1996

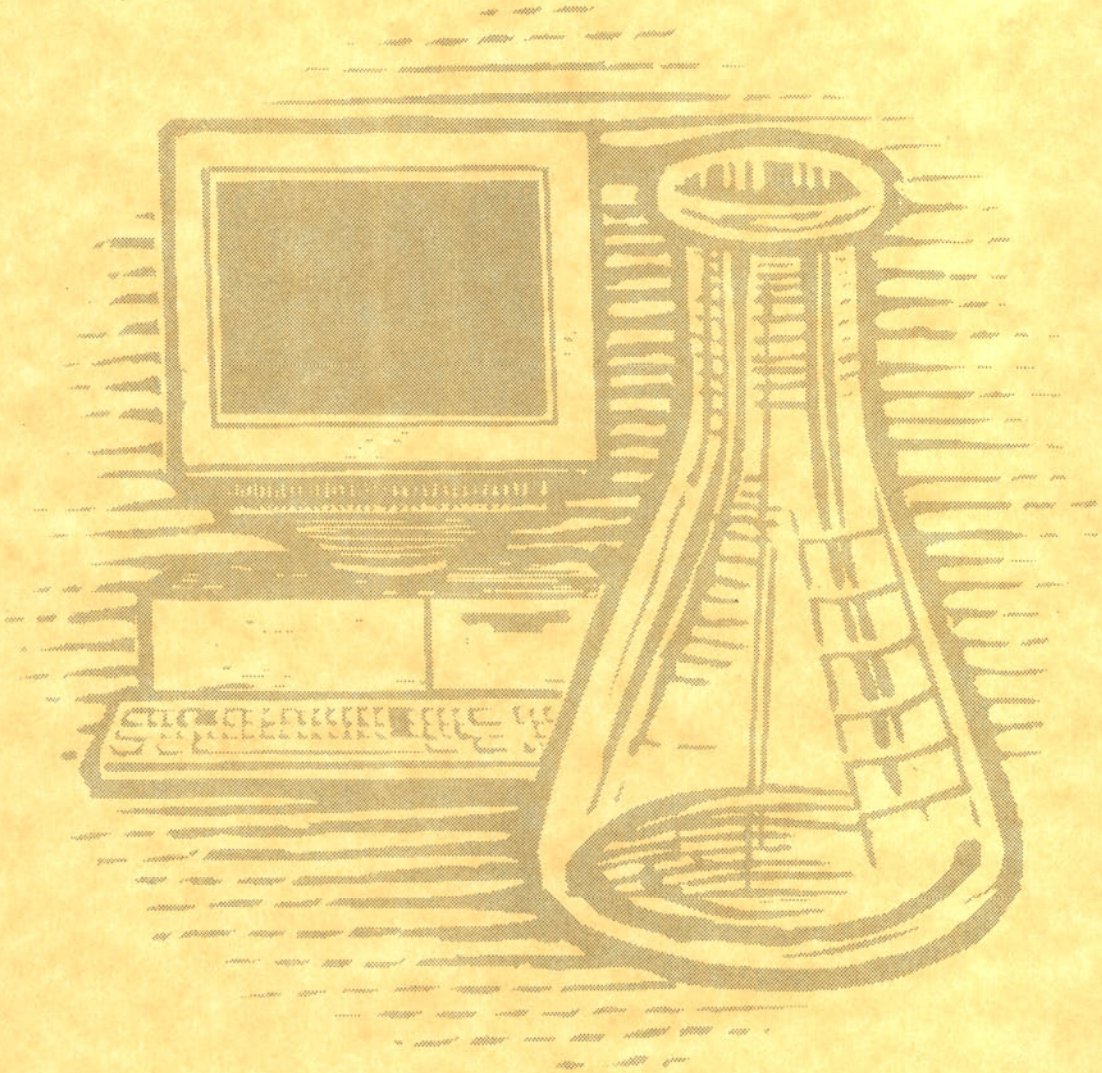
Center of Excellence Annual Report, July 1995-June 1996

College of Veterinary Medicine

Center of Excellence in Livestock Diseases and Human Health

ANNUAL REPORT

July 1, 1995 - June 30, 1996



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

CONTENTS

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

V. Benchmarks

Table 1. External Funding Levels Since Establishment of the Center of Excellence in Livestock Diseases and Human Health

Table 2. Faculty Accomplishments

Table 3. Externally Funded Research Projects

VI. Plans for Next Year

1996-97 Center of Excellence Members

Research Projects

VII. Budget Form

VIII. Appendix

Five-Year Review Report

External Scientific Review Report

THE UNIVERSITY OF TENNESSEE
COLLEGE OF VETERINARY MEDICINE

Office of the Dean
P. O. Box 1071
Knoxville, TN 37901-1071
Phone: 423/974-7262
Fax: 423/974-4773
E-mail: mshires@utk.edu

August 2, 1996

The College of Veterinary Medicine Center of Excellence has just concluded its twelfth year of existence and its seventh year as an accomplished center. The benchmarks set at the inception of this Center have been exceeded every year. For instance, this year the average number of peer reviewed publications per member is over seven, indeed a remarkable achievement.

Despite recent level funding the center is growing and our faculty are achieving great success in the very competitive area of federal/national support. One of the greatest achievements, largely due to the center, is the award of an NIH Training Grant. This grant is a collaborative effort between the College of Veterinary Medicine, Department of Pathology and the Biology Division of the Oak Ridge National Laboratories and is to train outstanding researchers in the area of molecular pathobiology of environmental diseases. The proposal was for $700,000 over a five year period.

This year, we were not only reviewed by our external review committee, which review occurs every few years, but we also had the pleasure of a review on behalf of the Tennessee Higher Education Commission (THEC) which stated in its written review that:

> "The Center has been very successful in attracting external funding. Over the past five years, over $19 million has been awarded to the Center to support these research projects. While the College of Veterinary Medicine is among the smallest in the nation, it ranks fourth in external research funding."

The external reviewers' written report stated:

> "In conclusion, we congratulate the Dean and the faculty on the fine accomplishments of the Center. . .continues to be an important asset to the University and the State."

We will continue to refine our Center to best match areas of the most impact on Tennesseans. Currently, the researchers of the Center cover a wide spectrum of areas—bovine mastitis, human and animal reproduction, infectious diseases, vaccines, animal models for important human diseases such a polycystic kidney disease, cancer, and host defensive mechanisms important in immune mediated diseases.

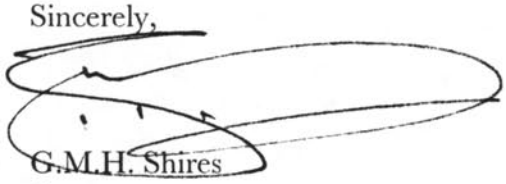
This Center of Excellence continues to be a wonderful investment with returns of almost $2.5 million per year of external funding on a state investment of roughly $500,00 (5:1). Would that we could all invest so well.

The forging of links and partnerships with other recognized institutions such as Oak Ridge National Laboratories has enabled collaborative proposals to be submitted for funding from external agencies that heretofore we were unable to access. These relationships should broaden our expertise, especially in the molecular biology/transgenic mouse areas.

One note of caution is that our state support has been level for a number of years while costs have risen exponentially. We are very thankful for the support but with the increased price of everything from per diem for mice to rapidly increasing spare parts for an aging electron microscope, the Center really does need a raise. The College of Veterinary Medicine is a major success story which shows the Tennessee taxpayers how well their money is being invested in their, and Tennessee's, future.

We thank you for your support and we are proud to be a part of this success.

Sincerely,



G.M.H. Shires
Dean

vjb

1995-96 CENTER OF EXCELLENCE MEMBERS

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

James D. Godkin, Ph.D.
Professor
Department of Animal Science

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

Alfred M. Legendre, D.V.M., M.S.
Professor
Department of Small Animal Clinical Sciences

Ted P. McDonald, Ph.D.
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

Mark S. Miller, 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

Leon N.D. Potgieter, B.V.Sc., Ph.D.
Professor and Head
Department of Comparative Medicine

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

Jill E. Sackman, D.V.M., Ph.D.
Assistant Professor
Department of Small Animal Clinical Sciences

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

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

A. Eric Schultze, D.V.M., Ph.D.
Assistant Professor
Department of Pathology

Robert M. Shull, D.V.M.
Professor
Department of Pathology

David O. Slauson, D.V.M., Ph.D.
Distinguished Professor and Head
Department of Pathology

Daniel A. Ward, D.V.M., Ph.D.
Assistant Professor
Department of Small Animal Clinical Sciences

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

Programmatic Report

Center of Excellence
Program Report (1995-96)

The Center of Excellence has been in existence for over eleven 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 1995-96 (153 total, a mean of 7.29 per member). It is a tribute to our members that they have been able to maintain funding levels in spite of a very unfavorable funding climate.

