DNA Vaccines
Enhancing animal production, profitability, and well-being by improving animal health.

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Over the years, the Veterinary Medical Experiment Station has supported a wide range of research projects touching almost every critical aspect of human life, from the food we eat and the clothes we wear to our physical, emotional, and economic health and the quality of our environment. This tradition continues as is evident in the profiles of 1997-98 research described in this report. The past year’s projects encompass efforts aimed at improving productivity and health of poultry and livestock, bettering life’s quality for companion animals, and tackling tough interdisciplinary problems in biotechnology and disease surveillance.

Prior to their initiation, each of these projects was evaluated for scientific merit, importance to animal health, consideration for experimental animal welfare, and role in meeting the research objectives of the Veterinary Medical Experiment Station.

These objectives are the following:

To improve the health and productivity of domestic livestock, poultry, fish, and other income-producing animals and wildlife through research.

To assist in preventing disease epidemics by providing laboratory resources and highly skilled scientific personnel.

To assist in protecting human health through the control of animal diseases transmissible to man.

To improve the health of companion animals which serve to enrich the lives of humankind.

To train new scientists in animal health research in order to provide continuity and growth in this area of veterinary medicine.
All programs and activities of the Veterinary Medical Experiment Station are conducted without regard to race, color, national origin, age, sex, or handicap.
Report Of The Director

It is with pleasure that I present the 22nd (and for myself, the first as Director) Annual Report of the Veterinary Medical Experiment Station. It has been an exciting year, highlighted by the completion of the new research building of the Poultry Diagnostic and Research Center, which was officially opened on June 12, 1998. This excellent facility provides state-of-the-art research laboratories dedicated to the enhancement of poultry health and production. Our second new building, the Animal Health Research Center, is nearly complete as well and should be online in the fall of 1998. Together, these two facilities will ensure that the VMES attracts and retains top-notch animal researchers engaged in the science and technology that sustains Georgia’s animal and human populations.

Many other exciting developments are underway. Within the next few months, we hope to initiate a national and international search for an Eminent Scholar in Animal Vaccine Development, a position created by the Georgia Research Alliance and the Georgia General Assembly. This scholar’s positive impact on our VMES program will be immense and will greatly benefit the state’s animal industries.

In efforts to raise the critical mass of the station’s personnel and resources, VMES researchers are engaged in university-wide collaborative programs such as the Interdisciplinary Environmental Toxicology Program, and federally funded research training grants. In the near future, several of our researchers will be involved in new initiatives in genomics and computational biology, emerging and reemerging animal diseases, and food safety. A combined DVM/PhD degree program is in the planning stages, and when initiated, will meet a critical need for new clinical and basic scientists in veterinary medicine. Through efforts such as these, the VMES ensures its leadership role in animal health research.

Our mission remains important to the people of Georgia. The Veterinary Medical Experiment Station plays a major role in research on animal health problems of present and potential concern to our state’s livestock and poultry industries. Our food animal industries are valued at more than $3.2 billion. In addition, sales of livestock, poultry, and their products account for more than half of Georgia’s annual farm income. A commitment at the state level to conduct research on animal health is a smart investment, particularly in view of the limited availability of federal funding specifically targeted for animal health research.

Station researchers, using a science-based approach, addressed many challenging animal health problems this year in areas of infectious diseases, disease diagnosis, and disease treatment and prevention. The 22nd Annual Report provides a brief description of many of the VMES supported projects during the fiscal year of 1997-98. Additional information on these projects can be obtained by contacting the VMES office or the investigators themselves. A list of publications resulting from these studies is included in this report for your perusal.

Finally, beginning with this issue and in each subsequent VMES Annual Report, we plan to focus on a specific new research area, technology, or breakthrough that is sure to have a critical impact on animal health. This will be done through a cover illustration and an accompanying article. This year our topic of interest is DNA vaccination (page 5).

I hope that you find this year’s report of interest and welcome your comments regarding our present and future research efforts.

Harry W. Dickerson, BVSc, PhD
DNA Vaccines

Ever since Dr. Edward Jenner’s famous experiment in 1796, which introduced vaccination as a preventive measure against small pox, doctors have been using vaccination to prevent many diseases in humans and animals. Conventional vaccines consist of the disease agent that has been killed or modified so it no longer can cause disease. When the vaccine is administered, the body recognizes it as a foreign substance and an immune response, which protects the individual from that specific disease, is induced. If the disease agent is encountered again, antibodies and lymphocytes (immune cells) attack and kill it.

After an immune response is induced as a result of a natural infection or vaccination, the body typically makes antibodies and lymphocytes against proteins that make up the disease agent. In general, the flow of molecules at the cellular level is DNA to RNA to protein. The genetic information contained in the DNA is transferred to RNA, which is used by the cell machinery to synthesize proteins, which are the building blocks of the cell or disease agent. So, each protein that makes up the disease agent has a corresponding gene (segment of DNA). Using molecular biology, we can extract DNA from a disease agent and isolate the gene that contains the information for the protein that induces a protective immune response.

DNA vaccines are genes from a disease agent that are injected directly into the body. The cells of the body take up the DNA, and proteins are synthesized through the natural flow of molecules in the cell (DNA to RNA to proteins). Because those proteins resemble the proteins that make up the disease agent, they are recognized as foreign by the body, and an immune response is induced. This is the basis behind DNA vaccination.

A tremendous amount of research has been conducted on DNA vaccines, and the future of DNA immunization appears very bright. DNA vaccines have been shown to be safe and extremely effective for a wide variety of disease agents.

DNA (B) is extracted from the disease agent (A) and made into a DNA vaccine (C). The DNA vaccine is injected intramuscularly (D) into a chicken, which produces sensitized macrophages (E). These sensitized macrophages communicate their information to immune cells (F), which produce antibodies (G). The antibodies, in conjunction with immune cells, destroy the disease agent.
Poultry

Georgia’s poultry industry dominated the state’s animal agricultural dollars with more than $2.5 billion in annual revenue in 1996. The state’s poultry industry is continuing to expand as broiler production in Georgia increased from 20.6 million per week in 1995 to 22.2 million per week in 1996. The urbanization of northern Georgia is causing the broiler expansion to occur primarily in the state’s southern section. Because of the intensive management system, poultry producers emphasize disease prevention. VMES scientists have responded to industry demands by developing vaccines to prevent infectious diseases. They are also helping to improve poultry health by developing inexpensive, rapid, and accurate methods for disease diagnosis. Although the primary poultry health concerns are respiratory diseases, recent efforts have been initiated to control type J avian leukosis virus, a major cause of the tumor, myeloblastosis. Researchers are also focusing on the reduction of potential human pathogens on poultry products nationwide.

Increasing Resistance to Marek’s Disease via Immune Modulation

The overall objectives of this project are to establish the importance of natural killer (NK) cell-like activity in the innate ability of chickens to resist Marek’s disease virus (MDV) infection and to then determine whether modulation of this natural immunity (NK cell activity) could be used as part of Marek’s disease prevention programs.

We have assessed NK-like activity of chickens having haplotypes reported to confer either resistance, N-2a chickens (B13), or sensitivity, P-2a chickens (B21), to MDV. The results from cytotoxicity assays indicate N-2a chickens have greater killing capabilities by NK cells than the P-2a chickens. The N-2a chickens displayed greater killing at one, two, and three weeks of age, with the increase becoming significant by the third week. We have also compared NK activities in two commercial lines of broilers: Arbor Acres line and Perdue line. Between these two broiler lines we found the Perdue birds to have significantly higher natural cytotoxic ability. Studies were performed to assess the efficacy of possible immune modulators on susceptibility to Marek’s disease. NK cell activity was assayed at day 7 postvirus challenge (day 14 postmodulation). Surviving birds were euthanized, and necropsy with histopathology was performed at six weeks for determination of disease susceptibility, organ involvement, and severity of disease. In the broiler line (Arbor Acres), the immunomodulator significantly increased the NK-like cytotoxic activity. Comparison of immunomodulated birds with birds that received only virus suggests that the immunomodulator may be a protective factor against Marek’s disease in this broiler line.

