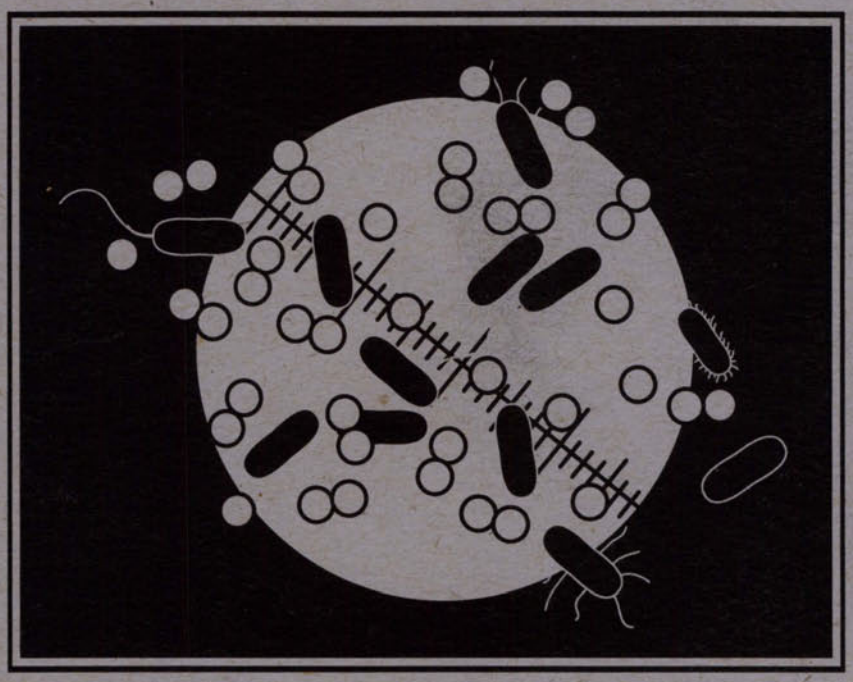
1997

Center of Excellence Annual Report, July 1996-June 1997

College of Veterinary Medicine

Center of Excellence in Livestock Diseases & Human Health



ANNUAL REPORT

July 1, 1996 - June 30, 1997

Mike Shires, Dean
College of Veterinary Medicine The University of Tennessee
Knoxville, Tennessee

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THE UNIVERSITY OF TENNESSEE
COLLEGE OF VETERINARY MEDICINE

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August 14, 1997

In these times of fiscal restraint, it is a pleasure to report on the success of The University of Tennessee College of Veterinary Medicine's Center of Excellence in Livestock Diseases.

A quick perusal of this document will show that despite the shrinkage of funds from the USDA, NIH, and other federal funding agencies, and the increased competition for these dollars, our researchers have been extraordinarily successful. The graph in Table I. indicates a thirteen percent decline in expenditures from grant funds for the last two years from a plateau in 1993 through 1995. Although we would like to reverse this trend we understand the reasons behind it. Basically, tightened funding and more competition has had a major effect; however, we have lost Dr. Ted McDonald from our research pool due to his retirement as well as another senior researcher. Their contributions to this Center have been consistent over the years and we will have to rebuild this annual funding by starting at the bottom with young and promising researchers. We have already begun this process by recently hiring a young researcher with an excellent funding history who we anticipate will be successful in grant awards and by placing two promising post-doctoral research students in the clinics on a half time basis.

Despite a fall in grant funds our expenditures from current grants was over $2 million, which is a significant amount for this College. We have consistently managed, at the very least, to maintain this level since 1988. The expenditures reflected in the COE program are slightly over a 4:1 return on state dollars invested in research. If one calculates this investment in relation to the total amount of grants in this College from which these expenditures arise, a minimum of a 32:1 investment from state dollars will be shown. This certainly rivals, if not exceeds, the current surge in the stock market.

At the same time, if one studies the benchmarks achieved this year, it will be seen that we have averaged over 7 articles in refereed journals per researcher. If this amount is added to book chapters and proceedings there is a total of 249 publications, excluding abstracts, for the researchers in this Center during the year. In 1988 there were 23 scientists involved in the Center which resulted in 102 publications and in 1996/1997 there were 24 scientists resulting in 249 publications. Those results prove a steady increase over the last nine years and a healthy return on the initial and subsequent award of funds.

The reorganization we previously put into effect with respect to the committee responsible for evaluating and selecting scientists and proposals for funding, has been working extremely well. The investigators are fully informed of the scores given their proposals and if they are not funded they are provided the reasons and, perhaps, suggestions for improving proposals next time. The guidelines related to who should apply and what is required for successful funding are much clearer and easier to follow.

Our mission has not changed in that we are still primarily motivated to:

- help fund productive established researchers
- fund promising new investigators
- when necessary, help bridge funding gaps
- fund students who are interested in a research career
- continue to help with stipends for post-doctoral students

We have also set aside small amounts to assist departments in providing maintenance contracts on equipment used by Center scientists. Another investment is a small amount of money to help the Lab Animal Program better serve our scientists with respect to equipment and housing for research animals.

Dr. Leon Potgieter, the Assistant Director of the Center of Excellence, has been a tremendous asset in organizing the Center and in managing the day to day functions. He is ably assisted by Ms. Diane Leslie who also helps coordinate the Graduate Program. This College is indebted to these two for their hard work and expertise. It is not easy, nor does one make many friends, when unbiased rules are routinely applied to all researchers without favors.

This Center continues to produce significant research and resulting scholarly works at a very small cost to Tennessee taxpayers and provides a huge return on their investment. With the changing scene related to federal agencies and funding, we will continue to forge new partnerships as opportunities arise. Obviously, the major changes at the Oak Ridge National Laboratories will create new partnerships and we are already hard at work along these lines.

Sincerely,

G.M.H. Shires
Dean

vjb

CENTER OF EXCELLENCE
FACULTY FUNDED 1996-97

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Department of Comparative Medicine

Philip N. Bochsler, D.V.M., Ph.D.
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Department of Pathology

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Thomas J. Doherty, M.Sc.
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Donita Frazier, D.V.M., Ph.D.
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James D. Godkin, Ph.D.
Professor
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Kevin A. Hahn, D.V.M., Ph.D.
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Diane Hendrix, D.V.M.
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Terry W. Schultz, Ph.D.
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J. Erby Wilkinson, D.V.M., Ph.D.
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Programmatic Report

Center of Excellence

Program Report (1996-97)

Dr. Leon N D Potgieter, Assistant Director

The Center of Excellence has been in existence for over twelve years. Although external funding levels have reached a plateau over the last five to six years (approximately $2.3 million/year), the Center continues to grow in terms of its benchmarks. The Center of Excellence can be proud, in particular, of the number of peer-reviewed articles published by participants in 1996-97 (total of 176 and a mean of 7.33 per member – a record for the Center). A factor that has impacted the Center is the retirement of two very productive researchers and the resignation of a third over the past 18 months. Drs. Ted McDonald and Walter Farkas retired after many years of productive research at the University of Tennessee. Unfortunately, the uncertain budget projections for the State for the immediate future will allow us to fill only one of these positions.

