the disease. From January 2000 to December 2003, the MDA, the USDA and private veterinary practitioners tested every cow in the state for the disease. Testing more than 1 million animals cost taxpayers tens of millions of dollars.

MSU veterinarian and pathologist Scott Fitzgerald was one of several researchers who conducted postmortem examinations of more than 60,000 hunter-harvested deer from around the state in the late 1990s. Today, Fitzgerald is studying whether other species, including crows, might act as reservoirs for the disease.

Testing a cow for TB involves injecting the skin near the animal's tail with a protein derived from TB bacteria. If the skin around the injection site becomes raised and swollen, then the entire herd is

Eradication — A Complex and Difficult Task



John Baker, acting director of the Michigan Agricultural Experiment Station and associate dean for research in the MSU College of Veterinary Medicine, was also involved in the state's bovine TB eradication efforts.

In March 2002, Baker was part of a delegation from MSU, the MDA and the MDNR to Washington, D.C., that successfully made the case for $6 million in federal funding for the bovine TB eradication effort. He also made several visits to the core infection area to participate in education and outreach activities with state regulators.

For a time, bovine TB was a hugely contentious issue in Michigan, largely because of all the confounding variables associated with the disease.

"To a veterinarian, the eradication of bovine TB in cattle is straightforward," Baker said. "Use testing to identify the infected animals and herds, and then remove these animals from the population."

A range of issues and questions complicated these eradication efforts, however. First, there was doubt about whether bovine TB bacteria could be self-sustaining in the deer population. Then, there were questions about the role of supplemental feeding in boosting deer populations and fostering disease transmission. And, of course, there's the importance of deer hunting to the economy and culture of Michigan.

"Moving forward, any successful eradication program needs to embrace not just sound scientific principles of infectious disease control — it also needs to address the sociological dynamics of this disease problem in Michigan," Baker said.

::: Geoff Koch

I Thought We'd Wiped Out TB — Bovine and Otherwise

A brief history of the disease in the United States leading up to Michigan's mid-1990s

Bovine TB was supposed to have been wiped out in the United States. Among the first regulations in the country for protecting the food supply was the Meat Inspection Act of 1906. It was inspired in part by the 1906 novel *The Jungle* by Upton Sinclair, which described unsanitary conditions in Chicago stockyards.

"There were men who worked in the cooking rooms, in the midst of steam and sickening odors, by artificial light; in these rooms the germs of tuberculosis might live for two years, but the supply was renewed every hour," Sinclair wrote.

The Meat Inspection Act required inspection of cattle, hogs, sheep and goats intended for interstate commerce, as well as the monitoring of slaughter and processing procedures. Bovine TB remained a problem, however, largely because the bacterium that causes the disease has an extremely slow rate of growth and a tendency to remain dormant.

In the early 1900s, scientists understood that the bovine form of tuberculosis was distinct from the human form. Evidence was mounting that the bovine form could be passed between animals and humans, and that in humans the bovine type could produce symptoms — lesions, coughing attacks and chronic wasting — clinically indistinguishable from those of the human strain.

It was an era when TB was responsible for one out of every nine U.S. deaths. And by one estimate, 10 percent of these deaths were from the bovine strain of the bacteria. Death was only one measure of the disease's cost — countless others were permanently crippled or lingered in pain as they wasted away.

In response, in 1917 the federal government embarked on a national campaign to eradicate bovine TB from the United States. The campaign led to an unprecedented peacetime use of the state's police power as federal and state authorities sent testers to every dairy and cattle operation in the nation and ordered the destruction of 3.8 million animals, with only partial compensation to the owners.

This campaign brought the disease under control by 1941, generating returns to the livestock sector of roughly 10 times the total program costs and saving tens of thousands of human lives.

As TB eradication progressed, it became apparent that testing on farms was becoming increasingly inefficient as a method to locate diseased animals. In 1959, the emphasis was switched to tracing animals with lesions found by meat inspectors at slaughter.

If an animal tested TB positive at a slaughterhouse, then an epidemiological investigation was launched to locate the lesioned animal's herd of origin and any other herds that may have been exposed to this animal. To eliminate any possibility of TB remaining in a herd, it was recommended that all animals in an infected herd be destroyed.

Since the second half of the 20th century, this epidemiological detective work has been the main method used to locate TB-infected herds. To encourage the collection and submission of tissue samples at slaughter, meat inspectors are given a cash award if the submitted tissue is found to be infected with TB. A second, larger award is made when the herd of origin is located.

In 1979, Michigan was among the last states to be granted TB-free status by the USDA. By the 1990s, annual surveys found only a smattering of cattle herds nationwide to have tuberculosis.

Then a new problem arose. Following the discovery of TB in an elk exported from the United States, Canada banned the importation of cervid species (animals in the deer family, including elk) from the United States in December 1990. TB was confirmed in an elk herd in the United States in 1991.

In 1994, tuberculosis was confirmed in a deer shot by a hunter in Michigan's northeastern Lower Peninsula. By 1995, the disease was identified as self-sustaining in Michigan's wild deer population.

::: *Geoff Koch*

quarantined and subjected to additional testing.

False positives — animals that react to the skin test but subsequently turn out to be free of the disease — add significant costs to the state's testing efforts. In a normal herd, 5 percent of the animals will yield false-positive results, according to the MDA.

In a February 2005 *JAVMA* article, Kaneene and several collaborators shed light on one aspect of the false-positive puzzle — the potential of other common bacterial infections in cattle to gum up testing efforts.

Cattle can carry other types of TB-related bacteria, such as the strain causing Johne's disease (pronounced "Yonees"). Johne's disease causes diarrhea and weight loss in cattle and can afflict up to 20 percent of the cattle population in some U.S. regions. Unlike bovine TB, Johne's disease isn't associated with a threat to human health, and it is not subject to anywhere near the same regulatory scrutiny.

Scientists had suspected that cattle carrying the bacteria associated with Johne's disease might be more likely to return false-positive results when tested for bovine TB. But in looking at more than 1,000 cattle from 10 Michigan herds, Kaneene and MAES researchers Dan Grooms, Steve Bolin and Carole Bolin saw scant evidence of such a link.

As a result, researchers may have to look elsewhere in their efforts to reduce the number of false positives. It's important work because false positives lead to "unnecessary culling of cattle, increased time costs associated with handling of cattle, increased cost of follow-up testing, and psychological stress to producers and veterinarians," wrote the scientists, whose work on false positives continues.

Kaneene and others are working on ways to trim these costs by cutting the time it takes to get a definitive answer on whether an animal is TB-positive. And Fitzgerald, the MSU veterinarian and pathologist, is studying whether other wildlife populations — such as pigeons, ducks and opossums — might also act as low-level reservoirs of bovine TB.

"Any successful eradication program needs to embrace not just sound scientific principles...but also the sociological dynamics of this disease."

LOOKING AHEAD TO TB-FREE STATUS?

Though open questions remain, there's much to celebrate in the state's fight against bovine TB. In the core infection area in the northeastern Lower Peninsula, the disease prevalence has dropped by 65 percent since 1995, the MDNR reported in March.

In April, Minnesota reopened cattle trade with parts of Michigan deemed lower risk by the USDA. Michigan has asked the federal government to declare the Upper Peninsula free of bovine tuberculosis. If the USDA agrees, the Upper Peninsula will become the first part of Michigan to regain TB-free status since it was revoked statewide in 2000.

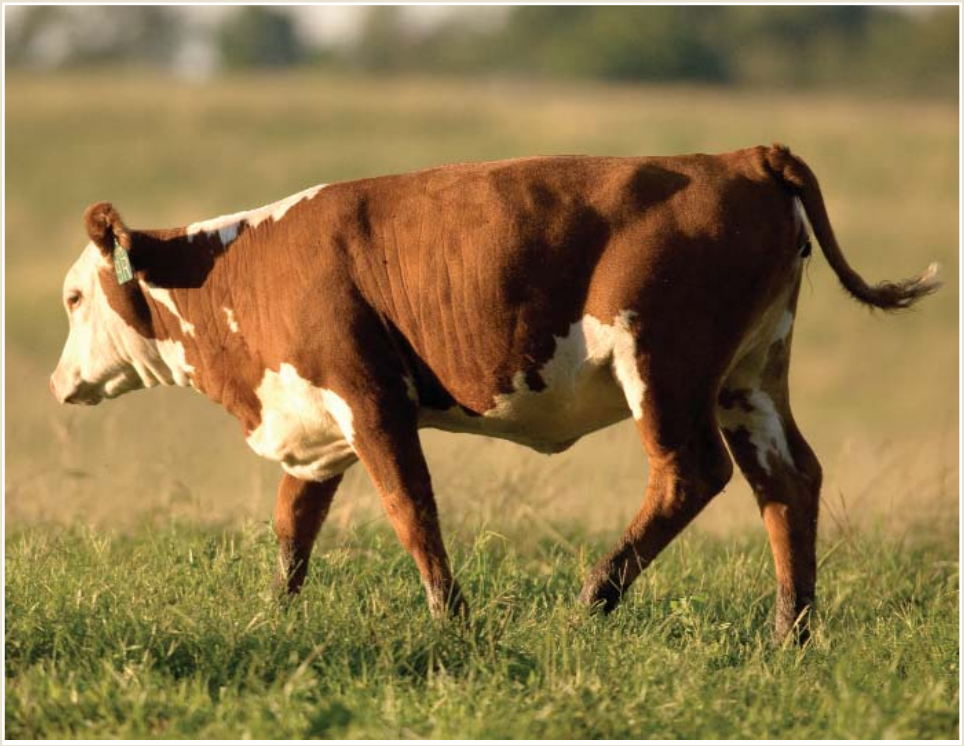
Perhaps the best news is that the impact on human health has been negligible. Though cattle on 34 farms and close to 500 deer have tested positive, the Michigan bovine TB strain has turned up in only two of the state's residents.

In one case, the strain was found during an autopsy of an elderly person who died in 2002. Bovine TB was not the cause of death, the MDCH reported.

And in January 2005, a hunter who cut his hand while gutting a deer became the first living person diagnosed with the Michigan bovine TB strain. The man, who killed the deer in Alcona County in October and sought medical attention after spotting telltale lesions in the animal's chest cavity, was treated with antibiotics and is expected to recover, according to the MDCH.

Throughout the course of the outbreak, the MAES was one of a handful of contributors to the effort to fight the disease. Other MSU scientists and MSU Extension educators were involved, as were people from an alphabet soup of state and federal agencies.

But the MAES research — which helped to cool rhetoric between hunters and farmers, guide regulatory efforts, ease strains on cattle producers and veterinarians involved in testing efforts, and answer questions about the basic science of the disease — has yielded practical benefits.



From January 2000 to December 2003, the MDA, the USDA and private veterinary practitioners tested every cow in the state for bovine TB. Testing more than 1 million animals cost taxpayers tens of millions of dollars.

"Academic scientists sometimes work on basic research and may have to wait for a long time to see the application of their results in solving a specific problem," Kaneene said. "But here, it was rewarding to see our research applied to make real progress against this disease."

::: *Geoff Koch*

Breathing seems to be the most reflexive and simplest thing to do. How many of us actually notice when we take a breath? But for people with asthma, cystic fibrosis and other respiratory diseases, breathing can become a challenging, complicated task.

According to statistics in "Epidemiology of Asthma in Michigan: 2004 Surveillance Report," published by the Asthma Initiative of Michigan and the Michigan Department of Community Health, almost 214,000 children and more than 654,000 adults in Michigan currently have asthma. The percentage of adults with asthma in Michigan (9.3 percent) is slightly higher than that of the country (7.7 percent). Seventeen percent of public middle and high school students in Michigan say that they have asthma now. The prevalence of asthma is higher among black students than white students.

