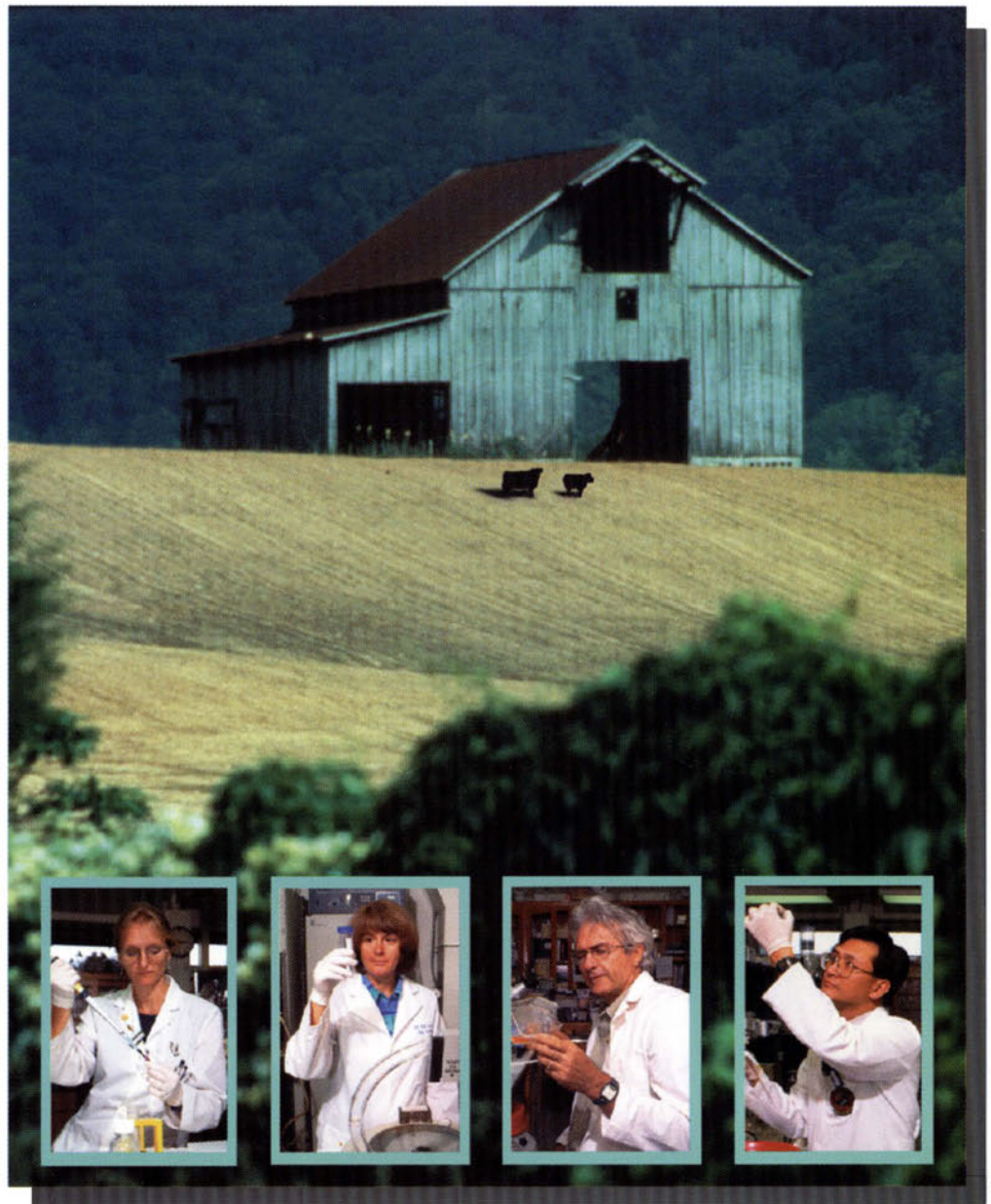


CENTER OF EXCELLENCE IN LIVESTOCK DISEASES AND HUMAN HEALTH



ANNUAL REPORT

1997-1998

College of Veterinary Medicine ■ The University of Tennessee, Knoxville

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DEAN'S MESSAGE

Dr. G.M.H. Shires, Dean, College of Veterinary Medicine

August 1998

I hope that you enjoy the new format for this annual report. It certainly makes it more attractive and, I am sure, much more readable. Dr. Potgieter and his staff, along with the College's Office of Veterinary Medical Communications, put many long hours into this production. We offer our thanks to them for a job well done.

Once again, the faculty of the Center of Excellence have been most productive and, as usual, have performed far above the required benchmarks. Many of them have been invited to present at international meetings as well as national scientific forums.

Careful management of the funds and strict adherence to guidelines have allowed the COE to provide quite generous start-up packages for new researchers as well as a modest amount of money for equipment purchases for several researchers. The return on the state of Tennessee investment is still a very good one and it would certainly enhance our research program if this investment could be increased as the cost of equipment and, therefore, the cost of doing research, rises every year.

The careful dispensation of the funds from this Center has been instrumental in assisting new researchers in successfully obtaining extramural funding as well as supporting some of our established researchers who may have a gap in their external funding. The COE continues to be the backbone which gives support to our entire research effort and is a sound investment in relation to funds from external sources.

My thanks to the state of Tennessee for its continuing support of the Center. Thanks also to the researchers who continue to be so productive and to our research leadership who are such excellent stewards of the COE. I hope you enjoy this publication.

PROGRAM REPORT

Dr. Leon N.D. Potgieter, Director of Research and Graduate Programs

I am pleased to report on an active year for the Center of Excellence in Livestock Diseases and Animal Health in 1997. Once again the Center has met its objectives admirably. The number of peer-reviewed scientific publications published by faculty supported by the Center continues to be truly astounding. These faculty have presented their work as seminars or as posters at local, regional, national and international scientific meetings and other venues. Research results are disseminated, not only in prestigious, peer-reviewed international journals, but also in popular journals and magazines distributed regionally and nationally. Several of our investigators, such as Drs. Rouse, Schuller, Brian, Stephen Oliver and Jack Oliver, have been invited to give keynote presentations at international scientific meetings.

The annual report this year has been prepared in a format different from previous years. We have chosen to focus on the activities and achievements of those individuals and research teams whose laboratories constitute the core of the Center. These investigators deserve tremendous credit for bringing recognition to the College of Veterinary Medicine, the Institute of Agriculture and the University of Tennessee. Furthermore, they continue to ensure that the Center maintains its strong competitive position and contribute to the fiscal health of our research environment. This report format emphasizes the strength of the Center and gives a clearer indication of how it meets its objectives.

Accomplishments

It should be evident from reading the summaries of the laboratories featured in this report that the Center:

1. Improves the quality of human life by improving animal health.
2. Augments livestock disease research capabilities in the Institute of Agriculture.
3. Identifies and characterizes laboratory and animal models of important human diseases.
4. Studies animal/laboratory models for better understanding of human health.
5. Studies the mechanisms of disease development and characterizes causative agents of common diseases im-

- portant to the state of Tennessee.
6. Improves the capabilities of the College of Veterinary Medicine, the College of Agricultural Sciences and Natural Resources and the Agricultural Experiment Station to deal with these diseases.
 7. Improves the facilities to enable the College of Veterinary Medicine to study more effectively infectious and toxic diseases of animals.
 8. Disseminates through the Extension Service practical information required to reduce the incidence of livestock diseases.
 9. Develops new strategies for the prevention of disease.
 10. Improves facilities and expertise in order to provide improved research training.
 11. Develops innovative approaches to the treatment of human diseases.

Research Funding

An important goal of the Center of Excellence is to support researchers and to promote research by a variety of mechanisms. The Center of Excellence in Livestock Diseases and Human Health emphasizes the following six specific areas: Infectious Diseases/Population Medicine, Toxicology, Reproduction, Host Defense, Molecular Genetics, and Carcinogenesis. The Center's underlying philosophy is to enhance young (or new) investigators' capacity to compete for extramural funding and to assist established researchers to maintain their extra-mural support. The Center does not serve as a primary source of research funding for faculty. The main criteria used for funding proposals include scientific merit, likelihood of leading to extramural funding and relevance to the Center's objectives. Proposals are reviewed by the Research and Graduate Programs Advisory Committee, and has a representative from every department of the College of Veterinary Medicine, chaired by Dr. David Slauson. .

The Center supported the following projects over the past year:

1. **Dr. David Bemis:** Recombinant *Bordetella bronchiseptica* fimbriae as carriers of unrelated antigens.
2. **Dr. Philip Bochsler:** Cloning bovine CD14, a pathogenrecognition receptor.
3. **Dr. David Brian:** How two terminal genetic structural elements regulate replication of the coronavirus RNA genome.
4. **Dr. Kevin Hahn:** Reversal of cisplatin resistance using ethacrynic acid: Evaluation in an osteosarcoma animal model.

5. **Dr. Alan Mathew:** Characterization of mastitis-causing agents in swine.
6. **Dr. Charmi Mendis-Handagama:** Regulation of mesenchymal cell differentiation into Leydig cells in the neonatal rat testis.
7. **Dr. Joyce Merryman:** The role of c-Jun amino-terminal kinases in squamous cell carcinoma of the lung.
8. **Dr. Linda Munson:** Role of platelet-derived growth factor in endometriosis and endometrial carcinoma.
9. **Dr. Jack Oliver:** Vascular cell injury by toxicants of tall fescue grass.
10. **Dr. Steve Oliver:** Characterization of M proteins from environmental streptococci and evaluation of their role in the pathogenesis of bovine mastitis.
11. **Dr. Bart Rohrbach:** Investigation of the role of endophyte-infected tall fescue as a risk factor for laminitis in the horse.
12. **Dr. Barry Rouse:** Evaluation of the kinetics and the mechanism by which mouse IL-10 induces immune suppression.
13. **Dr. Hildegard Schuller:** Molecular biology of neurotransmitter receptors in lung cancer cells.
14. **Dr. Terry Schultz:** Structure-activity relationships for skin sensitizing chemicals: nitrogenous aromatic electrophiles.
15. **Dr. Erby Wilkinson:** SCURFY; genetic rescue, identification of the gene and immunobiology.

Equipment

Requests from 13 investigators for 24 pieces of equipment were funded by the Center of Excellence over the past year. The investigators benefiting from these Center grants were Drs. David Bemis/Steve Kania, David Brian, Alan Mathew, C. Mendis-Handagama, Darryl Millis, Jack Oliver, Stephen Oliver, Barry Rouse, Terry Schultz, Hildegard Schuller, Hwa-Chain Wang and Dan Ward. Criteria taken into consideration for allocation of these funds included justification of need, equipment availability in adjacent laboratories, and the number of investigators who may benefit.

Student Awards

One mechanism by which the Center of Excellence promotes biomedical research is to provide summer opportunities for veterinary students to do investigational work in research laboratories of the College of Veterinary Medicine. This past year the Center funded eight requests from first- and second-year students. At the end of the summer, they provided a summary of their work to be entered into a competition judged by Phi

Zeta, the veterinary honor society. The program appears to be very successful; several students presented their findings at national scientific meetings, and several manuscripts have been submitted for publication in peer-reviewed journals.

Personnel Changes

The Center is sure to benefit by the recent recruitment of two investigators Drs. Hwa-Chain Wang and Joseph Bartges, who were provided with generous COE start-up funds this past year. Dr. Wang's expertise is in molecular mechanisms involved in cancer and Dr. Bartges interest is in animal models of nutritional diseases.

Dr. Edward Schroeder, Director of the Office of Laboratory Animal Care, retired during the year. We are pleased that this position was filled promptly by Dr. Dorcas Schaeffer following a national search. The College is currently conducting a search to fill the remaining open laboratory animal veterinarian position.

