1992

Center of Excellence Annual Report, July 1991-June 1992

College of Veterinary Medicine

Center Of Excellence In Livestock Diseases And Human Health

Annual Report July 1, 1991- June 30, 1992

College of Veterinary Medicine
The University of Tennessee
Knoxville, Tennessee

Mike Shires, Dean

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COLLEGE OF VETERINARY MEDICINE

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The Center of Excellence in Livestock Diseases and Human Health provides much needed support for some important research in the CVM. Funds are used to help support research by productive investigators with a track record of extramural funding. New investigators with projects having the most potential for securing extramural support and who can also obtain some departmental cost-sharing are also very carefully considered for support. In selected cases the COE funds are invested in some "start-up funds to enhance and accelerate the research of new faculty with promising research programs.

The COE funding has been very successful in assisting some of our new faculty in submitting grants and successfully competing for outside funding. This support has helped cement ties with The Thompson Cancer Survival Center and their funding of research projects with Dr. Donita Frazier and Dr. Kevin Hahn.

The concept of the COE stimulates collaboration between a multitude of different researchers and encourages sharing of equipment, ideas and many resources. Successful projects by researchers such as Drs. Linda Munson, Erby Wilkinson, Philip Bochsler, Doug Dawson and David Dean were all strengthened by initial COE support. These successful grants from outside funding agencies have included NIH, USDA, U.S. Air Force, EPA, as well as private corporations such as the American Cyanamid Company and the Upjohn Company. Several patents by Drs. Jack Oliver and Leon Potgieter have also resulted from projects initially funded, in part, by the COE.

In these times of declining outside funding and increasing competition, the COE funds have also been used to bridge any gap in funding that some of our established researchers may temporarily encounter.

Through the Venture Grant Program, the COE also helps fund a limited number of promising pilot projects submitted by residents and graduate students.

A significant part of the continued growth and success of the College of Veterinary Medicine research program can be attributed to COE support in its many forms. Despite the financial hardships in the last two budgetary years, the CVM has managed to proceed with most of its plans due to careful fiscal control and COE support.

Continued support from the COE will help us expand our research and continue to provide answers to some of the myriad of disease problems. Focusing on a few selected areas of research has also stimulated collaboration and sharing of ideas, equipment and other resources. The spirit of cooperation existing within our College is greatly enhanced by the support offered through the COE and the democratic and open process through which support is given.

The COE is a significant factor in the success of this College and, to my mind, is an excellent example of minimal expenditure for maximum return. Continued support will help to maintain and, hopefully, expand our strong research foundation.

Sincerely,

G. M. H. Shires
Dean

GOALS

Goal 1: To improve the quality of human life through better animal health.

Goal 2: To augment livestock disease research capabilities in the Institute of Agriculture.

Goal 3: To identify and characterize animal diseases that are analogous to human diseases.

Goal 4: To study these animal models for better understanding of human disease.

Goal 5: To understand the pathogenesis an characterize the causative agents of common disease important to Tennessee.

Goal 6: To improve the capabilities of the College of Veterinary Medicine, the College of Agriculture and the Agricultural Experiment Station to deal with these diseases.

Goal 7: To improve facilities to enable the College of Veterinary Medicine to study more effective infectious and toxic diseases affecting animals.

Goal 8: To disseminate through the Extension Service the practical information required to reduce the incidence of livestock diseases.

Goal 9: To develop new strategies for the prevention of disease.

Goal 10: To enhance the College's ability to recruit superior faculty and graduate students and to attract more external funding for research.

Goal 11: To improve facilities an expertise in order to provide improved research training.

Goal 12: To develop innovative approaches to the treatment of human disease.

Programmatic Report

I. PROGRAMMATIC REPORT

1.A PERSONNEL CHANGES

1.A.1. *Personnel Additions*

Dr. Charmi Mendis-Handagama and Dr. Teresa Rowles, who hold appointments in the Department of Animal Science are being added this year to the Center of Excellence Faculty. Dr. Mendis-Handagama received her D.V.M. from the University of Sri Lanka, Peradeniya and her Ph.D. from Monash University, Melbourne, Australia. Dr. Teresa Rowles received her D.V.M. from The University of Tennessee and her Ph.D. from Texas A&M University.

1.A.2. *COE Members Leaving*

Dr. Clinton Lothrop resigned from the University in February 1992 to accept a position in the Scott-Ritchey Research Center at Auburn University. He will maintain close ties with the college in collaboration with both the Growth Factor and Oncology groups.