Nationally, 20.3 million Americans report having asthma, and 9 million children under 18 have been diagnosed with asthma, according to statistics from the American Academy of Allergy, Asthma and Immunology. From 1982 to 1996, the prevalence of asthma increased by 97 percent among women and 22 percent among men. Overall the prevalence of asthma increased 75 percent from 1980 to 1994. Asthma rates in children younger than 5 increased more than 160 percent during the same period. In 2000, there were 10.4 million asthma-related outpatient visits to physician offices and hospital clinics (4.6 million of these involved children under 18). Approximately 5,000 deaths from asthma occur annually, and direct healthcare costs related to asthma in the United States total more than $9.4 billion annually; indirect costs (lost productivity) add another $4.6 billion, for a total of $14 billion. Inpatient hospital services represented the largest single direct medical expenditure, more than $4 billion.

MAES researcher Jack Harkema, university distinguished professor in the Department of Pathobiology and Diagnostic Investigation, uses mice and rats to study chronic respiratory diseases that are similar to those in humans.

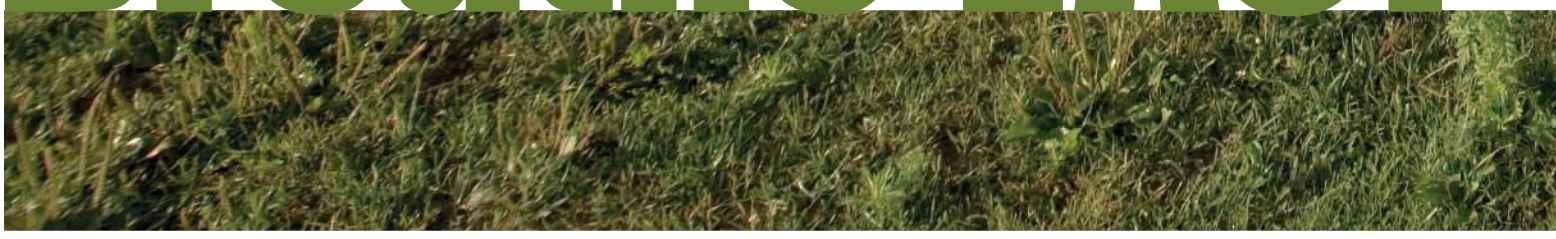
"Mice have respiratory systems that are similar to human systems," Harkema said. "They also have similar immune systems and inflammatory responses to respiratory disease. We can use these animal models of human respiratory disease to investigate the cellular and molecular mechanisms that underlie these diseases in the lung."

In humans, chronic respiratory diseases are asthma, cystic fibrosis, chronic obstructive pulmonary disease (COPD), emphysema and chronic bronchitis.

Cystic fibrosis is a genetic disease affecting

By studying respiratory diseases in horses, mice, cats and other animals, MAES scientists hope to provide new options for treatment and understand why these diseases are becoming more prevalent in humans.

Breathe EASY



MAES scientist N. Edward Robinson, who holds the Mathilda Wilson Chair, is studying heaves, an asthma-like disease in horses. Robinson is collecting data to determine how prevalent the disease is in Michigan.

approximately 30,000 children and adults in the United States. A defective gene causes the body to produce thick, sticky mucus that clogs the lungs and leads to life-threatening lung infections. These thick secretions also obstruct the pancreas, preventing digestive enzymes from reaching the intestines to help break down and absorb food. The mucus also can block the bile duct in the liver, eventually causing permanent liver damage in about 6 percent of people with cystic fibrosis. But it's usually lung disease that kills cystic fibrosis patients.

"The primary gene associated with cystic fibrosis was identified a while ago," Harkema explained. "We suspected that the alteration in this specific gene may cause other genes to malfunction in the lungs, which resulted in a lack of water in the airways and the development of abnormally thick mucus."

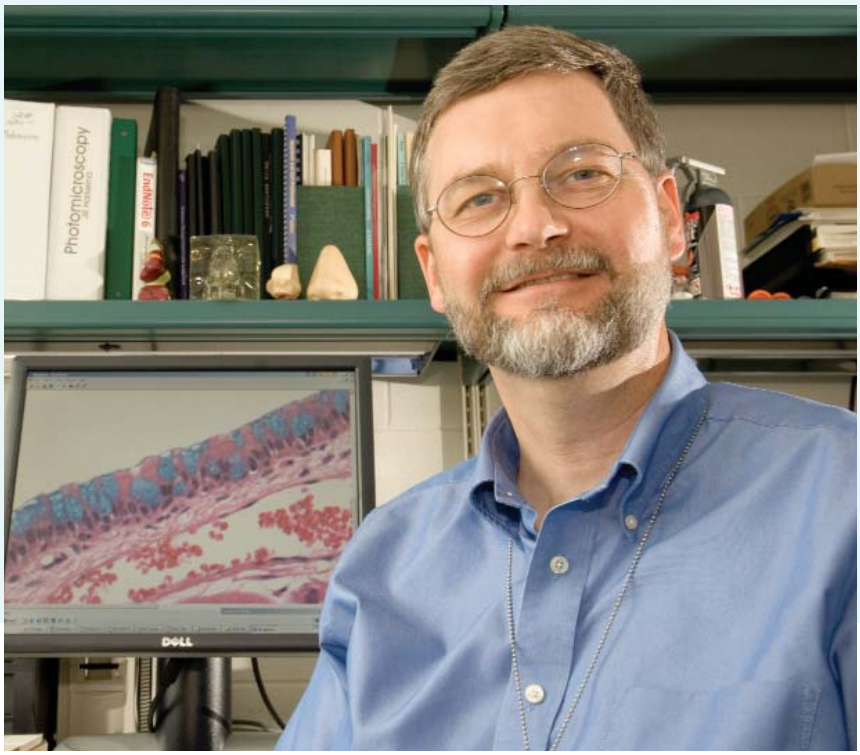
Based on research by Harkema and his colleagues at the University of North Carolina, Chapel Hill, scientists now know that dehydration of the airways is a major factor in the development of the lung problems in cystic fibrosis patients. Their research findings were published in the May 2004 issue of *Nature Medicine*.

"We now understand that adequate airway hydration is critical for normal lung defense from bacteria," said Marcus Mall, of the School of Medicine at the University of North Carolina and the study's lead researcher.

In people with cystic fibrosis, lung airways absorb an excessive amount of salt, which reduces the amount of water in the mucus lining the airways and causes it to become very thick and sticky. The hair-like cilia that ordinarily move the thin, watery mucus out of the lungs stop working when the mucus gets too gooey. Stuck in the airways, the mucus develops into a fertile breeding ground for countless infectious bacteria.

Harkema and the UNC researchers genetically modified the lungs of mice to absorb extra salt and water, and a cystic fibrosis-like lung disease resulted. The new mouse model doesn't contain the cystic fibrosis genetic disorder, only its characteristic lung disease. Their work demonstrated for the first time that over-absorption of sodium ions out of the airway is sufficient to cause mucus dehydration and the development of cystic fibrosis-like lesions in the lungs of mice.

"Cystic fibrosis doesn't normally develop in animals," Harkema said. "This was the first time that pulmonary pathology similar to that in cystic fibrosis patients was convincingly developed in a laboratory mouse. We hope this model will be used by other scientists to design better drugs for treating



Jack Harkema *(left)*, MAES researcher and MSU distinguished professor, has found that dehydration of the airways is a major reason why cystic fibrosis patients develop lung problems. Harkema and University of Michigan scientists collaborated to design and build AirCARE 1 *(right)*, the country's only mobile air research lab.

this devastating disease. These genetically altered mice may also be used to study other chronic respiratory diseases, such as asthma and chronic bronchitis. Of course, the ultimate goal is to develop effective ways to prevent this deadly disease."

Harkema and his colleagues at MSU also are studying the effects of air pollutants on the respiratory system.

The Ozone Effect

Ozone is an alternative form of oxygen that contains three oxygen atoms rather than two and is usually found in the Earth's upper atmosphere. It's responsible for filtering out much of the sun's ultraviolet radiation. But closer to the Earth's surface, ozone is a problem. It's produced as part of industrial air pollution and is the main component of smog. Ozone is very reactive and corrodes masonry, causes paint to darken and is unhealthy to breathe.

"We've found that the airways produce more mucus when they're exposed to ozone," Harkema said. "Exposure to high concentrations of this irritant found in urban smog may cause individuals who already have too much mucus in their airways [people suffering from asthma, chronic bronchitis or cystic fibrosis] to produce even more mucus, which results in clogged airways and difficulty with breathing."

Working with James Wagner, also a researcher in the MSU Department of Pathobiology and Diagnostic Investigation, Harkema has uncovered a symbiotic relationship between ozone and other pollutants and allergens.

"Ozone increases inflammation in the lungs, no matter what the original source of the inflammation is," Harkema explained. "It makes asthma or allergy symptoms worse and may cause asthma attacks. Jim Wagner and I are working with researchers at the University of California-Berkeley to develop antioxidant compounds that would reduce ozone's aggravation of these symptoms. The Berkeley scientists develop these novel compounds, and at MSU we test them on laboratory rodents to see if they work. If the treatment is effective in laboratory rodents, then these compounds will be used by researchers at the University of North Carolina, who will design clinical studies to determine their effectiveness in preventing pollution-induced exacerbation of chronic lung disease in humans."

To study ozone and particulate matter air pollution in communities with high levels of asthma and other respiratory diseases, Harkema and scientists from the University of Michigan are working together on the Collaborative Air Research Effort (CARE). They designed and built AirCARE 1, the only mobile air research laboratory of its kind in the country. The 53-foot-long, 8-foot-wide, 36,000-pound trailer contains three specially designed laboratories that allow scientists to conduct inhalation toxicology studies of real-world air pollution.

"So far, most of our work has been done in southwest Detroit," Harkema said. "There are high levels of childhood asthma in that part of the city, and we're finding that the kids there are exposed to high levels of particulate matter."

Harkema explained that the Environmental Protection Agency (EPA) is especially interested in particulate matter because research has shown that, as levels of particulate matter in air pollution go up, deaths and hospital admissions increase.

"We're not sure if it's related to the size of the particles or the chemical composition," he said. "Those are things we're starting to work on with the mobile lab. The U-M researchers can identify where the particles are coming from — fingerprinting them, so to speak. We think that the metal content might be important, but it could also be the size of the particle. The smaller the particle, the more toxic it may be. High numbers of ultrafine carbon particles [nanoparticles] are often found in urban air pollution. We want to determine if these very, very small particles are actually the most toxic to the lungs and the rest of the respiratory tract."

The overarching issue for the scientists is the effect that the mixture of contaminants in the air has on the lungs.

"We're looking at whether the combination of pollutants, allergens and bacterial agents work together and cause bigger problems for people than if they were just exposed to one at a time," Harkema explained. "In other words, what happens if you're exposed to particulate matter and ozone? Or bacteria and ozone? Does the order matter? And how do environmental pollutants affect infectious diseases?"

A Genetic Fingerprint for Asthma

Combining the influence of environmental factors with genetic makeup to determine who is susceptible to asthma is the research goal of Susan Ewart, acting associate dean for research for the College of Veterinary Medicine and director of the MSU Molecular Respiratory and Equine Genetics Laboratory.

"I'm an equine specialist," she said. "I started studying pulmonary diseases in horses that keep the animals from reaching their peak performance. As I got deeper into the research, I found that mice are easier to work with. But I still do work with horses."

By using mice as models, Susan Ewart *(right)*, director of the MSU Molecular Respiratory and Equine Genetics Laboratory, is trying to discover the exact genes responsible for asthma. Because the disease is caused by genetic susceptibility AND environmental factors, people who have the genes could be given counseling for their specific needs.

Using mice as models, Ewart is attempting to locate the exact genes responsible for asthma.

"We know there are a number of genes involved, and we also know that many diseases, such as asthma, are caused by both genetic susceptibility and environmental factors," Ewart explained. "So if you inherit the palette of genes responsible and are exposed to the environmental aspects, then you get the disease. Our long-term goal is to be able to identify people with genetic susceptibility to these types of chronic diseases and then offer them counseling about their environment, diet and exercise that is tailored to their specific needs."

Using two strains of mice — one that was very susceptible to asthma and one that was very resistant — Ewart and her research team placed the rodents in identical environments and then tracked which ones developed asthma. They then looked at the genetic makeup of these mice to see if there were specific genes that were in all the asthmatic mice.

"We know the general location of the genes and have pulled a subset for further study," she said. "We want to narrow it down to the specific genes involved."