The Center experienced considerable scrutiny this past year. First as part of the Tennessee Higher Education Committee five-year review and second by the external scientific review team (chaired by Dr. Peter Eyre, Dean, Virginia-Maryland Regional College of Veterinary Medicine). I am pleased to report that the Center received excellent reviews (see Appendix) and support the direction in which the Center is evolving. As suggested by the external review team, we will continue to seek an external scientific review every three years.

The essence and direction of the COE is determined by the key participants in the program. And, like any good program, the Center must be flexible to accommodate changes in personnel and yet maintain its overall goals. We are likely to have several new participants in the next year or two as a result of recruiting for research positions vacated because of retirement and resignation. This infusion of new researchers into the Center can only further stimulate the vitality of our research program. However, we realize also that subtle differences in research emphasis may also be a consequence of filling these positions. Furthermore, changes in personnel and the nature of external funding over the last year has provided also an opportunity for reviewing

current COE research focus areas (Inflammation and Host Defenses, Growth Factors and Molecular Genetics, Infectious Diseases and Population Medicine, *In Vitro* Toxicology and Toxicokinetics, and Carcinogenesis and Developmental Therapeutics).

Two personnel changes occurred during the year. **Dr. Ted McDonald**, Professor, Department of Animal Science retired from the University of Tennessee after 41 years of service and **Dr. Mark Miller** joined the staff at Bowman Gray School of Medicine at Wake Forest University in Winston-Salem, North Carolina.

Strategic Plan

After **Dr. Potgieter** took on the responsibility as Director of Research and Graduate programs (including direct administration of the COE), it was proposed that the Dean eliminate all standing research and COE advisory committees and replace them with a single committee to advise the college on all research and graduate issues. It was envisaged that this committee would have a critical role in the research and graduate training policies of the college and also be responsible for reviewing all internal funding proposals for research or research equipment. Although the mechanism by which this committee functions is still evolving, it has been very active since its inception, is fulfilling its objectives, and its influence is growing.

As a consequence, the definition, policies and procedures of the COE and the description of the research focus areas have been targets of ongoing discussion. Mechanisms to promote greater participation and/or communication were explored.

One goal of the Center that should receive greater attention is to identify faculty with research potential and provide appropriate venture opportunities. Therefore, this goal was placed as one of the four priorities for funding by the Center. Also, the notion that specific faculty were

"invited to be members" of the Center is to be discontinued. It was decided to solicit proposals from all eligible faculty (those with "significant" research appointments) and all who then receive funding from COE would be listed as "Faculty Funded for the Fiscal Year." Of course, only proposals that met the broad objectives of the Center would be considered.

Now all the projects supported by COE (supporting or venture) are folded into a single competition; all researchers funded will be listed as "Faculty Funded for 199X - 199X" in future COE reports. Also, the COE will continue to fund a modest number of summer stipends for veterinary students to promote careers in research.

The Center of Excellence will continue to fund equipment purchases; requests will be solicited from COE-funded researchers and recommendations for purchase by the Research and Graduate Programs Advisory Committee will be made to the Dean and Executive Committee.

An argument was made in the five-year report that there is considerable merit in modifying research focus areas within the Center. These arguments are valid, but in defining areas of focus, we should also reflect our areas of strength within the Center. Some researchers have shifted emphasis of their research on human disease slightly from exclusive use of animal models to include also *in vitro* systems. This shift should be reflected in descriptions of the goals and areas of research focus. We proposed, therefore, to use the term animal/laboratory model whenever animal model has been used in the past. This then will more accurately reflect what several researchers are doing than the current terminology.

We proposed also to not only change the areas of research focus from the five that have been operative in the immediate past to reflect the disciplines involved, but also to indicate the connection with the mission of the Center. The new groups are:

Mission 1: Livestock Diseases -
Focus Groups:

Infectious Diseases/Population Medicine
Toxicoses
Reproduction

Mission 2: Animal/Laboratory Models of Human Diseases -
Focus Groups:

Host Defense
Molecular Genetics
Carcinogenesis

This terminology reflects the relationship of our research to the mission of the Center, the nature of the disciplines involved, and also the strengths of our researchers. Furthermore, an established researcher is available to be assigned, based on their funded programs, to each of these sections to serve as coordinators/leaders.

The coordinators for the six research focus groups are as follows:

Infectious Diseases/Population Medicine:	David Brian
Toxicoses:	Terry Schultz
Reproduction:	Linda Munson
Host Defense:	David Slauson
Molecular Genetics:	Erby Wilkinson
Carcinogenesis:	Hildegard Schuller

The charge to the coordinators is to identify participants in each field, promote the formation of research alliances among potential participants (particularly between applied and basic disciplines), summarize and present research progress by faculty funded by COE periodically, and promote dissemination of research activity of the Center.

Major Research Activity in the Center of Excellence

Goal 1 -

To Improve the Quality of Human Life Through Better Animal Health

Several investigators contributed to this goal. **Dr. Stephen Oliver** worked on bovine mastitis to help ensure a safer food product. He has developed a highly accurate and specific method for identification of *Streptococcus* bacteria in milk.

Endometriosis affects one of every seven women in the United States, resulting in pain and infertility. In this disease, the cells that normally line the uterus grow inside the abdominal cavity, causing organs to adhere together and become constricted and dysfunctional.

Dr. Linda Munson's goal has been the development of a model for endometriosis in order to test factors that worsen this condition. She has developed a mouse model in which human uterine lining cells are transplanted into the abdominal cavity. This model will be used to develop new therapies for endometriosis.

Dr. Kevin Hahn and co-workers have conducted clinical and laboratory research trials on client-owned pet animals with naturally-occurring cancer to identify new methods for the diagnosis and treatment of human beings with cancer. Results from these trials have led to new concepts in how anticancer drugs should be given to increase the potential for tumor control (cure) and decrease the likelihood of side effects, especially in smaller-sized patients (pediatric patients).

Dr. David Brian's laboratory investigated coronaviruses that infect many species, including cattle. By studying the molecular biology of bovine coronavirus replication, **Dr. Brian** has identified potential sites in the viral genetic material for targeted anti-viral therapy and uncovered two potential mechanisms of persistent infection. Most excitingly, they have discovered a potent specific antiviral molecule, a ribozyme that cleaves a vulnerable site within the viral replication gene and blocks virus propagation. Coronaviruses infects and produces serious disease in cattle and Brian's research provides potential opportunities for resolving the acute and chronic coronavirus infection problems in cattle, but has applications for controlling coronavirus infections in humans as well.

Dr. Jack Oliver's area of research emphasis continues to be the understanding and control of the adverse effects associated with animals consuming toxic tall fescue grass. Tall fescue is grown on 3.5 million acres in the State of Tennessee, and most of this grass is infected with a fungus that produces toxins that harm animals (cattle, horses, sheep) that consume the grass. Conservative estimates place the animal loss to Tennessee cattle producers alone at nearly $100 million. In conjunction with other researchers at the University of Tennessee and the Agricultural Experiment Station, **Dr. Oliver's** major activity has been concerned with a field-trial study to determine the effectiveness of a for preventing tall fescue toxicosis. Results of this study proved that a vaccine approach to the control of fescue toxicity was possible.

The overall research focus in **Dr. Philip Bochsler's** laboratory has been the investigation of bacterial diseases of cattle. The general purpose of this research is to gain a better understanding of host-defense responses of cattle to disease-producing organisms. A better understanding of these responses is essential for understanding the pathogenesis of important diseases of cattle, and is important for the ultimate goal of designing improved strategies to deal with these diseases. In his work, he has studied the regulation of nitric oxide synthesis and is in the process of characterizing the role of nitric oxide in host defense against bovine respiratory tract disease-producing organisms.