Dr. Jeanne Maddux resigned in May 1992 to move to Alaska.

1.A.3. *Graduate and DVM Student Opportunities*

With the transition to a four-year, semester system, the College has been able to initiate a program to provide veterinary students experience in animal model-based biomedical research. This 12-week summer program focuses on first and second year veterinary students who have maintained a high academic standing and who have shown an interest in research. This experience should accelerate completion of their Ph.D. programs.

The Department of Comparative Medicine, UT/Memphis, in collaboration with the Comparative and Experimental Medicine Program is seeking to establish a postdoctoral graduate program in laboratory animal/comparative medicine. This program will be for the purpose of preparing graduate veterinarians to become productive members of the biomedical research community as specialists in laboratory animal medicine, and to attain board certification in the American College of Laboratory Animal Medicine.

1.B. RENOVATION OF FACILITIES AND EXPANSION OF SERVICES

1.B.1 *Animal Facilities Improvements*

With support from the Center of Excellence, Dr. Edward Schroeder, Laboratory Animal Veterinarian was able to apply for, and receive funding from the National Institutes of Health, for improving the use of space by incorporating isolation technology and labor saving equipment. The improvements have allowed a measure of flexibility and efficiency and has provided a higher level of animal care. With newly funded faculty coming into the college, as well as the onset of new faculty positions, these renovations have made it possible to have a variety of rodent species in special environments. In addition, the new equipment has improved cleaning methods and reduced the risk of cross contamination when cages are changed.

1.B.2 *Library Services Added*

The library has instituted several new services that impact on agriculture and veterinary medicine. With the addition of AGRICOLA, the largest and most comprehensive source of U. S. agricultural information, and CAB ABSTRACTS, an International research database of agricultural information and the source of information for veterinary medicine, human nutrition, developing countries, leisure, recreation, and tourism, faculty have the major indexes for agriculture and veterinary medicine available for searches anytime.

1.C. SPECIAL MATERIALS AND EQUIPMENT

A protein microsequenator, a DNA synthesizer, an upgraded HPLC, and a Doppler ultrasound attachment were purchased for college-wide use. Individual departments were also allocated funds for specific equipment items (e.g., Queue incubator, electroelution unit; Gene amplification polymerase system and gel dryer; and Coulter counter) for individual and department-wide use.

1.D MAJOR PROGRAMMATIC ACTIVITY

1.D.1 *Research '92*

Research '92 was the college's 5th annual presentation of current research.

Through the UT Office of Research and Technology Development, the college was awarded a *Hertel Grant*, to partially sponsor the program. The first day of activities entailed the Distinguished Lecture Series which was presented at the University Center on the Main Campus followed by a Reception and Poster presentation. On day two, the program returned to the Veterinary Teaching Hospital with 11 presentations by senior and junior faculty, graduate students, and residents. The exposure provided campus-wide attention to many of the excellent research activities taking place at the College of Veterinary Medicine, and brought enhanced interaction among various members of the campus and off-campus biomedical sciences community and College of Veterinary Medicine faculty.

Additionally, Research '92 provided an easy way for potential graduate students to learn of research activities within the College of Veterinary Medicine that may be of interest to them, and provided positive publicity for research at the College and University.

1.D.2 *Minority Recruitment*

Because of a genuine interest by faculty, students, and staff, more minority applicants are giving consideration to the various programs within the college. Specific interest areas are the DVM program, graduate student program, and residency programs in both Rural and Urban Practices.

With the addition of teachers to the Minority High School Apprentice Program sponsored by the National Institutes of Health, we are already experiencing extra incentive and visibility and more interest in veterinary medicine and the biomedical sciences from students.

The college has added 10 students from the Upward Bound Program to its summer science experience. This six-week program includes students from different states.

1.D.3 *Collaborative Research Projects*

With recent notification from the NIH National Eye Institute of funding for his competitive renewal entitled *Immunopathological Mechanisms in Herpetic Stromal Keratitis*, **Dr. Barry Rouse** in collaboration with Dr. Deborah Distephano

in the Department of Ophthalmology at The University of Tennessee, Chattanooga, will continue to further define the role of CD^{4+} T lymphocytes in Herpes simplex virus (HSK) as well as the part played by CD^{8+} T cells at modulating the HSK reaction.