I am pleased to announce that we have been able to recruit Dr. Hwa-Chain Wang, an established and accomplished researcher in basic mechanisms of cancer therapy. He brings with him a well-funded research program. We have been fortunate also in recently recruiting Dr. Joe Bartjes, an eminent investigator in clinical nutrition. He has been well funded for research on nutrition in development of degenerative joint and other diseases. Both these investigators could have significant roles in the Center of Excellence in the future. I may add that the existence of the **Center of Excellence was a major factor in the recruiting of researchers of this caliber**.

It is a tribute to our current COE participants that they have been able to maintain funding levels and increase productivity in spite of a very unfavorable funding climate and loss of research personnel. Drs. Barry Rouse, Hildegard Schuller and David Brian continue to be the main pillars of the Center's funding base. They are well supported by Drs. Erby Wilkinson, Terry Schultz, Linda Munson, Stephen Oliver, Sharon Patton, Charmi Mendis-Handagama, Alan Mathew, James Godkin, Darryl Millis and Melissa Kennedy. It is a pleasure to announce that Drs. Kevin Hahn and Jack Oliver also have received major awards. Dr. Hahn's award from Bayer amounts to approximately $450,000 for five years and involves use of an animal model (with naturally occurring tumors) for the treatment of certain cancers. Dr. Jack Oliver received nearly $200,000 from USDA for the study of mechanisms of fungus toxicity in cattle associated with tall fescue

grass pastures. These awards clearly illustrate the national recognition for excellence of our investigators. The research potential of our recent recruits and the productivity of our current participants makes me optimistic for the future of the Center of Excellence and that it will have a significant impact on the welfare of the people of Tennessee.

Major Research Activity in the Center of Excellence:

Goal 1: To Improve the Quality of Human Life by Improving Animal Health

Drs. Jack Oliver, Stephen Oliver, Philip Bochsler, David Brian, Alan Mathew, Donita Frazier and Sharon Patton made significant contribution to improving animal health over the past year.

Mastitis in an inflammation of the mammary gland that affects almost 35% of dairy cows worldwide. Several different types of bacteria can invade the udder and cause inflammation resulting in mastitis. The National Mastitis Council estimates that mastitis costs U.S. dairy producers in excess of $2 billion dollars annually. In Tennessee, costs associated with mastitis likely exceed $35 million dollars each year. Thus, mastitis continues to be one of, if not, the most significant limiting factor to profitable dairying in Tennessee, the U.S., and throughout the world.

Dr. Stephen Oliver is characterizing factors that affect resistance of the udder to mastitis and mechanisms that permit bacteria to invade the udder. His goal is to develop and evaluate procedures to enhance resistance of the udder. A major research focus has been on *Streptococcus uberis,* a frequent cause of mastitis. Strategies for controlling this pathogen are poorly defined and inadequate. During the last year, **Dr. Oliver** has identified some factors that allow *Streptococcus uberis* to invade the udder and cause mastitis. His laboratory is currently characterizing and evaluating these factors. The long-term goal of this research is to develop a vaccine to control this important mastitis pathogen.

Dr. Sharon Patton's laboratory is studying the risk factors involved in the transmission of *Toxoplasma gondii* in the U.S. It causes one of the most widespread protozoan diseases, infecting approximately 13% of the world population in both temperate and tropical countries. Congenital infection occurs when a woman is infected for the first time during pregnancy. It is estimated that 4,100 of the 4.1 million infants born annually in recent years in the US have the congenital infection. Toxoplasmic encephalitis is the second most common AIDS-related opportunistic infectious of the central nervous system. Estimated medical costs of congenital

toxoplasmosis ranged from $368 million to $8.8 billion annually in the U.S., and in 1992 the cost for treating toxoplasmosis in AIDS patients was between $23 and $106 million dollars.

Humans are infected with postnatal *Toxoplama gondii* by eating tissue cysts in undercooked meat or food or by ingesting water contaminated with sporulated oocysts from cat feces. **Dr. Patton's** laboratory has focused on the infection in swine. Toxoplasmosis has been identified as an emerging disease problem for the swine industry because of a perceived potential transmission from pork to humans. Consumer assurance of the safety of the pork they eat is vital to the swine industry. If perceived as an unclean product, the demand for pork and its image in the marketplace will deteriorate. This research will assist in providing answers on the pork/toxoplasmosis issue before it becomes a major industry problem that may impact Tennessee producers.

Dr. Melissa Kennedy's work focused on the Coronaviridae. These viruses cause disease in many species of birds and mammals, including humans. They have been associated with diseases of the respiratory tract, nervous system,and reproductive system. She has characterized some of the molecular inter-relationships among several coronaviruses and has developed and evaluated molecular techniques to detect these viruses in affected and carrier animals.

Dr. Donita Frazier has been working on the chemical modification of drugs by multiple enzyme systems since this is the most important factor in the body's regulation of drug concentrations. It constitutes the major mechanism for altering the biological effects of a compound and for its clearance from the body. The largest concentration of enzymes involved in these reactions (primarily cytochrome P450) is located in the liver, but significant concentrations also exist in the intestine. Although cytochrome P450 enzymes occur in all animal species, minor changes in structure or tissue distribution, may allow great differences in the breakdown and elimination of specific drugs. A lack of consideration of the rates of inactivation and elimination of drugs in animals intended for food may result in drug residues in consumed meats. Also, ineffective concentrations of antibacterial drugs could occur, resulting in inadequate bacterial killing, leading to bacterial contamination of meats. Moreover, low antibiotic concentrations may favor development of resistant strains of bacteria. **Dr. Frazier** is determining the activities of specific cytochrome P450 enzymes in various tissues of swine and poultry and the role of these enzymes in the breakdown of quinolone antibiotics.

Goal 2: To Augment Livestock Disease Research Capabilities in the Institute of Agriculture

Drs. Philip Bochsler, Melissa Kennedy, Stephen Oliver, Jack Oliver, David Brian, James Godkin, Linda Munson, and Joyce Merryman made significant contributions in livestock disease research by the Center this past year.

Dr. Jack Oliver and co-workers have continued to research the mechanism(s) by which the fungal-produced toxins, prevalent in tall fescue grass, affect primarily herbivores. His laboratory seeks to find methods to significantly reduce losses that occur to the cattle industry, currently estimated at $10 million annually in Tennessee alone (see Goal 5).

Respiratory diseases of cattle are a cause of significant economic loss for cattle and dairy operations in the state of Tennessee. White blood cells (leukocytes) are an important part of the immune system, contributing to a defense against infectious agents in the lungs of cattle as well as other animals.