In 2003, Ewart began collaborating with Wilfried Karmaus, an epidemiology researcher at MSU, and he introduced her to Hasan Arshad, a researcher at the David Hide Asthma and Allergy Research Centre on the Isle of Wight in the United Kingdom. In 1990, Arshad and his colleagues recruited 1,400 of the 1,500 children born that year on the Isle of Wight to participate in a longitudinal study on allergies, now in its 15th year.

The investigators have collected information about the children's environments and data from physical exams at ages 1, 2, 4 and 10. Using this information, they hope to identify how each allergic disease progressed through each child, whether there were combinations of allergies and whether disease onset was early or late. Ewart is studying the DNA from these children to identify genes that contribute to allergic disease progression.

"We're studying the natural history of any allergic disease in each child," Ewart said. "Over the course of time, this can change. Some infants can wheeze and look like they will develop asthma, but it resolves itself. They seem to grow out of it. Others have no symptoms as an infant and develop asthma as preschoolers; this is more common in males. Others will have no symptoms until adolescence; this is more common in females. We want to know why this happens and get a better sense of who gets what when.

"It's very complex to figure out if there are similarities or differences in the kids' genetic makeups," she continued. "For example, do all kids who get asthma as infants have similar genetics? There is a lot of information to sort out."

According to Ewart, there are only a few longitudinal studies of children and asthma, and only one

other includes genetic information, so this research is rather distinctive. In 2006, the children will turn 16 years old, and the researchers are looking for funds to study them at this important stage in their development.

"In my lab, we go back and forth between human information and our mouse models," she said. "We use what we see in mice to augment our human studies, and we test what we see in humans in the mice. It's allowed us to start to answer some questions about how asthma functions at the genetic level."

Help for Horses

Heaves is an asthma-like equine disease that is chronic in older horses. Horses develop it when they inhale dust that contains mold and other allergens. Heaves causes coughing and difficulty breathing. In the South, horses on pasture are the ones that usually develop heaves, primarily in the summer and usually when it's hot and humid. In the northern United States, heaves usually affects horses kept in a barn and is usually associated with poor ventilation and giving hay as feed. There is no cure for heaves, but the symptoms can be alleviated somewhat by controlling the horse's environment to reduce exposure to dust and with medications.

"We understand the physiology of heaves quite well," said N. Edward Robinson, MAES large animal clinical sciences researcher, who holds the Mathilda Wilson Chair. "What we don't understand is why some horses are susceptible and some horses aren't. It's similar to people with asthma. There's an overactive airway inflammation response that seems to have a genetic predisposition."

Since the 1600s, scientists and horse owners have known that dusty hay can trigger heaves. Recommendations for owners of horses with heaves include keeping the horse away from hay and keeping the animal outside year round.

Even though Robinson has been studying heaves for many years, he is still amazed that no statistics are available on the prevalence of airway diseases in horses in the United States.

"We have some data on severe cases of heaves but none on less severe cases, so we don't really understand how the disease begins," he said. "And we aren't sure if the recommendations for the treatment of heaves are good for its prevention. So we decided to start collecting data on the prevalence of the disease in Michigan and the factors that affect its development. We also want to know if it's inevitable that horses progressively get worse when they get heaves. In the past, it's been a gloom-and-doom scenario when an older horse developed a chronic cough."

Robinson and his colleagues took mucus samples from 260 horses in Michigan and also looked at the cell types in the mucus to see if the lungs were inflamed. They found that about 20 percent of

Heaves has been a problem in horses for hundreds of years and is chronic in older horses. The condition can be triggered by dusty hay. There is no cure, but the symptoms can be controlled with medication and changes to the horse's environment.

Because dusty hay plays a role in heaves, Robinson compared various types of hay bale shapes and sizes, as well as pasturing, to see which caused the most respiratory inflammation in horses. He found that large round bales are associated with the most severe inflammation, probably because the horses have to bury their noses in the bales to get at the good hay.

Michigan horses have some type of airway inflammation, many with no clinical signs, especially when they're on pasture in the summer. They also found that large round hay bales — rather than other types of bales and pasture — are associated with the most severe inflammation. Being outside in the winter also increased the risk of airway inflammation, which contradicted the recommendations for horses with heaves.

"In the winter, the horses with the healthiest airways are those that are kept inside and eat from square hay bales," said Robinson. "In the summer, being outside is good. In the past, we have recommended keeping horses outdoors year round as the best way to keep the airways healthy. But we might have to temper our recommendations. Round bales might not be the best way for a horse to eat hay, especially if it's outdoors in cold weather."

Round bales are convenient for producers because they require little labor and are more economical to produce. Robinson speculated that the bales caused more inflammation because horses bury their noses in the bales when they eat to get to the good hay inside and in doing so directly breathe in the dust from the hay.

To track the progression of the disease, Robinson would like to follow 10-year-old pleasure horses for several years and see what happens.

To gather more data on the effects of airway diseases, Robinson collaborated with Susan Holcombe, associate professor of large animal clinical sciences, to study the consequences of inflammation on racing performance in racehorses at the Thistledown Racetrack in Cleveland. The scientists examined 150 horses each month for 16 months. Holcombe looked at the effect any inflammation had on the horses' performance, and Robinson looked at the prevalence of inflammation.

"We found that most inflammation and the associated mucus occurred in younger horses, and for each subsequent year the horse was there, the prevalence went down," Robinson explained. "Most importantly, small accumulations of mucus in the airways significantly decreased racing performance."

The results on prevalence of airway disease in racehorses match data from Britain and Australia, where similar surveys have been done. The next objective is to figure out the cause of the inflammation. Researchers in Britain think the cause is bacterial, but Robinson and his colleagues are beginning to look at the horse's environment to see if those factors have an effect.

Searching for Treatments for a Deadly Lung Disease

Idiopathic pulmonary fibrosis (IPF) is a lethal disease that damages the air sacs in the lungs, leading to scarring of the lungs and reduced transfer of oxygen to the blood. More than 200,000 people in the Untied States have IPF (the "idiopathic" in the name means researchers do not know what causes it) and there are no effective treatments or cure for the disease. IPF occurs more often in people 50 and older and most people with IPF survive only about 5 years.

Currently, there is no animal model for the disease that causes similar changes in the lungs of animals. Because of this, researchers have a difficult time understanding the disease and testing possible treatments.

Today, thanks to the work of MAES veterinary pathologist Kurt Williams, people with IPF may soon have renewed hope, and researchers may be able to start new studies on the mechanism of the disease.

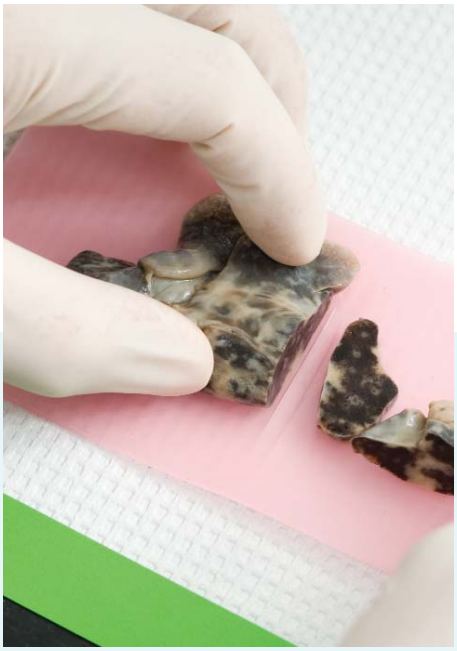
Through his work in the Diagnostic Center for Animal and Population Health, Williams has identified a disease in cats that is very similar to IPF in humans. According to Williams, laboratory mice can get lung fibrosis, but it doesn't look like IPF microscopically and doesn't progress as the disease does in humans. In cats, as in humans, the disease is progressive and invasive.

"IPF causes complex changes in the lungs," Williams explained. "In my work in the Diagnostic Center, I noticed that the lung tissue of some cats that came in seemed to have undergone similar changes. So we started collecting data and published a paper on our findings in 2004. I'm very interested in what can be done to help people with IPF, as well as cats with the disease."

Using his discovery, Williams hopes to develop a new animal model of IPF. He is now studying the conditions that may cause the disease, as well as investigating what happens at the cellular level in hopes of uncovering a treatment. His next step is to try to recreate the disease and study how it develops in the lung.

"I've enjoyed studying a real-world disease and then being able to apply some of my work to help people," Williams said. "In people, IPF is relatively uncommon, but because it's untreatable, it's devastating. We went from the necropsy floor to the lab — there is a lot to be learned from the Diagnostic Center, and it's a tremendous resource for MSU and the state to have."

::: *Jamie DePolo*



MAES researcher Kurt Williams found a disease that affects cats' lungs that is very similar to idiopathic pulmonary fibrosis, a lethal lung disease in humans. By studying how the disease progresses in the lungs of cats, Williams hopes to figure out the conditions that cause the disease.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On the Front Line of Michigan Security

The new Diagnostic Center for Population and Animal Health protects the state's people and animals from disease.

On a typical day, the MSU Diagnostic Center for Population and Animal Health (DCPAH) receives between 600 and 1,200 pieces of mail. Most of these contain samples of blood or other tissues of animals that are suspected of harboring a disease.

"There may be one sample per box or 300 per box — we don't know until it's opened," said Steve Bolin, MAES pathobiology and diagnostic investigation researcher, who is also chief of the DCPAH Immunodiagnostics and Parasitology sections and serves as associate director of the center. "Each sample comes with a form that tells us which tests to run — more than one test may be done on each sample. Our technicians sort everything into specific refrigerators for each lab. A signal light then goes on in the lab to let them know that a new sample is in and ready for testing. Now that we're all in one building, rather than being spread out across five buildings on campus, the intake process is more efficient."

Dedicated in September 2004, the new DCPAH facility allows MSU scientists to run more than 1.3 million tests per year, making it one of the top three diagnostic labs in the country, according to Willie Reed, DCPAH director, who is also chairperson of the Department of Pathobiology and Diagnostic Investigation in the College of Veterinary Medicine. The tests range from rabies to West Nile virus to bovine tuberculosis (TB) to chronic wasting disease, and the center's clients are in all 50 states and several foreign countries.

"Our mission, as it has been for the past 30 years, is to protect animals and humans from the health threats of disease and toxic substances," Reed said. "We do this through accurate and rapid detection of infectious diseases to prevent spread and minimize animal losses and human illness."

"We don't offer treatment, just diagnosis," said Richard "Mick" Fulton, chief of the Anatomic Pathology-Necropsy

Carole Bolin, MAES scientist, is chief of the Bacteriology Section of the Diagnostic Center for Population and Animal Health. Because of the Diagnostic Center, Michigan is a national model for integrating systems for animal and human health.

Section of the DCPAH. "We figure out why the animal died or is sick. Our clients range from private citizens and private veterinarians to state and federal governments."

The original collection of campus labs, known as the Animal Health Diagnostic Laboratory, was created in the 1970s in response to the accidental introduction of PBB, a chemical fire retardant, into the food supply.

Steve Bolin, MAES scientist and associate director of the center, runs tests for bovine tuberculosis, West Nile virus and chronic wasting disease in his lab. Last year, the center did 6,000 tests for chronic wasting disease in four weeks — a huge volume of work.

"We grew rapidly," Reed said, "and became one of the busiest labs in the country in terms of the number of tests run and the complexity of problems we dealt with. The bovine TB issue that started a few years ago underscored the need for new facilities — located in one spot — so samples could quickly and easily be examined and go to different labs for tests. We were struggling to handle the large number of deer and cattle submitted to the lab. We wanted to be able to make more rapid diagnoses safely and securely. With our old setup, we couldn't make the final diagnosis of bovine TB here at MSU. We had to send the samples to the USDA lab in Ames, Iowa, which increased the turnaround time for providing the results of the tests. In our new facility, we can make the final diagnosis here, which is more efficient for everyone."

"Our old immunodiagnostics section lab was just about twice the size of my office in the new building," said Bolin, showing off his somewhat compact new office space. He runs tests for diseases such as bovine TB and West Nile virus. "Sometimes we'd have to tell people that we couldn't test their samples because we were so cramped for space. They had to wait a week."