A collaborative project with Oak Ridge on which **Dr. Erby Wilkinson** serves as principal investigator is entitled *The Immunobiology of the Scurfy Mouse* and relates to cellular immunology and the role of the microenvironment of the thymus in the production, selection, and export of functional T cells. The Scurfy (*sf*) mutant mouse forms an interesting model for such studies. Scurfy mice develop a severe x-linked lymphoproliferative disease that primarily affects skin and lymphoid organs and is an early cause of death. Several pieces of evidence implicate the thymus in development of the scurfy phenotype, and investigations are underway to better understand the pathogenesis of this disease. Such data is likely to enhance the investigator's understanding of the role of the thymus in T-cell differentiation. **Dr. Barry Rouse** is also a collaborator on the Scurfy mouse project.

In another collaborative effort, **Dr. Hildegard Schüller** is now embarking on a major venture as evidenced by her recent submission of an NCI Program Project. This $7 million project encompasses two medical schools within the United States and one outside the country, and three faculty members in the college. The project will link basic and clinical approaches to targeting mitogenic signal transduction pathways for the development of novel means of lung cancer therapy. While most lung cancer types generally do not respond to conventional radio- and chemotherapy, small cell cancer, a highly malignant neuroendocrine form of the disease, often demonstrates an initial response. However, in most cases, multi-drug-resistance develops, thus rendering the mortality rate of lung cancer in general at 90%. Preliminary data strongly suggests that B859-35 and similar agents may inhibit the continuous proliferation of lung cancers whose proliferative activity depends on Ca^{2+}/calmodulin/protein kinase C mediated signal transduction loops. **Dr. Schüller** is a leading researcher in the field of basic lung cancer research at both a national and international level. Funding of this

project would help establish an oncology center within the College of Veterinary Medicine.

Dr. Terry Schultz in collaboration with Dr. Mark Kot is examining ways of monitoring and modeling biological chaos using an environmentally controlled microbial system. A major effort is underway to examine the usefulness of double-Monad systems. This unique blend of experimental and modeling science in the past two years has been funded by the National Science Foundation and is currently being funded by the Department of Energy.

FETAX is fast becoming recognized as the premier non-mammalian system for the study of toxicant effects on development. A standard guide for conducting the assay has been published by the American Society for Testing and Materials. FETAX is now required for evaluation of sediment toxicity in the state of Washington. **Dr. Doug Dawson** is involved in an interlaboratory validation study with researchers from Oklahoma State University, the U. S. Army, the University of Maryland, Stover Biometric, and other laboratories around the country. Upon completion of the project, the EPA is expected to require FETAX testing in the process of pesticide registration.

1.D.4 *Dissemination of Information*

Research at the college has been highlighted by the media nationally, statewide, and locally during the past year. CNN featured ongoing research related to production of the red panda, a threatened species. The features aired several times in June as part of the CNN evening news, then was aired as a segment in a half hour CNN series called "Science and Technology Week." A public television series called "The Gentle Doctor" spent two days at the college in taping a segment for the nationally broadcast series about veterinary medicine. The feature will air during the 1992-93 seasons. Veterinary research is routinely featured on Tennessee television news programs in Knoxville. In addition, a television station from Nashville produced a lengthy news feature on the college in 1992. Newspaper articles have covered a wide range of research news and profiles of college faculty. Topics have included cancer research, toxic agents affecting cattle, auto-immune disease, as well as features on a new department

head and on other members of the faculty. Members of the Infectious Diseases and Population Medicine Group continue to work through Extension Service veterinarians to transfer the latest information on livestock diseases to the public. The college is also featured regularly in UT publications, including *UT Agriculture*, a magazine distributed to the Tennessee agricultural community and alumni; *UT Alumnus*, sent to graduates and contributors of the university statewide; *Torchbearer*, a UTK alumni publication; and *Context*, the UTK faculty and staff newspaper. Additionally, the college disseminates information through its own newsletter, *Veterinary News*, sent to Tennessee veterinarians and college alumni, and through other informational brochures for veterinarians and the general public. Information is also dispersed through the UT Extension Service veterinarians. They have regular newspaper columns statewide and respond to a variety of questions from Tennessee farmers and pet owners. They contribute to an extension service newsletter called *Veterinary Topics*, which is distributed to Tennessee veterinarians.