Dr. Philip Bochsler is investigating the mechanisms by which white blood cells provide protection against infectious agents that cause bovine pneumonia. This research is being done to understand the mechanism(s) by which organisms produce respiratory diseases in cattle. This research may eventually assist in formulating improved strategies for prevention and therapy of these infectious diseases. He has determined that certain lung cells (alveolar macrophages) produce nitric oxide in response to certain organisms. **Dr. Bochsler's** research suggests that this substance appears to have an important role in destroying infectious agents in the lung. He has evaluated factors that influence production and bacterial killing by this biological product.

Coronaviruses cause some of the most costly respiratory and gastroenteric diseases in livestock and fowl. In recent years, new coronavirus pathotypes have emerged in the bovine and porcine species as a result of virus mutation. Coronaviruses also cause a variety of debilitating chronic disease in animals as a result of long-term persistent infection, a condition that is thought to contribute significantly to the emergence of new virus variants. Because of the special challenges of inducing immunity at mucosal surfaces and because coronaviruses mutate rapidly, vaccines to control coronavirus often are not effective. Therapeutic measures to cure persistent

infections are not available because it is not known in detail how or where the chronic coronavirus infection is maintained.

Dr. David Brian's research has included coronaviruses that infect many species, including cattle. By studying the molecular biology of bovine coronavirus replication, he has identified potential sites in the viral genome for targeted antiviral therapy and uncovered two potential mechanisms of persistent infection.

Dr. Alan Mathew recently determined, by biochemical analyses, that organisms associated with mastitis (milk fever) in swine herds are mostly of environmental origin and exist primarily in unsanitary areas. This is in contrast to animal pathogens commonly associated with mastitis in dairy cows. Animal pathogen reservoirs are typically within the host animal. This finding should enable **Dr. Mathew** to develop therapeutic and/or management strategies for control of mastitis/milk fever in sows. He also has tested feed and water treatments to determine their effectiveness in preventing intestinal diseases that often occur following weaning in young pigs. He specifically tested products naturally derived from the breakdown of carbohydrates in the intestine, known as volatile fatty acids. Natural concentrations of volatile fatty acids in the gastrointestinal tract decrease rapidly following weaning and may be responsible for the reduced resistance to common intestinal infections such as *E. coli*.

Vitamin A (retinol) is essential for reproductive processes. Severe retinol deficiency may inhibit reproductive cyclicity, ovarian development and ovulation. Moderate deficiency may result in abortion, fetal resorption or congenital abnormalities.

Dr. James Godkin studies the mechanisms by which vitamin A and derivatives regulate cell growth and development of reproductive tissues. He has discovered and characterized several proteins that specifically bind to these derivatives. Recent studies determined the role of ovarian sex steroids and vitamin A derivatives in regulating production of these proteins in various tissues of the reproductive tract. An important discovery was that vitamin A treatment improved embryo quality in ewes. Research continues on developing treatments to manipulate production of these critical proteins during ovulation and pregnancy, through optimizing reproductive efficiency.

Goal 3: To Identify and Characterize Laboratory and Animal Models of Important Human Diseases

Dr. Eric Schultze has worked on the development of a mouse model for a certain type of anemia and iron storage disease of humans. His research focused on characterizing the results of genetic changes in a region called the *fitness 1* locus in chromosome 7 of mice. Mice with mutations in the *fitness 1* locus are stunted and develop growth abnormalities involving the spinal column (scoliosis). *Fitness 1* mice also have a marked deficiency in the number of red blood cells (anemia) and evidence of liver dysfunction. He has evaluated the transportation of iron and copper and the concentrations of these metals in the tissues of the *fitness 1* mice. Microscopic examination indicated that the bone marrow and spleen of these mice were abnormal. Red blood cell formation in the bone marrow was decreased, but was markedly increased in the spleen, probably due to the abnormal distribution of iron within the various organs. Analysis of *fitness 1* mice organs for abnormalities in the concentrations of several other biologically important metals indicated that the problem is largely limited to iron and copper. Currently, the laboratory is examining the concentration of hemopexin and iron transport protein, found in the blood of people and mice, to determine if alterations in this protein might account for the abnormal iron metabolism in these mice.

Drs. Dorcas Schaeffer and Erby Wilkinson continued to study the many abnormalities of the Tg737 mouse mutant. This mouse has major abnormalities in many organs including the kidney, liver and pancreas; these abnormalities resemble several genetic diseases of humans. They have further characterized the abnormal cells of the liver and determined that the main problem is the failure of the stem cells to differentiate into normal mature liver cells. These mutant cells also constitute a target cell for cancer formation. Studies of these mice indicated that the pancreas develops normally, but atrophies soon after birth. The animals lose weight and eventually die. The cause of the pancreas lesion is due to a failure of the duct stem cells to mature like the abnormal stem cells of the liver.

Dr. Erby Wilkinson has studied two models of autoimmune disease of humans. One is the "scurfy mouse," and they have now determined that the disease is caused by the activation of

a certain subset of immune cells (T lymphocytes). These T cells produce a number of cell products that activate other inflammatory cells and cause the wasting and inflammation that results in the death of the animals. His laboratory has generated considerable information on how these cells develop and become activated. They have also located the scurfy gene in a small region of the X chromosome. This is a major breakthrough and ensures that the gene can be identified shortly. **Dr. Wilkinson** and his co-workers have screened over 100 lines of mice with chromosomal abnormalities for immunological abnormalities. They have identified 10 lines of mice with genetically inherited mutations that cause different alterations of the immune system. Many of these mice lines could be useful animal models of human disease.

Dr. Linda Munson has established a promising mouse model for human endometriosis, an important reproductive disease in women involving the uterus. She has established that immuno-deficient (SCID) mice which have had human endometrial epithelial cells on a matrix implanted into the abdomen survive at least six weeks and even form rudimentary glandular sctructures.

Dr. Diane Hendrix has established a laboratory model for studying the healing characteristics of the injured cornea under various conditions (such as exposure to various treatments). The model involves the harvesting and growth of corneal epithelial cells (the outermost layer of the cornea).

Dr. Melissa Kennedy has identified a coronavirus in a colony of howler monkeys experiencing gastroenteritis, and in one case, weight loss and death. Because coronaviruses cause a variety of diseases in humans, this virus in primates may serve as a model for human disease. Characterization of the virus at the genetic level is ongoing, but it appears to contain some genetic material similar to a bovine coronavirus and to a feline coronavirus. This analysis will be extended to other regions of the viral genetic material. If these results prove consistent, it would be the first time that coronavirus genetic material with characteristics of two very different coronaviruses has been identified. These findings may impact significantly our understanding of coronaviruses and their pathogenesis in its host.