The Department of Animal Science announced that Dr. Patricia Tithof joined the department to fill a position in physiology in July. Dr. Tithof's research interest is in line with the Center's focus and we look forward to her participation.

Dr. Linda Munson, who had been supported by the Center for several years, resigned in August 1997. I hope that in the near future the College will receive approval to fill her position, in addition to one in the Department of Animal Science. These positions have had significant research assignments and could improve the critical mass of the Center of Excellence.

Funding Levels

The total funding for the Center of Excellence has not changed significantly. Both extramural and state funds have remained steady. The state's investment in the Center of Excellence in Livestock Diseases and Human Health remains a healthy one; our extramural funding still is good, in spite of a difficult and very competitive funding climate.

I am very encouraged in that several faculty this past year have secured new multi-year funding for COE-related research. They include:

Dr. Jack Oliver: Reactivity of bovine vasculature to ergovaline and ergine of toxic tall fescue. From the National Research Initiative of the United States Department of Agriculture. Total award \$188,000.

Dr. Terry Schultz (co-investigator): The role of bioavailability in determining acceptable limits for the bioremediation of polychlorinated biphenyls. From the Department of Energy. Total award \$441,000.

Dr. Hwa-Chain Wang: Pathway leads to apoptosis in SRC-transformed cells. From the National Cancer Institute (NIH). Total award \$517,500.

Dr. Stephen Oliver: (a) Influence of prepartum intramammary infusion of Pirsue or Albacillin on mastitis and lactational performance of heifers. From Pharmacia and Upjohn Company. Total award \$65,000;
(b) Lactation/Mastitis Research. From the I. Schattner Foundation, Inc. Total award \$65,000;
(c) Evaluation of specific immune responses and protection during early lactation following immunization during the non-lactating period with novel streptococcal antigens. From Pfizer, Inc. Total award \$85,000.

I look forward to another good year for the Center of Excellence in Livestock Diseases and Human Health. I am confident that the support provided by the Center for some of our promising investigators will constitute the embryogenesis of established research programs.

RESEARCH TRAINING

Dr. David Slauson

The College of Veterinary Medicine funds at least ten positions for Ph.D.-level training of students with a professional medical degree. Some of these students are based in the Department of Pathology (as part of their residency/Ph.D program), and some are awarded without restriction. Most of these students become linked with investigators conducting Center of Excellence-related research. The presence of this dynamic group of young investigators significantly bolsters the achievements of the Center. Faculty benefiting from these graduate students include Drs. Rouse, Schuller, Wilkinson and Potgieter.

In addition, the University of Tennessee College of Veterinary Medicine is one of few veterinary colleges to be chosen

as a site for a NIH Institutional Training Grant. This five-year training grant on the "Molecular and Cellular Pathobiology of Environmental Disease" is funded through the National Institutes of Environmental Health Sciences. The grant began in 1995 and is funded through the year 2000; current annual funding is \$122,968. This training grant, initiated by Dr. David Slauson, is centered in the Department of Pathology, but also involves scientists from other departments, as well as important collaborators in the Life Sciences



Dr. David Slauson (center) with (from left to right) Dr. Sharon Witonsky, Dr. Barbara Sheppard, and Dr. Brian Jull.

Division at the Oak Ridge National Laboratory. Dr. David O. Slauson, Program Director for the grant and Pathology Department Head, said that the NIH funds provide stipend support for three years of advanced research training for DVM graduate students who already have at least two years of disease-oriented residency training. "We are very honored to have been selected for this important award," Slauson said. "As far as I know, we are one of only two Colleges of Veterinary Medicine in the entire country to have such an environmental pathology training grant." Slauson indicated that the research training sponsored by this new NIH grant emphasizes basic molecular and cellular biology of disease, including environmental disease. "Our purpose here is to produce well-trained individuals who understand disease at the tissue and whole animal level, as well as at the most sophisticated edges of contemporary molecular and cellular pathogenesis," Slauson continued. There

are currently three DVM graduate students supported by these NIH funds and working in the laboratories of COE-associated scientists.

The summaries below illustrate the sort of quality individuals that we have been able to attract to the University of Tennessee with this NIH Training Grant:

Dr. Barbara Sheppard is working on the Ph.D. degree in Dr. Hildegard Schuller's Experimental Oncology Laboratory on a project involving growth regulation of the cells of origin of small cell lung cancer. Dr. Sheppard received her B.S. degree in biology from Virginia Polytechnic Institute in 1986 where she was on the Dean's List for her last seven consecutive semesters. Dr. Sheppard then received a M.S. degree in physiology in 1989, also from VPI, and was awarded her D.V.M. degree from North Carolina State University in 1993. Dr. Sheppard was in private practice in Delaware for a year before entering the Pathology Residency Program at the University of Florida in 1994. Dr. Sheppard came to the University of Tennessee in 1996 to begin her graduate program.

Dr. Brian Jull is working on the Ph.D. degree in Dr. Schuller's laboratory, pursuing a difficult project that involves defining metabolic pathways involved in the regulation of growth of cells that become small cell lung cancer cells. Dr. Jull received his undergraduate degree in Animal Science *cum laude* from the University of Kentucky where he was a consistent member of the Dean's List. He received his D.V.M. degree *summa cum laude*, near the top in his class from the College of Veterinary Medicine at Auburn University in 1993. Dr. Jull was in private practice in Kentucky before joining the pathology residency training program at the University of Tennessee in 1995. Dr. Jull was appointed to the NIH training grant in 1997.

Dr. Sharon Witonsky is working in Dr. Erby Wilkinson's Cellular Pathobiology Laboratory on projects involving mouse models of genetic diseases. Dr. Witonsky was a Phi Beta Kappa undergraduate in biology and chemistry at Earlham College, and received her D.V.M. degree from the University of Minnesota in 1993 where she was an outstanding student. She came to UTCVM in 1993 as a graduate student, and has been engaged in research as well as clinical training in internal medicine here, aiming at specialty board certification and a Ph.D. degree in Comparative and Experimental Medicine. Dr. Witonsky was appointed as an NIH Postdoctoral Fellow in 1997.

"We believe that the graduates of this program will be able to contribute to an enhanced understanding of the environmentally-caused disorders of man and animals," said Dr. Slauson," both in terms of the morphologic expressions of disease and in terms of its molecular and cellular pathogenesis. "With trainees of this quality coming out of the University of Tennessee, College of Veterinary Medicine, we can all be rather proud," said Dr. Slauson.

INFLAMMATION LABORATORY

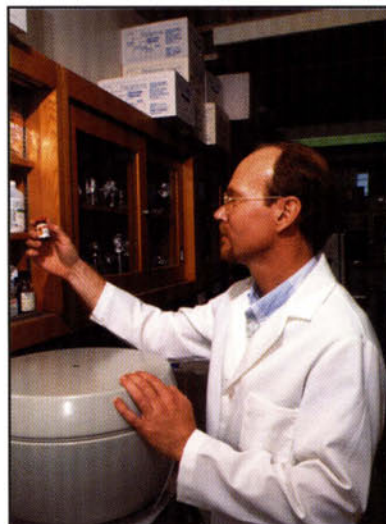
Dr. Philip N. Bochsler

Fellows and staff: Dr. Z. Yang, Dr. Gary L. Mason

Pneumonia, mastitis, and enteritis/diarrhea of newborns are all diseases which result in significant economic loss for cattle and dairy operations in Tennessee. Leukocytes (white blood cells) are an important part of the immune system and contribute to defense against many of the infectious agents which cause these diseases. Yet the reasons for occasional breakdown in the defense systems often are unknown. The main focus of Dr. Bochsler's laboratory is the basic mechanisms by which leukocytes can provide protection against infectious agents that affect cattle. The research concentrates on the actions, interactions, and synthesis of immunologically active products of white blood cells and cells lining blood vessels. Of particular interest is the responses of these cells to a component (endotoxin) of certain bacteria (Gram negative), that commonly cause serious bovine diseases. Better understanding of bovine white blood cells and the immune system will help uncover the essential events in disease production by infectious agents. This information should eventually frame the basis for improved strategies of prevention and therapy.

When liberated from gram-negative bacteria in sufficient quantity, bacterial endotoxin elicits symptoms and adverse effects that may progress to multiple organ failure and death. Endotoxin binds to various substances in the blood, and on certain cells, is part of its action and metabolism. Dr. Bochsler determined that, unlike humans, the receptor to which endotoxin binds is present on the surface of bovine blood vessels. This suggests that these cells have a very high sensitivity and low activation threshold to this bacterial toxin. It explains also some aspects of important vascular and white blood cell responses to endotoxin in several diseases of cattle. He also was able to isolate and analyze the gene encoding the surface structure (receptor) of the vascular lining cells to which endotoxin binds.

Dr. Bochsler has investigated the factors affecting nitric oxide production in lungs of cattle. Nitric oxide (NO) is a short-lived



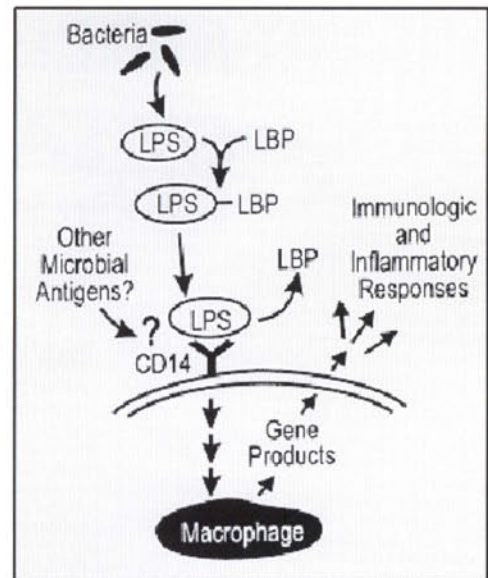
Dr. Philip N. Bochsler.

chemical reactant produced by many cells of the body, and has an important role in host defense against certain microbes, such as bacteria. He showed that nitric oxide is produced by lung scavenger cells (alveolar macrophages), but the question of whether sufficient quantities of this substance is produced for bacterial killing remains unanswered. It was determined also that common respiratory tract viruses of cattle (herpes and parainfluenza) impairs production of nitric oxide by alveolar macrophages.

Another approach taken by Dr. Bochsler and his group was to determine the relationship between bovine respiratory virus infection and fibrin formation in the lung. Fibrin formation in the lung is important because it is a common complicating factor in bovine pneumonia and may interfere with successful resolution of the disease.

They found that inoculation of lung scavenger cells with a variety of bovine respiratory viruses increased production of a substance (tissue factor) that is an initiator of fibrin formation. A bacterial component (endotoxin) often enhanced production of this substance by virus-treated scavenger cells. This work has advanced our knowledge of the mechanisms involved in the development of bovine respiratory tract disease.

Dr. Bochsler's research has been supported by the Center of Excellence and USDA.



Mechanism by which bacterial products (LPS) attach to scavenger cells (macrophage) causing the release of biologically-active products.