1.D.5 *Major Research Areas*

GROWTH FACTORS GROUP

The major emphasis of **Dr. Robert Shull's** research program is to treat dogs with mucopolysaccharidosis I by insertion of the gene for the deficient enzyme α-L-iduronidase into their bone marrow cells. Canine iduronidase has been purified, sequenced, and the gene cloned. Retroviral vector technology is being used to insert the gene into cultured bone marrow stem cells which will then be returned to the dog. A major effort is being made to use various novel stem cell factors as c-kit ligand to stimulate stem cells to divide and incorporate the new gene. If this is successful, the canine experiments may pave the way for replacement gene therapy in children with similar diseases. They are also planning on investigating the effects of direct injections of recombinant enzyme into MPS I-affected dogs. Notification from NIH that their competitive renewal has been funded assures **Dr. Shull's** collaboration with scientists at UCLA and USC in Los Angeles for at least 5 more years.

One of **Dr. Linda Munson's** long range research goals is to understand the regulation of placental growth by endogenous growth factors. Her proposed research investigates the role of transforming growth factors (TGFs) in controlling proliferation and adhesion of trophoblastic and endometrial epithelial cells at the maternal/fetal interface in developing bovine placentas. She is exploring the possibility that a novel mechanism of communication occurs between fetal and maternal tissues in the developing placenta called "juxtacrine."

The research performed in **Dr. James Godkin's** laboratory focuses on the fetal-maternal interactions that are responsible for the maintenance of pregnancy and the growth and development of the embryo. His work has concentrated on proteins produced by fetal placental membranes. Most recent studies have centered on vitamin A (retinoid)-associated proteins. It has been recognized for over 50 years that vitamin A (retinol) is essential for reproduction. Recently a natural vitamin A metabolite, retinoic acid (RA), has been identified as a morphogen that dictates pattern formation in developing embryos. The action of retinoids (vitamin A and its analogs) is believed to be mediated by a plasma/extracellular transport protein, retinol-binding protein (RBP), two intracellular binding proteins (CRBP, CRABP), and RA nuclear receptors (RAR's). They have recently discovered that all of the placental extraembryonic membranes and the uterus synthesize RBP. They are currently investigating the molecular expression of the retinoid associated proteins in developing embryos and maternal uterine tissues.

Cloning the gene for thrombopoietin (TPO) remains one of the major goals of **Dr. Ted McDonald**. The role of TPO in regulation of thrombocytopoiesis has recently become clearer and the use of TPO in treating patients with platelet production disorders appears appropriate. During the last year, they have made progress in cloning the gene for thrombopoietin by adding to the amino acid sequence of the molecule and gained helpful insight into TPO's stability in various aqueous solutions.

During the last year, they have used TPO as a radioprotective agent for treating mice after whole-body irradiation. The results show that irradiated mice

treated with TPO had higher platelet counts and increased $\%^{35}S$ incorporation into platelets than did irradiated controls. These results suggest that TPO therapy will modulate the severe thrombocytopenia that occurs in irradiation-induced bone marrow suppression and indicates great clinical promise for this regulatory factor.

ONCOLOGY GROUP

Dr. Mark Miller, in collaboration with **Dr. Hildegard Schüller,** has been studying the effects of cigarette smoking as a causative agent in lung cancer. They have been using an animal model system, developed at The University of Tennessee by **Dr. Schüller,** to explore the molecular mechanism of cancer causation with the ultimate goal of trying to develop novel anti-cancer drugs that would be targeted to the specific genetic lesions responsible for tumor growth.

The animal model they have employed involves the treatment of hamsters with nitrosamines, a class of carcinogenic compounds that are prevalent in cigarette smoke, under conditions of increased oxygen levels. This treatment regimen results in the formation of a specific type of lung cancer that exhibits neuroendocrine features. This animal model is the only known model that produces neuroendocrine lung tumors. Their results have shown that the hamster tumors show the same types of genetic lesions as found in human small cell lung cancers. They will also continue to explore ways to inhibit tumor growth based on their findings of enhanced gene expression in these tumors. They have also been studying the potential effects of cigarette smoking combined with ethanol consumption during pregnancy. These studies should provide further information on environmental risk factors for lung cancer formation, and emphasize the potential risks to the fetus of exposure to ethanol and potential carcinogenic agents found in cigarette smoke.

Recent efforts of the Predictive Toxicity Program has centered studies of aryl alcohols and aldehydes. Specifically, **Dr. Terry Schultz's** laboratory has identified that addition of one or more aromatic rings to the carbon atom attached to a hydroxyl group is a sufficient alteration in molecular structure to cause a change in mechanism of toxic action. They have completed the

development of the gas-tight lethality assay. Moreover, they have tested large numbers of electrophilic aldehydes. Comparing relative toxicities for aldehydes in the gas-tight assay with those in the more conventional growth assay revealed that the presence of peptides and nucleic acids in the medium used in the growth assay modulates the toxic response of the direct-acting electrophiles by acting as nucleophiles. These findings have been validated by analyses of data from other test systems and go a long way in explaining the disparities in the literature on aldehyde toxicity.