Diagnostics for Avian Enteric Coronavirus Infections in Commercial Poultry

Virus neutralizing polyclonal antibodies were developed in rabbits using multiple immunizations of adjuvant plus purified cell culture-origin sucrose gradient purified avian enteric coronavirus (AEC). The antibodies were used to develop 1) an indirect immunofluorescent antibody detection system (IFA) for either AEC or anti-AEC antibody after infection; 2) fluorescent detection of AEC in frozen tissue sections; and 3) immunohistochemical detection of AEC in formalin-fixed tissue sections. The IFA system was adapted to 96 well microtiter plates to increase throughput. The latter antibody technique is currently being used as part of the eradication plan to detect flocks naturally infected with AEC, so they can be eliminated to prevent spread to other poultry farms. Bovine enteric coronavirus was found to infect commercial turkeys. Infection of poultry with this virus leads to confusion in AEC eradication programs. We have developed seven monoclonal antibodies (Mabs) against AEC surface proteins. These Mabs are being used in the IFA test to differentiate AEC infection from bovine coronavirus (BCV) infection in cell cultures and birds.

Genes coding for the S surface viral protein of multiple AEC isolates have been sequenced and primer sets constructed to identify these genes. Polymerase chain reaction (PCR) assays have been developed based on these primers. These PCR primers and additional primer sets are currently being investigated for in situ use as probes for AEC. In addition, sequences coding for AEC viral protein S are being cloned into vectors for production of vaccinal quantities of this viral protein for test immunization.

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**Differential Diagnosis of Infectious Laryngotracheitis Viruses by PCR**

Infectious Laryngotracheitis is a severe acute respiratory disease of chickens caused by Infectious Laryngotracheitis Virus (ILTV), a member of the family *Alphaherpesviridae*. During 1994-1995, ILT outbreaks were reported in Georgia, Alabama, Arkansas, and Delaware. These outbreaks caused severe financial losses to the poultry industry. The major obstacle against the effective control and prevention of the disease is the inability to clearly and easily determine the source of outbreaks. Therefore, discrimination of ILTV strains of different pathogenicity, and particularly of field isolates from vaccine strains, is a major necessity. The main objective of this project is to develop a polymerase chain reaction (PCR) test capable of distinguishing among ILTV strains circulating in the field. We have identified restriction enzyme site differences in the gE gene, and the upstream region of the ICP4 gene. Digestion of PCR products with specific enzymes, deduced from the sequence data obtained during this year’s project, has allowed us to characterize field isolates as either “chicken embryo origin (CEO) like,” or “tissue culture origin (TCO) like” vaccine strains. Most importantly, we have identified restriction enzymes that produce restriction fragment length polymorphism (RFLP) patterns unique to some of the field isolates analyzed. These indicate that specific mutations are acquired by field isolates at these particular areas of the genome, for example, digestion of PCR products of the seven field isolates with enzymes *DdeI*, *MnlI*, and *Ple*.

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**Antimicrobial Peptides in Broiler Chickens**

Antimicrobial peptides are important components of innate disease resistance in vertebrate and invertebrate animals. These peptides arm phagocytic leukocytes and mucosal epithelial cells of the gastrointestinal and respiratory tract with a broad spectrum of antimicrobial activity and serve as the first line of defense against microbial pathogens. Recently, we discovered the cDNA sequences for two chicken and two turkey heterophil antimicrobial peptides, referred to as beta-defensins. We will now attempt to sequence the genes that encode the avian defensins and then study the regulation and expression of these genes. We have cloned the cDNA sequences for a chicken peptide and are in the process of producing a recombinant chicken beta-defensin.

Recombinant peptides will be used to characterize the complete spectrum of antimicrobial activity against avian pathogens. Moreover, development of resistance to these endogenous antibiotics by pathogenic bacteria can be studied using recombinant defensins. Ultimately, it may be possible to manipulate this endogenous defense system to enhance disease resistance in poultry.

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**Recombinant Vaccines for Infectious Bronchitis Virus**

The main objective of this proposal is to develop a recombinant vaccine for infectious bronchitis virus (IBV). A plasmid expression vector that works in an avian cell line is being used to express the immunogenic spike glycoprotein of IBV. The expressed protein is being characterized and tested for its suitability as a subunit vaccine in chickens. In addition, a newly redesigned nucleic acid vaccine for IBV, which provides higher expression of the IBV spike glycoprotein, was tested and found to be efficacious when given to young chickens by intramuscular injection at 1 and 14 days of age. We are currently examining the immune response generated by that vaccine, as well as testing for its suitability when given in ovo.

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*Victoria Leiting works on DNA fingerprinting of Mycoplasma organisms.*
Avian Mycoplasmosis

The avian mycoplasmas, *Mycoplasma gallisepticum* (MG) and *Mycoplasma synoviae* (MS) occur as egg-transmitted infections causing respiratory, joint, and tendon disease in chickens and turkeys. The objectives of this study were to improve detection and control measures for avian mycoplasma infection, to study pathogenesis, and to determine the incidence of avian mycoplasmas by DNA “fingerprinting.” A polymerase chain reaction (PCR) with random primers (RAPD), developed for rapid identification of specific strains of MG and other avian mycoplasmas is now routinely used to identify (fingerprint) specific strains and identify sources of infection. A library of avian mycoplasma isolates containing several hundred isolates has proven to be very useful in studying strain variation. In addition, PCR primers that detect all known mycoplasmas, followed by cutting the PCR product with specific enzymes, were utilized to identify specific strains of MG. MG strains could be categorized into at least six groups by this method. This may provide a method of “fingerprinting” that would not require prior isolation of the organism, which is often very difficult and might take up to three weeks.

MG vaccine strain ts-11, previously shown by us to be effective in multiple age commercial egg operations for MG control and eradication, has been studied in broiler breeders. This strain was very effective in the field, and measurable protection continued for the life of the flock. MG, which is pathogenic for chickens and turkeys, is widespread in wild house finches and now seems to be on the decline. Few new cases were identified. A model for consistent reproduction of clinical synovitis with field strains of MS was developed. This method will prove useful in studies evaluating antibiotic medication and/or vaccination. In collaboration with Dr. Dusan Bencina at the University of Ljubljana in Slovenia, the hemagglutinin (HA) of MS was identified as a virulence factor. HA positive clones were pathogenic, whereas HA negative strains were not. These results improve our ability to detect and control MG and other mycoplasmas in commercial poultry.

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Neuraminidase is a Conserved Antigen of *Pasteurella multocida*

“Sometimes there breaks out in the poultry-yard a disastrous disease, commonly known as chicken cholera. The animal which is prey to this infection is without strength, trembles and has drooping wings.” Louis Pasteur spoke these words in 1880 when he revealed his fowl cholera vaccine to the Paris Academy of Sciences. Pasteur, now known as the father of modern microbiology, developed the first attenuated-live vaccine effective against infection. Live vaccine strains are still used today to prevent fowl cholera. However, the available live vaccine strains are often too pathogenic for use in chickens, and killed vaccines induce protection only against closely related strains of *Pasteurella multocida*, the bacterium responsible for the disease. We propose to create a recombinant vaccine that will induce protection against all *P. multocida* strains. We have cloned and sequenced a gene present in all strains of *P. multocida*. Furthermore, we have protected chickens from fowl cholera using recombinant protein from this gene. The long-term goal of our research is to create an effective broadly protective vaccine against fowl cholera that can be inexpensively used by Georgia poultry producers.

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The Distribution of Virulence Specific-Genes among Avian *Escherichia coli* Isolates

Although usually commensal residents in mammals and birds, a small percentage of *Escherichia coli* isolates can cause disease in their hosts. Virulence of any microbe is dependent on the organism’s genetics. We have examined the distribution of specific virulence genes among avian *E. coli* encountered in northern Georgia. Genes encoding for hemolysins and toxins were absent in avian *E. coli* as determined from either polymerase chain reaction (PCR) or Southern blots. Other genes, such as the capsule gene *kps* and sialic acid-binding lectin *sfa*, are present in avian *E. coli* but at a low frequency. Emphasis has been placed on looking at the distribution of *P*-fimbrial genes among avian *E. coli*. We looked specifically at the adhesin protein of the P-pili, PapG. This protein determines specificity of disaccharides recognized by the pili. In uropathogenic *E. coli*, there are three PapG alleles, PapG96, PapG1a, and PrsG, that recognize three different galactosyl disaccharides present on the glycolipids of red blood cells. The PapG allele, PapG1a, is the only adhesin that has been identified in avian *E. coli* by either PCR or Southern blot. This gene was present in 25% of the *E. coli* isolates examined.