Situated a bit south of the main MSU campus, the new DCPAH facility houses labs, offices and classrooms in one building that provides better personnel safety, high levels of biocontainment and the ability to offer expanded services. Because protecting human and animal health is critically important to Michigan, the state funded the construction of the facility through a special appropriation. State officials and MSU scientists analyzed emerging disease trends and tried to create a facility that was ready to handle just about anything that could potentially happen.

"We tried to take everything into account when we were planning and designing the building," Reed said. "We wanted to be able to deal with anything and everything — as much as we could possibly think ahead, we did."

The result is a diagnostic center that is one of the most advanced in the nation. The DCPAH is a member of the USDA National Animal Health Laboratory Network and the Centers for Disease Control (CDC) Laboratory Response Network. Both networks aim to diagnose and report diseases of concern, such as chronic wasting disease, foot-and-mouth disease, classical swine fever and avian influenza.

"For example, the BSE [bovine spongiform encephalopathy] case in Washington in 2003 triggered the national surveillance program, so we were ready to do testing as needed," Reed explained. "The labs in the networks perform just as federal labs do and have to have the capabilities to handle these agents of concern. Our goal is to detect them quickly before they spread. The USDA controls which facilities can run tests for these high-risk agents."

Cutting-edge Capabilities

The Diagnostic Center encompasses 10 sections or labs:

- Anatomic Pathology (which includes Surgical Pathology, Immunohistochemistry and Necropsy).
- Clinical Pathology.
- Endocrinology.
- Immunodiagnostics.
- Bacteriology.
- Parasitology.
- Virology.
- Nutrition.
- Toxicology.
- Epidemiology.

It also includes administrative, computer services and quality assurance units. Except for the Epidemiology Section, which analyzes incidences of disease and other data and issues reports on trends, all the sections offer specific diagnostic tests for clients. Scientists from the Michigan Department of Natural Resources also share a lab to test deer for bovine TB and to detect diseases in other wildlife.

Willie Reed, director of the Diagnostic Center, says the facility allows MSU scientists to run more than 1.3 million tests per year, making it one of the top three diagnostic labs in the country.

"The Diagnostic Center is equipped to address animal health in all species, from fish and wild animals to agriculture and companion animals," Reed said. "Not all labs can offer all these services."

The DCPAH has several biosafety level III (BL-3) labs and containment facilities. They are used to support the state's bovine TB eradication program, as well as to identify dangerous pathogens that threaten both human animal health, such as strains of *Salmonella* that are resistant to multiple drugs and West Nile virus.

"No other diagnostic center has a BL-3 necropsy floor," Reed said. "This gives us a unique opportunity to partner with state government to address emerging diseases."

"If some type of biological attack or outbreak occurred, it's probable that it would be seen in animals first," said Carole Bolin, MAES pathobiology and diagnostic investigation scientist, who is chief of the Bacteriology Section. "We are certified to work with nine agents of concern that are on the federal government's overlap list, which means they affect both animals and humans."

For security reasons, she couldn't name the specific agents the DCPAH is certified for, but the federal government's list includes the pathogens that cause anthrax, eastern equine encephalitis virus and tularemia. Over the past 20 years, nearly 75 percent of the approximately 30 new diseases discovered in humans were zoonotic, meaning they are transmissible between animals and people. Of the more than 1,650 human disease conditions, nearly 60 percent are caused by pathogens that also infect animals.

"Because agricultural animals are outside much of the time, they may be the first ones to contract anything in aerosol form — many of the agents on the overlap list can be transmitted via aerosols," Carole Bolin said.

TAKING ANIMAL DIAGNOSTICS TO AFGHANISTAN

Over the course of his 24-year career as a veterinarian, Mick Fulton was involved in the design and building of two animal diagnostic laboratories, including the progressive new Diagnostic Center for Population and Animal Health (DCPAH) at MSU. In March, the associate professor of pathobiology and diagnostic investigation went to Afghanistan to help Kabul University build a necropsy laboratory there, one of the first steps in helping the war-torn country begin to feed itself.

"They had an old curriculum and an old building," Fulton said. "I helped them redesign their necropsy lab and developed an equipment list for them. Once the necropsy lab is up and running, they'll be able to train students. This is the first step toward a national program.

"It's all part of a plan to provide the Afghans with a disease surveillance and reporting system," he continued. "This will, we hope, help them be more self-sufficient in feeding their people."

Besides assisting with some of the design and building of the DCPAH, Fulton also was involved when a similar facility was built while he was a resident and faculty member at Purdue University.

"I've been through the building process, so I know about space requirements, equipment requirements and generally how to get these things started," he said.

Fulton was asked by the USDA to help in Afghanistan and was in the country for two weeks.

"It's a great opportunity to be asked by your government to use your skills to help other people," he said. "You have to weigh the benefits from the good parts and the bad parts, and in this situation, the good parts outweighed the bad. I was a little apprehensive about the visit, but we had no problems at all."

Mick Fulton, chief of the Anatomic Pathology-Necropsy Section, helped Kabul University, in Afghanistan, build a necropsy lab.

::: Jamie DePolo and Tom Oswald

Jon Patterson, MAES researcher, serves on the Michigan Arbovirus Surveillance Group. He tests for West Nile virus in birds and also keeps track of the cases of West Nile in horses that come into the Diagnostic Center.

"If it is suspected that these agents of concern are involved, the Diagnostic Center does the testing," she continued. "We have a grant from the Michigan Department of Community Health [MDCH] to serve as an auxiliary lab in the Centers for Disease Control network. MDCH coordinates this. We're also ready to act as a backup to the Department of Community Health. For example, if there were a suspected anthrax outbreak, it might require thousands of tests, which would overwhelm the MDCH lab. We have the resources to provide the people and the space to do the testing."

(There are also agents of concern that affect only humans, such as smallpox, as well as agents that are a threat only to plants, such as *Ralstonia solanacearum*, race 3, biovar 2, which causes wilt disease in potatoes, tomatoes, peppers, geraniums and eggplant. *[For more on emerging plant diseases, see p. 20 in the winter 2005 issue of* Futures.*]*

"The DCPAH is why Michigan is a leader in coordinating and integrating systems for animal and human health," Carole Bolin continued. "We are a national model. The creation of the Diagnostic Center facility, which consolidated services and lab space, has helped with this great integration. If something happens, we have the inherent capabilities, we have the knowledge and training, and we have the surge capacity to handle a large volume, which is key. Yes, we have labs that focus on nine specific agents. But more importantly, we also have the advantage of having people with the knowledge to question things that they recognize as different. And we have the infrastructure in place that allows them to act on it."

"The Diagnostic Center represents a long-term commitment to public and animal health and safety, and better prepares Michigan to handle emerging issues," said Dan Wyant, former director of the Michigan Department of Agriculture. "This facility is a shining example of what can be accomplished with strong state, university and industry partnerships and collaboration — a model that Michigan has come to be known for."

Tracking Chronic Wasting Disease and West Nile Virus

Chronic wasting disease (CWD) is a fatal neurological disease of farmed and wild deer and elk. The disease has been found in wild and captive mule deer, white-tailed deer and North American elk, and in captive black-tailed deer. CWD belongs to the family of diseases known as transmissible spongiform encephalopathies (TSEs). TSEs include a number of diseases affecting animals or humans, including bovine spongiform encephalopathy (BSE, mad cow disease) in cattle, scrapie in sheep and goats, and Creutzfeldt-Jacob disease (CJD) in humans. Though CWD has not been found in humans or livestock, its close relationship to BSE and CJD have put it on the USDA Animal and Plant Health Inspection Service (APHIS) hot topics list.

In deer and elk, CWD causes loss of body condition, behavioral changes, excessive salivation, increased drinking and urination, depression, and eventual death. CWD is always fatal. There is no known treatment, vaccine or live animal test for CWD. The disease has been found in wild deer and elk in Colorado, Wyoming, Nebraska, Kansas, Montana, Oklahoma, South Dakota, New Mexico, Wisconsin, New York, Alberta and Saskatchewan.

CWD has not been detected in Michigan to date. In conjunction with the state departments of Agriculture and Natural Resources, DCPAH scientists are working to help ensure that the disease remains out of Michigan and that, in the event it is discovered, Michigan has a coordinated, immediate and effective response plan to minimize its impacts.

"The test for CWD involves looking at the animal's lymph nodes," said Steve Bolin. "Last year we did 6,000 tests, most in about four weeks. The test is a time-consuming process and the most we can do in a day is 400 — and that's doing one right after another with no breaks. Since we started doing testing in 2002, we've tested about 20,000 deer and haven't found any positives. We encourage hunters to kill animals that look sick and submit them for testing and urge the public to call and report sick-looking deer or elk."

West Nile virus was first found in the United States in 1999. Carried by birds, the virus is transmitted by mosquitoes and can infect humans and horses. People can become ill with flu-like symptoms, but if West Nile virus enters the brain, it can cause life-threatening encephalitis (inflammation of the brain) or meningitis (inflammation of the lining of the brain and spinal cord). Most cases of this type of disease occur in elderly people and people with impaired immune systems. Currently, there are no vaccines and no drug treatments for West Nile virus in humans. A West Nile

vaccine is available for horses.

"West Nile virus is an arbovirus — arthropod-borne virus," explained Jon Patterson, MAES pathobiology and diagnostic investigation researcher in the Anatomic Pathology-Necropsy Section of the DCPAH, who has served on the Michigan Arbovirus Surveillance Group since 1992. "In 1992, we were focused primarily on eastern equine encephalitis. Then West Nile started to be of interest. From 1999 to 2003, people would send in whole birds and we would look for a specific West Nile virus protein in the birds' hearts and kidneys."

Today, the testing is much more efficient. If a bird is suspected to be infected, a swab is taken from its mouth and that is sent into the DCPAH.

"We can do these tests in 15 minutes and report results faster, so that communities can take action against mosquitoes," Patterson said. "We have good participation from local health departments because they can see the value. If we find the virus in birds, it allows us to forecast infection coming in people and horses. Besides the bird testing, I also keep track of the cases of West Nile in horses that come into the DCPAH."

The bird family Corvidae, which includes large birds such as blue jays, crows, ravens and magpies, is the most susceptible to West Nile virus infection. The virus also has been found in more than 250 other avian species, though in birds not in the Corvidae family it is not immediately fatal and some even recover. Corvids usually die within a day of the onset of symptoms. Researchers want to know how West Nile virus behaves in both corvid and non-corvid birds to better understand the mechanism of the disease.

"A virus usually interacts with its animal host in a very specific manner," Patterson said. "An avian or mammalian cell requires the right receptor to become infected. If we could identify that receptor, we might be able to develop a vaccine."

In addition to his West Nile work, Patterson also participates in chronic wasting disease and bovine TB surveillance. The DCPAH performs about 2,500 necropsies (postmortem exams of animals) per year.

"Besides helping and educating our clients, we're also educating students," Patterson said. "Every vet student at MSU is required to take a rotation through the DCPAH necropsy section. We examine all types of animals — from lions to guinea pigs and everything in between. This new facility is allowing us to make people more aware of the connection between animal health and community health."

Tracking Disease in Cattle

Preventing and controlling intestinal diseases in cattle is one area of MAES microbiology and molecular genetics scientist Roger Maes' research. Bovine viral diarrhea (BVD) is one of the diseases that Maes, who also serves as chief of the DCPAH Virology Section, is studying.

Affecting both dairy and beef cattle, BVD is complicated because it is caused by several strains of BVD virus. Though it does not cause disease in humans, BVD can be difficult to control and very expensive for cattle producers because it causes abortion, early embryonic death, pneumonia, fever, lameness and immunosuppression, as well as diarrhea.

MAES scientist Roger Maes's research focuses on preventing and controlling intestinal diseases in cattle, such as bovine viral diarrhea. He is working to educate producers on how to identify persistently infected cows to protect their herds.

Infected cattle shed billions of viral particles per day, so the disease is highly contagious. Most animals that contract the disease die after about 2 years; those that are infected in the womb can become persistently infected and are known as carrier animals. The disease costs producers millions of dollars per year in lost calves and reduced production.