Present work by **Dr. Doug Dawson** involves basic research into the way chemical mixtures interact to induce malformations (i.e., birth defects) in developing vertebrate animals. This research has led to the development of a technique which can be applied to the fields of aquatic and developmental toxicology. Work is also underway examining a series of carboxylic acids, in order to determine the compounds that have the greatest potential to cause birth defects. This work leads to the development of mathematical equations which can then be used to predict the potential hazard for any structurally similar chemical, without having to test the chemical. Therefore, the methodology has the potential to reduce the numbers of animals needed in toxicological testing.

INFECTIOUS DISEASES AND POPULATION MEDICINE

Dr. Steve Oliver's studies from last year have identified suitable microbiological procedures for identification of Streptococcus uberis and other Streptococcus species. He recently reported on a new technique to differentiate Strep. uberis from the closely related Strep. parauberis by polymerase chain reaction and restriction fragment length polymorphism analysis of 16S ribosomal DNA. This technique will be of considerable importance in subsequent studies on the epidemiology and pathogenesis of Strep. uberis mastitis. An identification scheme for Streptococcus and Enterococcus species was also developed based on the same analysis. Procedures are now available for genetic identification of Streptococcus and Enterococcus species of bovine origin. **Dr. Oliver** has recently received funds from The Upjohn Company to work on a study entitled *Immunization of Dairy Cows Against Strepococcus uberis*.

A major challenge in both human and veterinary medicine today is the development of targeted methods to specifically interrupt virus infections that are persistent within the host and lead to chronic diseases. Coronaviruses are ubiquitous in nature causing a wide variety of disease in animals. **Dr. David Brian's** laboratory is the first in the world to report the existence of an intraleader open reading frame and its development (selection) during persistent infection. His objective is to examine in detail how variant leader structures regulate translation rates. In the last two years, two other virus families, the toroviruses (a cause of gastroenteritis in calves, horses, and possibly humans) and arteriviruses (a cause of equine arteritis) have been placed along with coronaviruses into a coronavirus superfamily. These all share a common strategy of RNA transcription, and possibly replication. Thus, what they describe as mechanisms of coronavirus persistent infection may be pertinent to these other families as well.

Infection with bovine viral diarrhea virus (BVDV) results in tremendous losses to cattle farmers annually. The major envelope protein of BVDV is the only virally-encoded polypeptide consistently precipitated with BVDV antisera, and is the target for neutralizing antibodies. **Dr. Leon Potgieter**'s laboratory has cloned and sequenced the genomic sequence encoding this glycoprotein from a noncytopathic strain of BVDV. Additionally, they have subcloned this viral sequence into a baculovirus expression system that provides for production of large amounts of properly processed viral protein. They hope to gain insight into the immune response induced by this important viral agent, as well as evaluate the potential usefulness of a recombinant vaccine consisting of BVDV structural proteins. **Dr. Potgieter's** goal is to use the viral protein produced in this system to define the immunogenicity of the major envelope protein and use it for immunization of cattle against this serious infection.

Recent studies have determined potential toxicity of individual alkaloids that are present in fescue grass infected with the fungus *Acremonium coenophialum*. **Dr. Jack Oliver's** laboratory has been the first to show, in cattle, biological activity associated with three of the five major alkaloid types found in toxic fescue. Results of these studies indicate that the various alkaloid types that

are present in toxic fescue, have greater or lesser effects on specific tissue receptors that control organ function. Thus, it appears it will be difficult to develop a singular chemical agent to block all of the various effects of toxic fescue alkaloids.

Other studies have led to the development of a model system in cattle that allows the effects of individual alkaloids to be studied over a period of time. Alkaloids are constantly administered to animals by a miniature pumping device that is implanted under the skin. This system mimics the natural situation where cattle consume the toxic alkaloids while grazing, but has the advantage of looking at toxicity caused by a single alkaloid, where the concentration and amount of alkaloid that the animal actually is exposed to is known.

Because of the difficulty of controlling the toxic fescue condition in cattle with drugs, **Dr. Oliver's** research group has examined the possibility of developing an anti-fescue-toxicosis vaccine. They have just received verbal communication from Schering-Plough that they will fund their project to develop this method of fescue toxicity control in cattle.