Dr. Susan Sanchez prepares an ELISA test to detect *Pasteurella multocida*. 

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Hemolysin is one type of virulence factor that assists in the pathogenesis of *E. coli*. Currently, hemolytic activity in *E. coli* has been attributed to one of two alpha hemolysin genes found in either uropathogenic of enterohemorrhagic *E. coli*. Hemolytic avian *E. coli* isolates, however, lack both these *E. coli* hemolysin genes. A “new” *E. coli* gene, *hylE*, was identified which lacked the conserved amino acid sequence and accessory genes common to alpha hemolysin. The *hlyE* gene was found to map at position on the *E. coli* chromosome where virulence genes are commonly found in uropathogenic *E. coli*. In cloning another *E. coli* hemolysin gene, an *E. coli* gene was identified that was similar to a *Salmonella* virulence gene. We are currently investigating the distribution of this “new” gene among *E. coli* pathogenic for poultry. Characterization of these virulence genes will assist in our development of probes and cross-protective vaccines against avian *E. coli*.  

**Investigation of Hatchery Disinfectant Efficacy and Effect on Broiler Production**

Hatchery sanitation has a significant impact on chick quality. The proper use of disinfectants is essential. A disinfectant with great promise as a hatchery sanitizer due to its low cost, efficacy, and low level of toxicity is hydrogen peroxide. Aerosol bacterial counts, egg moisture loss, hatchability, chick quality, and broiler productivity were measured in eggs exposed to hydrogen peroxide fogging and compared with eggs not exposed to disinfectant during the incubation period. The efficacy of hydrogen peroxide was also evaluated in the presence of severe challenge with *Staphylococcus aureus* contaminated eggs. There was a significant reduction in aerosol bacterial counts within the hatch when incubators were fogged with 3% hydrogen peroxide when compared with water-fogged machines, even in the face of high bacterial challenge. Eggs exposed to hydrogen peroxide lost a significantly greater amount of moisture during incubation, but hatchability was not affected. The use of hydrogen peroxide as a hatchery sanitizer did not affect broiler livability, body weight, or feed conversion but did reduce the incidence of retained yolk sacs in 42-day old chickens.  

**Incorporation of Computer-Assisted Learning in Poultry Disease Training**

The poultry industry in the United States is a $40 billion industry, which requires the attention of qualified experts in the field of poultry health. An explosion of knowledge is occurring in veterinary and agricultural sciences. The study of poultry health is highly specialized with a few select students entering the field. Because the majority of students lean in other directions, many veterinary and agricultural curriculums are unable to maintain poultry health courses. A computerized autotutorial learning system for the study of poultry diseases is being developed to fill this educational void. The main objective of this computer program is to support the teaching of anatomy and pathology of different poultry species. The disease topics are presented by organ system and etiology. Basic information such as a glossary, detailed postmortem directions, description of the types of poultry, and information on husbandry practices such as biosecurity is offered to the student to accommodate every level of knowledge. The format of the program uses the Internet through Netscape with only local use allowed. Links are provided within the program to allow the student to access a selected topic for study, or the student can proceed through the program from beginning to end. Images are incorporated in the text to allow the student to see the lesions associated with each disease.  

**Investigation of Natural Disease Outbreaks and Field Trial Studies**

Respiratory disease was investigated in one broiler operation. Viral serology, isolation, and polymerase chain reaction (PCR) were used to identify the primary agent as infectious bronchitis. Secondary bacterial infection with *Bordetella avium*, *Escherichia coli*, and *Ornithobacterium rhinotracheal* (ORT) was confirmed by bacterial culture of tracheal swabs. Modification of the vaccination program helped to alleviate the problem. *Aspergillus fumigatus* was isolated from young chicks with early mortality and respiratory problems. Recommendations from our clinical veterinarians helped the integrator to bring the problem under control. 

Hemagglutination-inhibition (HI) serology, virus isolation, and PCR tests revealed that Arkansas 99 strain of infectious bronchitis virus was the cause of a...
respiratory problem in a broiler operation. Modification of the vaccination program brought the problem under control. The estimated annual saving is more than $100,000.

The PCR technique has permitted generation of more useful and timely information than classical diagnostic techniques for infectious bronchitis and mycoplasmas. Research continues and new PCR tests will be applied to diagnostics as applications are developed.

Diagnostic Services Laboratory activity is represented by 5,107 accessions, 20,481 bacterial procedures, 979 antimicrobial susceptibilities, 56,832 enzyme-linked immunosorbent assay (ELISA), 17,632 infectious bronchitis hemagglutination-inhibition (IBV-HI) tests, 22,000 histopathology slides, 248 diagnostic PCR tests, and 579 necropsies.

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Isolation, Identification, and Control of Avian Viruses

Several molecular techniques, including polymerase chain reaction (PCR), reverse transcriptase-polymerase chain reaction (RT-PCR), restriction fragment length polymorphism (RFLP), and in situ hybridization, were used to analyze important sequences of the nucleic acid of field strains of infectious bursal disease virus (IBDV). One strain from Georgia was similar in sequence to Delaware E variant strain, a second strain was similar to the GLS strain also reported from the Delmarva area, and a third strain was similar to the pathogenic classic standard strain. The results obtained were similar with all the molecular techniques evaluated. Analysis of portions of the viral nucleic acid indicated that the genetic variation observed among the IBDV isolates are due to natural genetic drift rather than to selective pressures.

Four pathogenic adenoviruses isolated from field cases associated with inclusion body hepatitis were classified as group E adenovirus, using restriction patterns of extracted viral DNA generated by the restriction endonucleases BamHI and HindIII. These results confirmed the pathogenicity of the isolates.

A rapid method to identify strains of infectious bronchitis virus (IBV) has been developed. Using neuraminidase to treat the allantoic fluid obtained from chicken embryos, a hemagglutination reaction indicates the presence of the IBV. The method had a 98% correlation when compared with RT-PCR, which is considerably more expensive.

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Large Molecular Weight Plasmid Role in the Pathogenesis of Avian E. coli

Financial losses due to colibacillosis cost the poultry industry hundreds of millions of dollars annually. Virulence traits of bacterial organisms are encoded by specific genes located on the bacterial chromosome or on large molecular weight (MW) plasmids. *Escherichia coli* strain V-1 (V-1<sup>WT</sup>) is a well characterized, pathogenic avian strain isolated from a broiler chicken with colisepticemia, which contains several plasmids, two of which are high MW plasmids.

We are looking for a genetic marker (designated epv) that indicates the putative virulence gene located on the virulence plasmid, pWT3 (of *E. coli* strain V-1), and we want to determine what this virulence factor contributes to the mechanism of pathogenicity in avian disease. The organisms to be tested include *E. coli* strain V-1<sup>WT</sup>, *E. coli* strain V-1<sup>WT</sup> restored with the virulence gene, and appropriate positive and negative controls. The ability of the organisms to kill chicken embryo-onated eggs will be used as a measure of virulence for the organisms tested. Twelve-day-old chicken embryos will be inoculated with approximately $10^2$ colony forming units (CFUs) of the appropriate isolate, which is deposited into the allantoic fluid. In another procedure, $10^2$ CFUs will be inoculated into the yolk sac of six-day-old embryos. Embryos will be candled daily. The number of deaths will be recorded, and tissues will be taken for reisolation and histopathology. Previous statistical analysis has shown us the Embryo Lethality Assay performed with 20 embryos /group repeated at least three times is sufficient sampling for statistical analysis. Once the epv gene is delineated, we want to compare the mechanism(s) of pathogenicity between the wild-type organism and the wild-type organ-

Dr. Pedro Vilegas examines a tissue culture for lesions associated with infection of avian viruses.
ism without the epv gene. The results of the embryo lethality will then be used to decide the challenge model for adult chickens to further the understanding of the virulence mechanism(s) associated with pWT3 of *E. coli* strain V-1 wt.