"If a fetus is exposed to BVD between 50 and 100 days of gestation, the developing calf can't recognize it and fight it, so the calf is always infected with it," Maes explained. "These animals are permanent carriers of the disease."

According to Maes, the virus is in all the tissues of a persistently infected animal, so a test can be run even on a small piece of skin from the ear. If the test is positive for BVD, the calf is culled. The DCPAH tests about 30,000 samples per year. The new skin tests allow producers to collect samples from their cattle themselves. A number of BVD vaccines are available, but because the disease is caused by several strains of the virus, a vaccine may not protect against all types of the virus.

"We're working to educate producers about persistently infected cows and how to identify them," Maes said. "This will help protect herds from infection. BVD is a reportable disease, but it is not scrutinized as closely as bovine TB or chronic wasting disease."

::: Jamie DePolo

Battling

As part of the national Food and Waterborne Diseases Integrated Research Network, MAES scientists are working to understand and control high priority bacterial pathogens.

Bad Bacteria

It's been jokingly portrayed in television ads as the illness no one wants to name out loud, but diarrhea affects large numbers of people every year. In the United States, according to statistics from the National Institute of Allergy and Infectious Diseases (NIAID), diarrhea is the second most common infectious illness, accounting for one out of every six (16 percent) of all cases of infectious diseases. Bacterial and viral infections of the gastrointestinal tract can lead to diarrhea, and the agents that cause the illness are known as enteric pathogens. Many of these pathogens are transmitted through contaminated food or water. The World Health Organization says that diarrheal diseases account for 15 to 34 percent of all deaths in certain countries — conservative estimates place that death toll at 4 million to 6 million per year, with most of these occurring in children, the elderly and the immunocompromised.

"These pathogens are difficult to control, have no vaccines and have been identified as high priority by the National Institutes of Health [NIH]," said Thomas Whittam, MAES food science and human nutrition and microbiology and molecular genetics scientist, who heads the Microbial Evolution Laboratory and is a Hannah distinguished professor. "Our objective is to get over the hurdles and understand these tough-to-control pathogens."

Two years ago, the NIH awarded a team of researchers led by Whittam a $10.2 million research contract to explore the genetics of microorganisms that cause food- and waterborne infectious diseases. The award made MSU a part of the Food and Waterborne Diseases Integrated Research Network (FWD IRN), a network of research laboratories launched by NIAID, and established the Microbiology Research Unit (MRU) in the National Food Safety and Toxicology Center at MSU. The MRU at MSU is one of two such units nationwide. NIAID has established eight such research units nationwide in four research areas: microbiology, immunology, clinical and zoonoses. As principal investigator and project leader for MRU, Whittam also participates as a member of the FWD IRN executive committee.

"The FWD IRN links researchers together to carry out research and make breakthroughs on tough organisms," Whittam explained. "There is tremendous variability in these pathogens and a lack of animal models to study how the pathogens behave. MSU's strength is in bacterial pathogens — that's why we're a part of this."

The list of priority organisms was created from work done previously at the NIH. Ten years ago, the agency issued a call for proposals for research contracts on enteric pathogens. This led to the creation of the Enteric Pathogen Research Unit (EPRU), which developed the priority list. Before Whittam came to MSU in 2001, he was part of the EPRU.

In the MRU, Whittam and the other three project leaders — MAES large animal clinical sciences and microbiology and molecular genetics researcher Linda Mansfield, large animal clinical sciences researcher Mahdi Saeed, and microbiology and molecular genetics researcher Vince Young — are conducting research in the following areas:

- Advancing molecular techniques and databases to identify pathogenic strains of *E. coli* O157:H7, *Campylobacter* and *Salmonella*.
- Investigating factors involved in the emergence of new *Salmonella* strains.
- Developing animal models for understanding *Campylobacter* infection and pathogenesis.
- Developing microarray technology specifically targeted for rapid detection of diverse pathogens.

Tracking *E. coli*

Much of Whittam's research focuses on *E. coli*. He pioneered the application of population genetic methods to study variation in bacterial species. His work has revealed that the major disease-causing varieties of *E. coli* are organized into clonal groups and that some of these groups have evolved multi-

MAES scientist Thomas Whittam, who has appointments in the departments of Food Science and Human Nutrition and Microbiology and Molecular Genetics, heads the Microbiology Research Unit at MSU. Much of his research focuses on Shiga toxin-producing *E. coli*.

ple times. His investigations into *E. coli* O157:H7 demonstrated that the pathogen recently descended from a non-toxin-producing strain that causes infant diarrhea, and that the acquisition of a virulence plasmid and toxin genes were crucial steps in the pathogen's emergence.

In the MRU, Whittam has developed a DNA fingerprint database for Shiga toxin-producing *E. coli* (STEC). (The Shiga toxin is what causes disease.) The database is designed to facilitate research on Shiga toxin-producing *E. coli* by providing a standard reference collection of well-characterized strains and central online accessible databases.

"Our objective is to get over the hurdles and understand these tough-to-control pathogens."

"Our database is for research purposes," Whittam explained. "Other scientists can send us samples and we'll be able to characterize it for them."

Whittam is also working on developing animal models to study hemolytic uremic syndrome (HUS). HUS is one of the most common causes of sudden short-term kidney failure in children. Most cases occur because the digestive system has been infected with *E. coli* from contaminated meat, milk or water. The Shiga toxin in the bacterium leads to kidney failure. Not all children who ingest *E. coli* develop HUS, however. And HUS is not always fatal. After being seriously ill, some children do recover, though most of them are left with permanent kidney damage.

"There is a variation in susceptibility, and we're not sure why that is," Whittam explained. "Is there a substrain of *E. coli* that causes HUS? Or is that particular person more susceptible for some reason? There is no good animal model that mimics kidney failure or damage in humans for us to study these questions."

To start to tackle these questions, Whittam is working on a rabbit model. Some breeds of rabbits are susceptible to a similar disease.

"Many of the intestinal diseases transmitted by food and water have been tough to control, and vaccines have often failed," Whittam said. "If we can mimic the human diseases in laboratory animals, we can have a way to test new therapies, develop novel candidates for vaccines and learn to control infections in human populations."

To facilitate animal model research throughout the FWD IRN, the MSU MRU sponsored an animal model workshop in April for network scientists.

"We presented our models and the other scientists presented theirs," Whittam said. "We discussed what makes a good animal model for pathogenesis studies and identified priority animal models for inflammatory bowel disease as well as HUS.

"Animal model research is sometimes difficult to get funding for," he continued. "It almost has to work before you can say you want to study it.

MAES researcher Linda Mansfield is working to find an animal model for *Campylobacter*, the No. 1 food-borne bacterial pathogen in the United States. More than 2.5 million people contract campylobacteriosis each year, most from eating or handling raw or undercooked poultry.

But of course you have to do research before you know that."

Whittam also is collaborating with Dele Davies, chairperson of the MSU Department of Pediatrics and Human Development, to study Group B *Streptococcus* (GBS).

Though many people carry GBS and are not affected, it can be deadly in people with weakened immune systems. It is the most common cause of blood infections and meningitis in newborns when passed from mother to baby during delivery.

"The bacteria colonize in the vaginal tract and the woman has no symptoms," Whittam said. "Not much is known about the dynamics of the colonization process. We don't know what effects antibiotics have. And if the infection is treated and then comes back, is it the same strain of GBS or is it a different one?"

Whittam is applying the same techniques he used to create the STEC DNA database on GBS. By cataloguing well-characterized strains of the bacterium, researchers will be able to start to identify which strains are present and causing infection.

GBS also causes mastitis in cows, and GBS outbreaks have increased in the past 20 years.

"We're seeing more different types," Whittam said. "There have been outbreaks in nursing homes. The very old and the very young are at risk. The bacterium originated in cows, but the type in humans is distinct. This project has just started, and I'm very excited about the work."

Controlling *Campylobacter*

What's the No. 1 food-borne bacterial pathogen in the United States? If you said *E. coli* or *Salmonella*, you'd be wrong. It's *Campylobacter*, and, much like the other two pathogens, it causes bloody diarrhea, vomiting, cramps and fever. But because its associated disease, campylobacteriosis, happens as isolated, sporadic events, not as large outbreaks, most people haven't heard of it. The bacteria live in the gastrointestinal tract of animals and people. Chickens, pigs and dairy cows can all be infected with *Campylobacter* but have no symptoms. A few people who are infected with *Campylobacter* don't have symptoms, either. Most people, however, develop short-term bloody diarrhea. In immunocompromised people, *Campylobacter* can spread to the bloodstream and cause a life-threatening infection.

The bacterium is estimated to affect more than 2.5 million people each year — more than *E. coli* or *Salmonella.* People pick it up mostly by handling raw poultry or eating raw or undercooked poultry meat. Even one drop of juice from raw chicken meat can infect someone. *Campylobacter* can survive cold temperatures and can live in water, and it can colonize and spread in chicken processing chilling tanks. Some researchers speculate that

MSU's strength and experience in studying bacterial pathogens is why the university received a $10.2 million research contract to explore the genetics of microorganisms that cause food- and waterborne infectious diseases. The award made MSU part of the national Food and Waterborne Diseases Integrated Research Network.

freezing might kill it, but it has been found on frozen chicken. Thorough cooking will kill the bacterium. Like the other pathogens on the MRU priority list, *Campylobacter* has no vaccine for either animals or humans.

"You usually get campylobacteriosis about 24 hours after you've been exposed to the bacterium,"

"There are definitely lasting effects after Campylobacter... Our goal is to prevent the infection from happening in the first place."

said Linda Mansfield, MAES scientist and MRU project leader. "In most people, the symptoms aren't severe and they don't go to the doctor. Until recently, it was thought that there were no long-term effects from it. But recent research has linked it to Guillain-Barré syndrome and Reiter's syndrome, both of which are autoimmune disorders."

Guillain-Barré (pronounced Ghee-yan Bah-ray) syndrome (GBS), also called acute inflammatory demyelinating polyneuropathy and Landry's ascending paralysis, is an inflammatory disorder of the nerves outside the brain and spinal cord. It causes rapid weakness and often paralysis of the legs, arms, breathing muscles and face. GBS is the most common cause of rapidly acquired paralysis in the United States, affecting one to two people in every 100,000. The disorder came to public attention briefly when it struck a number of people who received the swine flu vaccine in 1976.

Reiter's syndrome is a type of arthritis that produces pain, swelling, redness and heat in the joints. It is one of a family of arthritic disorders called spondylarthropathies, affecting the spine and usually involving the joints of the spine and the joints in the pelvis that connect the tailbone (sacrum) and the large pelvic bone (illium). It can also affect many other parts of the body such as the arms and legs. People with Reiter's syndrome have inflammation of the joints, urinary tract and eyes, and sores on their skin and in their mouths.

"There are definitely lasting effects after people are infected with *Campylobacter*," Mansfield said. "Our goal is to prevent the infection from happening in the first place."

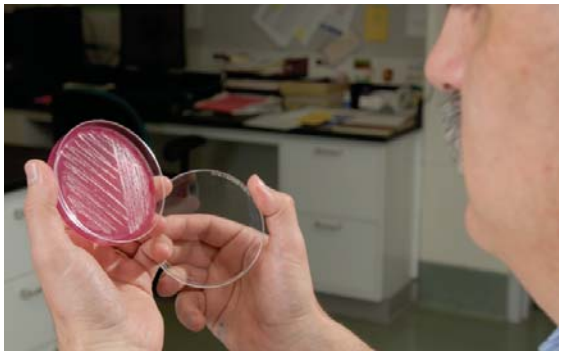
The consequences of *E. coli* and *Salmonella* infection have been well publicized, but *Campylobacter* has not received much media attention — even though Mansfield estimates that 80 to 90 percent of the chicken available in stores has *Campylobacter* on it. She's working to develop an animal model so campylobacteriosis can be studied to find the ways in which it can cause disease and to develop new treatments and preventive measures.