Goal 2 -

To Augment Livestock Disease Research Capabilities in the Institute of Agriculture

Drs. P. Bochsler, S. Oliver, J. Oliver, L. Potgieter, D. Brian, J. Godkin, L. Munson, and J. Merryman made significant contributions in livestock disease research by the Center this past year.

Dr. Philip Bochsler's study of nitric oxide produced by certain cells and its potential disease-producing role in the bovine lung will elucidate molecular mechanisms involved in the bovine defense response to disease organisms, and will add useful information concerning the development of some respiratory diseases of cattle. Bacterial and viral infections of the

respiratory tract of cattle occur commonly in Tennessee, and are a source of significant economic loss to the cattle industry. He has established that nitric oxide may be an important regulatory molecule affecting the host-defense response of cattle to microbes.

Further recognition for the feasibility of an immunological approach to the control of fescue grass toxicity occurred when **Dr. Jack Oliver** and co-workers were issued a patent for a vaccine to control fescue toxicity in animals (U.S. Patent No. 5,468,486, November 11, 1995). A comprehensive approach to monitoring toxin effect on normal body function of animals included documenting changes in the appearance of animals, recording body weight changes, and measuring a wide array of metabolic factors. This represented the most thorough study of tall fescue toxin effect on cattle that had ever been done. Animals that were grazing toxic tall fescue grass without benefit of vaccine, when compared to vaccinated cattle, grew at a slower rate, had evidence of suppressed liver function (certain metabolic enzyme levels were less), and had bone marrow suppression (total white blood cells and total red blood cells were less).

Dr. Leon Potgieter's work focused on the genetic variability of Respiratory Syncytial Virus strains recovered from cattle and sheep. A portion of the viral gene that varies among strains was targeted with a probe designed to react with the appropriate genetic material. He determined that two subgroups of the virus affecting these animals existed. This work suggests that a vaccine made with one strain of the virus might not provide adequate protection against respiratory disease caused by the virus.

Dr. David Brian continued to work on bovine coronavirus, concentrating on the molecular biology of its replication. With funding from the USDA and the NIH, **Dr. Brian** has been making an intense and systematic effort to understand how five separate genetic structural elements in the coronavirus genome function to regulate production of viral proteins. During acute infection, replication rates are high and during persistent infection, replication rates are low.

He studied the mechanism by which the five specific (untranslated) regions on the messenger molecules (RNA's) regulate the rate of viral protein synthesis (translation). They now have obtained new information about coronaviruses that defines a specific site regulating viral protein synthesis. This site, therefore, could be targeted for therapeutic control of coronavirus infection.

Dr. Linda Munson's work on the development of a mouse model of endometriosis and to test the role of a specific growth factor (platelet cell-derived) in the initiation and maintenance of endometriosis has been successful. She has made significant progress in developing and characterizing cell lines of human endometrial epithelial cells, optimizing their methods for identifying key proteins (peptides) and receptors in these cells. She confirmed that the growth factor receptors are present in human endometriotic tissues and strengthened the relevancy of the growth factor hypothesis. She also has made progress in transplanting endometrial cells into the mouse and confirming the continued expression of growth factor receptors in the transplanted cells. Transplanted cells are identified as human endometrial epithelial cells in the mice by tests with a monoclonal antibody which does not react with mouse tissues.

Recent studies by **Dr. James Godkin** have focused on the factors that influence early embryonic development leading to successful pregnancy in cattle and sheep. Vitamin A (retinol) is essential for reproductive processes. Severe retinol deficiency may inhibit reproduction cycles, ovarian development, and ovulation. Moderate deficiency may result in abortion, fetal resorption or congenital abnormalities. **Dr. Godkin** studied the mechanisms by which retinoids (vitamin A-like chemicals) regulate cell growth and development in reproductive tissues. Recent discoveries include the identification of retinol-binding protein (RBP), cellular-retinol binding protein (CRBP) and cellular-retinoic acid binding protein (CRABP) in the placenta, uterus, oviduct, ovarian follicle, egg and corpus luteum of cattle and sheep. He determined the role of ovarian sex hormones and retinol derivatives in regulating synthesis of retinol-associated proteins in these tissues. Research in progress is focused on developing treatments to manipulate production of these critical proteins during ovulation and pregnancy to achieve improved reproduction efficiency.

In addition to the studies of retinol-associated proteins, it was discovered that the uterus and placenta of sheep and cattle produce a family of growth factors known as transforming growth factor-beta. Three members of this family (TBF-B-1, B2, B3) and their messenger molecule (mRNA) are produced at different concentrations in the uterus during the estrous cycle and pregnancy. Sex hormone replacement studies demonstrated that each growth factor is regulated differently by ovarian hormones.

A major research focus of **Dr. Stephen Oliver** has been on the bacterium *Streptococcus uberis,* a frequent cause of mastitis in cows. Strategies for controlling this mastitis-causing organism are poorly defined and currently inadequate. During the last year, **Dr. Oliver's** laboratory has identified some factors that allow *Streptococcus uberis* to invade the udder and produce mastitis. One such factor is a capsule composed primarily of hyaluronic acid that surrounds bacteria in at least 50% of strains, and that inhibits bacterial destruction by mammary gland macrophages (scavenger cells). Another factor is a protein that may promote adherence of this organism to certain cellular proteins and to mammary epithelial cells. He hypothesized that the capsule and the protein are virulence factors involved in the development of *Strep. uberis* mastitis. The long-term goal of this research is to develop a vaccine to control this important mastitis-producing organism.

Certain malignant tumors (squamous cell carcinomas) are common in people and are often associated with environmental stresses such as ultraviolet radiation, cigarette smoke, and other carcinogens. Squamous cell carcinomas probably develop because their cells are not inhibited by a certain growth factor (TGF-β1). This appears to be a mechanism by which normal epithelial cells become malignant. Studies conducted by **Dr. Joyce Merryman** confirmed the resistance of squamous cell carcinomas to growth-inhibition normally induced by this growth factor. But these cells still respond by activating production of certain chemical signals within the cell. This led to the discovery that the growth factor was incapable of activating the normal mechanisms for repairing DNA in the tumor cells exposed to ultraviolet light. The repair mechanism is activated by the growth factor in normal cells under similar circumstances. This fundamental research may identify mechanisms for controlling the tumors.

Goal 3 -

To Identify and Characterize Animal Diseases that are Analogous to Human Diseases

Dr. Eric Schultze's 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. Work in the laboratory centered on the investigation of iron metabolism, a requirement for normal blood cell formation and bone growth.

Fitness 1 mice had less iron in their blood than normal mice do. The concentration of iron in the liver of *fitness 1* mice was increased, but the concentration of iron within the kidneys was significantly less than that of normal mice. From these data, it was concluded that the anemia in *fitness 1* mice is associated with abnormal iron metabolism. The evidence of excessive storage of iron within the liver, low serum iron concentration and biochemical evidence of liver dysfunction suggests that the *fitness 1* mouse is a good model for the disease hemochromatosis. The *fitness 1* mice constitutes a unique model that can be used to shed new light on the diagnosis and treatment of anemia and hemochromatosis in people. This research has broad implications for understanding the molecular control of blood cell formation, iron metabolism, and bone growth in mammals.

Tennessee is one of the top five air polluting states in the nation. To aid industry, state, and local governments in making accurate judgments regarding chemical toxicity methods predicting toxicity of chemicals such as quantitative structure-toxicity relationships and knowledge-based expert systems, need to be developed. Phenols are a group of poisonous bioreactive organic chemicals that have a wide variety of industrial uses. Bioreactive chemicals, such as phenols, cause unique problems for the development of methods that predict toxicity of a chemical.

Over the past year, **Dr. Terry Schultz's** laboratory has focused on developing models of predicting chemical interactions of industrial phenols. His laboratory has found that certain chemical properties (the ionization constant and the quantum chemical molecular orbital term, the lowest unoccupied molecular orbital energy) are important in predicting toxic potency of phenols.

Goal 4 -

To Study Animal Models for Better Understanding of Human Disease

Several COE researchers exploited animal models in their studies over the past year of disease processes in humans. The investigators were **Drs. C. Mendis-Handagama, Dr. T. McDonald, J. Sackman, B. Rouse, H. Schuller, E. Schultze, D. Ward, and E. Wilkinson.**

Dr. Charmi Mendis-Handagama continues her research on cellular mechanisms associated with hormone production in the mammalian testis and ovary using the rat model.