VIRUS MOLECULAR BIOLOGY LABORATORY

Dr. David A. Brian

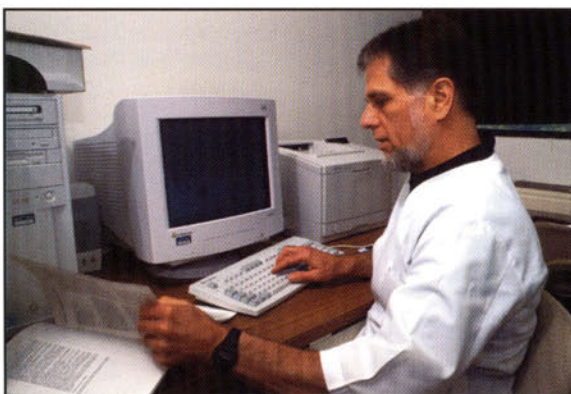
Fellows and Graduate Students: Dr. Savithra Senanayake, Dr. Jennifer Black, Gwyn David Williams, Catherine Cardullo

Dr. Brian's interest in basic molecular biology has resulted in discoveries of fundamental biological mechanisms of virus and cell replication for which he has received national and international recognition. His research exploits basic viral and cell biology discoveries for the control and therapy of important viral diseases of animals and people.

Coronaviruses cause some of the most costly respiratory and gastro-enteric diseases among livestock and fowl and disabling diseases of people. Efforts to control coronavirus infections have been frustrated by three major obstacles:

1. A weak immune responses in animals to coronavirus vaccination.
2. A logistical problem of inducing protective mucosal immunity in the newborn (often the most vulnerable victim of coronavirus infection).
3. An ability of coronaviruses to rapidly mutate into new pathogenic variants.

The primary research focus in Dr. Brian's laboratory is the molecular biology of coronavirus replication with the goal of determining how this virus induces disease. They have discovered a fragment of the virus gene (subviral replicon) of the bovine coronavirus that replicates in the presence of wild-type virus. This minigenome is being engineered experimentally to carry many kinds of potential antiviral molecules into cells. One molecule is an enzyme (ribozyme) designed to



Dr. David A. Brian.



Dr. Brian and staff.

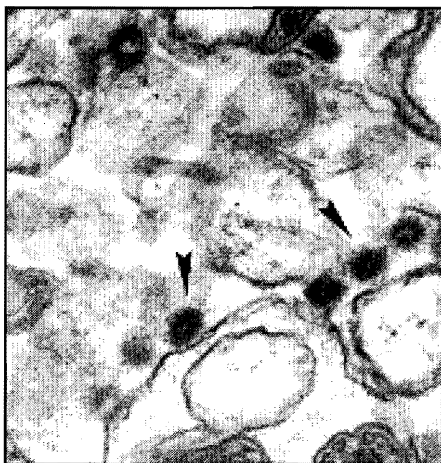


Figure 1: Electron microscope of bovine coronavirus replicating in human prostate cells. This is the first evidence of susceptibility of human prostate cells to coronavirus infection. Corona-viruses are identified by arrowheads.

destroy the gene on which the virus depends for replication (polymerase gene). This novel therapeutic approach could cure a virus-infected cell. Another molecule is a gene for virus protein (antigen) that might stimulate superior immunity against the coronavirus when inoculated into animals.

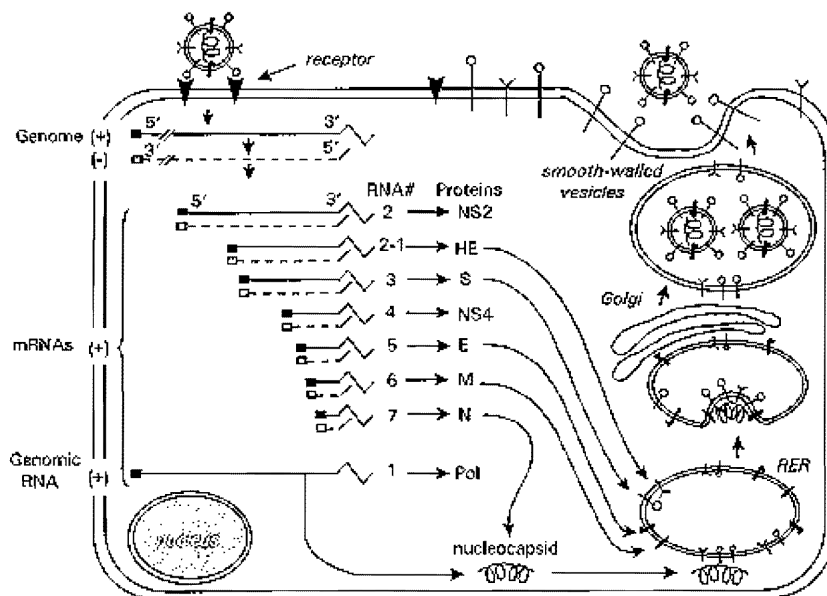
With funding from the USDA and the NIH, and modest support from the Center of Excellence, they are making an intense and systematic effort to understand how five separate genetic structural elements in the coronavirus gene (genome) function to regulate production of viral proteins. This information will have a significant impact in designing additional control and therapeutic strategies for the coronaviruses.

Through the study of the minigenome, Dr. Brian recently discovered regions at the ends of the virus genetic material that are potential sites for targeted antiviral therapy (promoter regions for the virus' replicating enzymes).

Of great interest is how a newly discovered segment in the virus gene regulates replication of the genome. The structure is absolutely required in its entirety for genome replication (RNA pseudoknot - a tRNA-like structure - in the 3' end of the bovine coronavirus genome). The hypothesis is that the RNA pseudoknot regulates production of viral proteins, which first must be accomplished before viral genetic material can be replicated. By understanding how this structure regulates this function, it may be possible to develop a therapeutic antiviral molecule. The structure-function relationship described for the pseudoknot is novel;

its function in this role (as a transfer RNA-like element) apparently has not been described for any other animal virus. An additional hypothesis is that the tRNA-like pseudoknot binds to a common cellular protein component of protein production machinery (histidyl tRNA synthetase). Because the latter is involved in polymyositis (as an antigen), an autoimmune disease in humans, a connection

Figure 2: Replication scheme for coronaviruses. Adapted from K. Holmes and M. Lai, *Virology*, 1996.



between coronavirus infection and autoimmune disease may exist. If so, this would also be a novel finding and may uncover a means by which this particular disease could be controlled.

TUMOR BIOLOGY LABORATORY

Dr. Kevin A. Hahn

Staff and Graduate Students: Dr. Ahmed Shoieb, Mary Anne Barnhill, Tracy Diehl, Marie Nolan and Jason Yarbrough

Many tumors and cancers can be treated effectively with certain drugs. Unfortunately, resistance to several drugs is becoming a serious problem in cancer therapy. Dr. Hahn's working hypothesis is that modification of the activity or function of a certain enzyme (glutathione-S-transferases) will result in the reversal of anti-cancer drug resistance and improve patients' response to therapy. Dr. Hahn's approach to confirming this hypothesis is to exploit a specific inhibitor of this enzyme and to determine whether it can reverse drug resistance in different systems.



Dr. Kevin Hahn.

Earlier work by Dr. Hahn established that the enzyme (glutathione-S-transferases) is responsible for resistance to the drug cisplatin and that the inhibitor (ethacrynic acid) reversed this resistance in cancer cells grown in the laboratory. Dr. Hahn currently is evaluating whether the inhibitor can reverse the drug resistance in an animal. He is using an animal model consisting of the nude mouse, implanted with drug resistant tumor cells or with drug sensitive tumor cells for comparison purposes. Dr. Hahn has shown also that the blood concentration of the enzyme (glutathione-S-transferases) is correlated with the successful treatment with another drug (doxorubicin) of dogs with lymphoma. Therefore, monitoring blood concentrations of this enzyme regularly during treatment may allow clinicians to identify drug-resistant patients early and initiate alternative treatments. This would decrease the likelihood of subsequent remissions and extend patients' life span.

In another approach to improve cancer therapy, Dr. Hahn is using a dog model in an detect the recurrence of lymphoma before it is clinically apparent. In this study they measured the concentration of a substance (Acid Glycoprotein) in blood in several dogs during clinical remission after having had lymphoma and treatment with doxorubicin. They found that blood concentration of

Acid Glycoprotein increased significantly just prior to the onset of a relapse. Therefore, an elevated level of this substance is useful in predicting lymphoma progression in patients after treatment. This also should be very useful in the management of drug-resistant tumors.

This research is funded by the Center of Excellence, Morris Animal Foundation and the Bayer Corporation.

TALL FESCUE TOXICITY LABORATORY

Dr. Jack W. Oliver

Staff: Dr. Eric Schultze, Dr. Robert Linnabarry, Kim Abney,
Elizabeth M. Bailey and Jane Czarra



Dr. Jack W. Oliver.

Tall fescue is the predominant cool-season grass grown in Tennessee and much of the Southeastern United States, and is common forage for cattle and other grass-eating species (herbivores). Most of the tall fescue grown in the U.S. is infected with a fungus (*Neotyphodium coenophialum*) that produces potent chemical agents known as ergot alkaloids. These alkaloids are harmful to livestock and result in serious economic losses to producers. The tall fescue toxicosis syndrome in herbivores is widely recognized as the primary grass-induced toxicity for animals in the U.S. There are more than 3.5 million acres of tall fescue in Tennessee, approximately 10% of the total U.S. acreage. Annual animal production losses to the state due to livestock consuming the infected forage are estimated at 100 million dollars. Production losses occur because of severely impaired weight gain, milk production and reproduction in animals that consume contaminated grass.

The ill effects caused by ergot alkaloids ("ergotism") is certainly not a new disease entity, having been recognized in people for hundreds of years. The disease in humans is associated with the eating of grains contaminated with a fungus (*Claviceps spp.*-"ergotized") that produces alkaloids similar to those present in infected fescue grass. Tissue lesions in people caused by ergotized grains were described in the 1930s, and outbreaks of a similar disease in cattle identified in the 1950s was associated with grazing on Kentucky 31 tall fescue grass. The incrimination of fungus contamination of tall fescue grass as the cause of toxicity in cattle was made by a group of researchers at the University of Georgia in 1977. However, despite numerous studies at Southeastern Land Grant Colleges designed to understand and alleviate the disease problem and intensive discourse among researchers worldwide, production losses continue in animals that graze contaminated tall fescue

grass.

The long-term goal of tall fescue research is to prevent the health problems in herbivores that consume the grass, while maintaining the drought and insect resistance imparted to the plant by the presence of the fungus and the ergot alkaloids. Development of an effective vaccine or chemical treatment is needed to counter the toxic effects in animals, that would allowing full usage of this valuable forage. Alternatively, identifying the specific toxic alkaloids in tall fescue grass will allow plant scientists to genetically manipulate fescue grass to eliminate toxic alkaloid production.

Research by Dr. Oliver and his co-workers on reducing the severity of the disease has, among other advances, resulted in development of an effective anti-fescue toxicosis vaccine (U.S. patent awarded). The nutrient content of tall fescue is excellent and this forage could be exploited even more widely if the associated health problems in herbivores could be prevented. The grass is well established, and valued for its vigor and root establishment making it an important factor in control of soil erosion, and an extremely popular turfgrass.