INFLAMMATION GROUP

Dr. Barry Rouse's laboratory is attempting to verify their hypothesis that herpetic stromal keratitis, a common cause of ocular impairment, including blindness, represents an inflammatory response by the host, within the eye, to some components of the virus. They are seeking to establish the mechanisms of this reaction and ultimately find some immunological means of controlling it. Their recent results have provided further direct evidence that a single subset of T lymphocytes, the CD^{4+} subset, are primarily involved in the immunopathology. This was shown by transferring cells of known identity and reactivity into animals whose own immune response had been compromised.

A second mission in **Dr. Rouse's** laboratory is involved with evaluating the optimal means of inducing CD^{8+} T lymphocytes with soluble proteins and nonreplicating viral antigens. They have used several approaches to this issue including the demanding task of generating primary CD^{8+} T cell mediated cytotoxicity completely *in vitro*. They have achieved success finding that two

conditions are particularly important. These are the delivery of antigen within pH sensitive liposomes and the use of a particular cell type, the dendritic cell, as a means of delivering antigen.

Bacteria of the gram-negative type produce a toxin that is commonly referred to as endotoxin. Because of its molecular structure, endotoxin is also referred to as lipopolysaccharide, or simply LPS. In most cases, LPS does not act directly on body tissues to cause sickness, but acts through the animal's own immune system.

There is evidence that humans and some animals are stimulated to synthesize a novel protein whenever they are exposed to the bacterial toxin LPS. This protein is found circulating in the blood, and binds to the LPS molecule. Because of this, it is called LPS-binding protein, or LBP. Once LBP and LPS are bound, they attach to a receptor on cell surfaces called CD^{14}. When this occurs, the immune system becomes even more aware of the presence of the bacterial toxin LPS. Although cattle are commonly afflicted by disease causing bacteria that produce the LPS toxin, this important protein (LBP) and receptor (CD^{14}) had not been studied in cattle. The purpose of **Dr. Philip Bochsler's** work is to study bovine LBP and CD^{14} in order to better understand how bacterial LPS affects cattle, which may ultimately contribute to improved treatment and control of gram-negative bacterial infections of cattle.

Some of the work in **Dr. David Slauson's** laboratory is directly aimed at major disease problems in livestock, including increased susceptibility of new born calves to life-threatening bacterial infections and the mechanisms of signal transduction in bovine leukocytes. In recent years, they have been able to document that leukocytes from new born calves exhibit marked functional differences in respiratory burst activation, an important bactericidal system, as well as in leukocyte membrane reactivity to complement stimulation. **Dr. Slauson** has also been studying the transmembrane and intracellular signalling pathways used by bacterial endotoxin in bovine lung macrophages.

Dr. Michael Breider has studied the effect of live and dead Pasteurella haemolytica on bovine pulmonary endothelial cell (EC) monolayer cultures. He

found the proliferation of live bacteria leads to severe EC toxicity and dead bacteria can produce a similar EC toxicity, although a larger inoculating dose must be given. The addition of polyclonal anti-P. haemolytica bovine serum and neutrophils protect the EC from live P. haemolytica, but not dead P. haemolytica. However, the addition of polymyxin B effectively protects EC, presumably by neutralizing the bacterial endotoxin. These studies clearly demonstrate that endotoxin is an important bacterial virulence factor, and the host defense system of neutrophils and immune serum may protect against proliferation of P. haemolytica in the lung but cannot protect against the endotoxin associated EC damage.

1.D.6 *Projects that Benefitted from COE Support*

Dr. Erby Wilkinson has just received verbal notification that his grant submissions to NIH titled *Molecular Genetics of Polycystic Kidney Disease in the Transgenic Tg737 Mouse* and *Immunobiology of the Scurfy Mouse* have both been funded to begin September 1, 1992. Both of these awards are a direct reflection of COE start-up monies. **Dr. Philip Bochsler's** USDA grant titled *Bovine Lipopolysaccharide Binding Protein and Mechanisms of Macrophage Activation* is a result of starter monies from COE and Dr. David Dean's NIH Fellowship application entitled *Signalling Pathways in LPS-stimulated Lung Macrophages* which was funded was strengthened because of COE support.

Additionally, several projects supported in part by COE have resulted in patents. **Dr. Jack Oliver** has received a patent, "Development of an Anti-Fescue Toxicosis Vaccine" issued by the U. S. Patent Office on 1/21/92, U. S. Patent Office #07/823, 146, UT Research Corporation File No. 91-16, and applied February, 1992, for a second patent "Biomedical Use of Loline Alkaloids," UT Research Corporation File No. 92-11. Dr. Hugo Eiler received a patent for "Method for Treatment of Bovine Retained Placenta," U. S. Patent No. 5,089,264, UT Research Corporation File No. PD 89-44 issued on February 18, 1992.