Mouse models are extensively used by **Dr. Barry Rouse** and co-workers in their studies of the immuno-biology of human herpesvirus type 1 (herpes simplexvirus). The objectives of their work are to understand the mechanisms of the disease processes and protective immunity and the development of effective vaccines. Significant progress was made this past year.

Dr. Hildegard Schuller has been studying the role of the autonomic nervous system in the induction and development of lung cancer. It has been known for years that nicotine stimulates brain cells because it binds to a certain receptor (nicotinic acetylcholine receptor) of the autonomic nervous system. **Dr. Schuller** has found also that this receptor is produced on some types of lung cells that give rise to the most common human lung cancers and that it regulates the growth of these cells. Nicotine is generally considered non-carcinogenic based on experiments in laboratory animals. However, it is becoming increasingly evident that, among smokers, only those who have a history of chronic lung disease are at high risk to develop lung cancer. **Dr. Schuller** has simulated this condition in hamsters maintained in an environment with concentrations of oxygen that are toxic to the lung. These animals developed lung cancer when given nicotine at a concentration (0.1 mg/Kg two times/week) equivalent to that in a moderate smoker. Healthy animals without lung injury did not develop tumors when treated with nicotine. These results prove, for the first time, that nicotine can cause lung cancer in individuals with chronic lung disease.

Another important finding in **Dr. Schuller's** laboratory was that theophylline blocks the growth of small cell lung cancer in the laboratory while it stimulates the growth of another lung cancer (adenocarcinoma) The mechanism by which theophylline regulates these two lung cancers is being studied in animal models. Theophylline is the active ingredient in drugs that dilate the

bronchi and that are widely used for the treatment of asthma and bronchitis. High concentrations of theophylline are contained also in black and green tea. If the animal experiments confirm the laboratory data, theophylline containing drugs, as well as tea should be avoided by human patients with lung adenocarcinoma whereas they would be beneficial for the treatment and for the prevention of metastatic spread of small cell lung cancer.

Dr. Jill Sackman is using a dog model to investigate gene therapy via cells that line the blood vessels (endothelial) cells. However, genetically-altered endothelial cells generally fail to adhere to blood vessel grafts used as a vehicle to deposit the cells in an animal. She has determined that the mechanism for poor adhesion is an altered or missing receptor on the cells. This information now allows the development of methods to circumvent the problem and will enhance the development of gene therapy to treat genetic vascular diseases in humans.

Dr. Ted McDonald's laboratory continues to work on the genetic basis of a disease of blood cells, the abnormal production of blood platelets. Certain precursor cells (megakaryocytes) that give rise to blood platelets may contain excessively-high numbers of chromosomes and result in over-production of blood platelets that may promote vascular disease. The mechanism by which this condition is inherited in mice has been determined and now the role of genetic control and thrombopoietin (a hormone affecting megakaryocytes) can be evaluated to establish potential mechanisms of controlling the disease.

Dr. Erby Wilkinson continues to focus on the development of disease caused by specific genetic mutations, and has exploited several mouse models for these diseases; either spontaneous mutant mice or mice in which mutations have been induced in the laboratory. **Dr. Wilkinson** has made some significant discoveries concerning the genetic kidney disease (autosomal recessive polycystic kidney disease). It is caused by a change in a specific gene that may be important in cell cycle regulation. He identified a unique protein that this gene codes for. Furthermore, he discovered cells in the liver of these mice that have characteristics of liver stem (precursor) cells making these mice good candidates for studies of liver cancer.

Dr. Wilkinson has also identified a mouse model of auto-immune disease caused by abnormalities in the interaction among certain lymphocytes in the developing thymus of the mouse embryo. He is investigating the cellular and molecular basis of the disease by specific laboratory-

induced mutations in these mice. Further studies this past year include the identification of mouse models of a variety of other genetic diseases affecting various tissues and organs.

Dr. Daniel Ward continues his research in the treatment of abnormal eyelashes (distichiasis) that cause eye irritation and the treatment of elevated intraocular pressure (glaucoma). Using a dog model, his laboratory has conclusively demonstrated that surgical placement of a fluid-draining device is superior to laser surgery for the treatment of severe glaucoma.

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. P. Bochsler, D. Brian, T. McDonald, J. Merryman, J. Oliver, S. Oliver, B. Rouse, H. Schuller, T. Schultz, E. Schultze, D. Ward and E.Wilkinson**.

Dr. Barry Rouse and co-workers have moved closer to understanding how herpes simplex virus infection of the eye causes an inflammatory reaction (herpetic stromal keratitis) which often results in blindness. It seems that the virus replicates in the surface epithelial cells of the cornea and this causes the release of chemical messengers, chemokines, which signal certain white blood cells (neutrophils) to enter the cornea. Although these cells are mainly confined to the deeper layers of the cornea (i.e., in the stroma), they are responsible for clearing virus. How they accomplish this is currently under study. **Dr. Rouse** has evidence that either the viral replication events or the antiviral efforts of the neutrophils damage the corneal tissues in such a manner that triggers the host's own defense system to react with these tissues resulting in chronic autoimmune disease. Herpetic stromal keratitis may well represent an auto-immune inflammatory response set off by viral infection. Repair of the lesion leaves a scarred cornea that acts as screen to light transmission and in thus partial or complete blindness.

Dr. Jack Oliver and co-workers have developed and refined a model assay system for the effects of tall fescue grass toxin on blood vessel (endothelial) cell function. Two of the major tall fescue compounds (alkaloids: ergine and ergovaline) were toxic to these cells. Presumably they affect endothelial cells of animals leading to the chronic inflammatory state responsible for tall fescue toxicity in cattle. Tall fescue toxicity may result in suppression of liver and bone marrow function and of the immune response which could explain the superior weight gain in cattle given a newly-developed vaccine against these toxins.

A test in ferrets, based on measuring adrenal hormones before and after stimulation of the adrenal glands, was developed in **Dr. Oliver's** laboratory to detect cancerous growth of these glands. Results of thyroid function testing in parrots indicates that stimulation of the birds with thyrotrophic releasing hormone will allow diagnosis of certain thyroid conditions. This test will be invaluable to detecting the most common hormonal disorder in birds because standard thyroid tests are too variable. No other thyroid stimulation tests are currently available for birds, so the new test procedure is an important development for improving the health of birds.

Dr. Daniel Ward has investigated factors that affect the ability of the pigmented epithelium of the retina to protect the interior of the eye from blood-borne toxicants. Similarly, he has shown that a certain growth factor which is produced in the eye and other tissues, also provides protection.

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

Dr. Barry Rouse's work with naked DNA vaccines, and inclusion within vaccines the DNA encoding regulatory molecules of the immune system, has been mentioned elsewhere in this report. However, it needs to be emphasized that this approach promises to greatly enhance the effectiveness of vaccines and to develop vaccines to protect against a variety of diseases for which vaccines have not been available in the past. Similarly, work in **Dr. David Brian's** laboratory has

resulted in the discovery of another powerful mechanism to deliver substances to an animal to induce immunity. They found that a defective portion of a coronavirus of cattle was incapable of producing disease but still had the capacity to divide in cells. This subviral replicon can be used, not only to immunize animals to coronavirus, but also to carry other immunizing proteins or therapeutic drugs into animals' tissues.

Dr. Jack Oliver, together with his co-workers, have collected additional information on the efficacy of a novel vaccine to prevent the toxic effects of alkaloids present in tall fescue grass. A patent has been issued for this vaccine and several commercial companies have expressed an interest in further development of this vaccine .

Data from **Dr. Robert Shull's** laboratory indicate the exciting prospect that curing certain genetic diseases by gene therapy involving a certain carrier virus is possible. In this project they used a harmless virus, adeno-associated virus, to carry the appropriate genetic material into and to restore the genetic defect in the tissues of dogs.

Goal 7 -

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

As mentioned in last year's report, space in the Clyde M. York Veterinary Medicine Building for research, teaching, and clinical services is in short supply. Collaborative COE research is being conducted also in McCord Hall (Animal Science), Walters Life Sciences (Microbiology), and in the Oak Ridge National Laboratory; but research space everywhere is at a premium. It appears that funding for an animal housing facility at Cherokee Farm is now in place. Construction should proceed this fall. Once the facility is completed, the veterinary student surgery will be moved to Cherokee Farm, thereby, freeing approximately 3,000 square feet, some of which will be designated for research space. Minor renovations and equipment allocations have been made over the past year to maximize efficient use of space and to promote a multi-user philosophy. Laboratory sharing among faculty with similar interests and/or similar equipment requirements has been encouraged and implemented.