The short-term goals of fescue toxicosis projects have focused on injury to cardiovascular tissues of animals consuming fungal-infected tall fescue grass. Although much remains to be learned, excellent progress has been made. Dr. Oliver's work has established that vascular damage may be the central event induced by ergot alkaloids in animals:

1. The ability of blood vessels to contract is increased by changes in blood vessel structure (alpha-adrenergic-2 receptors) that trigger vessel narrowing.
2. Soluble chemical factors released by the cells that line blood vessels further produce vessel contraction and narrowing (thromboxane A₂, angiotensin II).
3. Circulating ergot alkaloids from fungal-infected fescue result in the release of factors that promote blood clotting (Von Willibrand factor) and damages lining cells of blood vessels.
4. Damage to the lining cells of blood vessels and the

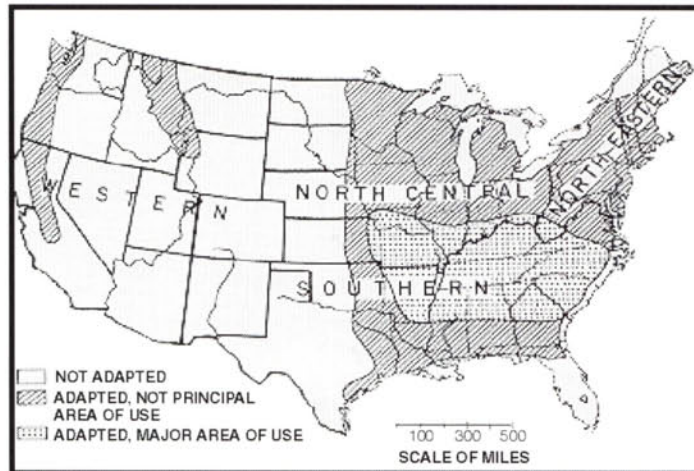


Figure showing tall fescue use/adaptation.
From R. Buckner & L. Bush (Eds.), *Tall Fescue* (1979), p.15.

associated attempt at repair (platelet aggregation and blood clotting), result in release of factors that cause vessel wall thickening (serotonin, thromboxane A₂, angiotensin II).

As a consequence of injury to blood vessels, blood flow to tissues is impaired thereby affecting the function of body systems. Examples include:

1. Decreased blood flow to the skin affects haircoat quality (unthrifty appearance) and contributes to heat stress in animals by interfering with heat loss from body surface.
2. Altered blood flow and blood clotting in the small vessels of lung tissues impairs oxygen distribution to tissues, and decreases heat loss via the lungs.
3. Altered blood flow to mammary tissues contributes to decreased milk production.
4. Altered blood flow to reproductive structures affects reproductive capacity.
5. Decreased blood flow to the intestines and the liver affect body metabolism and suppresses growth (decreased weight gains).

Dr. Oliver and staff.



The achievements of the researchers in the College was recognized in 1997 by an invitation to Dr. Oliver to deliver a plenary paper on the physiological manifestations of fescue toxicosis in ruminants at the Third International Symposium on Fescue Toxicity that was held in Athens, Georgia, May 28-31, 1997. Over 100 researchers from 14 countries attended this major, worldwide event. In October of 1997, USDA awarded a substantial competitive research grant to Dr. Oliver and co-workers for three years to continue study of mechanisms of toxicity caused by the fescue alkaloids. The study will allow continued in-depth examination of toxic mechanisms of alkaloids, and will establish relative toxic effects of the major alkaloids found in fungus-infected tall fescue.

MASTITIS RESEARCH LABORATORY

Dr. Stephen P. Oliver

Post-doctoral Research Associates and Staff: Dr. Raul Almeida, Dr. Weihuan Fang, Barbara Gillespie, Mark Lewis, Doug Luther, Susan Ivey, Lori Coleman

Research conducted by Dr. Oliver focuses on mastitis in dairy cows caused by environmental organisms. Objectives are to:

1. Characterize factors that affect resistance of the udder to mastitis.
2. Characterize factors and mechanisms, that permit mastitis pathogens to invade the udder and produce mastitis.
3. Develop and evaluate techniques for the prevention and control of mastitis in dairy cows.

Dr. Oliver's research program incorporates both applied and basic research. Applied studies concentrate on issues of concern to the dairy industry that can have an immediate beneficial impact. This research includes strategies for controlling mastitis in heifers and the influence of mastitis on reproduction of high-producing dairy cows.

Basic research is aimed at discovering innovative methods of mastitis control by exploiting biotechnological advances. This research includes development of nucleic acid probes for rapid and accurate detection of mastitis organisms and organisms responsible for food poisoning. Other studies being done concern virulence (severity) factors produced by and immunity to certain mastitis-producing organisms (streptococcus species) in cows. They also are attempting to identify disease-resistant genes of dairy cattle.

Mastitis is caused by several kinds of bacteria that are capable of infecting the udder. Mastitis pathogens invade the udder,



**Dr. Stephen P.
Oliver (center)
and staff.**

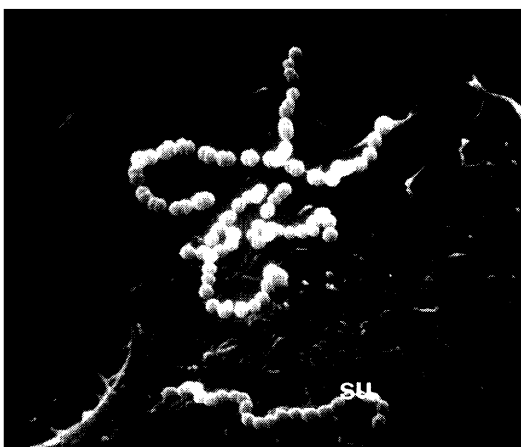


Figure 1: Electron microscope view of bacteria attached to a milk-secreting cell.

world.

Dr. Oliver has increased the awareness of scientists, extension specialists, dairy producers, pharmaceutical companies and other members of the dairy community of the importance of environmental pathogens in bovine mastitis. Furthermore, he has discovered fundamentally-important information that is critical for controlling the heterogeneous organisms that cause mastitis. The ultimate goal of Dr. Oliver's research is to enhance the quantity and quality of milk produced by and to reduce the economic impact of mastitis for dairy producers in Tennessee, the U.S., and throughout the world. One aspect of this work is to develop a vaccine to prevent mastitis and thereby eliminate the need for treatment with antibiotics.

Dr. Oliver was the first to show that mastitis in pregnant dairy heifers occurred frequently near calving and that many of these infections persisted into early lactation. His research has resulted in a simple, effective and inexpensive method for controlling mastitis in heifers. Intra-mammary antibiotic infusion before calving, was shown to be an effective procedure for:

1. Eliminating many infections in heifers during late gestation.
2. Reducing the prevalence of mastitis in heifers during early lactation.
3. Reducing the prevalence of mastitis in heifers throughout lactation.

Several studies over the past 13 years at the UT Dairy Experiment Station involved collection of milk samples for microbiological evaluation at intervals before calving, during lactation and during the dry period. About 15,000 samples are collected and processed each year from cows in this herd. Data from those studies have been computerized, producing perhaps the largest

mastitis database in the world. It now is being exploited for retrospective studies and will provide valuable information on the spread of mastitis pathogens, such as *Streptococcus uberis* and *Streptococcus dysgalactiae*, in high-producing dairy herds.

Recently they evaluated the influence of mastitis on reproduction in Jersey cows and found it profoundly impairs reproduction during early lactation. Consequently, two proposals were funded recently by the American Jersey Cattle Association to delineate mechanisms by which mastitis can influence reproductive performance.

Dr. Oliver has been actively seeking the identification of virulence (severity) factors produced by certain mastitis organisms (streptococcus species) and implications of immunity to them. In many dairy herds *Streptococcus uberis* and *Streptococcus dysgalactiae* are responsible for a high proportion of mastitis with varying degrees of severity in lactating and non-lactating dairy cows. Strategies for controlling these mastitis pathogens are poorly defined and inadequate. This research focuses on:

1. Genetic characterization of *S. uberis* and *S. dysgalactiae*.
2. Characterization of *S. uberis* and *S. dysgalactiae* with particular emphasis on factors involved in adherence and invasion into mammary epithelial cells.
3. Evaluation of immunity after immunization of dairy cows with components of *S. uberis* and *S. dysgalactiae*.
4. Effectiveness of experimental vaccines to *S. uberis* and *S. dysgalactiae* mastitis during the nonlactating period.

Dr. Oliver's research group determined that *S. uberis* and *S. dysgalactiae* readily adhered to and invaded cells lining the bovine udder (see Figures 1 and 2). Chronic infections then may develop, and their intracellular location may protect these bacteria from anti-microbial drugs and host defense mechanisms. Mastitis pathogens cultured in the presence of mammary epithelial (lining) cells in the laboratory synthesize proteins not detected when bacteria are cultured alone. These unique proteins likely are involved in virulence of bacteria including their capacity to adhere and invade mammary epithelial cells. Thus, culture of mastitis pathogens in the laboratory in the presence of mammary epithelial cells may result

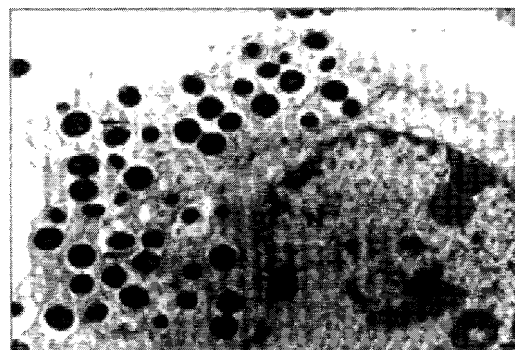


Figure 2: Electron microscope view of a section through a milk-secreting cell containing several bacteria.

in expression of bacterial virulence factors similar to that which occurs in the animal. This important discovery will be exploited for the development of vaccines and management of mastitis.

Dr. Oliver has communicated results of his research via scientific and popular press publications, and via presentations to several different target groups at state, regional, national and international meetings and conferences. There is considerable interest in this work throughout the dairy community, and Dr. Oliver has been a popular speaker and author on heifer mastitis and its control.



Dr. Oliver and staff.

In addition, Dr. Oliver has made several presentations to groups such as The University of Tennessee Agricultural Committee Board of Trustees, the Institute of Agriculture Development Board and the 21st Century Campaign Steering Committee, Tennessee Agricultural Experiment Station Department Heads' Conference, and the Tennessee Higher Education Commission Center of Excellence Review team. This spring, Dr. Oliver has given presentations entitled "The Univer-

sity of Tennessee Mastitis Research Program: Making a Difference Through Research" to the Tennessee House of Representatives Agriculture Committee, to The University of Tennessee Institute of Agriculture Alumni Council, and to The University of Tennessee Institute of Agriculture Development Board and Agriculture Steering Committee for the 21st Century Campaign.

Dr. Oliver's research in mastitis was recognized by the UT Institute of Agriculture in 1998 with the Pendergrass Award. The award, named for former vice president for agriculture Webster Pendergrass, is presented in tribute to a faculty member who has contributed most to the fulfillment of the Institute's goals.

Dr. Oliver's research has been supported for several years by the Center of Excellence, but his primary funding has been derived from substantial grants from foundations and the pharmaceutical industry.

VIRAL IMMUNOLOGY LABORATORY

Dr. Barry T. Rouse

Fellows, Staff and Graduate Students: Uday Kumaraguru, Teresa Sobhani, Dr. Johnson Thomas, Dr. Ila Davis, Massoud Daheshia, Dr. Shivaprakash Gangappa, Sirdhar Govindaswamy Dr. Nelly Kuklin, Shilpa Deshpande, Dr. Stewart Novinger, Dr. Zhiya Yu, and Sangjun Chun

Dr. Rouse's research deals with the issue of how the body recognizes and interacts with viral infections. The virus they study is herpes simplex virus, an agent that affects up to 80% of mankind. This virus causes a variety of diseases, but is rarely lethal. Following initial infection, the body usually fails to cast out the virus, and it persists in association with cells of the nervous system in a condition called latency. Unfortunately this state of affairs is not permanent, since periodically some latently-infected nerve cells reverse their interaction, and new virus is produced which may cause a secondary expression of lesions. Such recrudescent lesions occur frequently in some individuals and are the cause of considerable pain and distress. Much remains unresolved regarding the nature of the interaction of the herpes simplex virus with its host. One such unresolved issue is why the reactivation episodes are clinically significant in some individuals, but unnoticed in others. A likely answer to this question lies in the effectiveness of one or more components of the immune defense system. However, this is a difficult issue to study in the human host.