New faculty who have just been awarded startup funds from COE to enhance extramural opportunities are:

- Dr. Kevin Hahn, an assistant professor with joint appointments in Environmental Practice and Urban Practice, is involved in both basic and clinical oncology research. He is collaborating with Drs. Donita Frazier and Masoud Panjehpour to determine what treatment schemes induce the most sub-lethal DNA damage in surviving tumor cells. Their long-term objective of this research is to enhance tumor control.

- The development of in vitro models of central nervous system disorders or toxicities is of increasing importance both as screening and mechanistic tools. Free radicals, such as oxygen centered radicals, have been implicated in aging, which has special relevance in the central nervous system in investigations of senile dementias. Dr. Teresa Rowles is currently evaluating several neural cell lines of human origin. Such determinations will be useful in future grant applications for mechanistic and screening studies in the areas of ischemia/reperfusion and neurotoxicities.

- The Leydig cell produces the steroid testosterone in mammals. Testosterone is required for the development and function of the male reproductive tract. Dr. Charmi Mendis-Handagama will attempt to identify whether peroxisomes are involved in the transport and metabolism of cholesterol during steroidogenesis in Leydig cells, and study the mechanisms involved in biogenesis of peroxisomes in Leydig cells in response to LH stimulation.

- Dr. Linda Bravo, a 2nd-year Resident in the Department of Urban Practice is being funded by COE for a project entitled *Serum Cytokine Concentrations in Normal Dogs and in Dogs with Lymphoma before and after Chemotherapy.* Collaborating with **Dr. Clinton Lothrop**, Auburn University, Dr. Kevin Hahn, Departments of Environmental and Urban Practice, and The Thompson Cancer Survival Center, they will seek to determine the appropriate levels of recombinant cytokines to use in dogs post chemotherapeutic treatment.