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 state-wide 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 state-wide readership by the Institute of Agriculture), Veterinary News (for practitioners), Veterinary Medical Topics (published twice yearly by the extension service), and two alumni publications (UT Alumnus and Torchbearer), and in Context (UT faculty/staff newsletter). Research being conducted by the Center is disseminated also via a computer-based program, the World-Wide Web. The University of Tennessee, College of Veterinary Medicine has a home-page (http://www.vet.utk.edu/vet/default.html).

Goal 9 -

To Develop New Strategies for the Prevention of Disease

Dr. Barry Rouse has been investigating DNA vaccines composed of laboratory-propagated DNA that encodes proteins of herpes simplex virus as well as proteins that act to regulate the immune response. His laboratory was the first to show that genetic vaccines could induce protective immunity against the virus and more recently have demonstrated that DNA encoding HSV proteins can produce immunity in the reproductive tract following intra-nasal immunization. This opens up the prospect of developing a new approach to the control of the virus, an important venereal disease. Recent experiments have also revealed that the inclusion of DNA encoding molecules that regulate the immune system may markedly influence the nature and

effectiveness of the immune response. These findings have far-reaching implications in the production of vaccines.

Work done in the laboratories of **Drs. Jack Oliver, Hildegard Schuller, and David Brian** may also culminate in novel strategies for preventing infectious diseases, certain toxicities, and cancer (see information under Goals 4 and 6).

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 a Coulter multisizer cell counter and an image analysis system. This equipment should enhance significantly the capacity of researchers to work with cells in the laboratory and to record and analyze nucleic acid or protein data.

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, Godkin, S. Oliver, Rouse, Schuller, 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. Karrie Brenneman** is

completing her first year in the program and will be reappointed for her second year. She is working in the laboratories of **Dr. Erby Wilkinson** and Dr. Rick Woychik. Her doctoral research will involve mice with specific experimentally-induced genetic disease.

Dr. Barbara Sheppard is the second trainee, and was appointed July 1, 1996. Dr. Sheppard has special interests in diseases of the nervous and immune systems. She hopes to work on the development of diseases at cellular and molecular levels.

Four graduate students and seven residents received modest COE support for their research. Funds were allocated on a competitive basis.

Nine 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

Dr. Kevin Hahn's research concerns reversing the resistance of some tumors to anticancer drugs. Using dogs with lymphoma as an animal model, **Dr. Hahn** and co-workers have identified how the tumor cell environment affects the cell's response (survival or death) to the anticancer drug. These results have led Dr. Hahn and co-workers to pursue further research to identify, develop, and evaluate new drugs which may change the tumor environment allowing anti-cancer drugs to be more effective in treating drug-resistant tumors.

Dr. Robert Shull continues to make progress in research concerning restoration of a genetic defect in children (mucopolysaccharidosis I enzyme deficiency) in a dog model of the disease. In collaboration with Dr. Emil Kakkis, the long-term effects of genetically-engineered products administered to reconstitute the function of the gene in dogs were studied. This year new emphasis was placed on investigation of gene therapy administered into muscle. Five dogs were treated with the important conclusion that such gene therapy can be severely limited by an immune response to the desired enzyme produced in animals.

Another exciting project involved direct intramuscular injection of a novel harmless carrier virus (vector) constructed from adeno-associated virus. The vector contained the genetic material encoding the enzyme missing in affected dogs. Tissues of the treated animals contained high

levels of the desired enzyme, and the stage now has been set for exploring adeno-associated virus-based gene therapy.

Benchmarks

Table 1.

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

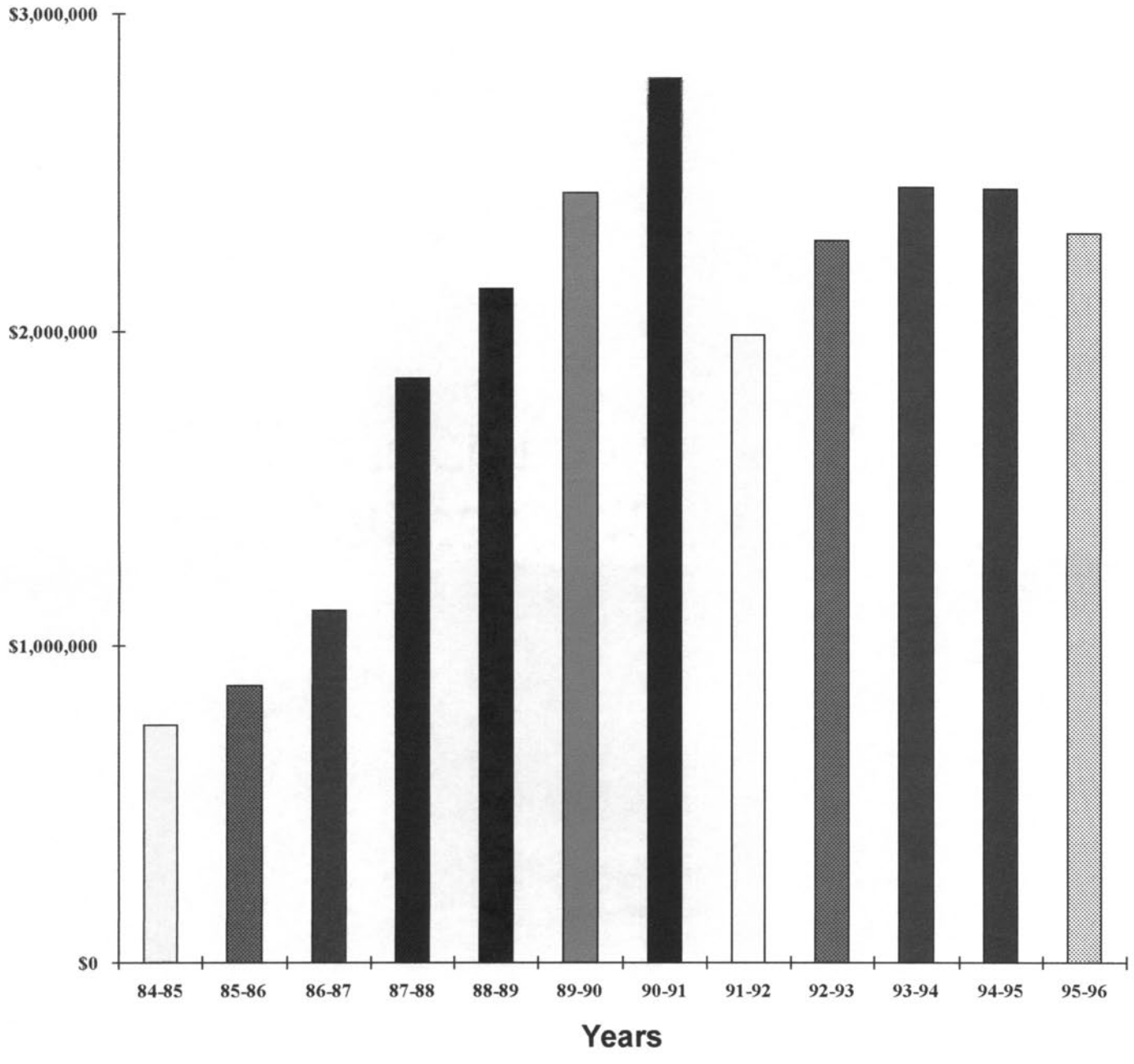


TABLE 2

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) 1992-93		Year 10 (Year 05 as Accomplished Center) 1993-94		Year 11 (Year 06 as Accomplished Center) 1994-95		Year 12 (Year 07 as Accomplished Center) 1995-96	
	Target	Actual	Avg	Actual	Avg	Actual	Avg	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)	95	(5.00)	132	(6.29)	153	(7.29)
Books or Book Chapters		7	(0.30)	17	(0.65)	14	(0.54)	6	(0.32)	7	(0.35)	9	(0.47)	5	(0.24)	5	(0.27)
Published Proceedings		21	(0.91)	37	(1.42)	42	(1.62)	24	(1.26)	17	(0.85)	11	(0.58)	37	(1.76)	65	(2.95)
Total Publications	2.82	102	(4.43)	122	(4.69)	153	(5.89)	113	(5.95)	102	(5.10)	104	(5.47)	174	(8.29)	223	(10.62)
Abstracts	0.30	33	(1.43)	66	(2.54)	48	(1.85)	47	(2.47)	53	(2.65)	55	(2.89)	42	(2.00)	64	(3.05)
Invited Participation at:																	
Regional Meetings	0.50	36	(1.56)	19	(0.73)	28	(1.08)	13	(0.68)	15	(0.75)	18	(0.95)	41	(1.95)	55	(2.62)
National Meetings	1.25	55	(2.39)	28	(1.08)	44	(1.69)	36	(1.89)	47	(2.35)	47	(2.47)	65	(3.10)	70	(3.18)
Faculty in Center		23		26		26		19		20		19		21		22	
Number of Visitors	11	10		17		17		12		12		13		15		18	