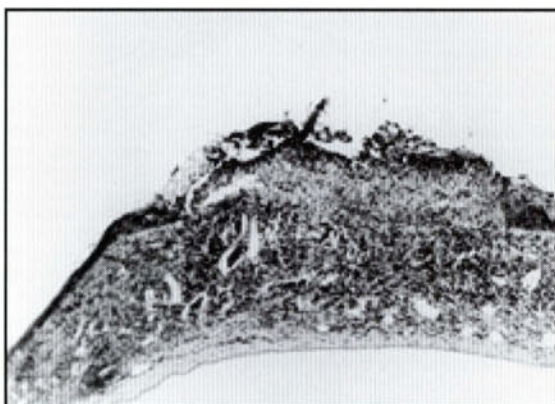
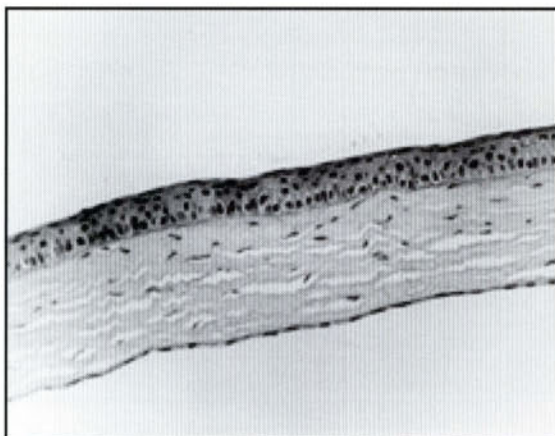


Dr. Barry T. Rouse.

The Center of Excellence supports some aspects of this research, but it is funded primarily by very substantial grants from the National Institutes of Health. Their research has generated national and international interest, and the laboratory is recognized as one of the premier viral immunology programs in the country.

Value of Animal Models

Dr. Rouse's approach to understanding the interaction between HSV and the immune system has been to use model infections in experimental animals, using the mouse and a variety of



1) Normal cornea (top photo)
2) Diseased cornea (bottom photo).

routes of infection. Their aim is to identify immune defenses that best correlate with protection, seeking a means of vaccination and immune manipulation to enhance the efficiency of appropriate immune defenses.

Immunity to Herpesvirus Infections

Currently, Dr. Rouse's major approach is to use novel vaccines composed of nucleic acids, which encode selected proteins of HSV as a way of inducing protection. They combine this approach with the co-administration of molecules that can manipulate the quality of immune responses induced. Thus, it is known that molecules (so-called cytokines) released by the body's own T lymphocytes and other white blood cells may profoundly influence crucial events of the immune response.

Accordingly they have found that the presence of some of these cytokines results in prompt and effective immune induction whereas the presence of others may lead to a type of immunity that is less effective. They

are exploring the use of DNA, encoding various cytokines, given at different intervals in relation to either infection or immunization for their effect on the level of immune protection. Their results may provide clues useful for the design of future herpesvirus vaccines.

Disease Caused by Immune Responses to Herpesviruses

The immune response to a virus is not always a beneficial protective event. In some situations aspects of immunity seem to account for development of lesions. Such situations are usually referred to as immune pathologies. At least one disease process caused by herpes simplex virus infection may represent an immunopathological event, the Herpetic Stromal Keratitis (HSK) syndrome. HSK involves the cornea of the eye and is the most common infectious cause of vision impairment in the USA. Many thousands of persons are affected, and a significant number require corneal transplants. Dr. Rouse is attempting to understand the various events that result in keratitis with the ultimate objective of finding steps amenable to manipulation for minimizing lesions. They have identified many of the host cells and their products involved in lesion development

in mice. They showed also that, if the animals are genetically unable to generate immune responses or if certain aspects of immunity are suppressed, keratitis does not develop. This is the primary evidence supporting the notion that herpes keratitis is, in fact, an immunopathological lesion, i.e. without a response by the immune system, damage to the eye would not result.

It would not be wise to totally suppress immunity in an attempt to control HSV, because, without some immune protection, the virus may spread beyond local sites (such as the eye) and cause damage to the nervous system. This may have lethal consequences. There may be more subtle ways of adjusting the immune response such that protection will be preserved and pathology diminished. One way, discovered in Dr. Rouse's laboratory, that seems to accomplish this objective is to adjust the cytokine environment of the cornea using DNA vaccines encoding cytokines. One cytokine, called IL-10, appears particularly useful for this purpose.

Although replication by the virus in the eye appears as an essential event to set off keratitis, they found that the continued presence of the virus is not needed for persistence of the inflammatory process. Indeed it could be that the virus somehow sets off an inflammatory event that, in its latter stages, becomes an autoimmune reaction.

According to this idea, herpes simplex virus may damage the cornea, causing a slight change in tissue composition such that it then becomes the target of the immune response. Some research results even suggest that a component of the virus itself may act as a molecular mimic of the host protein that then drives autoimmunity. Dr. Rouse and his co-workers are striving to evaluate these ideas on the role of the immune response in herpes keratitis using a variety of genetically-defined animal model systems. They hope that their research will culminate in an understanding of the molecular and cell-specific steps that occur during keratitis, and that clues will emerge as to how best to manage this tragic disease in people.



Dr. Rouse and staff.

EXPERIMENTAL ONCOLOGY LABORATORY

Dr. Hildegard M. Schuller

Fellows, Staff and Graduate Students: Dr. Howard K. Plummer III, Dr. Diann L. Weddle, Dr. Barbara J. Sheppard, Dr. Brian A. Jull, Michelle R. Williams, and C. Brian Porter

Lung cancer is the leading cause of cancer deaths in all industrialized countries. East Tennessee has one of the highest lung cancer rates in the nation. Although cancers at other organ sites are more than twice as common, their cure rate is considerably higher. The most common cancer in men is prostate cancer with a cure rate of 84%. Breast cancer is the leading type of cancer in women with a cure rate of 74%. By contrast, 158,700 (89.3%) of the 177,700 patients diagnosed with lung cancer in the year 1997 died within 12 months of diagnosis.



Dr. Hildegard M. Schuller.

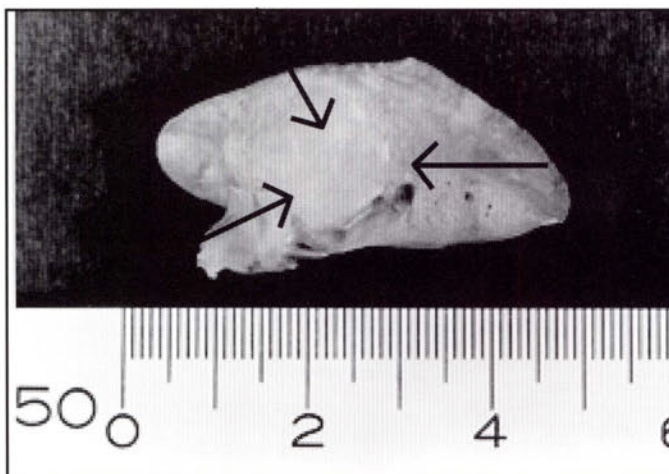
Smoking and exposure to second hand smoke are the most intensively studied and best-documented risk factors for the development of lung cancer. Contrary to cancers at other organ sites, the incidence of lung cancer continues to rise in all industrialized nations. Moreover, teen smoking in the U.S. has increased at an alarming rate, thus setting the stage for even higher numbers of lung cancer cases 30-40 years from now. Another important contributing factor to the rise in lung cancer cases is the growing number of lung cancers developing in individuals who have never been exposed to primary or second hand smoke. This trend, which has been globally observed during the last two decades in all industrialized countries, is particularly evident for pulmonary adenocarcinoma. Of the six types of lung cancer recognized by the World Health Organization (WHO) classification, two (small cell carcinoma and adenocarcinoma) account for 90% of all lung cancers, with 30% of these cases unrelated to a history of exposure to primary or second hand smoke.

The lung cancer "epidemic" is closely related to an increase in chronic lung diseases such as bronchitis, bronchiolitis, asthma, emphysema, and chronic obstructive pulmonary disease. For all lung cancer types, chronic lung disease has

been identified as a risk factor even without a history of exposure to smoke. This disease complex, which often is referred to as "allergies," has the same geographic distribution as lung cancer with which it shares some risk factors such as smoking and air pollution. It has been stated that East Tennessee is "the land of allergies."

Dr. Schuller's research has been dedicated to the study of lung cancer for over 20 years. It is her belief that effective strategies for the prevention and therapy of this disease complex can only be based on an in-depth understanding of the regulatory mechanisms which govern the growth of normal lung cells and the cancers arising from such cells. Contrary to other researchers who are searching for the "magic molecular event" responsible for the genesis of all lung cancers, she hypothesized that different lung cell types and different types of lung cancer may be governed by different regulatory mechanisms. These in turn may be differently affected by known risk factors for the disease.

Dr. Schuller's achievements in lung cancer research have been recognized nationally and internationally. Her research has been supported by the Center of Excellence, but her primary support comes from substantial grants of the National Cancer Institute and the pharmaceutical industry.



Lung tumor induced in a hamster by a metabolic product of nicotine and increased intrapulmonary carbon dioxide.

Recent Achievements

Dr. Schuller's recent research has been prompted by the epidemiological evidence which links small cell lung carcinoma to both smoking and chronic lung disease. Her group is exploring whether factors exist unique to tobacco constituents and chronic lung disease that might interfere with growth regulation in these types of cancer cells and the normal cells from which they originate (pulmonary neuroendocrine cells). Using this approach, they found that the growth of these normal cells is regulated by an aspect of the nervous system (autonomic) via the release of a chemical messenger from nerve endings (the neurotransmitter acetylcholine). They have identified the molecular mechanism that triggers specific growth of this cell type. The first discovery was that the chemical messenger binds to a specific surface structure unique to these cells.

They now have dissected the chemical events that are triggered by the binding of the chemical messenger to the receptor. It



Dr. Schuller and staff.

culminates in the release of a growth factor, serotonin, into the blood stream. The release of this growth factor selectively stimulates the growth of the neuroendocrine cells. Their studies showed that nicotine and its product produced in the body stimulate the production of high levels of this growth factor by binding to the receptor on these cells. Minute amounts of these tobacco-specific agents therefore act as powerful and selective growth stimulators for these cells in smokers.

Their experiments also showed that carbon dioxide selectively sensitizes the receptor to nicotine, thus dramatically promoting the release of the growth factor and growth stimulation in response to these tobacco-specific toxicants.

Chronic lung diseases impair pulmonary ventilation, thus increasing the concentration of carbon dioxide in the lungs. The increased carbon dioxide therefore drastically increases the likelihood for the development of small cell lung cancer in smokers. In a hamster model developed by Dr. Schuller, this hypothesis gains powerful support from their finding that nicotine and its metabolic product, which is non-carcinogenic in healthy animals, causes lung tumors in hamsters under conditions of increased intrapulmonary carbon dioxide.

Their findings explain why small cell lung cancer is virtually never found in nonsmokers and why among those who smoke, this cancer type develops primarily in individuals with chronic lung disease. Moreover, these data provide a basis for the development of novel drugs and treatments for this lung cancer type.