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**Evaluation of Mechanism of Tendon Failure in Heavy Meat Type Birds**

In heavy meat type birds, lack of tendon integrity and associated lameness are poorly understood. The specific role of growth rate, management practices, and strain of bird in the genesis of the problem is not clear. Tendons may fail with no apparent lesion to explain cause. A procedure to detect alteration in fibrillar collagen type would help define a prefailure change in tendon quality. Utilization of monoclonal antibodies to procollagen type I and collagen type III in an immunodection procedure has been developed to show differential responses of avian tendon to heat, exercise, and rupture. Eighteen day-old embryonic tendon explants grown at 43°C had decreased procollagen and expression. Treadmill exercise for four weeks increased procollagen collagen with no change in collagen III. In ruptured tendons, the staining in tendon fibers was diminished for both procollagen I and collagen III. The peritenon and epitenon, however, had increased reactivity to both collagen types indicative of prior injury to the tendons. Changes in level of expression of collagen type correlated with changes in the regulatory proteins TGFβ messenger RNA.

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*Dr. George Rowland prepares tissue sections of avian tendon to aid in determining why these tissues fail in heavy meat birds.*
Fish

Georgia’s aquaculture industry continues to expand with its greatest increase in channel catfish. Since 1995, pond acreage for catfish farming has grown from 6,000 to 8,000 acres. Major areas of disease concern continue to be losses caused by channel catfish virus and the bacteria *Flavobacterium columnare* and *Edwardsiella ictaluri*. Furthermore, there have been extensive losses in Georgia this spring because of the protozoan parasite *Ichthyophthirius multifiliis* or Ich. In addition to Georgia’s food fish industry, there is an increasing interest in ornamental fish production. As Georgia’s aquaculture industries continue to grow, research aimed at improving the health of aquatic animal species will ultimately help growers reduce production costs and improve profits.

**Role of Signaling Phosphoproteins in Catfish Antibacterial Innate Resistance**

Non-specific cytotoxic cells (NCC) are the teleost equivalent of mammalian natural killer cells. NCC lyse protozoa and tumor cells and NCC may participate in anti-bacterial resistance by the release of cytokines and amplification of inflammatory responses. We have recently identified an antigen receptor (i.e., natural killer receptor protein-1/NCCRP-1) on the membrane of NCC. Cross-linkage of this receptor with monoclonal antibody or tumor/protozoan antigen initiates a downstream signaling process that eventually activates cytotoxicity. A major consequence of this activation/signaling process is the phosphorylation of many different intermediate proteins necessary for NCC function. In the present study, we identified different “species” of phosphoproteins. NCCRP-1 was phosphorylated on both tyrosine and serine residues. This was identified in Western blots using monoclonal antibodies specific for phosphoryrosine and phosphoserine residues. BOX-1 motifs are proline-rich consensus sequences found on the N-terminus of NCCRP-1 and on different cytokine receptors, on growth hormone receptors, and so on. These motifs are the known docking sites for JAK kinases. NCC membrane lysates were treated with the chemical cross-linker DSS, and it was found that JAK-2 was physically associated with NCCRP-1.

Additional data suggesting that NCCRP-1 is an important signaling phosphoprotein was the presence of STAT-6 in NCC cytosol preparations. Evidence that this protein may be associated with transcriptional activation was shown by demonstrating that STAT-6 translocates to the NCC nucleus. These studies demonstrated that NCCRP-1 may be responsible for both signaling responses and gene transcriptional activation.

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**Catfish Immune Response to Plasmid Vaccination**

Channel catfish (*Ictalurus punctatus*) farming accounts for approximately half the total aquaculture production and farm gate value in the United States. Compared with terrestrial food animal production industries, very little is known about the health management aspects of channel catfish, especially with regard to infectious disease. As with most commercially important food animals, there is a pressing need for safe, effective, and inexpensive vaccines in the channel catfish culture industry. DNA-mediated vaccines, or plasmid vaccines, are a rapidly emerging variation of subunit vaccines. The long-range goal of this research is to develop safe, effective, and affordable plasmid vaccines for infectious diseases important to the channel catfish culture industry. The current objective in pursuit of this goal is to investigate the catfish immune response, both humoral and cellular, generated by immunization with a plasmid vaccine. Our laboratory has demonstrated that foreign protein genes under the control of mammalian transcription promoters will be expressed by channel catfish cells both *in vitro* and *in vivo*. Our expectations are that, at the end of this project, we will have demonstrated that channel catfish will mount a humoral and cell-mediated immune response against an *in vivo* expressed foreign antigen delivered by plasmid vaccination. These observations will provide preliminary data that will facilitate funding for future research towards the development of vaccines targeted against specific channel catfish disease agents, such as channel catfish virus and the bacterium *Edwardsiella ictaluri*.

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*Ca tf ish Antibacter ial Inna te Resistance*

Ca tf ish Immune Response to Plasmid Vaccination
Cattle and Other Ruminants

Cattle, sheep, and goats are three of Georgia’s important food-animal ruminants. They are considered ruminants because their four-chambered stomach enables them to digest copious roughage, which is inedible for direct human consumption. These three industries have gone through recent dynamic changes. The beef and dairy industries have liquidated their herds because of a relatively large cattle supply, high grain market, and low milk and beef prices. Today’s cattle producers are working with narrow profit margins and must watch their expenses more closely than ever. Consequently, biomedical researchers are challenged to provide these industries with ways to maintain healthy animals, which will help reduce production costs. Mastitis, Johne’s disease, brucellosis, pasteurellosis, pneumonia, Infectious Bovine Rhinotracheitis (IBR), Parainfluenza-3 (PI-3), and leptospirosis continue to challenge the immune systems of Georgia’s cattle herds. Ruminant herd health as it pertains to food safety is also a major concern to consumers and producers. Scientists need to investigate pathogenic *Escherichia coli*, *Salmonella*, *Campylobacter*, and other food-borne organisms as to their origin, transmission, and prevalence.

Surface Immunity against Fescue Toxicois

Tall fescue is a major cool weather forage in the humid areas of the eastern and southern United States. The fescue plants are naturally infected with an endophyte fungus (*Neotyphodium coenophialum*) that is important for persistence of the grass and for maximum forage production. Endophyte-infected tall fescue contains ergot alkaloids. Cattle grazing endophyte-infected tall fescue absorb these alkaloids and develop fescue toxicosis, which results in decreased weight gains and calving rates. The negative effect of fescue toxicosis is estimated to exceed $750 million annually. Various strategies have been developed to reduce or prevent fescue toxicosis. Nevertheless, to date, no management or treatment procedure has proved successful. Our research group has been investigating the possibility of immunizing cattle against the effects of the ergot alkaloids. We have developed a vaccine that stimulates antibodies that will bind to the ergot alkaloids. In the present study, we are investigating whether the induction of surface immunity (production of antibodies in the mucus covering the digestive tract) will prevent the absorption of the ergot alkaloids in ingested fescue forage. Phase one of the study will determine if surface antibodies can be induced by a combination of injection of the vaccine and nasal infusion of the vaccine. The surface immune system is a unit, and stimulation at any internal surface will result in antibody production at all internal surfaces. Based on the results of this phase, an efficacy trial will be done where immunized and placebo-immunized cattle will be grazed on endophyte-infected tall fescue. The efficacy of this vaccine will be determined by measuring the urinary excretion of ergot alkaloids. We have determined that cattle excrete ergot alkaloids 24 hours after starting to graze endophyte-infected tall fescue. If these trials are successful, more extensive trials will be designed to determine the optimum dose and the number of vaccinations needed to provide long-term protection against fescue toxicosis. Donald L. Dawe, Frederick N. Thompson, Nicholas S. Hill*, and John A. Stuedemann**
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The Role of Parasite Adhesion Proteins in the Disease Process

Parasites exploit molecules on the surface of host cells by producing adhesion proteins capable of binding to them. The parasite’s goal is to enhance its survival, which as a consequence contributes to the development of disease in humans and animals. The adhesion proteins produced by the parasite are therefore of considerable interest, as blocking their interaction with host molecules should interfere with an important step in the disease process. The focus of work in this laboratory is to better understand these interactions between parasite adhesion proteins and the host molecules they bind. The starting point of this research is a family of adhesion molecules in the parasite *Plasmodium falciparum*, an agent of human malaria. During the past year, the complete sequence of the gene encoding a new adhesion molecule has been obtained, and work is underway to determine how it interacts with
target molecules on host cells. Using the DNA sequence of this gene, several other putative adhesion molecules have been identified. There are significant similarities between *P. falciparum* and several parasite pathogens of veterinary importance, most notably species *Babesia* (parasites of cattle, horses, and dogs). The techniques and reagents developed for the study of adhesion molecules in *Plasmodium* are now being used to detect similar molecules in *Babesia*. The discovery of novel adhesion molecules in *Babesia* will allow these techniques to be adapted to the detection of adhesion molecules in a wider array of pathogenic parasites that impact human and animal health, such as *Cryptosporidium* and *Eimeria*. These adhesion molecules are expected to provide important new targets for development of vaccines and antiparasite drugs.