TABLE 3

RESEARCH PROJECTS FUNDED EXTERNALLY

REPORT PERIOD 1995-96

PROJECT DIRECTOR	TITLE OF GRANT	FUNDING AGENCY	TOTAL AWARDED	ESTIMATED EXPENDITURES
Philip Bochsler	The role of nitric oxide as a mediator of host defense in cattle.	USDA 1433 Funds	$ 6,852.00 10/1/95-9/30/96	----------
	Purification and characterization of bovine lipopolysaccharide-binding protein (renewal)	USDA	$ 184,000.00 9/1/93-8/31/96	$ 55,279.67
	Molecular basis of endothelial cell sensitivity to lipopolysaccharide	USDA	$ 95,000.00 9/15/92-8/31/95	$ 3,935.46
David Slauson (Co-PI)	The bovine CD14 receptor: A link in endotoxin-mediated macrophage activation	USDA	$150,000.00 9/15/92-8/31/95	$ 22,756.76
David Brian	Bovine coronavirus vector for mucosal immunity to phaemolytica leukotoxin	USDA	$140,000.00 9/15/95-9/14/97	$ 12,287.44
	Mechanisms of coronavirus RNA amplification.	National Institutes of Allergies and Infectious Diseases	$118,696.00 7/1/96-6/30/2001	----------
	Mechanism(s) of coronavirus RNA replication and packaging	USDA	$200,000.00 9/1/92-6/30/96	$ 92,464.23
James Godkin	Retinoids in bovine follicular and oocyte development	USDA Formula Funds	$ 5,000.00 10/1/95-9/30/96	----------
	Retinoid-binding protein and receptors in bovine placental development	USDA NRI	$212,000.00 9/1/93-8/31/97	$122,418.05

Kevin Hahn **H. Schuller, A. Legendre (Co-PI)**	Treatment of dogs with spontaneously occurring osteogenic sarcoma	BYK Gulden	$ 63,890.00 1993-96	$ 9,221.14
	Phase II evaluation of oxorubicin in the cat	American Animal Hospital Association	$ 10,000.00 1994-96	$ 9,782.13
Ted McDonald	Development of assays for thrombopoietin	Genentech	$144,300.00 3/31/88-3/31/96	$ 48,714.49
	Characterization of thrombopoietin	AMGEN	$ 74,794.00 7/1/93-6/30/96	--------
Charmi Mendis-Handagama	Regulation of testosterone production in adult rat testis	National Science Foundation	$ 18,000.00 8/15/94-1/31/97	$ 5,022.69
Linda Munson	Contraceptive health surveillance center for zoo and wildlife species.	Geraldine R. Dodge Foundation	$ 30,000.00 10/95-9/96	$ 12,286.11
	Continuing safety assessments of contraceptives for non-domestic felids	American Association of Zoo Parks and Aquarium	$128,414.00 1993-97	$ 30,891.93
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 10/1/95-9/30/96	--------
	Anti-fescue toxicosis vaccine study (Co-PI)	Merck and Company	$ 60,000.00 1/1/95-12/31/96	--------
	Endothelin response to tall fescue stimulus of bovine endothelial cells (Co-PI)	USDA	$ 60,002.00 3/1/95-8/31/96	--------
Stephen Oliver	Identification, characterization, and evaluation of *Streptococcus uberis* virulence factors	USDA Formula Funds	$ 7,000.00 10/1/95-9/30/96	--------
	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	$ 499.95

Stephen Oliver (cont'd)	Application of DNA markers to assess the gene associated with high somatic cell count and mastitis in Jersey cattle	American Jersey Cattle Association	$ 6,400.00 1995-96	$ 6,400.00
	DNA fingerprinting of mastitis pathogens	Dairying Research Corporation	$ 3,000.00 1995	$ 3,000.00
	Experimental infection of bovine mammary glands with *Strep. Uberis*	Sanofi Animal Health	$ 20,200.00 1995	$14,999.51
	Influence of intramammary antibiotic therapy at calving on mastitis and lactational performance of heifers during early lactation	The Upjohn Company	$ 38,250.00 1995	$17,069.00
Leon Potgieter	Significance of strain variation within the ruminant respiratory syncytial virus	USDA	$123,310.00 9/1/93-8/31/95	$ 14,056.12
	Amplification, cloning, and expression of structural protein genes of BVD virus	The Upjohn Company	$ 85,000.00 1990-98	$ 11,319.88
	Identification of C3 binding components that facilitate invasion by *Babesia bigemina* (Co-PI)	USDA	$130,000.00 1992-95	----------
	Detection of feline infectious peritonitis virus and feline enteric coronavirus (Co-PI)	Morris Animal Foundation	$ 14,500.00 1994-96	$ 4,065.64
Barry Rouse	Immunity mechanisms in herpesvirus infections	National Institute of Allergy and Infectious Diseases - NIH	$512,245.00 1995-00	$253,362.52
	Mucosal immunity in control of herpetic infection	National Institute of Allergy and Infectious Diseases - NIH	$538,847.00 1993-97	$164,475.66
	Mechanisms of herpetic stromal keratitis	National Eye Institute - NIH	$868,717.00 1992-97	$227,648.88
	Genetic vaccines and immunity to herpes simplex	NIH	$218,607.00 1994-95	$ 67.24
	Liposome microencapsulation of vaccine antigens	NIH	$785,274.00 1990-95	----------

Jill Sackman	Evaluation of the mechanisms of genetically modified endothelial cell loss from synthetic vascular grafts *in vivo*	American Heart Association	$ 80,000.00 11/94-96	$ 35,116.38
Hildegard Schuller	NNK effects on receptor pathways in normal and neoplastic lung cells	National Cancer Institute - NIH	$599,126.00 1/94-12/96	$260,310.49
	Regulation of the proliferative response of pulmonary neuroendocrine cells to nicotinic agonists	Verum Foundation for Behavior and Environment	$128,484.00 1/10/96-12/31/97	$ 15,552.17
	Anticarcinogenic effects of dexniguldipine-MCL in hamsters	BYK-Gulden, Inc.	$380,133.00 1/1/93-12/31/96	$ 35,897.25
	Characterization of induced neuroendocrine lung cancer	National Cancer Institute - NIH	$550,791.00 2/92-1/96	$ 19,179.12
Terry Schultz	Structure-biodegradability/toxicity relationships of substituted naphthalenes	Dupont Corp.	$ 40,000.00 6/95-6/97	---------
	Development of bioremediation risk management	Environmental Protection Agency	$ 34,749.00 9/94-9/96	$ 23,276.47
	Photo-induced toxicity in *Tetrahymena*	University of Minnesota	$ 19,063.00 1/1/94-12/31/96	$ 6,815.16
Robert Shull	Molecular study of MPSI; gene therapy in a canine model	University of California - NIH	$255,055.00 8/1/94-7/31/98	$125,940.86
David Slauson	Cellular pathobiology of environmental disease	NIEHS - NIH	$117,496.00 7/1/95-6/30/00	$ 40,736.84
John Wilkinson	Scurfy Mouse	Lockheed Martin	$ 67,700.00 7/1/95-12/31/96	$ 34,028.67
	Scurfy Mouse	Lockheed Martin	$ 41,391.00 10/1/95-9/30/96	$ 20,641.74
	Mammalian genetics and development	Lockheed Martin	$ 70,850.00 10/1/95-9/30/96	$ 48,925.48