BIOLOGICAL ACTIVITY TESTING AND MODELING LABORATORY

Dr. Terry W. Schultz

Staff and Graduate Students: Glendon Sinks, Betsy Gregory and Anna Bearden

Modern society uses and misuses hundreds of thousands of organic chemicals. While the need for information to aid industry and government in hazard and risk assessment of chemicals has never been greater, only limited toxicological assessment has been done on a small fraction of these chemicals. At the same time the resources allocated to generate these data are being reduced. As a consequence, the field of structure-toxicity has been developed and is providing important answers in a timely and resource-efficient manner. Today, structure-toxicity models are considered reliable tools for use in hazard and risk assessment. Dr. Terry W. Schultz, at the University of Tennessee's College of Veterinary Medicine has been a leader in the development of this science.

Structure-toxicity relationships correlate toxic potency of chemicals to their chemical properties. Since properties of chemicals are related to their structure, structure-toxicity studies investigate the sort of chemical structure that will produce a well-defined adverse or toxic response. Structure-toxicity studies have been conducted for over a century. A. F. A. Crois defended his thesis entitled: "Action de l'alcool amylique sur l'organisme" before the Faculty of Medicine, University of Strasbourg, Strasbourg, France on January 9, 1863. He noted the relationship between the toxicity of simple alcohols and their water solubility. This relationship demonstrated the central axiom of structure-toxicity modeling - the toxicity of molecules is reflected in their chemical structure. The science of structure-toxicity is truly an integrated one (see figure, opposite page).

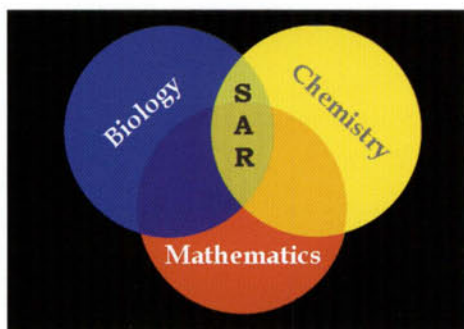
The objective of structure-toxicity analyses is to define, as accurately as possible, the limits of variation in the structure of a chemical that are consistent with the production of a specific toxic effect. Moreover, such analyses examine ways in which alterations in structure and overall properties of the molecule influence



Dr. Terry W. Schultz.

toxicity. If enough data related to toxicity become available, a hypothesis can be developed regarding the molecular basis of interaction between the toxicant and the site of its toxic action in the body or cell.

Dr. Schultz directs the Biological Activity Testing and Modeling Laboratory in the College of Veterinary Medicine at the University of Tennessee, which has had a long-standing interest in structure-toxicity modeling. The U.S. Department of Energy and the U.S. Environmental Protection agency are the primary sources of funding for this research. The Center of Excellence also has invested in this research, which during the past 15 years it has provided expertise to industry and agencies not only in Tennessee, but also to the entire nation. Moreover, Dr. Schultz has built a solid international reputation in the field through collaborative efforts throughout the world.



Quantifiable toxicology involves numerous disciplines.

Since the establishment of the Center of Excellence in Livestock Disease and Human Health in 1985, the Biological Activity Testing, and Modeling Laboratory has tested an average of more than 100 chemicals per year. This work has developed the largest chemical toxicity database in the world. The long-term goal of this program is to develop a computer-aided, knowledge-based system that will predict acute toxic potency from molecular structure. The current version accurately models the toxicity to humans of about 75% of the industrial organic chemicals.

The short-term goal of this program is to develop a better understanding of man-made chemicals that cause disruption of endocrine (hormonal) systems. In particular, their current project focuses on identifying the molecular structural features associated with industrial organic chemicals that mimic estrogens. Recent achievements by this group include the prediction of the capacity for chemicals to form highly toxic, free radicals (reactive products) by certain biochemical mechanisms (either by photo-induction or by mimicking synthetic cytochromes).

As we enter the 21st century, the Biological Activity Testing and Modeling Laboratory stands ready to assist industry and government to address toxicological problems by acquiring specific data and to develop tools to be used in predicting toxicity from molecular structure.

ANTICANCER MOLECULAR ONCOLOGY LABORATORY

Dr. Hwa-Chain R. Wang

Dr. Wang's long-term research goals concern tumor-specific intracellular molecular signaling network and to uncover signaling pathways that can be induced by anticancer agents, leading cancer cells to a programmed cell death (apoptosis).

Short-term goals are to identify intracellular signaling elements whose activation is involved in induction of apoptosis of cancer cells. A corollary to this is to identify novel anticancer agents which may selectively induce apoptosis of cancer cells, while sparing normal cells. Ultimately, he expects to apply the understanding of intracellular signaling control to anticancer therapeutics.

Currently, Dr. Wang focuses on two approaches. The first is to understand the molecular and cellular function of a novel intracellular enzyme, which is activated in cells at the late stage of cellular malignancy and in cells undergoing programmed cell death induced by forms of acute stress. The second is to study molecular and biological activities of a novel natural anticancer agent, which selectively induces programmed cell death of cancer cells.

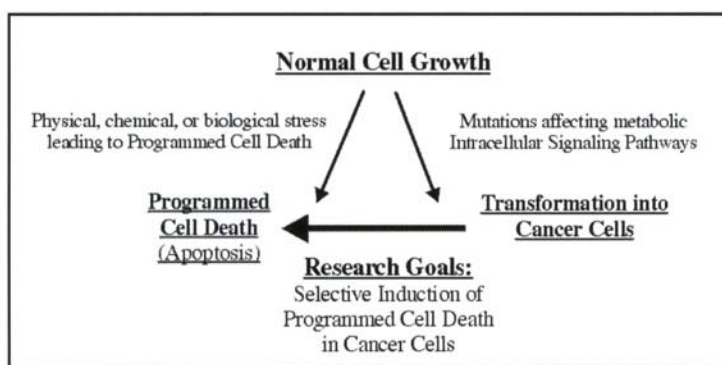
Dr. Wang has identified a novel enzyme (kinase SAMK/Krs1) that is activated in cells at the late stages of transformation into cancer cells. The same enzyme is also induced in cells undergoing programmed cell death as a result of a variety of physiological, chemical or physical stresses. Dr. Wang determined that the gene encoding this enzyme might represent a member of a new kinase enzyme family. He is investigating the molecular and biological roles of this enzyme gene in cancer development and programmed cell death. Uncovering the apparent novel signaling pathway that cross-links cancer development of cells to programmed cell death should be directly exploitable for development of anticancer



Dr. Hwa-Chain R. Wang.



Dr. Wang and staff.



Research goals.

agents. A novel natural substance was isolated from bacterial cultures, and Dr. Wang discovered, it induces programmed cell death in these cells whereas it merely inhibits growth in normal cells. Studies on the molecular activities of this drug on different intracellular metabolic signaling pathways suggest it selectively induces programmed cell death in cancer cells only. At least three important intracellular metabolic signaling pathways are affected. Dr. Wang has made progress in testing this phenomenon in cell cultures and is developing a unique model for testing in an animal model (mice). In the latter, he hopes to determine the efficacy of this anticancer agent at different stages of malignancy. His research therefore is unique in that it links the molecular, cellular and animal system approaches in the development of anticancer agents.

Dr. Wang's research is supported by the Center of Excellence, but his primary funding source is the National Cancer Institute.

therapeutics.

Investigation into the molecular mechanisms of potential anticancer therapeutic agents on a variety of cancer cell types, particularly human breast cancer cells, is ongoing. Cancerous mouse embryo cells and various human tumor cells are used to screen anticancer

MOLECULAR GENETICS LABORATORY

Dr. J. Erby Wilkinson

*Fellows, Graduate Students and Staff: Dr. Carla Sommardahl,
Dr. Sharon Witonsky, Dr. Joanne Zahorsky, Nancy Nielson,
Marilyn Cottrell*

Dr. Wilkinson's primary research focus is defining the role of certain genes and gene products in specific diseases. Many diseases of people and animals are the result of the cumulative effects of altered gene activity. Any given disease may result from the increased or decreased activity of normal genes, the activity of normal genes at the inappropriate time or place, or the activity of a mutant gene. Most diseases are the result of the cumulative effects of all these molecular events.

The group uses the tools of molecular and cellular biology, informatics, the emerging technologies of genetic manipulation of the mouse, and information generated in the Human Genome Project to develop animal models of human and domestic animal diseases. Unlike many other groups, all their efforts start with the identification of a mutant mouse with a particular disease. They then use the skills of clinicians, pathologists, and other researchers to define the disease and identify the nature and effect of the mutation.

They are actively involved in the development and identification of mutant animals, and have genetic 'tricks' to limit the number of animals needed to produce mutations in every gene in a specific region of chromosomes. By using "super mutagens," chemicals that produce many mutations in a cell, they are able to quickly produce and identify several mutations within a single gene. These types of mutations are particularly important because they represent a range of gene malfunctions that result in varying degrees of disease severity. This information is especially useful to the pharmaceutical industry, since any drug that is developed may only partially inhibit or enhance the function of a specific gene and its metabolic pathway.

In addition to these newest mutations, known as saturation mutants, the laboratory is also involved in the identification and analysis of spontaneous mutants and various mutants produced by



Dr. J. Erby Wilkinson.



(top) Normal mouse.
(bottom) Mouse
with scurfy.

genetic manipulations. They use all the tools of modern molecular biology and the traditional tools of immunology, pathology, in addition to developmental biology, to completely evaluate the role of specific genes in specific diseases. These studies, which are part of the federal government-sponsored human and mouse genome initiatives, include collaborations with a number of investigators at the Oak Ridge National Laboratory. Several projects have matured considerably in the past year, and several new

projects have been initiated.

They have identified a gene that causes a fatal congenital kidney disease in humans (polycystic kidney disease). The various forms of this disease represent a spectrum of diseases that are a significant health problem worldwide. One form is a significant cause of mortality in newborns. In addition to closely mimicking human polycystic kidney disease, this mutant line of mice is unique in that the mutant gene now has been cloned and characterized by Dr. Wilkinson's group. Thus, for the first time, a gene directly associated with polycystic kidney disease was identified. Studies are underway to further define normal structure and function of this gene to determine how mutations in the gene result in the pathologic changes seen in the disease, and to identify other genes affecting the severity of the disease.

In addition, they have identified and characterized unusually primitive cells in the livers and pancreas of these mutant mice. The existence of such cells and the impact of their manipulation may be important in the treatment of liver and pancreatic diseases. The researchers also demonstrated recently that the polycystic kidney disease gene is an important factor in cancer of the liver, kidney, and pancreas. From these studies, possible new avenues of therapy can be explored.

Other projects include the analysis of a number of mutations that alter the immune system. In one recently completed project, they determined the cellular basis for a severe, rapidly fatal disease of the immune system in certain (scurfy) mice. They are currently working with collaborators to identify the mutant gene and determine how it causes the disease. Another line of mutant mice has been analyzed because of a high incidence of tumors. The tumors have been characterized and they anticipate cloning the mutant gene over the next year. Their data indicates that a unique, uncharacterized gene responsible for suppressing these tumors contains a mutation.

INFORMATION DISSEMINATION OF RESEARCH TO THE GENERAL PUBLIC

Dr. Nancy Howell

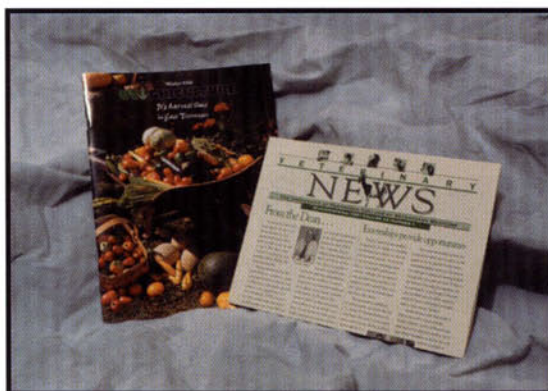
Providing the public with information about Center of Excellence research is an important activity of the College of Veterinary Medicine. To accomplish the goal of disseminating research information, the college utilizes many resources.