Goal 4: To Study Animal/Laboratory Models for Better Understanding of Human Disease

Several COE researchers utilized animal models in their studies over the past year of disease processes in humans. They included **Drs. Hildegard Schuller, Erby Wilkinson, Kevin Hahn, Barry Rouse, Eric Schultze, Terry Schultz, Joyce Merryman and Darryl Millis.**

Dr. Charmi Mendis-Handagama's research focuses on implications concerning the mechanisms of fertility in animals and humans. She is studying the process of Leydig cell formation in the developing mammalian testis using the rat model. Her research has revealed that thyroid hormones has this crucial role in the developing mammalian testis to establish the adult Leydig cell population. This important disclosure is a breakthrough in the field of pediatric endocrinology.

Dr. Hildegard Schuller continues to study the role of the autonomic nervous system in the induction and progression of different types of lung cancer. **Dr. Schuller's** research has previously shown that nicotine can cause lung cancer in individuals with chronic lung disease by binding to certain (cholinergic) receptors expressed in certain (neuroendocrine) lung cells. This initiates a cascade of intracellular chemical reactions that stimulate abnormal cell proliferation and tumor formation. This is a very important finding because it now allows for the development of cancer therapeutics that selectively block the growth of neuroendocrine lung cancer without affecting other lung cell types. **Dr. Schuller** determined that theophylline selectively blocks one step of these intracellular reactions. Theophylline is the active ingredient of drugs that dilate the bronchi, and which are widely used for the treatment of bronchitis and asthma. Accordingly, these drugs are already approved for the safe use in human patients and can be immediately tested as therapeutics for small cell lung cancer. Theophylline is also contained at a high concentration in green and black tea, and an experiment in hamsters is currently underway to test the potential chemopreventive effect of green tea on neuroendocrine lung cancer.

In a series of experiments in collaboration with **Dr. Merryman, Dr. Schuller** has addressed the question in the laboratory of why chronic lung disease is a risk factor lung cancer and promotes the development of lung cancer caused by nicotine. This research has identified carbon dioxide as an important messenger molecule for small cell lung cancer.

Drs. Dorcas Schaeffer and Erby Wilkinson reported on the Tg737 mouse that has major abnormalities in many organs such as the kidney, liver and pancreas resembling certain human diseases. They showed that the disease is influenced by a misplacement of a growth factor receptor on the wrong side of the cells that line the kidney tubules. This implies that inhibitors of this receptor, currently being developed by pharmaceutical companies, potentially could be used as a treatment for the disease. They demonstrated that partial replacement of the abnormal gene in this mouse dramatically retards progression of the disease. Gene therapy therefore should be a useful treatment for this common and deadly disease.

Dr. Erby Wilkinson's work targets animal models of immunological diseases in humans. He has completed analyses of transgenic mice with certain immune cells (T cells) that over-produce certain proteins. One of these proteins has the capability of activating replication of human immunodeficiency virus. With their enhanced immune responses these animals will be useful in identifying the factors involved in several important diseases with abnormal immune functions. Another mouse model studied in **Dr. Wilkinson's** laboratory is the Wiskott-Aldrich disease, a fatal disease of males characterized by immune deficiencies, bleeding and eczema. These animals also have markedly enhanced immune responses. The researchers have determined that T cells markedly stimulate the antibody-producing immune (B) cells in the animals. The latter discovery could lead to important advances to increase the immune response to harmful agents. Mechanisms to dissect the Wiskott-Aldrich gene, have been developed, a first step in producing potential treatments and cure.

Lymphoma is a common and fatal cancer in people, dogs and other animals. While there is no known cure, the progression of the disease can be slowed by administering anti-cancer drug therapy. Though these drugs are successful and many patients may enjoy an extended life span, relapses are common resulting from resistance of the cancer cells to the drugs that are used. Doxorubicin is an anti-cancer drug commonly used to control lymphoma.

Dr. Kevin Hahn and co-workers have conducted a one-year pilot study in the dog model addressing how lymphoma cancer cells become resistant to the anti-cancer effects of doxorubicin. He measured the amount of a specific protein in the blood that may appear when the cancer cells begin to develop drug resistance. He evaluated whether the presence of this protein could indicate lymphoma cells in a patient had become resistant to doxorubicin prior to and/or during

doxorubicin treatment. Preliminary results in the laboratory suggested that changing levels of this protein do reflect an increased resistance of the cells to doxorubicin exposure. The benefit of this study is the potential use of a simple blood test to determine whether a patient's cancer cells have already developed resistance to a particular anti-cancer drug prior to treatment. An elevated protein level would suggest using alternative anti-cancer drugs, thus providing better care for the tumor-bearing patient and avoiding the use of costly and unnecessarily toxic drugs.

Tennessee is one of the top five air polluting states in the nation. Methods predicting toxicity of chemicals could aid industry and state and local governments in making accurate judgments regarding chemical toxicity.

Over the past year, **Dr. Terry Schultz's** laboratory has focused on predicting the toxicity of highly reactive industrial materials using biological activity testing and mathematical modeling procedures. This past year efforts centered on quinones, an environmentally important class of aromatic compounds. Researchers established the exact chemical reactivity mechanisms of these compounds that relate to their toxicity. They identified also the nature of the chemical substructures related to toxicity. This information allows them to predict the toxicity of new compounds of this class.

Dr. Linda Munson has worked on human endometriosis and endometrial cancer using laboratory and animal models. These diseases are common reproductive diseases in women but little is known about the specific factors that influence their development. A signaling chemical, platelet derived growth factor, appears to influence the normal cyclical growth of uterine epithelial cells. Studies in **Dr. Munson's** laboratory have determined that various uterine epithelial cells express different levels of the growth factor receptor. Preliminary evidence indicated that uterine carcinoma cells all express the growth factor receptor. The laboratory studies indicate that estrogens may markedly enhance the expression of these growth factors on uterine epithelial cells and thereby promote their proliferation. These findings may impact current concepts of hormone replacement therapy in women.

Dr. Joyce Merryman's research has focused on the effect of environmental hazards on cells, especially ultraviolet radiation present in sunlight. Skin cancer is the most common type of cancer in Caucasians, with a lifetime risk greater than the risk for all other cancers combined. Ultraviolet radiation causes damage to the cellular DNA that ultimately may result in skin cancer.

Consequently, she has been investigating the role of tumor suppressor genes, growth-regulatory factors and intracellular communication pathways involved in the development of skin cancer. The development of an *in vitro* reconstituted skin model, a system whereby cells isolated from normal skin are grown in the laboratory in such a fashion that they resemble normal skin, is critical to these investigations. She now has perfected this technique so that ultraviolet radiation-induced damage to skin can be studied under tightly controlled conditions. With this model system, **Dr. Merryman** has been able to demonstrate the importance of a tumor suppressor gene in the development of skin cancer.

Dr. Darryl Millis' research involved the use of bone growth factor to enhance bone fracture healing. Delayed healing of fractures is relatively common in people and costs millions of dollars in additional treatment costs and lost productivity. Dogs also have delayed healing of fractures and it is through the use of a canine model of bone healing **Dr. Millis** has determined that growth hormone and insulin-like growth factor to be effective in promoting healing of fractures.