Wilkinson (cont'd)	Role of the agouti gene product on tumorogenesis	Lockheed Martin	$ 37,790.00 10/1/95-9/30/96	$ 26,185.94
	Histopathologic and clinical pathology analyses of mice from a colony containing chromosomal translocations	Lockheed Martin	$175,600.00 7/1/95-3/21/98	$ 32,792.80
	Genome analysis program	Lockheed Martin	$ 29,390.00 2/1/96-9/30/96	$ 8,156.46
D. Slauson Co-PI	Directed expression of the agouti gene product in transgenic mice: A potential model for obesity	Glaxo	$672,890.00 10/1/93-9/30/96	$368,572.47
	Small instrumentation grants program	NIH	$ 18,615.00 9/1/94-8/31/95	$ 2,089.30
	Molecular genetics and PKD in the transgenic TG737 mouse	NIH	$484,523.00 9/30/93-9/29/95	$ 58,340.30
Barry Rouse (Co-PI)	Immunobiology of the scurfy mouse	NIH	$691,666..00 9/30/92-5/31/95	$ 6,090.13

Plans For Next Year

1996-97 CENTER OF EXCELLENCE MEMBERS

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

James D. Godkin, Ph.D.
Professor
Department of Animal Science

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

Diane Hendrix, D.V.M.
Assistant Professor
Department of Small Animal Clinical Sciences

Melissa Kennedy, D.V.M., Ph.D.
Instructor
Department of Comparative Medicine

Allen 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

Darryl L. Millis, M.S., D.V.M.
Assistant Professor
Department of Small Animal Clinical Sciences

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

Sharon Patton, Ph.D.
Professor
Department of Comparative Medicine

Leon N.D. Potgieter, B.V.Sc., Ph.D.
Professor and Head
Department of Comparative Medicine

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

Jill E. Sackman, D.V.M., Ph.D.
Assistant Professor
Department of Small Animal Clinical Sciences

Dorcas O. Schaeffer, D.V.M., M.S.
Assistant Professor
Department of Comparative Medicine

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

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

A. Eric Schultze, D.V.M., Ph.D.
Assistant Professor
Department of Pathology

David O. Slauson, D.V.M., Ph.D.
Distinguished Professor and Head
Department of Pathology

Daniel A. Ward, D.V.M., Ph.D.
Assistant Professor
Department of Small Animal Clinical Sciences

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

Center of Excellence

1996-97

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 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. Brian's laboratory will focus on the understanding of the mechanisms used by coronaviruses for regulating genome replication and gene expression.

Dr. S. Oliver will identify virulence factors that play an important role in the development of *S. uberis* mastitis and to determine whether such factors must be considered in the development of a vaccine to control this organism.

Dr. Potgieter will work on preventing respiratory tract disease in cattle caused by respiratory syncytial virus infections. He hopes to determine whether current vaccines are capable of producing an adequate immunity to the disease because circumstantial evidence suggests that vaccines are inadequate under certain circumstances.

The Center also funded two projects; one on the mechanisms by which certain bacteria causing food-borne diseases establish themselves in the intestine in swine (Dr. A. Mathew) and the other on the implications of infections in swine with *Toxoplasma gondii* (an important parasitic disease of the nervous system and fetuses in humans) as a food-borne illness.

Toxicoses

Dr. T. Schultz will work on laboratory models capable of predicting toxicity of bioreactive phenols. This project will provide quantitative experimental toxicity data for a number of important industrial and environmental chemicals.

Dr. J. Oliver and co-workers will study the effect of tall fescue grass toxins on blood vessels of cattle. Chronic exposure to the toxins results in damage to the lining of blood vessels and mechanisms to prevent damage will be investigated. They also will work on improving the their patented vaccine to prevent the harmful effects of the toxins.

Dr. Ward will investigate the effects of certain growth factors (bFGF, TGFB) and chemical factors on a laboratory model of the protective outer blood-retinal barrier in the eye. It is hoped that he can establish the same barrier that exists in the eye for protection against blood-borne toxins.

Reproduction

Dr. Godkin will conduct studies on methods that regulate the effect vitamin A-like chemicals (retinoids) on ovarian function and early embryonic development. The long-term goal of these studies is to identify means of improving reproductive efficiency in livestock.

Dr. Munson will study the effect of a certain growth factor (PDGF) on the development of endometriosis, a cause of infertility.

Host Defense

Dr. Rouse will continue to work on the immunobiology of herpes simplex virus (HSV) infection. The objectives of this work are to understand the mechanisms of herpesvirus-induced disease processes; to get insight into the mechanisms of protective immunity against infection, and to develop effective vaccines against HSV infection and disease.

Dr. Bochsler will continue his research studies on the role of nitric oxide as a mediator of host defense in cattle. The goal of this study is further characterize nitric oxide generation by certain lung cells (bovine alveolar macrophages), to determine whether synthesis of nitric oxide is essential for killing of an important disease-producing organism of the respiratory tract of cattle, to investigate the effect of several bovine respiratory viruses on the ability of bovine alveolar macrophages to synthesize nitric oxide and to study the regulation of enzymes/factors responsible for synthesis of nitric oxide.

Molecular Genetics

Dr. Mendis-Handagama will use certain tumor cells (Leydig cell line) to address the basic questions on cholesterol transport mechanisms in the synthesis of hormones in the mammalian testis and also investigate hormonal production in aging and developing testes using the rat model.

Dr. Wilkinson will investigate the molecular mechanisms of several human genetic diseases in mutant mice. These include polycystic kidney disease, auto-immune disease and growth regulation.

Dr. Sackman is studying methods for to improve adhesion of genetically-altered blood vessel cells to blood vessel grafts in her work on treatment of genetic vascular diseases.

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

Carcinogenesis

Dr. Schuller will continue to determine the molecular mechanisms by which nicotine produces lung cancer and confirm whether drugs widely used for asthma and chronic bronchitis promote certain kinds of lung tumors in animal models.

Dr. Hahn will identify, develop and evaluate new drugs that may augment standard anti-cancer drugs by minimizing resistance of tumor cells to the latter drugs. He also will conduct clinical trials on client-owned pet animals with naturally-occurring cancer as models to identify new methods for the diagnosis and treatment of cancer.

Dr. Merryman will work on new techniques to effectively evaluate the role of a certain growth factor {(TGF)-β} in the development of cancer (squamous cell carcinomas).

Budget Forms

Schedule 7 Budget Form 1997-98

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

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

	1995-96 Actual			1996-97 Proposed			1997-98 Requested		
Expenditures	252,995	506,403	**759,398**	266,898	533,797	**800,695**	274,575	549,150	**823,725**
Salaries									
Faculty	31,287	62,668	**93,955**	29,637	59,363	**89,000**	30,969	62,031	**93,000**
Other Professional	50,555	101,262	**151,817**	35,118	70,343	**105,461**	37,296	74,704	**112,000**
Clerical/ Supporting	20,937	41,939	**62,876**	20,488	41,039	**61,527**	21,645	43,355	**65,000**
Assistantships	10,027	20,081	**30,108**	19,927	39,915	**59,842**	20,446	40,954	**61,400**
Total Salaries	**112,806**	**225,950**	**338,756**	**105,170**	**210,660**	**315,830**	**110,356**	**221,044**	**331,400**
Fringe Benefits	25,763	51,603	**77,366**	27,992	52,672	**80,664**	27,306	54,694	**82,000**
Total Personnel	**138,569**	**277,553**	**416,122**	**133,162**	**263,332**	**396,494**	**137,662**	**275,738**	**413,400**
Non-Personnel									
Travel	1,029	2,062	**3,091**	1,332	2,668	**4,000**	1,332	2,668	**4,000**
Software	2,234	4,475	**6,709**			**0**			**0**
Books & Journals	450	904	**1,354**			**0**			**0**
Other Supplies	44,653	89,088	**133,741**	73,488	147,197	**220,685**	69,430	138,245	**207,675**
Equipment	60,834	121,852	**182,686**	51,615	103,385	**155,000**	56,610	113,390	**170,000**
Maintenance	4,772	9,560	**14,332**	6,901	16,415	**23,316**	8,741	17,509	**26,250**
Scholarships	454	909	**1,363**	400	800	**1,200**	800	1,600	**2,400**
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	**114,426**	**228,850**	**343,276**	**133,736**	**270,465**	**404,201**	**136,913**	**273,412**	**410,325**
GRAND TOTAL	**252,995**	**506,403**	**759,398**	**266,898**	**533,797**	**800,695**	**274,575**	**549,150**	**823,725**
Revenue									
New State Appropriation		517,200	**517,200**		523,000	**523,000**		549,150	**549,150**
Carryover State Appropriation			**0**		10,797	**10,797**			**0**
New Matching Funds	258,600		**258,600**	261,500		**261,500**	274,575		**274,575**
Carryover from Previous Matching Funds			**0**	5,398		**5,398**			**0**
Total Revenue	**258,600**	**517,200**	**775,800**	**266,898**	**533,797**	**800,695**	**274,575**	**549,150**	**823,725**

Appendix

The University of Tennessee
College of Veterinary Medicine
Center of Excellence in Livestock Diseases and Human Health

The Tennessee Higher Education Commission policies governing the Centers of Excellence require that the centers be re-evaluated for continuation each five years after they are declared by the Commission as "Accomplished Centers."