"The only models we have to study *Campylobacter* are swine and ferrets," Mansfield

Linda Mansfield and Vijay K. Rathinam, a veterinarian working on his doctorate in Mansfield's lab, are trying to develop a mouse model to study *Campylobacter*. Swine and ferrets are also affected by the bacterium, but mice are easier to work with. The goal is to develop a vaccine for chickens to protect people from *Campylobacter*.

said. "We're trying to develop a mouse model for it because they're easier and faster to work with."

Mansfield is working with several strains of mice with dysfunctional immune systems because they allow her to see any response the mice have immediately and also because campylobacteriosis is a more serious disease in the immunocompromised. She fed the bacterium to the rodents orally to see if the *Campylobacter* would



Thomas Whittam is also studying hemolytic uremic syndrome (HUS), which is most often caused by meat, milk or water contaminated by *E. coli*. But not everyone exposed to *E. coli* gets HUS, so Whittam wonders if a substrain of *E. coli* is responsible for HUS.

colonize and produce invasive disease. So far, most normal mice appear to be resistant, and many of the mice with defective immune systems are highly susceptible to this bacterium. These results show hope that these mouse models will ultimately help Mansfield's research.

"The normal mice may not have the right receptors for *Campylobacter* on their cells or they may be introduced to another bacterium at a young age that makes them immune," she said. "Another likely explanation is that a normal immune system is needed to fight off *Campylobacter*. We've only been working on this for about a year, and we're continuing to test different strains of mice for the best model of what happens in humans with disease. We have noticed that some of the mice have developed a condition that is similar to inflammatory bowel disease (IBD) in humans."

Mansfield said some researchers suspect that some people develop IBD because they were exposed at an early age to *Campylobacter* or other microorganisms.

"It's a provocative idea and underscores all the more our need for animal models," she said. "We need the models to study how the disease develops, to develop vaccines and to test new treatments. The ideal would be to develop a vaccine for animals, especially chickens, that would protect people so we wouldn't have to vaccinate people.

"Some strains of *Campylobacter* have developed resistance to antibiotics, which is another reason why an animal vaccine would be good," she continued. "Then, if the vaccine worked well, we wouldn't have to worry about antibiotic resistance from *Campylobacter* showing up in people."

Because chickens have a higher rate of *Campylobacter* infection than pigs or dairy cows, the U.S. Department of Agriculture is focusing on eliminating the bacterium in poultry. This is expected to dramatically reduce infections in humans.

"Then we'll focus on what's left," Mansfield said.

::: Jamie DePolo

How Do Diseases

Emerge?

Like a biological crime scene investigator, MAES researcher Ned Walker pieces together the path that diseases take from insects to man.

MAES SCIENTIST NED WALKER HAS degrees in zoology, microbiology and entomology, and he has appointments in the departments of Entomology and Microbiology and Molecular Genetics. But he's really more of a detective. Walker studies how emerging diseases, such as West Nile virus and Lyme disease, emerge. In other words, how do these diseases move through the environment and end up infecting people?

"I take a landscape ecology approach," Walker said. "Both West Nile virus and Lyme disease are related to the ways humans modify the environment. We change the landscape to meet our needs and at the same time create desirable habitats for insects and animals that are carriers or incubators of the diseases. Then the disease becomes established because the environment is favorable. It's analogous to an invasive species, such as the emerald ash borer."

By identifying locations that are good habitats for the disease carriers (known as "vectors" in scientific terms), Walker then has a list of places that the diseases are likely to move into and can help advise local public health and other officials there on possible prevention strategies.

"Geographical information systems [GIS] have totally revolutionized this area of biology," said Walker, who uses these geospatial computer modeling tools to map relationships between various types of information. "We now have the ability to layer data, which helps us make correlative relationships between data that we couldn't do before."

Instead of looking at databases full of numbers of where West Nile virus has been found in crows in Michigan, where human cases have been found, where desirable mosquito environments are found, mosquito populations for the state, and other data sets full of numbers, Walker can now generate one map with all the variables on top of one another, allowing him to identify potential outbreak areas much more easily.

"It helps us formulate areas of future study," Walker explained. "We can look at smaller and smaller pieces of the landscape, and as we do this the biodiversity goes down. The range of hosts narrows, and some are more susceptible than others."

Tracking West Nile Means Tracking Mosquitoes

West Nile virus (WNV) was discovered in the African country of Uganda in 1937. Carried by birds, the virus is transmitted by mosquitoes and can infect

humans and horses. It was first found in this country in 1999 in New York City. Since that time, WNV has been detected in 47 states. The disease was first detected in 10 Michigan counties in 2001 in dead crows. The first human cases of WNV were reported in 2002. The state created the WNV Working Group in 2000 and implemented a surveillance system to monitor dead birds and mosquito ponds and advise local officials about mosquito suppression tactics.

Mosquitoes are responsible for spreading West Nile virus from birds to people. After studying outbreaks of the disease in Detroit and Chicago, MAES scientist Ned Walker thinks storm water retention ponds in new developments may play a role as breeding grounds for mosquitoes.

People older than 50, those who are immunocompromised and people with underlying health conditions have the highest risk of developing severe disease. Most people infected with WNV have no symptoms; about 20 percent have mild, flu-like symptoms. Those who develop a severe form of the disease can experience headache, high fever, stiff neck, tremors, seizures or convulsions, paralysis, coma and possibly death.

Many scientists think that the WNV cycle involves two types of mosquitoes: one that bites only birds and one that bites both humans and birds. But Walker suspects that the mosquitoes that supposedly bite only birds also bite humans.

"The *Culex pipiens* mosquito likes to come inside at night, and it may be biting people," he explained. "West Nile virus outbreaks usually happen during hot, dry weather when the mosquito that bites people and birds isn't around."

Recent research that Walker did in Detroit and Chicago also offers clues to why WNV outbreaks seem to be clustered in specific areas.

In both cities, Walker and his research associates found that WNV outbreaks were clustered in middle-class suburbs such as Royal Oak and Ferndale. These areas are home to many new housing developments.

"I think the outbreaks are related to the way storm water is channeled in these neighborhoods, such as with street catch basins and storm water retention ponds," Walker said.

Walker suspects these man-made urban bodies of water are perfect breeding grounds for the mosquitoes that transmit WNV.

"We're now talking to scientists in the Department of Civil and Environmental Engineering about the design of these systems and the legal basis for their installation," he continued. "This is another example of how we've passed legislation designed to help the environment and it's had unexpected outcomes."

To fight WNV, Walker advocates eliminating mosquito environments and organized community mosquito suppression. He's also a fan of bed nets to protect people from indoor biting at night.

Tracking Lyme Disease Means Tracking Ticks

Lyme disease got its name from the town in Connecticut where it was discovered in children in 1975. It was first reported in Michigan in 1985 and has been confirmed in only a few counties in the state. Lyme disease is caused by the bacterium *Borrelia burgdorferi*, which is spread to animals and people by infected black-legged ticks. Most of the annual 24,000 cases are in 12 states: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island and Wisconsin.

Lyme disease in humans is usually not a life-threatening illness; most often it's similar to a mild case of the flu. But serious problems involving the heart, joints and nervous system may develop in some individuals. The most tell-tale sign of Lyme disease is the bull's-eye rash that develops around the tick-bite site. Arthritis is the most common long-term effect of Lyme disease.

Dogs, cats, cattle, horses and other domestic animals are also susceptible, and their symptoms may include fever and lameness. Wild animals such as deer, raccoon and mice have no symptoms and apparently suffer no ill effects from the disease.

There is no human vaccine, but there is one for dogs.

In Michigan, most cases of Lyme disease have been clustered around Menominee County because black-legged ticks are found there. However, Walker and other scientists began hearing reports that black-legged ticks were being found on the west side of the Lower Peninsula.

"The baby ticks were getting on birds and moving around the state," he explained. "White-footed mice and chipmunks are also carriers of the disease and are favorite hosts of baby ticks. The spread of the disease correlates to favorable tick habitat — they like deciduous forests and dry, sandy soils."

Walker has developed a computer model that highlights favorable tick habitats around the state and shows possible locations for disease outbreaks. The state is using the information to monitor the areas and provide more education, such as the poster Walker helped develop (available for download at http://www.michigan.gov/emergingdiseases/0,1607,7-186-25796-104336—,00.html).

"Grand Haven and Saugatuck are hot spots for tick habitat," Walker said. "We're starting to see more human and dog cases in these areas. We're hoping we can be proactive and educate people about ways to protect themselves against ticks and Lyme disease."

::: *Jamie DePolo*

STRESSED OUT AT THE CELLULAR LEVEL

Functional genomics — research that determines the functions of genes and the proteins they encode in determining traits, physiology or development of an organism — is growing rapidly. The MSU Center for Animal Functional Genomics (CAFG) was created in 2001 with funding from the MAES, the Michigan Animal Industry Initiative and the Office of the Vice President for Research and Graduate Studies. Using technology that allows them to track animals' responses to stress from diseases, giving birth, shipping and other environmental factors at the cellular and molecular levels, CAFG researchers are beginning to understand why stress may make animals sick or more susceptible to disease.

"We are no longer looking at just the physical outcome — did the animal get better — but also at the cellular and gene levels to see what impact was actually realized," said Paul Coussens, director of the CAFG.

"In functional genomics research, we don't force preconceived ideas on the system — we let the cells tells us what's going on," said Jeanne Burton, head of the Immunogenetics Laboratory.

Coussens and Burton, both MAES animal science researchers and members of the CAFG, study the genes that are expressed or suppressed when the immune systems of animals respond to an infection or other stresses. Because human and animal systems are similar, their work offers exciting possibilities for a new understanding of the human immune system as well as new types of treatments. ▼

Ensuring a Happy Birthing Day

Premature birth rates in the United States continue to rise rapidly, despite efforts to predict premature birth and control it. Using cows as a model to understand why early birth happens may offer prevention strategies for pregnant women and their doctors.

According to statistics from the March of Dimes, between 1981 and 2002 in the United States the rate of premature birth increased 29 percent. In Michigan between 1992 and 2002, the percentage of babies born prematurely increased more than 10 percent. In an average week in Michigan, 2,619 babies are born; 304 of those (11.6 percent) are premature. In 2002, the total hospital bill for all babies born in the country was $33.8 billion. Almost half of that — $15.5 billion — was for babies with any type of diagnosis of prematurity or low birthweight. The United States has a goal to reduce premature births to 7.6 percent, but rates keep going up instead of down.

At an American College of Obstetricians and Gynecologists meeting in May, Kenneth Ward, chairperson of obstetrics and gynecology at the University of Hawaii, said that premature birth is the No. 1 problem in obstetrics today.

"The process of giving birth can also be a problem in dairy cows, and dairy cows that have difficult, still or premature births often become sick with opportunistic infectious diseases such as mastitis [a painful infection of the mammary gland that also affects women]," Burton said. "Our goal is to keep cows healthy. We're studying stress and sex hormones that influence the timing of birth in cows and are starting to understand the role they play in the molecular and cellular processes that lead to normal and abnormal births and how they influence cows' ability to fight infections such as mastitis."

Caused by bacteria such as *Escherichia coli* and *Staphylococcus aureus*, mastitis causes the udder to become red, swollen and painful to the touch. The bacteria and the body's immune response also can damage milk-producing tissue, causing scar tissue and abscesses to form and ultimately reducing milk production. Mastitis sometimes becomes so severe around the time of birth that cows even die from it because bacterial toxins and inflammatory molecules secreted by the immune system spread through the blood and cause multiple organ failure.

Mastitis is one of the most costly infectious diseases affecting the U.S. dairy industry, resulting in losses of more than $2 billion annually. The highest rates of mastitis occur in the first few weeks following the birth of the calf.

Burton and her research team — which includes scientists from the Republic of Ireland's version of the experiment station, Teagasc — are examining interactions between a key birthing hormone, glucocorticoid, produced by the adrenal glands, and neutrophils, a type of white blood cell that normally protects animals from opportunistic infectious diseases such as mastitis. Humans also have glucocorticoids and neutrophils.