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**A Survey of Genes Expressed in Bovine Skeletal Muscle**

Beef, a major food commodity, is comprised of the products of genes expressed in bovine muscle tissue, yet our knowledge of these genes is currently limited. Accordingly, as a first step toward the identification, characterization, genetic mapping, and monitoring of expression of muscle genes influencing beef quality traits, we have initiated a bovine muscle EST (Expressed Sequence Tag) project. This work involves the isolation and partial sequencing of numerous unique cDNAs from a bovine skeletal muscle cDNA library. The sequences can be analyzed in light of their homologies to the expanding databases of human sequences; inferences can be made about their map locations via comparative mapping; and the set of sequences provides a basis for further study into the molecular regulation of muscle structure and function.

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**Sequential Western Blot Analysis of Bovine Humoral Immunity to Paratuberculosis**

Johnne’s disease (paratuberculosis) caused by *Mycobacterium avium* subs. *paratuberculosis* (MPTB) is a chronic wasting disease of ruminants that spreads slowly and may be present in a herd for years prior to diagnosis. In the United States, it is estimated that the prevalence of infection is between 5-20%. Infected cows have diarrhea, decreased milk production, and body condition. Losses to the dairy industry alone exceed $1.5 billion per year. Though controversial, MPTB may also be a human pathogen. Crohn’s disease is a chronic transmural inflammatory disease of the intestinal tract that has clinical and pathologic features similar to paratuberculosis. The sequential humoral immune response to MPTB is not well studied, and this lack of information hinders development of serologic tests that target molecules recognized early in the immune response. The objective of this project is to analyze by Western blot, the sequential humoral immune response of calves infected with MPTB. Our long-term goal is to develop serologic diagnostic assays that have greater potential to diagnose this chronic disease than is currently possible. Detection of early infection would allow producers a better tool to identify and eliminate MPTB infected cattle and limit spread to other animals and the environment.

Holstein calves obtained from herds with MPTB test-negative status were orally inoculated with MPTB strain 19698. A Western blot assay to detect MPTB antibody has been developed utilizing enhanced chemiluminescence. Serum samples are collected and analyzed every four weeks for antibody to MPTB by Western blot. Preliminary data suggest that by 18 months postinfection, three of six MPTB challenged calves have developed an immune response to an antigen comigrating at the same apparent molecular mass. One other MPTB challenged calf has a similar weak immune response that is considered suspicious. This immune response is not seen in sera from any control calves. Antibody from only one of the MPTB challenged calves identified this antigen before 15 months indicating that the number of MPTB calves mounting an immune response to this antigen is significantly increasing. Identification of MPTB specific antigens may provide candidate molecules that can be targeted for improved diagnostic assays for this chronic disease.

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The Use of *in situ* Hybridization to Detect Bovine Cytokines in Tissue

Cytokines are a diverse group of low molecular weight proteins that modulate virtually all biological processes. In infectious diseases, cytokines are particularly important, because the outcome of an infection depends largely on the interplay between the infectious agent and the cytokines induced by the host and modulated by the agent. Studying the interactions between the infectious agent and the cytokine can best be done through *in situ* hybridization, a process allowing for visualization of the cytokine within the tissue using nucleic acid probes. We have made probes to many of the main bovine cytokines, including interleukin (IL)-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and IFN-α.

Using *in situ* hybridization, we have examined the presence of these cytokines in tissues from cattle infected with *Mycobacterium bovis* and foot-and-mouth disease. In tuberculous cattle, TNF-α and IL-10 are prominent cytokines. Interleukin-10 is noted for its ability to dampen the cellular immune response, perhaps allowing *M. bovis* to persist. In foot-and-mouth disease, two anti-viral cytokines, IFN-α and IFN-γ, are produced in the acute infection, but in quantities insufficient to overcome the extremely rapid proliferation of the virus.

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*In situ* hybridization for vesicular stomatitis viral nucleic acid in neurons of cerebral cortex.
Horses

The Georgia horse industry is experiencing significant growth as more than 250,000 horses reside in this state. Equine-related services contribute about $750 million to the state’s economy. These numbers are expected to rise as Georgia’s population continues to grow. The number of new equine training programs in the Southeast continues to expand, and more professional trainers have moved to the Southeast. With this growth comes an increasing concern about equine colic and laminitis. These diseases cause major losses to the equine industry. Thus, VMES researchers have focused on identifying better ways of treating horses with these diseases. To date, researchers have determined the effects of bacterial toxins absorbed during serious episodes of colic, developed treatment methods that inhibit action of some of the toxins, developed improved techniques to anesthetize horses, and identified the earliest changes that occur in the digit of horses that develop acute laminitis. It is the researchers’ collective goal to learn more about the development of these diseases so that appropriate measures can be designed to prevent them in the future.

Evaluation of the Effect of Polymyxin B Sulfate on ex vivo Endotoxemia in Horses

Gram-negative bacterial septicemia and acute gastrointestinal disease are leading causes of death in foals and adult horses, respectively. The high mortality rate in these diseases is associated with the release of bacterial endotoxin. Once in the blood, endotoxin binds to and activates leukocytes to secrete mediators, such as tumor necrosis factor, which in turn channel the host’s defense mechanisms toward self-destruction and shock. The purpose of this proposal is to evaluate polymyxin B sulfate, an antibiotic that binds endotoxin, thereby neutralizing its toxic effects.

This project involved an ex vivo model of equine endotoxemia in which three doses (100, 1000, and 10,000 units/kg) of polymyxin B sulfate or saline (time and drug control) were given as an intravenous bolus to eight healthy horses. Blood was drawn at various times before and after the administration of polymyxin B sulfate (or saline) and Escherichia coli or Salmonella minnesota endotoxin (1 ng endotoxin/ml blood) were added to heparinized blood ex vivo. After a 4-hour incubation, the plasma was assayed for tumor necrosis factor activity. To date, all eight horses have received the three doses of polymyxin B sulfate or saline, and tumor necrosis factor activity results have been compiled on six horses for all three doses of polymyxin B sulfate and on three horses that received the saline control.