The college produces a general newsletter twice annually, distributed throughout Tennessee and beyond, which highlights research activities. Features on on-going research, in addition to results from concluded research are included in the publication, *Veterinary News*, which is written for general audiences. Features appear in other University of Tennessee publications, including *UT Agriculture*, *UT Alumnus* and *Tennessee AgriScience*.

News releases are routinely distributed to state media, in addition to certain regional and national media. Television and print publications produce numerous features about the college each year, many related directly to research conducted through the Center of Excellence. Public displays about the college also frequently include highlights of COE research. In addition, Center of Excellence researchers are invited to share their research not only professionally, but as speakers to commodity groups, civic groups and other interested individuals.

Another method of information dissemination is through the college's site on the world wide web. Research is a major component of the site, with some COE projects, such as the tall fescue toxicity research, including detailed information concerning their progress.

Providing this material in the general media not only informs the public of important information, but helps the public better understand science and the practical applications of science to their daily lives.



Research information is distributed through a variety of UT publications, as well as local and national media.

BENCHMARKS

Table 1
CENTER OF EXCELLENCE FOR LIVESTOCK DISEASES AND HUMAN HEALTH
EXTERNAL FUNDING EXPENDITURE LEVELS SINCE ESTABLISHMENT

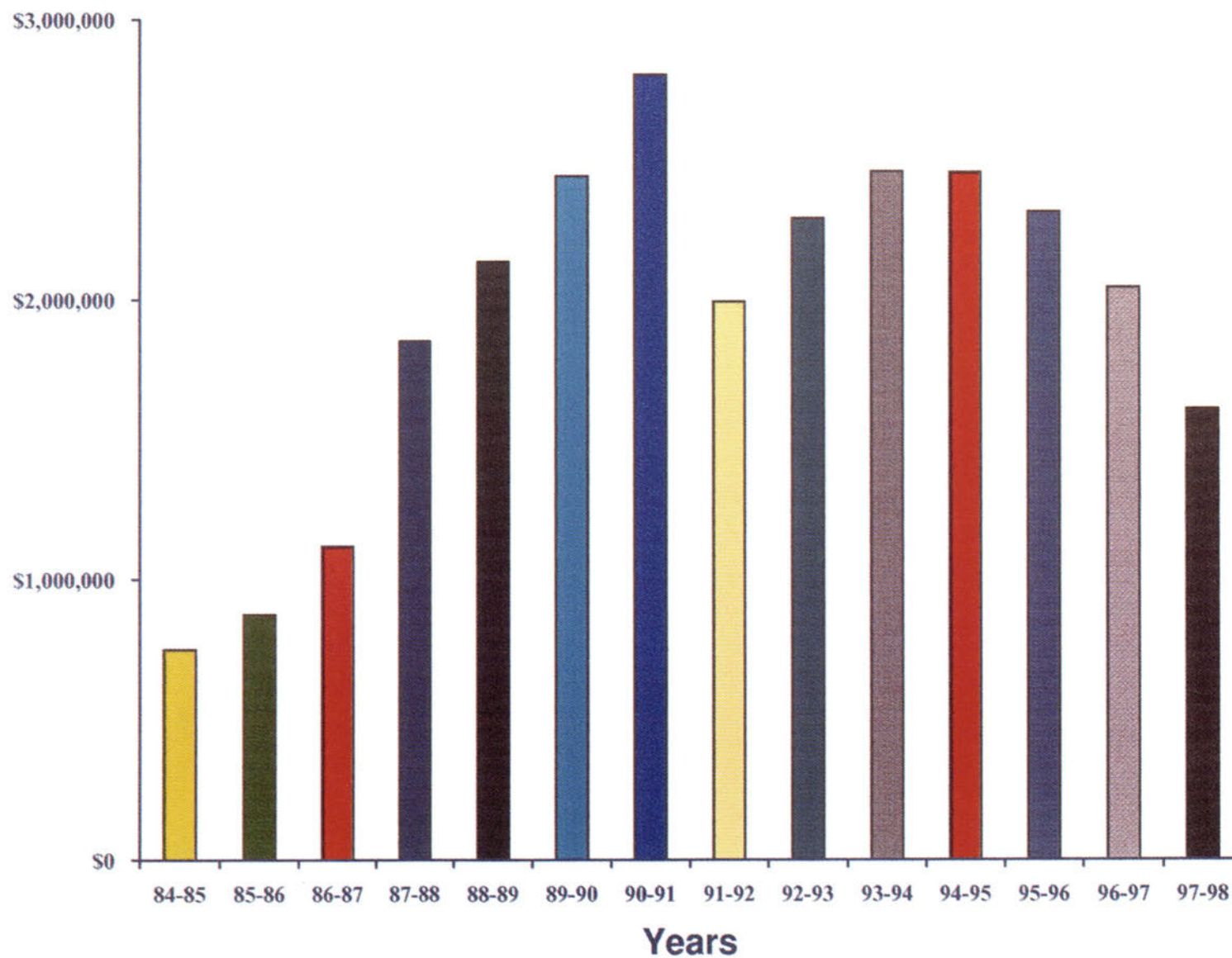


TABLE 2
CENTER OF EXCELLENCE IN LIVESTOCK DISEASES AND HUMAN HEALTH
BENCHMARKS OF FACULTY ACCOMPLISHMENTS

FACULTY MEMBERS ASSOCIATED WITH THE CENTER OF EXCELLENCE

	Year 5 (Final Year of Initial Commitment Center) 1988-1989			Year 6 (Year 01 as Accomplished Center) 1989-1990		Year 7 (Year 02 as Accomplished Center) 1990-1991		Year 8 (Year 03 as Accomplished Center) 1991-1992		Year 9 (Year 04 as Accomplished Center) 1992-1993	
	Target	Actual	Avg	Actual	Avg	Actual	Avg	Actual	Avg	Actual	Avg
Number of:											
Articles		74	(3.22)	68	(2.62)	97	(3.73)	83	(4.37)	78	(3.90)
Books or Book Chapters		7	(0.30)	17	(0.65)	14	(0.54)	6	(0.32)	7	(0.35)
Published Proceedings		21	(0.91)	37	(1.42)	42	(1.62)	24	(1.26)	17	(0.85)
Total Publications	2.82	102	(4.43)	122	(4.69)	153	(5.89)	113	(5.95)	102	(5.10)
Abstracts	0.30	33	(1.43)	66	(2.54)	48	(1.85)	47	(2.47)	53	(2.65)
Invited Participation at:											
Regional Meetings	0.50	36	(1.56)	19	(0.73)	28	(1.08)	13	(0.68)	15	(0.75)
National Meetings	1.25	55	(2.39)	28	(1.08)	44	(1.69)	36	(1.89)	47	(2.35)
Faculty in Center		23		26		26		19		20	
Number of Visitors		10		17		17		12		12	

	Year 10 (Year 05 as Accomplished Center) 1993-1994		Year 11 (Year 06 as Accomplished Center) 1994-1995		Year 12 (Year 07 as Accomplished Center) 1995-1996		Year 13 (Year 07 as Accomplished Center) 1996-1997		Year 14 (Year 08 as Accomplished Center) 1997-1998	
	Actual	Avg	Actual	Avg	Actual	Avg	Actual	Avg	Actual	Avg
Number of:										
Articles	95	(5.00)	132	(6.29)	153	(7.29)	176	(7.33)	179	(11.2)
Books or Book Chapters	9	(0.47)	5	(0.24)	5	(0.27)	5	(0.21)	104	(6.5)
Published Proceedings	11	(0.58)	37	(1.76)	65	(2.95)	71	(2.96)	72	(4.5)
Total Publications	104	(5.47)	174	(8.29)	223	(10.62)	249	(10.38)	355	(22.2)
Abstracts	55	(2.89)	42	(2.00)	64	(3.05)	71	(3.01)	56	(3.5)
Invited Participation at:										
Regional Meetings	18	(0.95)	41	(1.95)	55	(2.62)	68	(2.83)	76	(4.8)
National Meetings	47	(2.47)	65	(3.10)	70	(3.18)	76	(2.92)	74	(4.6)
Faculty in Center	19		21		22		24		16	
Number of Visitors	13		15		18		18		19	

Table 3

**RESEARCH PROJECTS FUNDED EXTERNALLY
REPORT PERIOD 1996-97**

PROJECT DIRECTOR	TITLE OF GRANT	FUNDING AGENCY	TOTAL AWARDED	ESTIMATED EXPENDITURES
David Bemis	<i>Bordetella bronchiseptica</i> adhesion molecules as protective immogens and markers of host specificity	USDA 1433 Funds	\$ 9,000.00 10/01/96-9/30/97	\$ 5,444.07
Philip Bochsler	Purification and characterization of bovine lipopolysaccharide-binding protein (renewal)	USDA	\$184,000.00 8/31/97	\$ 78,651.80
	The role of nitric oxide as a mediator of host defense in cattle	USDA 1433 Funds	\$ 6,852.00 10/01/95-9/30/96	\$ 6,852.00
	Mechanisms of innate resistance to enteric pathogens of bovine calves	USDA 1433 Funds	\$ 8,322.00 10/01/96-930//97	\$ 3,548.50
David Brian	Bovine coronavirus vector for mucosal immunity to phaemolytica leukotoxin	USDA	\$140,000.00 9/15/95-9/30/98	\$ 10,854.64
	Mechanism(s) of coronavirus RNA replication and packaging	National Institute of Allergies and Infectious Diseases	\$228,871.00 7/01/96-6/30/01	\$ 99,994.65
Thomas Doherty	Evaluation of gastric emptying in an endotoxin-induced ileus model in the horse	USDA 1433 Funds	\$ 5,000.00 10/01/96-9/30/97	\$ 1,195.00
Donita Frazier	Comparative cytochrome P450 drug metabolism pathways of fish, poultry, and swine	USDA 1433 Funds	\$ 4,000.00 10/01/96-9/30/97	\$ 101.00
James Godkin	Retinoids in bovine follicular and oocyte development	USDA Formula Funds	\$ 5,000.00 10/01/95-9/30/96	\$ 5,000.00
	Retinoid-binding protein and receptors in bovine placental development	USDA NRI	\$212,000.00 9/01/93-8/31/97	\$ 34,913.34
	Maintenance of pregnancy in cattle and sheep.	AES Hatch	\$ 15,000.00 7/01/96-6/30/97	\$ 3,748.37
Kevin Hahn	Serodiagnosis of Doxorubicin resistance in dogs	Morris Animal Foundation	\$ 3,000.00 9/01/96-11/30/97	\$ 2,003.77
Melissa Kennedy	Detection f feline infectious peritonitis virus and differentiation from feline enteric coronavirus	Morris Animal Foundation	\$ 19,000.00 9/01/94-8/31/96	\$ 12,623.03
	Characterization of 7A and 7B open reading frames of feline coronaviruses	Pfizer Company	\$ 8,750.00 7/01/96-7/31/97	\$ 8,699.75
	Identification and expression of FIPV-specific peptides and their use in FIPV-specific ELISA	Morris Animal Foundation	\$ 23,725.00 10/01/96-10/31/98	\$ 2,666.56