Goal 5: To Understand the Pathogenesis and Characterize the Causative Agents of Common Diseases Important to the State of Tennessee

The research focus of many COE investigators is to dissect mechanisms and causes of disease production in animals and humans. Researchers who contributed significantly to this field over the past year included: **Drs. Barry Rouse, Philip Bochsler, Jack Oliver, Thomas Doherty, Erby Wilkinson, Dave Brian, Hildegard Schuller, Joyce Merryman, Alan Mathew, Steve Oliver, Melissa Kennedy and Eric Schultze.**

Dr. Barry Rouse's laboratory has investigated the development of disease caused by herpesviruses and their prevention and treatment. Researchers have established that lesions of herpes keratitis are caused by the body's response to viral infection and become progressive with recrudescence. Their work established that anti herpes simplex certain immune cells (CD4+ TH1) orchestrate virus inflammatory responses. Functions mediated or dependent on such cells may provide logical targets to minimize the impact of inflammatory responses. Their data established

that one product of these cells, IL-10, modulates the degree of the inflammatory response, and that several other cell products given prophylactically could alter development of the viral immuno-inflammatory disease.

Dr. Jack Oliver and co-workers have recognized and documented that toxins produced by the fungus in tall fescue (and other grass/weed species) first cause changes in the blood vessels of animals, and are followed by generalized tissue/organ inflammation. In response to the toxins, the lining cells of blood vessels produced chemical substances that cause vessels to contract and the walls of the vessels to become thickened, changing blood flow to tissues and organs. Other chemicals were released that promoted blood clotting, likely interfering with air exchange in the lungs, and contributing to the well-known heat stress experienced by affected animals. In severe toxic cases, these same chemicals would prevent blood flow to peripheral areas (feet, tips of ears, and tail) resulting in death and loss of the tissues. Changes in normal blood components in response to toxin presence were documented, and changes indicated impaired functioning of the liver and blood-forming organs. These changes could slow the growth of animals and be responsible for the major economic problem associated with the disease. The finding of the irritative and destructive nature of the toxins on blood vessels will allow **Dr. Oliver** to focus attention on this primary lesion and to test the effectiveness of anti-inflammatory drugs for its prevention.

Dr. Thomas Doherty has studied the effect of endotoxin (part of a cell wall of certain bacteria) on the bowel function in animals. Endotoxin, even at a low dose, causes bowel motility to cease and results in a serious medical condition. Lidocaine, a local anesthetic, effectively blocks the effects of endotoxin in a laboratory model (rabbit). However, horses do not benefit in the same way from lidocaine indicating species differences exist in the ability of lidocaine to block the endotoxin effect.

Goal 6: To Improve 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

Drs. Barry Rouse, David Brian, Jack Oliver, Steve Oliver, Hildegard Schuller, Erby Wilkinson, David Bemis, Kevin Hahn, Alan Mathew and James Godkin have done research resulting in exciting discoveries regarding treatments and prophylaxis of various infectious and genetic diseases and cancer. These discoveries are discussed in some detail under Goals 1,2,4,9 and 11.

Goal 7: To Improve Facilities to Enable the College of Veterinary Medicine to Study More Effectively Infectious and Toxic Diseases of Animals

After several years of anticipation, the **Biotechnology Animal Science Facility** is nearing completion. This facility includes two large laboratory animal rooms and a student teaching area. I anticipate that over 2000 ft^2 will become available in the College of Veterinary Medicine Teaching Hospital on the second floor as the result of moving some aspects of the teaching program and laboratory animal housing to the new facility. Our strategic plan calls for converting at least some of the space for research activities.

An addition to the College of Veterinary Medicine was completed during the past year. It includes an **office complex** for the **Office for Laboratory Animal Care**, **offices** for the **laboratory animal veterinarians**, and space for the **computer support staff**. These programs impact the research program and their relocation has given some relief for housing graduate students and post-doctoral fellows.

The building addition also allowed the college to construct a cobalt radiation unit, with both clinical and research applications.

Goal 8: To Disseminate Through the Extension Service Practical Information Required to Reduce the Incidence of Livestock Diseases

The efforts of Dr. Nancy Howell, (public information coordinator), the veterinary extension personnel and researchers continue to ensure that the College of Veterinary Medicine is featured in many national, regional and statewide publications. Research projects and data pertinent to Tennessee interests constitute a significant proportion of the media releases and informational displays. Many of the research articles featured were written by COE personnel, who have also taken advantage of invitations to speak to commodity groups at Tennessee Agricultural Experiment Station field days and at formal extension service programs. Publications have appeared in *UT Agriculture* (published for a statewide readership by the Institute of Agriculture), *Veterinary News* (for practitioners), *Veterinary Medical Topics* (published twice yearly by the extension service), two alumni publications (*UT Alumnus* and *Torchbearer*) and in *Context* (UT faculty/staff newsletter). Research being conducted by the Center is disseminated also via the World-Wide Web. The University of Tennessee College of Veterinary Medicine has a home-page (http://www.vet.utk.edu/vet/).

Goal 9: To Develop New Strategies for the Prevention of Disease

Drs. David Bemis and Stephen Kania have been studying, at the molecular level, the bacterium *Bordetella bronchiseptica*, an important cause of respiratory tract disease in swine, horses, certain laboratory animals and certain companion animals. They identified a unique gene that encodes a major surface protein present only in virulent strains of the bacterium. It is a variant fimbrial protein that enhances the organism's capacity to attach to cells and thereby initiate infections. Because this new fimbrial protein is one of the major antigens recognized by the body during infections, it is a good candidate for use as a vaccine. Consequently, the gene has been cloned and sub-cloned. The fascinating potential of this study is that the gene appears to be

amenable to insertion of carrier immunizing molecules and therefore could serve as a carrier for multiple vaccines to protect the respiratory tract.

Dr. Barry Rouse has pioneered the technology of naked DNA vaccines that has become the new paradigm for the science of vaccinology. Infection of neonates with herpes and other viruses may occur at birth as a consequence of vaginal delivery to infected mothers. **Dr. Rouse** used a mouse model to investigate whether DNA vaccines could protect neonates from herpes simplex virus infections. Researchers demonstrated the efficacy of DNA vaccination in neonates both in the induction of specific antibody and cell-mediated immune responses and, more importantly, against challenge inoculation with the virus. Moreover, passive immunity did not interfere with the responses to DNA vaccination but did prevent immune responses to conventional vaccines. The use of small pieces of DNA encoding immunizing components of an organism could enormously improve the efficiency of vaccines used in human and veterinary medicine. It has been a particularly difficult to immunize young animals with passive antibodies.

Dr. Dave Brian has discovered, through recombinant technology, innovative mechanisms to deliver immunizing materials to an animal (see Goal 11).