As expected, incubation of blood with endotoxin induced tumor necrosis factor activity ex vivo. In horses given saline as a control, tumor necrosis factor activity was consistently induced by endotoxin. All three doses of polymyxin B sulfate significantly inhibited endotoxin-induced tumor necrosis factor. Inhibition was slightly better against E. coli endotoxin, as compared with S. minnesota. Preliminary results indicate that the 10,000 units polymyxin B sulfate/kg dose effectively inhibited 90% of endotoxin-induced tumor necrosis factor activity for up to 6 hours, whereas the 1,000 units/kg dose inhibited 75% of endotoxin-induced tumor necrosis factor activity for 3 hours. The latter dose would cost only approximately $10 for a single treatment for a 450 kg horse. Signs of drug toxicity were not detected. Our ultimate goal is to identify an affordable, safe, and effective dose of polymyxin B sulfate for the treatment of equine endotoxemia in the clinical setting. Michelle H. Barton and Anna Parviainen mbarton@calc.vet.uga.edu

Dr. Anna Parviainen is preparing serum for an ex vivo test for endotoxin-leukocyte binding in horses.
Endotoxin Antagonists: Characterizing their Interaction with Equine Monocytes

Diseases characterized by endotoxemia remain the largest cause of death in horses nationwide. In equine veterinary practice, endotoxemia occurs most frequently in horses with colic and foals with septicemia. For these reasons, we have initiated studies designed to identify the mechanisms by which endotoxin causes its deleterious effects and have initiated treatments to prevent these effects. The results of our previous studies indicated that peripheral blood monocytes play a key role in the development of many of the complications associated with endotoxemia. Consequently, the goals of this study were to characterize the binding of fluorescent endotoxin molecules to horse monocytes using flow cytometry and then to determine if unique endotoxin molecules isolated from nitrogen-fixing organisms from plants would serve as antagonists of endotoxin activity in horses. Initially, we determined that excessively high concentrations (10 µgrams/ml) of commercially available fluorescent endotoxins had to be used to detect their binding to the horse monocytes. These concentrations exceeded those measured in the circulation of horses with colic by more than 1,000-fold. We then adapted a new method to label endotoxins with fluorescent markers ourselves and were able to detect significant binding to horse monocytes at 6-10 ng/ml. The results of these experiments will allow us to more accurately characterize the binding of endotoxins to horse cells at concentrations that occur in natural cases of colic.

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Effect of a Hyaluronate Membrane on Adhesions and Anastomotic Healing in Horses

Intra-abdominal adhesions are a common cause of postoperative intestinal obstruction and mortality in horses. Adhesions become a clinical problem when they compress or distort the intestine and lead to intestinal constriction or incarceration, predisposing the patient to intestinal obstruction and signs of abdominal pain. A bioresorbable hyaluronate membrane (HA-membrane) has been developed to reduce postoperative adhesion formation in people. The HA-membrane is placed on the intestine to prevent serosal-serosal or serosal-peritoneal apposition during the early postoperative healing. Agents that reduce adhesion formation without adversely affecting normal peritoneal healing may reduce the morbidity and mortality associated with abdominal surgery in horses. The purpose of this study was to evaluate the effect of a bioresorbable HA-membrane on experimentally induced adhesion formation and anastomotic healing in horses.

The effect of a HA-membrane on postoperative adhesion formation was evaluated in 12 healthy horses using an established model of serosal trauma to induce intra-abdominal adhesions. Ventral midline celiotomies and two hand-sewn, jejunal resections and end-to-end anastomoses were performed. Two separate areas of the jejunum were briskly rubbed 100 times using sterile, dry gauze, and three simple interrupted chromic gut sutures were placed in the abraded area. In treated horses (n=6), HA-membranes were applied to the jejunum to completely cover the anastomoses and abraded areas of jejunum. Nontreated horses (n=6) served as controls. Horses in both groups were euthanatized ten days after surgery. The abdominal cavity was evaluated for adhesion formation and the jejunal anastomoses evaluated histologically for quality of healing.

Fibrous adhesions were associated with both abraded jejunal sites in all six control horses. Of the treated horses, only one abrasion site of one horse formed an adhesion. There were significantly fewer adhesions at the jejunal abrasion sites in the HA-membrane group as compared with the control group. There were no differences in anastomotic healing between groups.

The results of this study suggest that in horses at an increased risk of intra-abdominal adhesion formation, the use of HA-membranes during exploratory celiotomy may reduce the morbidity and mortality associated with abdominal surgery.

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Dr. Eric Mueller examines a client’s horse at the Large Animal Teaching Hospital.
Swine

Many of Georgia’s hog producers have recently converted their finishing units into farrowing houses. More hog operations are sending their two-week-old pigs to nurseries in neighboring states and to finishing floors and packing plants in the Midwest. Propelling this change was the closing of the state’s only major swine processing plant in June 1996.

With these changes in production scheme, biomedical researchers are focusing on the health needs of a sow production system. Georgia scientists are working to improve herd health by eliminating porcine reproductive and respiratory syndrome (PRRS), pseudorabies, and brucellosis. With respect to food safety, VMES scientists are testing ways to reduce the numbers of microbial agents in Georgia’s hog farms, thereby reducing human foodborne pathogens.

Inflammatory Cytokine Expression in Swine Lymphoid Tissue Experimentally Infected with Mycobacterium avium Serovar 2

Swine mycobacteriosis (tuberculosis) is a common cause of carcass condemnation in South Georgia swine. Once the infection is established in a swine herd, it is difficult to effectively prevent or eliminate the disease. Mycobacterium avium infections in swine are of great economic importance to swine producers in Georgia and other regions with high swine populations. The maximum incidence of detectable lesions often corresponds to traditional slaughter weights. As clinical signs are usually not apparent at slaughter, considerable financial loss to producers occurs due to carcass condemnations. Evaluation of in vivo mRNA cytokine profiles in lymphoid tissue from swine infected with M. avium should allow the elucidation of cytokine interactions involved in clearance of the organism and resolution of lesions. We hypothesize that the cytokine secretion profile in infected swine lymphoid tissue is altered from the normal state by local factors present on or secreted by M. avium; thereby preventing an appropriate immune response capable of effective clearance and prevention of disease. Our objective is to evaluate the inflammatory cytokine mRNA expression (TNF, IL-1, IL-6, and IL-8) of swine lymphoid tissue (mandibular lymph node and tonsil) experimentally infected (160 days postinoculation) with M. avium serovar 2 by morphological localization of cytokine mRNA by in situ oligoprobe hybridization. Preliminary data suggest a marked increase in TNF expression, a mild increase in IL-8 expression, and a mild increase in IL-1 expression in mandibular lymph nodes from infected swine. A mild increase in IL-6 expression was observed in tonsils from infected swine. This data on localized cytokine expression (in vivo) at a stage of disease where a cell-mediated response is active in resolution of the disease should allow development of more effective vaccine.

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Wildlife

Georgia’s wildlife habitat is continually changing as more people and domestic animals move into the countryside. This change brings concerns about disease interaction among wildlife, domestic animals, and humans. In addition, hunting, a popular form of wildlife recreation, adds hundreds of millions of dollars to Georgia’s economy, and as such, depends on the health of the state’s wildlife. VMES researchers are studying many wild species, including white-tailed deer, wild turkeys, wild swine, foxes, raccoons, skunks, small rodents, and songbirds, to learn more about each animal’s role in disease maintenance and transmission. Recent research projects have involved diseases such as rabies, *Escherichia coli* O157:H7, leptospirosis, ehrlichiosis, Lyme disease, pseudorabies, swine brucellosis, sarcoptic mange, and mycoplasmosis. Although research objectives vary by project, the main goals are to determine the importance of each disease to the health of wildlife, domestic animals, and people, and to devise ways to minimize that disease’s undesirable impact. At times, researchers have identified wildlife as a key part of a specific disease problem, but there also are numerous instances in which studies clearly demonstrate that wildlife is not involved. Either way, research provides the understanding that is required before rational solutions are possible to maintain a healthy environment for Georgia’s people and animals.

**P-selectin Regulation in Epizootic Hemorrhagic Disease Virus Infection**

The epizootic hemorrhagic disease viruses, along with the closely related bluetongue viruses, cause a devastating disease in white-tailed deer commonly known as hemorrhagic disease. These viruses occasionally cause disease in cattle, and the bluetongue viruses cause significant morbidity and mortality in sheep. Although it is known that these viruses infect and kill the cells that line blood vessels resulting in severe hemorrhage, infection of these cells no doubt triggers other events that either potentiate or ameliorate the disease. P- and E-selectin are proteins that are expressed on the surface of the cells lining the blood vessels when these cells are activated by a variety of insults. When expressed, these proteins direct the migration of cells involved in cellular immunity, inflammation, or hemostasis to sites of vascular injury. Little is known, however, about the expression or role of selectins during viral infections. We have found that both P and E-selectin are expressed on the cells lining the blood vessels during epizootic virus infection, both *in vitro* and *in vivo*. Expression was higher in cattle, which rarely develop disease following infection, than in the extremely susceptible white-tailed deer. This low-level of selectin expression in white-tailed deer following infection with epizootic hemorrhagic disease virus may partially explain the extreme susceptibility of deer to these viruses.