Glucocorticoids are secreted when the body is under stress. They get their name from their effect of raising blood sugar (glucose) levels needed for the acute "fight-or-flight" response. Cortisol (also called hydrocortisone) is the most abundant glucocorticoid in cows and humans. Cortisol and the other glucocorticoids also have a beneficial anti-inflammatory effect on the body, but this effect then reduces the body's acute immune response to infection, including neutrophil responses to bacteria that cause mastitis.

Neutrophils are normally short-lived and fast acting. Stored briefly in bone marrow and blood, they are the first line of immune defense, and thousands can accumulate in minutes when the body detects an infection. Neutrophils are filled with protein enzymes and oxygen free radicals to fight infection and are responsible for the swelling and pain around the infection site. Neutrophils spill out the enzymes and free radicals that fight the infection but can also hurt surrounding healthy tissue if not tightly regulated. After spilling their killing molecules to fight infection, neutrophils must die quickly to prevent further inflammatory tissue damage. The average life span of neutrophils in healthy animals is about 12 hours.

"We know that higher levels of glucocorticoids in the cow's blood are associated with an increased susceptibility to infectious disease, including mastitis," Burton said. "Neutrophils have glucocorticoid receptors that rapidly change the expression of genes in the cells, so they're dramatically affected by the higher levels of the hormones during stress. We're looking at circulating neutrophils to see what is happening to them when blood glucocorticoids are high during birth and other stressful times, such as truck transportation."

Giving birth is a stressful situation for a cow's body, so glucocorticoid levels go up. In addition, birth is stressful on the soon-to-arrive calf. When it's time for the calf to be born, it appears to take over the mother's neutrophil system by secreting large amounts of glucocorticoids that go into her bloodstream. Using functional genomics technology, Burton's research team has found that glucocorticoids change neutrophils into a different type of cell than they are when there is no stress.

"The glucocorticoids appear to be reprogramming the neutrophils so they have a different function," Burton explained. "Instead of expressing genes that help them fight bacterial infection, the neutrophils now use other gene systems that enable them to remodel the structural proteins of tissue, such as collagen. If you think about this, it's very important at birth for tissues such as the cervix, placenta and fetal membrane to change, to soften and rupture so the calf can pass through. As it turns out, much of this critical tissue remodeling is done by neutrophils that have diverted their efforts to the reproductive tract and placenta under the influence of fetal and maternal glucocorticoids."

In the past, it was thought that neutrophils just became dys-

MAES researcher Jeanne Burton *(center)* and Kelly Buckham *(left)* and Patty Weber *(right)* examine an autoradiograph of genes that are differentially expressed in bovine neutrophils as cows progress through parturition. Buckham is a Ph.D. candidate and Walsh fellow visiting Burton's lab from Ireland. Weber is the Burton lab coordinator and head technician. In the back, at the far left, Sally Madsen-Bouterse, another Ph.D. candidate in Burton's lab, sets up a quantitative real time RT-PCR assay to examine neutrophil gene expression during glucocorticoid treatment of the cells.

functional during birth. This was the explanation for why cows had more infections at this time — the neutrophils were dysfunctional. While there isn't a name for this second role of neutrophils, they're definitely not dysfunctional. They're just "altered functional," according to Burton — transformed by the glucocorticoids and maybe too busy helping with the birth process to fight infection in the mother.

"Is it possible that successful birth of a healthy calf has a higher priority in an evolutionary sense than temporary infection-fighting ability in the birthing cow?" Burton asked rhetorically. "I ask myself, 'Why is nature doing this?' I think biologically we're still cave people. Stress hormones bring out the 'fight-or-flight' response in us. In our chronically stressed lives today, that's not very helpful. But if we think back to how things were, it makes some sense. The stress response that leads to glucocorticoid production usually meant a fight or flight, after which body tissues might have been seriously damaged. It could possibly have been more important to animal survival that neutrophils be reprogrammed for urgent tissue remodeling and repair than to be poised to fight a possible infection.

"Shortly after the tissues are repaired, new neutrophils are normally produced in bone marrow, and these cells can resume the business of fighting infections," Burton continued. "Amazingly, neutrophil responses are very similar during fight-or-flight reactions to stress and the birth process."

The transformed neutrophils can't flip back to their infection-fighting former role. Once they've been changed, they stay changed until they die. The transformation also allows neutrophils to live slightly longer than normal, possibly because of the time it takes to do tissue remodeling. Burton has found that these transformed neutrophils can live 36 to 48 hours, about three to four times the life span of an untransformed, infection-fighting neutrophil, and long enough to help a successful birth happen.

She's also studying how the whole neutrophil system returns to fighting infection.

"After a normal birth, it takes about a day and half for the glucocorticoid levels to drop back to normal," Burton explained. "However, it appears to take about two to three weeks for the neutrophil system in the bone marrow to revert back to creating bacteria-fighting neutrophils. And that's usually when mastitis hits the hardest. Now that we have a better understanding about what makes birth happen at the cellular and molecular levels, we're thinking about how we might facilitate the timing of the birth process and a quicker return to normal infection-fighting capabilities of neutrophils."

But in a stressful or premature birth situation, glucocorticoid levels may remain high, which may delay the neutrophil system's reversion to disease fighting. This might explain why cows that have difficult births or abort the calves have more infections.

Because of the parallels in neutrophil responses to stress between cows and humans, Burton has begun collaborating with human medicine scientists studying premature birth in women.

With premature birth rates rising, scientists are looking for a cause. Burton's work with cows suggests that stress and stress glucocorticoids may play a role. In a normal birth situation, the baby initiates the birth process by secreting glucocorticoids. In a stressed or premature situation, the mother's body may be initiating the birth process. A single mother-to-be who works, goes to school and has little or no support network may be under tremendous stress, which could cause her glucocorticoid levels to be chronically higher than normal. Might this contribute to premature birth? Undetected infections also can bring on potent stress responses. Might undetected infections also contribute to premature birth?

"We're working to meld the bovine information with the human information," she said. "Ultimately, we'd like to know what causes premature birth and if it can be controlled. In humans, the process is more complex. There may be undetected stress from subclinical infection at a distant site or damage to blood vessels in the uterus or placenta. Nutrition also may play a role, as may drug and tobacco use. The causes may not always be hormonal. But it's very exciting. It could be that we can help prevent premature birth in women by understanding the effects of stress hormones on neutrophils of birthing cows."

Fingerprinting Disease

A genetic "fingerprint" of bovine immune system response to Johne's disease is helping researchers understand how the disease progresses.

The bacterium *Mycobacterium avium* subspecies paratuberculosis (MAP), known as paratuberculosis, causes Johne's (pronounced "YO-nees") disease in cattle. A chronic intestinal infection, Johne's causes diarrhea, weight loss, decreased milk production and death. The disease incubates in infected cows for 2 to 7 years, and even though they may show no symptoms, the animals can begin shedding large numbers of bacteria — up to several thousand organisms in 1 gram of feces. Cattle that are heavily infected will also shed the bacterium in milk. Currently, there are no vaccines or antibiotics that will cure Johne's disease.

There is some evidence, though it is controversial, that the MAP bacterium is infectious in people. Some scientists have connected MAP to Crohn's disease because the organism has been found in a significant portion of Crohn's disease patients.

"Johne's is a significant, global problem in the dairy industry," said Paul Coussens. "Producers lose more than $1 billion per year in the United States because of it. There is also an increasing concern for human health because of the growing connection of paratuberculosis with Crohn's disease. Paratuberculosis has been detected in the intestinal tissue of about 70 to 90 percent of Crohn's disease patients."

Paratuberculosis is a very potent pathogen, and the immune systems of cattle react strongly to it. Macrophages, large white blood cells that devour invading pathogens, are some of the first to respond. But researchers have found that the paratuberculosis bacterium actually lives inside macrophages in the bovine gut.

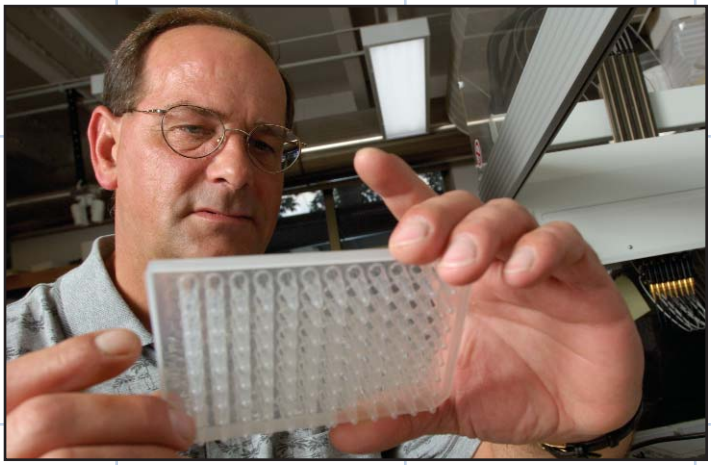
"Macrophages are supposed to engulf and kill these invading bacteria," Coussens explained. "But for some reason, the invaders have taken over the cell that is supposed to kill them. We want to know how paratuberculosis survives in the macrophage."

In addition to surrounding and killing pathogens, macrophages also stimulate other immune cells, such as T cells, by presenting them small pieces of the invading pathogen. T cells are lymphocytes, smaller white blood cells that attack and destroy body cells that have become infected or become cancerous. T cells also secrete cytokines, proteins that act as messengers between cells. There are three main types of T cells: killer T cells (cytotoxic T cells), helper T cells and suppressor T cells.

When a cow is first exposed to paratuberculosis, its immune system responds by creating more killer T cells to fight the infection. However, after a cow has been infected with paratuberculosis for a long period of time, this killer T cell response stops. The immune systems shifts to trying to create antibodies to fight the infection, but this is ineffective.

"If a cow has been infected with paratuberculosis, it can be asymptomatic and live with the disease as long as the T cells are fighting it," Coussens explained. "But when the killer T cell response stops, then the animal begins to develop Johne's disease. That's the second big question: why does the T cell response stop? We know a lot about the immune system, but there is a lot more we don't know."

So Coussens decided to look at what was happening at the cellular level — which genes were being expressed at which times and what happened as a result of this expression.



By identifying the genetic signature of cattle infected with paratuberculosis, MAES scientist Paul Coussens wants to create a new diagnostic tool for that disease and possibly other illnesses. His work is at the forefront of what's known about the immune system and may have implications for humans.

Coussens and a graduate student in his lab, Abe Aho, found that in cows with paratuberculosis, two proteins — interleukin-1 alpha (IL-1α) and tumor necrosis factor receptor-associated protein 1 (TRAF1) — were present in much higher levels than in uninfected cows.

"You wouldn't normally find these genes expressed at such high levels in cells," Coussens said. "But they were highly expressed in the gut tissues in the cows that had been exposed to paratuberculosis."

Both IL-1α and TRAF1 are messenger proteins of the immune system and are involved in fighting infection. IL-1α is expressed by macrophages to fight infection. TRAF1 helps to carry signals from the environment outside the cell to the nucleus, so TRAF1 ultimately determines how the cell responds. Other research suggested that high levels of IL-1α can cause the symptoms of Johne's disease: weight loss, fever and chronic diarrhea.

"When we looked at the cells in the intestines of infected cows, we saw only macrophages — not neutrophils or T cells," Coussens said. "Interleukin-8, another messenger protein, is also highly upregulated in infected cows, so we should see T cells and neutrophils. But they're not there. The T cell response has just stopped."

While examining macrophages in culture, Coussens and visiting scholar Shi-Kai Chiang made an interesting discovery. IL-1α enhances TRAF1 expression, and high levels of TRAF1 disrupt

normal communications between macrophages and T cells. High levels of TRAF1 also kept the macrophages alive longer.

"So these macrophages become the perfect place for paratuberculosis to live without being detected," Coussens explained. "IL-1α pulls other macrophages into the area by telling them to come and fight the infection. As new macrophages come in to fight, they're exposed to high levels of IL-1α, which enhances TRAF1 expression in incoming macrophages. Now the new macrophages can't communicate with T cells to tell them something is wrong and they don't die like they're supposed to — it's a perfect hiding place."

This process happens over time, about 2 to 5 years. In tracking the immune system response, Coussens started to see high levels of another cytokine, interleukin-10 (IL-10), as the T cell response was dropping off. He suspected this might be responsible for the diminished T cell response.