Goal 10: To Improve Facilities and Expertise in Order to Provide Improved Research Training

Equipment

As in previous years, several multi-user pieces of equipment were bought for COE researchers over the past year. Strategic equipment purchases last year include: **robotic liquid handling system, microplate scintillation and luminescence counter, air thermo-cycler, ELISA plate reader, automated histochemistry unit, preparative protein purification system, automated burette titrator** and several powerful **laboratory computers**.

Graduate Students and Postdoctoral Researchers

In the past, the training component of the Center of Excellence has been small, but one of high quality. This past year, funds were used to support stipends for graduate students or

postdoctoral researchers for **Drs. Brian, Munson, S. Oliver, Rouse, Schuller, Schultz, and Wilkinson.**

A major achievement by the Center of Excellence has been the funding by the National Institutes of Health of a large institutional training grant. The success of this grant application was largely due to the efforts of **Dr. David Slauson**, the primary author of the proposal. The grant will support five selected graduate students/residents in the Comparative and Experimental Medicine Graduate Program. The training program will be a collaborative effort of the Department of Pathology and the biology division of the Oak Ridge National Laboratory, and will emphasize "cellular pathobiology of environmental disease." The central goal of this training effort is to provide outstanding research opportunities for young pathologists in highly focused quality research laboratories with excellent quality control. **Dr. Sharon Witonsky** is completing her Ph.D. in this program; her work has involved characterization of immune mediated diseases of certain lines of mice. **Dr. Barbara Sheppard** was appointed July 1, 1996. **Dr. Sheppard** has special interests in diseases of the nervous and immune systems.

Twelve veterinary students received modest COE summer stipends to allow them to participate in research in laboratories directed by COE faculty. Funds were allocated on a competitive basis.

Four faculty also received modest funding for "venture" grants. The criteria for allocating the latter included scientific merit and potential of the work to lead to future funding.

Goal 11: To Develop Innovative Approaches to the Treatment of Human Disease

Drs. Dorcas Schaeffer and Erby Wilkinson have treated a genetic disease in an animal model by partial replacement of an abnormal gene (see Goal 4). Their study of abnormal stem cells of the pancreas may lead to identification of factors that can promote regeneration of the pancreas following injury.

Dr. David Brian, studying the molecular biology of coronaviruses, discovered a particle (subviral replicon) representing only a portion of the virus, but still capable of multiplication in

cells. He has exploited the discovery by creating a molecular "Trojan Horse" to destroy certain viruses. The particle has been cloned and engineered to carry into infected cells a ribozyme—a potent specific antiviral molecule that cleaves a vulnerable site within an essential viral gene (RNA polymerase gene) and blocks virus replication. The subviral replicon also has been engineered to carry immunogens of other viruses making it a new vaccine vector.

Dr. Barry Rouse has developed methods of preventing and treating herpesvirus-induced, immuno-inflammatory disease by administering small pieces of DNA encoding products produced by certain cells involved in the immune response. This pioneering work promises to provide practical methods for dealing with immune-mediated disease that has frustrated the medical profession for a long time (see Goal 5).

Dr. Hildegard Schuller is evaluating the use of theophylline to specifically inhibit the growth of neuroendocrine lung cancers because of a discovery that it may interfere with a chemical chain reaction involved in these cancers (see Goal 4).

Benchmarks

Table 1.

Center of Excellence for Livestock Diseases and Human Health
External Funding Expenditure Levels Since Establishment