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**Survey of Wild White-tailed Deer in Georgia for Escherichia coli O157:H7**

Cattle are a source of the human foodborne pathogen *Escherichia coli* O157:H7. Deer also are suspected as a source because of recent isolations of the bacteria from deer feces and confirmation of venison as the source of two small clusters of human disease...
in Oregon. The objective of this study was to determine if white-tailed deer in Georgia carry E. coli O157:H7.

During summer 1997, more than 300 fresh deer fecal samples were collected from the ground at five Georgia wildlife areas. During autumn 1997, nearly 400 fecal samples were collected directly from hunter-killed deer at the same locations plus an additional area. Fecal samples were cultured for E. coli O157:H7.

All samples collected from the ground were culture-negative. Three samples (0.8%) collected directly from deer were positive for E. coli O157:H7. The three isolates were from 77 deer sampled (3.8%) during November at one area. Two of the three isolates had identical DNA fingerprints. All three isolates produced Shiga-like toxins 1 and 2. Samples of frozen processed meat from the three positive deer were culture-negative for E. coli O157:H7.

Results of this study suggest that the overall prevalence of E. coli O157:H7 is low in free-ranging deer; however, there may be focal areas where deer harbor the bacteria. Cattle were present in the vicinity where the positive deer were found, but they also were present at other sites where deer were culture-negative. Additionally, the results suggest that contamination of meat did not occur during field dressing and processing of the three deer carrying E. coli O157:H7.

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Experimental Infection of Deer Mice with Vesicular Stomatitis Virus

Vesicular stomatitis (VS) is a viral disease of cattle, horses, and swine, that causes substantial economic losses to livestock producers. The epidemiology of this disease is currently undefined, but it is suspected that the virus is maintained in a vertebrate/insect vector cycle involving wildlife. To determine if native wild rodents may be involved in this cycle, a pilot study involving experimental infection of 100 deer mice (Peromyscus maniculatus) with vesicular stomatitis virus (VSV), New Jersey (NJ) serotype, was performed. The virus used in this study was originally isolated from sand flies collected on Ossabaw Island, Georgia. Viremia was detected in infected mice during postinoculation days one through three. Virus was isolated from various tissues from 96 of 100 mice from postinoculation days one through seven, and virus isolation results were confirmed by polymerase chain reaction (PCR), immunohistochemical detection of virus in tissues, and in situ hybridization of viral RNA in tissues. Following this pilot study, a series of experiments were conducted to compare the outcome of infection in deer mice with two different strains of VSV-NJ. The Ossabaw Island strain was compared with a VSV-NJ isolate from a recent VS outbreak (1995) in Colorado, with emphasis on development of viremia, clinical outcome, and distribution of virus in tissues. The Colorado strain of VSV-NJ produced a significantly higher level of viremia and caused central nervous system disease sooner than the Ossabaw Island strain of VSV-NJ. Further experiments using this deer mouse model are planned to investigate the effects of route of inoculation and dose of virus on development and extent of viremia, the effects of pregnancy on infection, and eventually, the potential for viremic deer mice to infect appropriate insect vectors. Results from this study provide the first evidence that a vertebrate host can become viremic and thus provide a source of VSV-NJ to biting arthropods and eventually livestock. Results also indicate that the deer mouse can provide a valuable research tool to further study vector competence of suspected biting insect species.

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Companion Animals

Companion animals reside in 55 million U.S. homes. These animals include an estimated 66 million cats, 58 million dogs, 88 million fish, 40 million birds, 13 million small animals (rabbits, hamsters, and gerbils), and 8 million reptiles. Companion animals’ popularity can be attributed to aging baby boomers looking to pets for companionship after their children leave home. And while U.S. pet ownership is at an all-time high, these animals are living longer than their predecessors because of medical advances. Longer life, however, means more age-related diseases and ailments, such as cancer, neural degeneration, kidney dysfunction, poor circulation, decreased respiratory capacity, and decreased liver function.

It is up to biomedical researchers to come up with treatments for these and other diseases and ailments that affect companion animals. Nevertheless, unlike other research areas, no federally funded support exists for studies that specifically benefit companion animals. Yet, many of these studies affect human medicine. For example, artificial hip studies were initially performed on dogs in order to develop a model for replacing diseased hips in humans. Now older dogs routinely undergo joint replacement. This is just one of many examples of how biomedical research benefits both human and animal health.

Canine Hepatocerebellar Degeneration: A Potential Model of CDGS1

Canine Hepatocerebellar Degeneration (CHD) is an insidious and debilitating neurologic disorder that has been described in Bernese Mountain Dogs, although it is conceivable that other breeds may also be affected. We have determined that this syndrome is an autosomal recessive inherited cerebellar cortical degenerative disease that has consistent hepatic involvement. CHD is biochemically and morphologically similar to a recently mapped human genetic disorder known as Carbohydrate-deficient Glycoprotein Syndrome type 1 (CDGS1). We are studying a group of related purebred Bernese Mountain Dog puppies with CHD and intend to examine both the pathogenesis of Purkinje cell degeneration in this newly described disease in dogs as well as probe the underlying molecular genetic basis of the disease. Development of a genetic test for carrier animals will provide an effective and humane way to breed healthy animals and to prevent the perpetuation of this disease within the breed.

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Dr. Paige Carmichael explains the pathogenesis of CHD to a group of visiting pathologists.
Diabetes mellitus is an important endocrine disease in the cat. About 50% of diabetic cats have the noninsulin-dependent form characterized by several metabolic alterations, most prominently hyperglycemia caused by increased hepatic glucose output, increased gluconeogenesis, and hyperlipidemia. Currently, diabetic cats are treated either with insulin or the oral drug, glipizide. Both treatments are associated with problems. Cats have variable responses to insulin, and large fluctuations in glucose occur frequently making insulin treatment a frustrating experience for the owner and dangerous for the cat. Glipizide treatment is not successful at all in many cats or is successful only for a limited time period. Both lead to an increase in insulin concentrations, which causes weight gain and deterioration in the insulin resistant state. The thiazolidinedione, troglitazone, has recently been approved for the treatment of diabetes in people. This drug improves insulin resistance, hyperglycemia, and hyperinsulinemia in both diabetic and nondiabetic obese patients and leads to a normalization of the hyperlipidemia. This drug might also be valuable in the treatment of the diabetic cat.

To use troglitazone in the diabetic cat, we established pharmacokinetic parameters for troglitazone by single dose intravenous and oral administration studies in healthy normoglycemic cats first. This information is necessary before troglitazone can be given to diabetic animals.

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Canine distemper virus infects both pet and wild canids producing severe disease of the immune, respiratory, gastrointestinal and nervous systems. Untreated animals that survive the acute illness usually die from fatal encephalitis. The neuropathology produced by CDV is similar to that produced in Multiple Sclerosis. In spite of this, little information exists concerning the exact cellular mechanisms of this virus in the nervous system. Current control of the virus in the pet dog population entails vaccination. In spite of these control measures, CDV is still a leading cause of infectious encephalitis in dogs. In Georgia alone, CDV was second only to parvovirus in the number of infectious disease cases reported to the Georgia Veterinary Diagnostic Laboratories between 1993-1995 (420 cases/3 years). The reasons for continued existence of the disease include unvaccinated animals, vaccine failure, persistence of the virus in wild canids, and the existence of an inadequately controlled roaming dog population. A study of CDV in the gray fox population of the southeastern states found that the disease occurred in 78% of the dead or sick foxes studied. It is noteworthy that 75% of the animals were from Georgia. In addition, CDV infection has also been reported in coyotes in Georgia and South Carolina. Therefore, it is likely that CDV will continue to be a significant threat to domestic canids and wildlife in Georgia. This warrants additional research in understanding its mechanisms of action at the cellular level, as well as the development of more effective treatment and control measures. The objective of the current study is to develop an _in vitro_ model system that can be used to study the action of CDV at the cellular level. Currently, we are using mouse spinal cord tissue to grow motor neurons in cell culture, and electrical recordings to measure the activity of these cells before and after infection with CDV, in an effort to better understand the cellular action of CDV.