"Interleukin-10 represses the immune system, it doesn't kill anything," Coussens explained. "IL-10 can shut off the activation of T cells. Its job is to prevent long-term chronic inflammation. It's very hard on the body to be fighting an infection for years at time. So by the time an animal with paratuberculosis presents symptoms of Johne's disease, there are virtually no T cells fighting the infection."

Coussens' work is at the forefront of what's known about the immune system and may have implications for human chronic disease. People infected with tuberculosis who develop the disease also have little or no T cell response to the infection, and understanding more about bovine immune systems will offer clues to the human immune system.

"We think that because the infection is so long-lasting, the body decides that this is the way it's supposed to be and that the immune system is over-reacting," Coussens said. "It's basically saying, 'This bacteria must be a normal part of the microflora' — the non-pathogenic organisms that normally live in the intestine without causing any disease."

So cows that are infected with paratuberculosis, whether or not they are showing clinical symptoms of Johne's disease, have immune systems that have been changed so they express higher levels of different genes than uninfected cows. By determining this genetic fingerprint or signature of infected cows, Coussens is working to create a new diagnostic tool for paratuberculosis and possibly other diseases.

"In collaboration with scientists from University College Dublin, we're looking at other diseases, such as bovine tuberculosis, brucellosis, trypanosomes [African sleeping sickness], to determine if there are gene expression signatures of each," Coussens said. "We want to know if any of the signatures are similar — does the immune system respond in the same way to any of these diseases? Some of the general gene expression patterns are indeed the same, but we also see differences between each type of infection. In collaboration with other scientists from the U.S. Department of Agriculture National Animal Disease Center in Ames, Iowa, and at other land-grant universities in the United States, we have expanded this program to include several virus infections in cattle. We now believe we can develop general signatures for each type of disease — so a bacterial disease has one type of genetic signature, a viral disease has another and a parasitic disease has another. Then if an animal presents us with an unknown disease, we can figure out what type of general immune response is happening."

Ultimately, Coussens sees the genetic signatures improving the diagnostic process. Veterinarians would not have to examine an animal for each possible infection. A simple, genomic-based blood test could quickly determine whether the animal was infected, the class of disease pathogen that was causing the infection and possibly even the specific organism responsible. This work has obvious implications in biosecurity issues — the ability to determine rapidly the type of infectious agent present would help to direct quick and appropriate responses from local, state and federal agencies.

"We could test for many different pathogens at one time," Coussens said. "It may also help us learn more about disease resistance and genetics — are different genes expressed in resistant animals?"

::: Jamie DePolo

MSU Hosts Second International Symposium on Animal Functional Genomics

In 2003, the MSU Center for Animal Functional Genomics (CAFG) hosted the first International Symposium on Animal Functional Genomics. Because of the success of the first, the CAFG is planning a second symposium, scheduled for May 2006 at the Henry Center on the MSU campus.

"The purpose of the second international symposium is to bring together international researchers, industry representatives and administrators who seek updated information on the design, analysis, interpretation, integration and application of high throughput gene expression profiling for the study of cells and organ systems that underlie economically relevant phenotypes in agricultural animals. The focal areas will include statistical genomics, bioinformatics and data mining, animal health, reproduction, and growth and metabolism," said MAES researcher Jeanne Burton, who, along with MAES scientist Guilherme Rosa, is chairing the event. "We're limiting it to 130 people so we can have some really good discussion."

Burton said she and Rosa expect several key outcomes from the second symposium, including:

- The exchange of updated information about animal functional genomics research, including use of data from animal models and cell lines to address issues of production animal agriculture.
- The sharing of visions for future impacts and applications of functional genomics research on animal production systems throughout the world.
- The discussion of strategies on how to implement new technologies, methodologies and gene expression information to bridge gaps between discovery and application.

The second International Symposium on Animal Functional Genomics, May 16-19, 2006, is designed around 11 keynote lectures to be delivered by internationally renowned functional genomics scientists. Selected abstracts and posters also will be presented by symposium delegates. A formal call for abstracts and details of symposium presentations, registration and hotel booking will be announced soon on the symposium Web site at www.isafg.msu.edu.

::: Jamie DePolo

MICHIGAN STATE UNIVERSITY

SESQUICENTENNIAL

A Legacy of Combating Disease in People and Animals

Michigan State University is celebrating its 150th anniversary in 2005. MSU is the pioneer land-grant institution, and its history is closely tied to the history of agriculture, natural resources and rural communities in the state. The Michigan Agricultural Experiment Station was founded on Feb. 26, 1888 — 33 years after MSU was founded — and the MAES has played a significant role in shaping MSU's research legacy and its priorities for the future. Each issue of Futures *in 2005 will feature a special sesquicentennial article highlighting the intersection of MAES and MSU history.*

The MAES has supported research in veterinary science since it was created in 1888. Keeping livestock healthy and free from disease has been the focus of much research, and many times this work has benefited human health. I. Forest Huddleson, who enrolled at the Michigan Agricultural College as a graduate bacteriology student in 1915, was an early pioneer in brucellosis research, and his work made major strides in controlling the disease.

Through the 1940s, brucellosis, also known as Bang's disease, was a major problem for the livestock industry. It affects cattle, sheep, goats, pigs, elk and sometimes dogs. The disease is difficult to detect because infected animals have no symptoms. Producers suspect the disease only after cows spontaneously abort or give birth to weak calves.

After receiving his master's degree, Huddleson was named a faculty member in 1916. He went on to receive his D.V.M. and Ph.D. degrees from MSU in 1925 and 1937, respectively. His research focused on brucellosis as an agent of Bang's disease, which at the time was not thought to affect humans. Huddleson's research demonstrated that the bacterium, *Brucella abortus,* could be transmitted to people through unpasteurized milk and caused a disease known as undulant fever, which is accompanied by long-term fatigue and flu-like symptoms. He predicted that it would become a major human disease and was quickly proven correct.

Continuing to study brucellosis, Huddleson developed a test to detect brucellosis bacteria in animals and a treatment for the disease, called brucellin. Both of these products were manufactured at Michigan State and then distributed worldwide to help people and animals. Huddleson also created a treatment procedure for people with advanced disease, which can be fatal. He was internationally known for his brucellosis research and traveled around the world helping countries treat and control the disease. For his work, he was presented numerous awards, including an honorary doctorate from the University of LaPlata in Argentina, an honorary doctorate from the University of Kentucky, the Borden Award from the American Dairy Association, the Kimble Award from the American Public Health Association, and the Distinguished Professor and Distinguished Alumnus awards from Michigan State University.

"Despite his accomplishments and renown, Dr. Huddleson was essentially a very modest, almost retiring, man," says Norman McCullough, a brucellosis researcher at the National Institutes of Health. "Dedicated to research, his personal involvement, 'working with his own hands' rather than directing others, continued until he retired. The glamour never faded. Near the end of his career he remarked that each new experiment was so intensely interesting that he hurried to his laboratory each morning anticipating the possibility of a great breakthrough unfolding from the new data to be analyzed that day. He was a researcher who followed his problem wherever it took him, exploiting new methodology and instrumentation as they became available. Retrospectively, in his research methods and scientific outlook he was often ahead of his time."

His endless enthusiasm for research and learning lives on through his many students, including Alfred H. Hershey, who received the Nobel Prize in Physiology and Medicine in 1969.

::: Jamie DePolo

Research *in the news*

Grand Ledge Farmer Pledges Multimillion Dollar Gift to Fund Agriculture and Natural Resources Work

David Morris, a farmer in Grand Ledge, Mich., has pledged an estate gift valued at approximately $7.5 million to endow research, teaching and outreach activities in the Michigan Agricultural Experiment Station (MAES), MSU College of Agriculture and Natural Resources (CANR) and MSU Extension (MSUE).

Morris' gift, announced during Ag Expo at MSU, will fund four agriculture-related endowments:

- The Betty and David Morris Endowment in Livestock Research will provide the MAES with discretionary funds for livestock research, including teaching and research fellowships.
- The Betty and David Morris Endowment for Support of Programs in Communities, Agriculture and Natural Resources will provide support through the MAES and MSUE for programs affecting communities, agriculture and natural resources.
- The Betty and David Morris Discretionary Fund in the CANR will provide sustained support for the college, allowing the dean to address critical issues and needs that arise.
- The Betty and David Morris Chair in State and Local Government Finance and Policy will endow an existing position within the Department of Agricultural Economics that works with state and local government. This faculty position engages in research, education and outreach focused on policy analysis that helps governmental units attract people and businesses to communities, improve the efficiency and effectiveness of government services, and advance Michigan's economic competitiveness.

"It is tremendously gratifying that David Morris has chosen to include Michigan State University in his estate plans," said MSU President Lou Anna K. Simon. "His foresight and generosity will provide support to research, outreach and academic programs that meet emerging needs of Michigan citizens."

David Morris and his late wife, Betty, operated a cash crop and livestock operation focused on feeder cattle, hogs, corn and soybeans. The Morris farm, which became a centennial farm in 2000, grew from 245 acres to 1,689 acres under their management.

"Dave Morris' generous planned gift will allow us to leverage other sources of funding to address critical issues," said Jeffrey Armstrong, CANR dean. "Mr. Morris is a strong believer in using the fruits of his labor for the betterment of others, and we are honored to have been chosen to help ensure that his and Betty's legacy will enhance Michigan's communities, agriculture and natural resources for generations to come."

MAES Plant Biologist Finds Corn Fungus is Nature's Master Blaster

A common corn fungus is by far nature's most powerful known cannoneer, blasting its spores out with a force that is 870,000 times the force of gravity, according to research done by a team of scientists that included an MAES researcher. Corn growers don't have to worry about being pegged by the fungal supergun, however — the tiny spore travels only 5 millimeters (2/10 inch) before falling to the ground.

Nevertheless, the fungus *Gibberella zeae* outguns the previous record holder, the fungus *Pilobolus*, by almost a hundredfold. It also outperforms a rifle, which launches its bullet with less than 1/10 that acceleration.

The researchers — MAES plant biologist Frances Trail and Iffa Gaffoor, a graduate student in her lab, and Steven Vogel of Duke University — published their findings in the June 2005 issue of *Fungal Genetics and Biology*. The study was supported by the U.S. Department of Agriculture and the Michigan Agricultural Experiment Station.

According to the scientists, the "bioballistics" of the fungus offers a dramatic lesson in the physics of scaling. At the infinitesimal scale of the fungus' spore, atmospheric drag plays an enormous role — hence the need for an extremely high ejection speed to achieve even the most modest spore dispersal.

The purpose of the study that revealed the fungus's extraordinary launch capabilities was to better understand the biological mechanism behind the fungal supergun. Basically, the gun is powered by the buildup of pressure inside the spore-containing fungal fruiting body, the perithecium. Such pressure is due to water flowing across a membrane into the perithecium as it tries to equalize the concentration of a salt solution inside the chamber. In the case of the fungus, the question was whether the sugar mannitol or potassium ions were responsible for the osmotic pressure that generated the propulsive force.

In their experiments, Trail and Gaffoor created a fungal "shooting gallery" consisting of a small glass chamber in which they mounted a block of gel-like agar containing mature perithecia. They arranged the agar so that the perithecia would launch their spores onto a removable glass cover slip. The researchers measured the length of the fungal blasts and calculated the mass of the spore. That mass turned out to be very low for a fungal spore, explaining why the fungus could achieve such extraordinary launch speeds.

Vogel fed data from the laboratory experiments and spore mass calculations into a computer program he had developed to determine the ballistics of such projectiles. One result was the record acceleration of 870,000 times the force of gravity for the spores and a launch speed of nearly 80 miles an hour.

The analysis of the fungal shooting ability led the biologists to determine that the osmotic pressure from potassium, not mannitol, likely generated the force necessary for the powerful blast.

An obvious question is why the fungus even bothers. Given the short range of its spores, why bother accelerating to 80 miles per hour to go a mere 5 millimeters? Because there is almost no air movement at the surface where the spore grows, according to the scientists. So the real object of the launch is to get the spore even a little way from the parent so that it can get into air currents that will allow the spore to move even farther away.

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