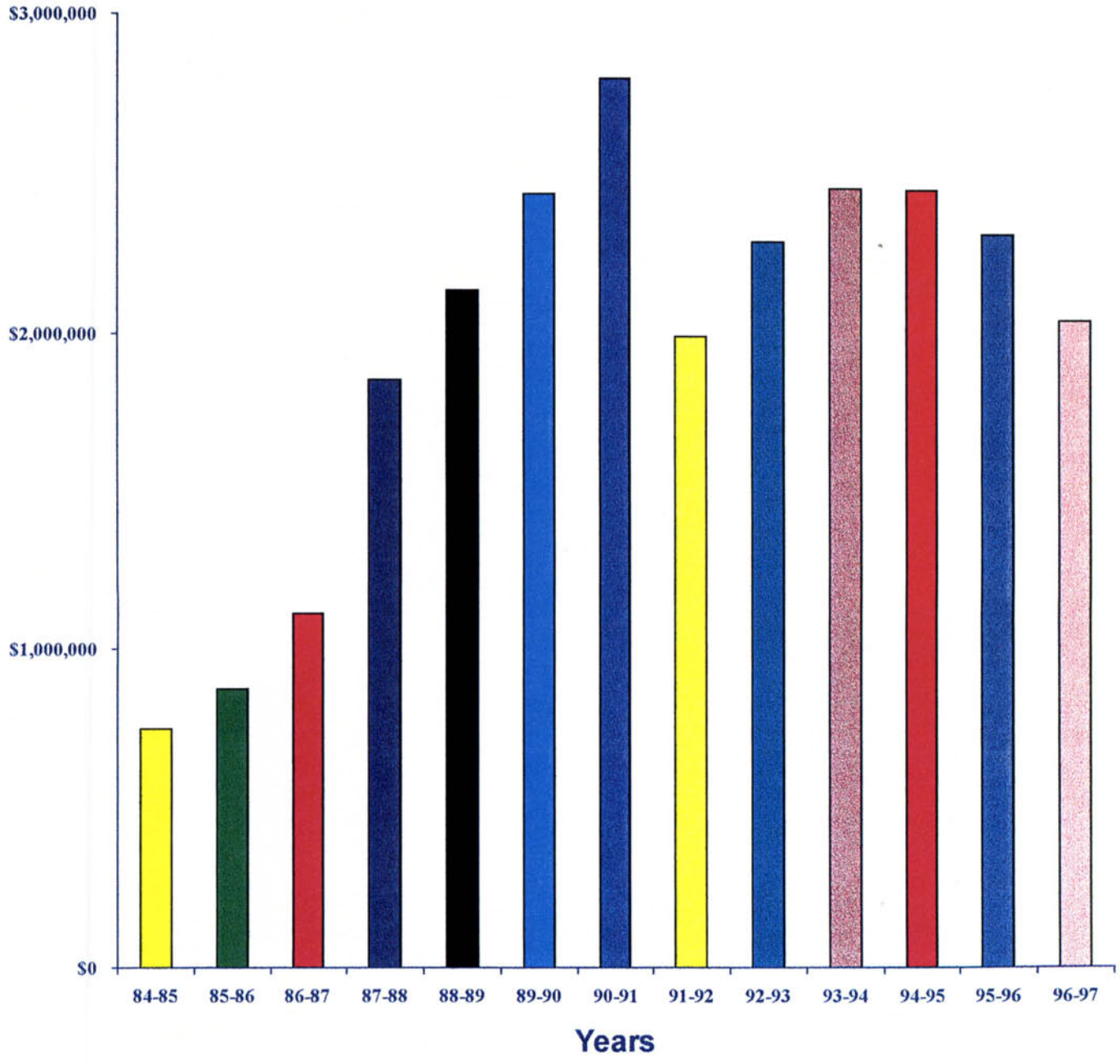

TABLE 2

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	
	Target	Actual	Avg	Actual	Avg	Actual	Avg	Actual	Avg
Number of:									
Articles		74	(3.22)	68	(2.62)	97	(3.73)	83	(4.37)
Books or Book Chapters		7	(0.30)	17	(0.65)	14	(0.54)	6	(0.32)
Published Proceedings		21	(0.91)	37	(1.42)	42	(1.62)	24	(1.26)
Total Publications	2.82	102	(4.43)	122	(4.69)	153	(5.89)	113	(5.95)
Abstracts	0.30	33	(1.43)	66	(2.54)	48	(1.85)	47	(2.47)
Invited Participation at:									
Regional Meetings	0.50	36	(1.56)	19	(0.73)	28	(1.08)	13	(0.68)
National Meetings	1.25	55	(2.39)	28	(1.08)	44	(1.69)	36	(1.89)
Faculty in Center		23		26		26		19	
Number of Visitors		10		17		17		12	

	Year 9 (Year 04 as Accomplished Center) 1992-1993		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	
	Actual	Avg	Actual	Avg	Actual	Avg	Actual	Avg	Actual	Avg
Number of:										
Articles	78	(3.90)	95	(5.00)	132	(6.29)	153	(7.29)	176	(7.33)
Books or Book Chapters	7	(0.35)	9	(0.47)	5	(0.24)	5	(0.27)	5	(0.21)
Published Proceedings	17	(0.85)	11	(0.58)	37	(1.76)	65	(2.95)	71	(2.96)
Total Publications	102	(5.10)	104	(5.47)	174	(8.29)	223	(10.62)	249	(10.38)
Abstracts	53	(2.65)	55	(2.89)	42	(2.00)	64	(3.05)	71	(3.01)
Invited Participation at:										
Regional Meetings	15	(0.75)	18	(0.95)	41	(1.95)	55	(2.62)	68	(2.83)
National Meetings	47	(2.35)	47	(2.47)	65	(3.10)	70	(3.18)	76	(2.92)
Faculty in Center	20		19		21		22		24	
Number of Visitors	12		13		15		18		18	

TABLE 3

RESEARCH PROJECTS FUNDED EXTERNALLY

REPORT PERIOD 1996-97

PROJECT DIRECTOR	TITLE OF GRANT	FUNDING AGENCY	TOTAL AWARDED	ESTIMATED EXPENDITURES
David Bemis	*Bordetella bronchiseptica* 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

Kennedy - Continued	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 *Escherichia coli* and *Salmonella choleraesuis* in pigs	USDA 1433 Funds	$ 4,000.00 10/01/95-9/30/96	$ 4,000.00
	Weaning and colonization of *E. coli* 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
	Effect of galactosyl lactose on calf starter diets (Co-PI)	Snow Brand Milk Products Co.	$ 30,000.00	----------
Charmi Mendis-Handagama	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 ostectomy 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 cylcoaxygenase-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
	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
Linda Munson	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	----------
	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 *Streptococcus uberis* 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	*Toxoplasma gondii* 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 *Toxoplasma gondii* in swine populations: A comparison of the seroprevalence of *Toxoplasma gondii* 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 *Leptospira 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	----------
	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 *Tetrahymena*	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
	Directed expression of the agouti gene product in transfenic 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	

Plans For Next Year

CENTER OF EXCELLENCE
FACULTY FUNDED 1997-98

David A. Bemis, Ph.D.
Associate Professor
Department of Comparative Medicine

Philip N. Bochsler, D.V.M., Ph.D.
Assistant Professor
Department of Pathology

David A. Brian, D.V.M., Ph.D.
Professor
Department of Microbiology

Thomas J. Doherty, M.Sc.
Assistant Professor
Department of Large Animal Clinical Sciences

Kevin A. Hahn, D.V.M., Ph.D.
Associate Professor
Department of Comparative Medicine

Alan G. Mathew, Ph.D.
Assistant Professor
Department of Animal Science

Charmi Mendis-Handagama, D.V.M., Ph.D.
Assistant Professor
Department of Animal Science

Joyce I. Merryman, D.V.M., Ph.D.
Assistant Professor
Department of Pathology

Linda Munson, D.V.M., Ph.D.
Assistant Professor
Department of Pathology

Jack W. Oliver, D.V.M., Ph.D.
Professor
Department of Comparative Medicine

Stephen P. Oliver, D.V.M., Ph.D.
Associate Professor
Department of Animal Science

Barton W. Rohrbach, V.M.D, M.P.H.
Associate Professor
Department of Large Animal Clinical Sciences

Barry T. Rouse, B.V.Sc., Ph.D.
Professor
Department of Microbiology

Hildegard M. Schuller, D.V.M., Ph.D.
Professor
Department of Pathology

Terry W. Schultz, Ph.D.
Professor
Department of Animal Science

J. Erby Wilkinson, D.V.M., Ph.D.
Associate Professor
Department of Pathology

Center of Excellence Plans for 1997-98

No major changes in the direction of research within the Center are anticipated for the next year. Most researchers have embarked on long-term research goals and some less-established members are focusing on development of a fundable research niche. Generally, the Center's research falls within two categories, **livestock diseases or animal/laboratory models of human diseases**. Researchers have concentrated on a limited number of focus areas within these two broad categories (Livestock diseases: infectious diseases/population medicine, toxicoses and reproduction; Animal/laboratory models: host defense, molecular genetics and carcinogenesis). The general research goals for each of the research focus groups are as follows:

Infectious Diseases/Population Medicine

Dr. David Brian will focus on the molecular biology of bovine coronavirus replication; to study mechanism(s) of persistent infections and to identify targets for antiviral therapy and for engineering effective vaccines.

Dr. Stephen Oliver will research virulence factors that have an important role in the development of bovine mastitis caused by bacteria and whether such factors must be considered in the development of vaccines.

Dr. Sharon Patton continues to investigate the epidemiology and risk factors of *Toxoplasma gondii*, a parasite responsible for serious disease in fetuses, neonates and immuno-deficient individuals. It affects humans and various animals.

Dr. Melissa Kennedy will characterize molecular inter-relationships and diagnosis of coronavirus infections in animals. She will concentrate on identifying persistently infected animal and carriers of the virus.

Dr. Alan Mathew will continue his study on factors influencing the incidence and severity of mastitis in sows. He also will investigate the influence of diet on the resistance of post-weaning pigs to intestinal infections.

Dr. David Bemis has identified a major immunizing protein and virulence factor of *Bordetella bronchiseptica*, an important disease-producing agent of swine, horses, laboratory

animals and other animals. He will focus on characterizing the immune response to this protein produced by recombinant DNA technology.