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Due to the increasing numbers of valuable canine patients being seen by the Veterinary Medical Teaching Hospital for reproductive problems, this research has been undertaken to provide new clinical therapeutic modalities for many of these otherwise untreated diseases. Although assisted reproduction rarely offers a cure, it does allow for the procreation of valued but otherwise sterile patients. The following is a summary of the canine specific

**Assisted Reproductive Techniques for the Treatment of Canine Infertility**

*Dr. Gina Michels performs a physical examination on a diabetic cat.*
research paid for by VMES funds where we investigated the harvesting of oocytes, in vitro maturation of oocytes, in vitro capacitation of canine spermatozoa, and two in vitro fertilization techniques.

Harvesting of oocytes by the dissection method was significantly (p<0.05) the best collection technique and will provide adequate numbers of oocytes for subsequent maturation and fertilization studies. When the oocytes were matured in several media, we found that the addition of estral serum from a dog was significantly (p<0.05) best for oocyte maturation. The matured oocytes were fertilized using fresh, chilled, and frozen dog semen, and we found that the addition of progesterone and caffeine significantly (p<0.05) increased the sperm binding and penetration of the egg’s zona pellucida. These treatments lead to successful in vitro fertilization of oocytes with 41.8% penetration by sperm cells at 24 hours and the production of male and female pronuclei in 8% of oocytes.

The successful maturation and fertilization dog oocytes will allow us to develop in vitro techniques to treat infertile dogs at the College of Veterinary Medicine. This will be the only fertility recourse for some of these extremely valuable, infertile dogs.

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Artificial Infection of Ticks with Canine Ehrlichiosis Agent

Canine monocytic ehrlichiosis is an acute hemorrhagic disease caused by Ehrlichia canis and transmitted by the brown dog tick, Rhipicephalus sanguineus. The tick maintains infection with these bacteria for an extended time, thereby serving as both vector and reservoir. In this study, a system was developed for artificially infecting ticks through capillary feeding of cell culture material and blood. Two groups of pathogen free, unfed adult ticks were allowed for 24 hours to imbibe cell culture material containing E. canis or Ehrlichia chaffeensis, a human pathogen not known to be transmitted by R. sanguineus. Additional ticks were fed uninfected cell culture material. Ticks were then removed from the feeding apparatus, held in humidity chambers, and groups of individuals serially sampled and tested for evidence of infection. Results demonstrate that artificial feeding resulted in apparent infection with E. canis, but not E. chaffeensis, in some of the ticks, although overall efficiency of infection was relatively low. Artificially fed ticks survived more than 60 days postfeeding, and no significant differences were found in survival of ticks fed infected culture material as compared with those fed uninfected cells. Additional evaluation of the mechanisms involved in infection of ticks with Ehrlichia spp. is integral to our understanding of the transmission of these important veterinary pathogens.

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Financial Highlights

Research Funding

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*Excluding carryover funds

Georgia Livestock and Poultry: Inventories and Values*

<table>
<thead>
<tr>
<th>Species</th>
<th>Number on Farms and/or Produced</th>
<th>Production Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>Beef 1,392,000, Dairy 98,000</td>
<td>$497,220,000, 355,680,000 b</td>
</tr>
<tr>
<td>Hogs</td>
<td>1,640,000</td>
<td>209,200,000</td>
</tr>
<tr>
<td>Poultry</td>
<td>Broilers 1,182,800,000, Non-broilers 19,869,000, Eggs 4,867,000,000, Turkeys 175,000</td>
<td>2,276,890,000, 17,112,000, 358,941,000, 2,591,000</td>
</tr>
<tr>
<td>Horses and Ponies</td>
<td>251,000</td>
<td>125,500,000</td>
</tr>
</tbody>
</table>

*Based in part on information published by the Georgia Agricultural Statistics Service, Athens, Georgia

*Includes value to dairy cattle and milk produced

Georgian Farm Cash Receipts

- Crops and Farm Forest (43.8%)
- Poultry and Eggs (44.3%)
- Dairy Products (4.2%)
- Meat Products (6.9%)
- Other Livestock (0.8%)
Research Contracts and Grants

Allen, S.W. Pharmacokinetics and efficacy of transdermal fentanyl patches in cats and their effect on serum cortisol concentrations. American College of Veterinary Surgeons, $10,000.

The use of Monocryl in feline ovariohysterectomy. Mallinckrodt Veterinary, Inc., $4,000.


The effects of endotoxin on equine leukocyte receptor expression. U.S. Department of Agriculture, $16,561.


Brown, T.P. Study of spiking mortality of turkeys. North Carolina State University, $64,310.

Diagnostics for avian enteric coronavirus infections in commercial poultry. U.S. Department of Agriculture, $10,205.


The effects of carprofen on the ground reaction forces in a canine chronic stifle osteoarthritis model. Pfizer, Inc., $28,279.

Crowell-Davis, S.L. Effect of litterbox location on normal and inappropriate elimination behavior in cats. The Pet Care Trust, $8,758.

Dickerson, H.W., Jr. Can a DNA vaccine induce cutaneous immunity in fish? Cornell University, $20,065.


Evans, D.L. Analysis of chicken lymphocytes responding to Campylobacter extracts. U.S. Department of Agriculture, $10,000.


Ferguson, D.C. Production of a highly sensitive canine thyrotropin immunoassay using bioluminescence. Georgia Institute of Technology, $46,000.


Hanson, W.L. Evaluation of potential antileishmanial drugs in animal models. U.S. Army, $207,000.


Maurer, J.J. Identification of virulence specific genes in avian Escherichia coli by RAPD PCR. U.S. Poultry and Egg Association, $22,247.

The distribution of virulence specific genes among avian Escherichia coli isolates. U.S. Department of Agriculture, $1,990.


Filarialsis repository research services. National Institutes of Health, $227,160.

Standardization of a model for canine ehrlichiosis using tick (Rhipicephalus sanguineus) induced infections of Ehrlichia canis in beagles. Georgia State University/Georgia Research Alliance, $30,000.

Standardization of a model for canine ehrlichiosis using tick (Rhipicephalus sanguineus) induced infections of Ehrlichia canis in Beagles. Merial Limited, $30,000.

McGraw, R.A. Genetics of between-breed resistance to nematode infection in sheep. Louisiana State University, $136,146.


Dextrorotatory opioids as probes for PCP receptors. National Institutes of Health, $488,249.


Nettles, V.F. Assess possible risk factors for exposure to Ehrlichia. Centers for Disease Control and Prevention, $40,949.


Development and evaluation of alternate baits for delivery of V-RG rabies vaccine to wildlife. Georgia State University/Georgia Research Alliance, $66,650.

Development of scientific information on animal traps for selected wild vertebrate species. U.S. Department of Agriculture, $53,334.

Southeastern cooperative wildlife disease study. Southeastern Association of Fish and Wildlife Agencies, $194,920.


In vivo evaluation of resorbable urethral stent in the canine cystoscopy model. Indigo Medical, Inc., $80,000.

Ritchie, B.W. Post-graduate support in zoo/exotic animal pathology. Zoo Atlanta and Riverbanks Zoo, $36,000.


Sander, J.E. Enumeration of bacteria before and after disinfection of various types of SLAT material used to house broiler breeders. Riverdale Mills Corporation, $4,029.

Investigation of hatchery disinfectant efficacy and effect on broiler production. U.S. Department of Agriculture, $2,660.

Stallknecht, D.E. Mycoplasma gallisepticum in house finches and other wild birds. Georgia State University, $34,249.


Thompson, F.N. Evaluation of vaccines against fescue toxicosis. U.S. Department of Agriculture, $22,634.


Isolation, identification, and control of avian viruses. U.S. Department of Agriculture, $6,585.
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Selected Publications


Berman, E., Murray, T.F.: Domoic acid neurotoxicity in cultured cerebellar granule neurons is predominantly mediated by NMDA receptors that are activated as a consequence of excitatory amino acid release. J. Neurochem. 69:693-703, 1997.