Alan Mathew	Evaluation of fiber blends, enteric microflora, and diet digestibility in cats with ileal cannulas	Iams Company	\$113,054.00 2/01/96-12/31/97	\$ 50,298.01
	Effect of volatile fatty acids on postweaning colonization of <i>Escherichia coli</i> and <i>Salmonella choleraesuis</i> in pigs	USDA 1433 Funds	\$ 4,000.00 10/01/95-9/30/96	\$ 4,000.00
	Weaning and colonization of <i>E. coli</i> in the intestine of young pigs	AES HATCH	\$ 52,000.00 10/01/93-9/30/97	\$ 10,931.43
	Characterization of mastitis causing agents in swine	AES HATCH	\$ 11,666.00 10/01/96-9/30/97	\$ 11,666.00
Charmi Mendis-Handagama	Effect of galactosyl lactose on calf starter diets (Co-PI)	Snow Brand Milk Products Co.	\$ 30,000.00	-----
	Regulation of testosterone production in adult rat testis	National Science Foundation	\$ 18,000.00 8/15/94-1/31/97	\$ 12,911.72
	Increasing the sperm counts in testes of bulls using the transient hypothyroid treatment	URCEO, France	\$ 24,000.00 1/97-1/99	-----
Darryl Millis	The use of canine recombinant somatotropin to enhance fracture healing in dogs	Monsanto Company	\$ 47,320.00 5/01/96-7/01/97	\$ 39,320.22
	Pilot study of a new anti-inflammatory drug for synovitis	G.D. Searle and Company	\$ 50,749.00 9/19/96-6/30/97	\$ 39,652.84
	Length of treatment time with canine recombinant somatotropin for osteotomy healing in an unstable gap fracture healing model	Protiva Company	\$ 65,342.00 01/01/97-12/31/01	\$ 30,519.79
	Initial dose determination of a new cyclooxygenase-2 inhibitor for the prevention of lameness induced by chemical synovitis in dogs	Protiva Company	\$ 83,215.00 06/01/97-5/31/98	\$ 11,359.47
Linda Munson	Modulation of osteoarthritis with somatotropin and polysulfated glycosaminoglycans in dogs using the pond-nuki model	Protiva Company	\$ 77,413.00 06/01/97-5/31/99	\$ 4,202.03
	Contraceptive health surveillance center for zoo and wildlife species.	Geraldine R. Dodge Foundation	\$ 30,000.00 10/01/95-1/31/97	\$ 17,713.89
	Continuing safety assessments of contraceptives for non-domestic felids	American Association of Zoo Parks and Aquarium	\$128,414.00 10/01/93-8/31/97	\$ 50,829.84
	Contraceptive health surveillance center for zoo, wildlife, and companion animals	Geraldine R. Dodge Foundation	\$ 25,000.00 01/01/97-12/31/97	-----
Jack Oliver	Characterization of serum clinical chemistry analyte profiles of cattle grazing endophyte-free and endophyte-infected tall fescue grass	USDA 1433 Funds	\$ 10,000.00 10/01/95-9/30/96	\$ 10,000.00
	Anti-fescue toxicosis vaccine development	USDA 1433 Funds	\$ 11,000.00 10/01/96-9/30/97	\$ 11,000.00
	Anti-fescue toxicosis vaccine study (Co-PI)	Merck and Company	\$ 60,000.00 1/01/95-12/31/96	-----

Jack Oliver (continued)	Endothelin response to tall fescue stimulus of bovine endothelial cells (Co-PI)	USDA	\$ 60,002.00 3/01/95-8/31/96	-----
	Comparison of plasma cortisol concentrations after stimulation with freshly reconstituted and previously frozen and stored cosyntropin clinically normal dogs (Co-PI)	American College of Veterinary Dermatology	\$ 2,250.00 7/01/96-6/30/97	-----
	The effect of exogenous oral melatonin administration on sex hormone prolactin and thyroid concentrations in healthy sexually intact adult dogs (Co-PI)	American College of Veterinary Dermatology	\$ 3,000.00 4/01/97-3/31/98	-----
Stephen Oliver	Identification, characterization, and evaluation of <i>Streptococcus uberis</i> virulence factors	USDA Formula Funds	\$ 7,000.00 10/01/95-9/30/96	\$ 7,000.00
	Efficacy of two novel experimental postmilking teat disinfectants for the prevention of mastitis in dairy cows under natural exposure conditions	Farnam Companies, Inc.	\$ 69,600.00 1995-96	\$ 3,395.19
	Influence of clinical and subclinical mastitis during early lactation on reproductive performance of Jersey cows	American Jersey Cattle Association Research Foundation	\$ 6,000.00 1996	-----
	Influence of intramammary antibiotic therapy at calving on mastitis and lactational performance of heifers during early lactation	The Upjohn Company	\$ 38,250.00 1995-97	\$ 20,534.00
	Evaluation of specific immune responses and protection by novel streptococcal antigens	Pfizer Company	\$108,848.00 4/97-12/98	-----
	Lactation/mastitis research	Robert L. Schattner Foundation	\$ 65,000.00 6/97	-----
	Hormonal changes associated with clinical mastitis during early lactation in Jersey cows (Co-PI)	American Jersey Cattle Association Research Foundation	\$ 6,000.00 1996	-----
Sharon Patton	<i>Toxoplasma gondii</i> in swine populations: A comparison of the percentage of sows and market-weight pigs infected from the NAHMS, farm management practice relationships, and economic costs	National Pork Producers	\$ 24,500.00 9/01/96-8/31/97	\$ 10,454.21
Patton - Continued	Epidemiology of <i>Toxoplasma gondii</i> in swine populations: A comparison of the seroprevalence of <i>Toxoplasma gondii</i> in hogs and market weight pigs in the NAHMS, farm management practice relationships, and economic costs	USDA 1433 Funds	\$ 11,000.00 10/1/95-9/30/96	\$ 11,000.00
Bart Rohrbach	Randomized clinical trial to evaluate the effect of vaccination against <i>Leptospira</i> spp to prevent ERU in horses.	Fort Dodge	\$ 27,845.00 5/15/97-8/15/-98	-----
Barry Rouse	Herpes zosterfilization	Smith-Kline Biological	\$124,746.00 7/1/90-12/31/04	-----

Barry Rouse (continued)	Mucosal immunity in control of herpetic infection	National Institute of Allergy and Infectious Diseases – NIH	\$728,711.00 1993-97	\$ 209,616.29
	Immunity mechanisms in herpesvirus infections	National Institute of Allergy and Infectious Diseases – NIH	\$783,510.00 1995-00	\$ 254,241.53
	Mechanisms of herpetic stromal keratitis	National Eye Institute - NIH	\$1,047,093.00 1992-97	\$ 221,919.82
Hildegard Schuller	Anticarcinogenic effects of Dexniguldipine-HcL in hamster	BYK Gulden	\$379,283.00 1993-97	\$ 20,442.60
	NNK effects on receptor pathways	National Institute of Health	\$599,126.00 1994-97	\$ 134,065.81
	Regulation of the proliferative response of pulmonary neuroendocrine cells to nicotinic agonists	Verum Foundation for Behavior and Environment	\$128,484.00 1/96-12/97	\$ 42,533.82
	Transplacental pancreatic carcinogenesis by NNI	National Institute of Health	\$506,499.00 7/31/97	\$ 184,945.48
Terry Schultz	Development of a bioremediation risk assessment scheme	US Environmental Protection Agency	\$ 54,749.00 9/94-9/97	\$ 5,443.27
	Structure-biodegradability/toxicity relationships of substituted naphthalenes	Dupont Corporation	\$ 40,000.00 6/95-6/97	\$ 40,000.00
	The role of bioavailability in determining environmentally acceptable endpoints for bioremediation of polychlorinated biphenyls (Co-PI)	US Department of Energy	\$441,037.00 3/97-2/00	-----
	Photo-induced toxicity in <i>Tetrahymena</i>	University of Minnesota	\$ 19,063.00 1/94-12/96	\$ 19,063.00
A. Eric Schultze	Vascular cell injury by toxicants of tall fescue grass (Co-PI)	USDA Formula Funds	\$ 5,000.00	-----
J. Erby Wilkinson	Role of agouti gene in tumorogenesis	Lockheed Martin	\$ 76,710.00 10/01/95-9/30/97	\$ 41,562.97
	Collaborative studies on the cellular and molecular basis of disease in the scurfy mouse	Lockheed Martin	\$ 24,000.00 7/29/96-7/28/97	\$ 21,208.71
	Genome analysis program	Lockheed Martin	\$ 75,195.00 2/96-9/30/97	\$ 38,971.91
	Histopathologic and clinical pathology analyses of mice from a colony containing chromosomal translocations	Lockheed Martin	\$ 102,250.00 7/1/95-3/21/98	\$ 49,181.39
	Role of the agouti gene product on tumorogenesis	Lockheed Martin	\$ 67,000.00 7/01/95-12/31/96	\$ 25,720.20

J. Erby Wilkinson (contined)	Directed expression of the agouti gene product in transgenic mice: A potential model for obesity	Glaxo	\$ 672,890.00 10/93-9/96	\$ 77,389.90
	Mammalian genetics and development	Lockheed Martin	\$ 70,850.00 10/95-9/96	\$ 21,924.52
	Scurfy Mouse	Lockheed Martin	\$ 41,391.00 10/95-9/96	-----

CENTERS OF EXCELLENCE/CENTERS OF EMPHASIS
ACTUAL, PROPOSED, AND REQUESTED BUDGETInstitution Veterinary Medicine Center Livestock Diseases and Human Health

	1997-98 Actual			1998-99 Proposed			1999-2000 Requested		
	Matching	Appropri.	Total	Matching	Appropri.	Total	Matching	Appropri.	Total
Expenditures	251,200	502,400	753,600	258,350	516,700	775,050	271,268	542,535	813,803
Salaries									
Faculty	34,133	68,266	102,399	37,424	74,848	112,272	39,295	78,591	117,886
Other Professional	36,781	73,561	110,342	44,227	88,453	132,680	46,438	92,876	139,314
Clerical/ Supporting	19,608	39,216	58,824	24,843	49,685	74,528	26,085	52,169	78,254
Assistantships	14,598	29,197	43,795	15,561	31,123	46,684	16,339	32,679	49,018
Total Salaries	105,120	210,240	315,360	122,055	244,109	366,164	128,157	256,315	384,472
Fringe Benefits	22,323	44,645	66,968	26,682	53,365	80,047	24,411	48,823	73,234
Total Personnel	127,443	254,885	382,328	148,737	297,474	446,211	152,568	305,138	457,706
Non-Personnel									
Travel	481	962	1,443	500	1,000	1,500	525	1,050	1,575
Software	450	900	1,350			0			0
Books & Journals	197	394	591			0			0
Other Supplies	45,455	90,912	136,367	41,826	83,653	125,479	43,918	87,835	131,753
Equipment	69,713	139,426	209,139	47,287	94,573	141,860	49,651	99,302	148,953
Maintenance	7,932	15,864	23,796	8,333	16,667	25,000	8,750	17,500	26,250
Scholarships	4,340	8,679	13,019	11,667	23,333	35,000	12,250	24,500	36,750
Consultants			0			0			0
Renovation			0			0			0
Other (Specify)			0			0			0
			0			0			0
			0			0			0
			0			0			0
Total Non-Personnel	128,568	257,137	385,705	109,613	219,226	328,839	115,094	230,187	345,281
GRAND TOTAL	256,011	512,022	768,033	258,350	516,700	775,050	267,662	535,325	802,987
Revenue									
New State Appropriation		502,400	502,400		516,700	516,700		535,325	535,325
Carryover State Appropriation		9,622	9,622			0			0
New Matching Funds	251,200		251,200	258,350		258,350	267,662		267,662
Carryover from Previous Matching Funds	4,811		4,811			0			0
Total Revenue	256,011	512,022	768,033	258,350	516,700	775,050	267,662	535,325	802,987

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Center of Excellence Annual Report



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