Toxicoses

Dr. Terry Schultz will expand on his research on predicting the toxicity of highly reactive industrial materials using biological activity testing and mathematical modeling procedures.

Dr. Jack Oliver and co-workers will study the effect of alkaloid fungal toxins in tall fescue grass on blood vessels of cattle. Chronic exposure to the toxins results in damage to the lining of blood vessels and mechanisms to prevent damage are being investigated. They also will continue to elucidate mechanisms by which these alkaloids, so prevalent on tall fescue grass, affect only herbivores. They also will work on improving their patented vaccine to prevent the harmful effects of the toxins.

Dr. Donita Frazier will complete work on the cytochrome P450 enzymes that could affect the amount of drug or chemical residues in food animals.

Reproduction

Dr. James Godkin will research treatments to manipulate production of vitamin A derivatives during ovulation and pregnancy to optimize reproductive efficiency in food animals.

Dr. Charmi Mendis-Handagama will continue her research focus on hormonal mechanisms of fertility in animals and humans.

Host Defense

Dr. Barry Rouse will concentrate on factors that modulate the severity of harmful inflammatory responses to herpesvirus infections. His approach is to use products of immune cells, produced by recombinant DNA technology, to ameliorate the degree of the host response to the virus. **Dr. Rouse** has pioneered the use of naked DNA vaccines and will continue to evaluate the utility of this approach for preventing infectious diseases.

Dr. Philip Bochsler will continue to investigate the mechanisms by which white blood cells provide protection against infectious agents that cause bovine pneumonia. **Dr. Bochsler** also is studying the role of nitric oxide as a mediator of host defense in the lungs of cattle. Knowledge

of the function of leukocytes and other immune mechanisms operative in the bovine lung will assist in formulating improved strategies for prevention and therapy of bovine respiratory tract disease.

Dr. Diane Hendrix will determine, in a laboratory model, the effect of various commonly used antibiotics on the healing of wounds to the cornea.

Molecular Genetics

Dr. Eric Schultze will work on a mutant mouse model of a specific type of anemia and iron overload disease in people. He will characterize the molecular control of blood cell formation, iron metabolism and bone growth.

Dr. Erby Wilkinson is characterizing and studying several diseases in mutant mice that resemble serious genetic diseases of humans. They include various auto-immune diseases, other immune-mediated diseases and Wiskott-Aldrich disease (see Goals 3 and 4). They have already had some success in curing and preventing some of these diseases. He will collaborate with **Dr. Dorcas Schaeffer** in further characterizing another disease in mutant mice that develop various organ abnormalities due to defect(s) in various stem (precursor) cells.

Dr. Darryl Millis uses a canine model to investigate factors that influence healing of bone fractures. His work has focused on the use of growth hormone.

Carcinogenesis

Dr. Hildegard Schuller will continue her work on the molecular mechanisms by which nicotine produces lung cancer and confirms whether drugs widely used for asthma and chronic bronchitis promote certain kinds of lung tumors in animal models. **Dr. Schuller** will continue the experiment in a hamster model to test the potential chemo-preventive effect of theophylline on this lung cancer type. Along with **Dr. Joyce Merryman**, she will continue to address the question why chronic lung disease is a risk factor for lung cancer.

Dr. Kevin Hahn will conduct clinical trials on animals with naturally occurring cancer as models to identify new methods for the diagnosis and treatment of cancer. **Dr. Hahn** also is

attempting to identify, develop and evaluate new drugs that may augment standard anticancer drugs by minimizing resistance of tumor cells to the latter drugs.

Dr. Joyce Merryman is studying the mechanism by which cells are affected by environmental hazards, especially ultraviolet radiation present in sunlight. Ultraviolet radiation causes damage to the cellular DNA. resulting in the necessary changes for skin cancer to develop. **Dr. Merryman** will investigate the role of tumor suppressor genes, growth-regulatory factors and intracellular communication pathways that are involved in the development of skin cancer.

Budget Form

Schedule 7 Budget Form 1998-99

CENTERS OF EXCELLENCE/CENTERS OF EMPHASIS
ACTUAL, PROPOSED, AND REQUESTED BUDGET

Institution llege of Veterinary Medicine **Center** Livestock Diseases and Human Health

	1996-97 Actual			1997-98 Proposed			1998-99 Requested		
	Matching	Appropr.	Total	Matching	Appropr.	Total	Matching	Appropr.	Total
Expenditures	257,150	514,300	**771,450**	251,550	503,100	**754,650**	264,127	528,255	**792,382**
Salaries									
Faculty	29,542	57,084	**86,626**	28,333	56,667	**85,000**	29,750	59,500	**89,250**
Other Professional	35,326	72,653	**107,979**	35,888	71,775	**107,663**	37,682	75,364	**113,046**
Clerical/ Supporting	22,043	44,087	**66,130**	9,927	19,855	**29,782**	10,423	20,848	**31,271**
Assistantships	13,482	26,963	**40,445**	15,413	30,826	**46,239**	16,184	32,367	**48,551**
Total Salaries	**100,393**	**200,787**	**301,180**	**89,561**	**179,123**	**268,684**	**94,039**	**188,079**	**282,118**
Fringe Benefits	22,122	44,243	**66,365**	21,095	42,190	**63,285**	22,150	44,299	**66,449**
Total Personnel	**122,515**	**245,030**	**367,545**	**110,656**	**221,313**	**331,969**	**116,189**	**232,378**	**348,567**
Non-Personnel									
Travel	518	1,035	**1,553**	1,278	2,557	**3,835**	1,342	2,685	**4,027**
Software	279	559	**838**			**0**			**0**
Books & Journals	99	197	**296**			**0**			**0**
Other Supplies	42,955	85,910	**128,865**	73,654	147,309	**220,963**	77,337	154,674	**232,011**
Equipment	82,467	164,934	**247,401**	50,843	101,685	**152,528**	53,385	106,769	**160,154**
Maintenance	4,267	8,535	**12,802**	7,452	14,903	**22,355**	7,824	15,649	**23,473**
Scholarships	7,278	14,555	**21,833**	7,667	15,333	**23,000**	8,050	16,100	**24,150**
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	**137,863**	**275,725**	**413,588**	**140,894**	**281,787**	**422,681**	**147,938**	**295,877**	**443,815**
GRAND TOTAL	**260,378**	**520,755**	**781,133**	**251,550**	**503,100**	**754,650**	**264,127**	**528,255**	**792,382**
Revenue									
New State Appropriation		514,300	**514,300**		503,100	**503,100**		528,255	**528,255**
Carryover State Appropriation		6,455	**6,455**			**0**			**0**
New Matching Funds	257,150		**257,150**	251,550		**251,550**	264,127		**264,127**
Carryover from Previous Matching Funds	3,228		**3,228**			**0**			**0**
Total Revenue	**260,378**	**520,755**	**781,133**	**251,550**	**503,100**	**754,650**	**264,127**	**528,255**	**792,382**

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