The Center was re-evaluated on February on February 9, 1996 and listed below is an excerpted report on the Center taken from THEC Five-Year Review submitted Mary 28, 1996.

The center of Excellence in Livestock Diseases and Human Health has a unique role in addressing the needs of animal agriculture in Tennessee and in providing a new dimension to human health research. The College of Veterinary Medicine has been a pioneer in the use of animal models to investigate several human diseases. It is unlikely that significant progress in understanding these diseases could have been made if these models had not been available. Center research focuses on the following specific five areas: inflammation and host defenses, growth factors and molecular genetics, infectious diseases and population medicine, *in vitro* toxicology and toxicokinetics, and carcinogenesis and developmental therapeutics.

To address its mission, the Center has established the following goals:

1. To Improve the Quality of Human Life through Better Animal Health
2. To Augment Livestock Disease Research Capabilities in the Institute of Agriculture
3. To Identify and Characterize Animal Diseases that are Analogous to Human Health
4. To Study Animal Models for Better Understanding of Human Disease
5. To Understand the Pathogenesis and Characterize the Causative Agents of CommonDiseases Important to the State of Tennessee
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
7. To Improve Facilities to Enable the College of Veterinary Medicine to Study More Effectively Infectious and Toxic Diseases of Animals
8. To Disseminate through the Extension Service Practical Information Required to Reduce the Incidence of Livestock Diseases
9. To Develop New Strategies for the Prevention of Disease
10. To Improve Facilities and Expertise in Order to Provide Improved Research Training
11. To Develop Innovative Approaches to the Treatment of Human Diseases

One research project has focused on white blood cells, which are an important part of the immune system and contribute to host defense against infectious agents. This research has studied the role of white blood cells in mediation of host defense against infectious diseases of cattle. A better understanding of the bovine immune system is essential for understanding diseases in cattle and is important in designing strategies for prevention and treatment of infectious diseases in cattle.

Another research project (supported both by the National Institutes for Health and the Belgian pharmaceutical firm, SmithKline Beecham) is searching for successful vaccines against herpesvirus infection.

Another project has the goal of improving reproductive efficiency in livestock by reducing stillbirths.

Certain diseases in humans also affect animals and these animals can be used to model treatment in human subjects. One research project at the Center has focused on gene therapy for canine genetic enzyme deficiency, a model for the identical disease which occurs in human children.

Another such project focuses in a mouse model of polycystic kidney disease, the most common inherited disease in humans and a major cause of disease and death. Using this mouse, Center researchers have been able to identify the first gene known to be associated with this costly and deadly disease.

Bovine mastitis costs Tennessee producers of dairy products over $60 million annually, and tall fescue toxicosis in cattle costs Tennessee producers another $85 million annually. Center researchers have a model vaccine (developed with support from a large pharmaceutical firm) that may save Tennessee farmers millions of dollars every year.

Another project has received nationwide attention: the first evidence that mothers who smoke during pregnancy may significantly increase the risk of cancer in their children. These findings may have a dramatic effect on prevention and treatment of lung cancer.

The Center has been very successful in attracting external funding. Over the past five years, over $19 million has been awarded to the Center to support these research projects. While the College of Veterinary Medicine is among the smallest in the nation, it ranks fourth in external research funding.

The Committee recommends to the governing board and the Commission that this Accomplished Center be continued.

The University of Tennessee, College of Veterinary Medicine
Center of Excellent in Livestock Diseases and Human Health

Report of External Review Team, March 25, 1996

- OVERVIEW

Since the last visit (October 1992), the Center has continued to make good progress. It's overall management is good and we were especially appreciative of the positive influence of Dr. Leon Potgieter, Assistant Director, who has clearly created a better focused, goal-oriented philosophy. This is good for the future of the Center, and should lead to even greater productivity. There has been some restructuring since the committee's visit in 1992. The new "focus groups" for the period 1996-2000 are different from those described in the 1990-95 report. These changes seem appropriate and reflect the willingness of the College to encourage the evolution and maturation of the Center.

The internal peer review process for proposals submitted for funding by the Center is functioning especially well. Because of the potential risk that the Center may be seen as a "club" and might exclude some faculty who may have potential to make significant research contributions, competition for Center grants is now open to all faculty rather than a restricted group of participants in programs of the Center. The resources of the Center should fit well with the mission of the College and be of benefit to the whole faculty.

We feel that the External Review Board will continue to play a useful role, especially in the political future of the Center. A four-member board (with two members rotating off periodically) seems appropriate. Visitation every three years provides a good interval for review.

Extramural funding remains high; yet it has leveled off in recent years. This does not necessarily represent a concern in the currently unfavorable funding climate. Efforts of the Center to better define the focus group should enhance their competitiveness for extramural funding.

The involvement of the new COE participants (resulting from faculty retirements) will stimulate the Center and further change its character, especially through recruitment of faculty who will enhance the CEO's goals.

- PROGRAM REPORTS

1. Inflammation and host defenses

This unit continues to fare well under good leadership. Here is a good example of the incorporation of new scientists who are changing the flavor of the COE. Dr. Rouse continues to be a major contributor who has garnered exceptional NIH support and plays a vital role in graduate education. The group's partnership with the Oakridge Laboratories is a major strength, and includes a recently funded NIH grant that will enhance graduate training opportunities for the College.

2. Growth factors and molecular genetics

The review team observes that this group, while continuing to be productive, seems to be less focused than may be desirable. There are many projects of differing character, headed in different directions. The review team is concerned about the future leadership of this unit and recommends that ways be found to restore focus and collaborative synergism to the group. Collaboration with Oakridge Laboratories in research involving transgenic animals will be a valuable focus for this group.

3. Infectious diseases and population medicine

This is a good program which is producing excellent work. Nevertheless, the review team strongly urges the College leadership to encourage the development of the quantitative areas of population medicine and epidemiology. This aspect is all but absent from the group's current interests and may prove to be a negative political issue with agricultural groups and legislators. We understand that the epidemiologists among the college faculty are not participating in the COE. Perhaps there is an opportunity for the Dean to appoint an epidemiologist to the team, as the current peer review system for membership may fail to fill this important need.

4. In vitro toxicology and toxicokinetics

While this program remains an active and important part of the Center, it has suffered major losses of people and funds. Our impression of this unit is one of several good people going separate ways. The group should reexamine its goals and common interests. Great benefit would accrue from better connections with the State's diagnostic labs, medical schools, and the Oakridge Laboratory.

5. Carcinogenesis and developmental therapeutics

This is a productive and innovative research enterprise that is unified behind a sovereign director. There is no question about the thematic focus of this unit. Nevertheless, the review team expresses concern for the growth of young scientists joining this group. Some attention might be given to the development of a more nurturing team-oriented

environment for the good of the College. No doubt this group will continue to be highly productive.

In conclusion, we congratulate the Dean and the faculty on the fine accomplishments of the Center. We are honored to serve as reviewers of its programs. The COE continues to be an important asset to the University and the State. Dr. Potgieter has provided an important influence on the Center's success.

It will be helpful to review regularly the leadership, membership, and thematic focus of each research program in relation to the mission and goals of the COE and the College.

- Peter Eyre (Virginia Tech)
  Chair of Review Team

- John M. Bowen, University of Georgia

- Talmage T. Brown, North Carolina State University

- John A. Phillips, Vanderbilt University

June 7, 1996

PEmmw050296.1

Publication #R180101-12-001-97