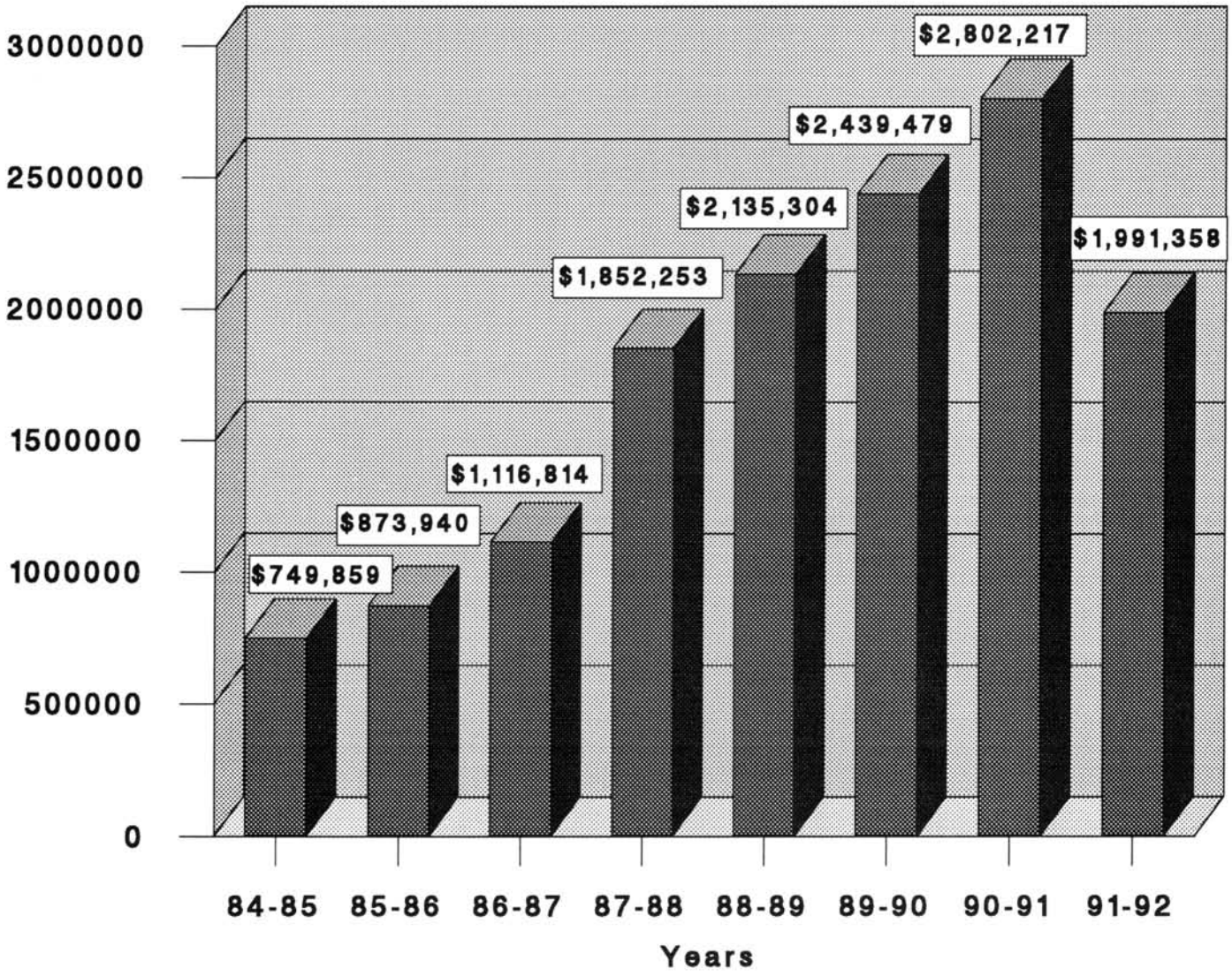
Benchmarks

TABLE 1. 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)* 1988-89			**Year 6** *(Year 01 as Accomplished Center)* 1989-90		**Year 7** *(Year 02 as Accomplished Center)* 1990-91		**Year 8** *(Year 03 as Accomplished Center)* 1991-92	
	Target	Actual	Avg	Actual	Avg	Actual	Avg	Actual	Avg
A. **NUMBERS OF**									
1. ARTICLES		74	(3.22)	68	(2.62)	97	(3.73)	83	(4.37)
2. BOOKS OR BOOK CHAPTERS PUBLISHED		7	(0.30)	17	(0.65)	14	(0.54)	6	(0.32)
3. 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)
B. ***NUMBER OF INVITED PARTICIPATIONS AT:**									
1. Regional Meetings	0.50	36	(1.56)	19	(0.73)	28	(1.08)	13	(0.68)
2. National Meetings	1.25	55	(2.39)	28	(1.08)	44	(1.69)	36	(1.89)
C. **ABSTRACTS**	0.30	33	(1.43)	66	(2.54)	48	(1.85)	47	(2.47)
NUMBER OF FACULTY INCLUDED IN CENTER		23		26		26		19	
NUMBER OF VISITORS	11	10		17		17		12	

FIGURE 1



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

The University of Tennessee
College of Veterinary Medicine

RESEARCH PROJECTS FUNDED EXTERNALLY
REPORT PERIOD 1991-92

PROJECT DIRECTOR	SOURCE	TOTAL AMOUNT AWARDED	ESTIMATED EXPENDITURES 7-1-91/6-30-92
BOCHSLER, P. N. J. M. Maddux & M. A. Breider co-investigators *Bovine Lipopolysaccharide Binding Protein and Mechanisms of Macrophage Activation*	USDA Competitive 9/1/91-8/31/93	140,000	59,970
BREIDER, M. A. *Effects of Pasteurella haemolytica Pathogenic Factors on Bovine Pulmonary Endothelium*	USDA Special 9/15/87-9/30/90 (Extension to 9/30/91)	146,616	2,000
BRIAN, D. A. *Coronavirus Structure and Replication*	NIH 9/1/89-8/31/94	565,311	94,080
DAWSON, D. A. *Joint Action of Developmental Toxicants*	Society of Toxicology/ U.S. Air Force 7/1/89-7/6/91	80,750	654
DAWSON, D. A. **SCHULTZ, T. W.**, Co-investigator *Mixture Teratogenesis: Relation to Mechanisms and QSARs*	NIEHS/NIH 4/1/91-3/31/93	138,043	68,472
DEAN, D. (Research Fellowship) *Signalling Pathways in LPS-Stimulated Lung Macrophages*	NIH Training Grant 11/30/91-11/30/94	97,500	18,200
GODKIN, J. & **Baumbach, G. A.**, Co-investigator *Bovine Fetal-Maternal Interactions*	USDA Competitive 9/1/88-8/31/91	237,000	13,166
LOTHROP, C. D. *The Molecular Biology of Cyclic Hematopoiesis*	NIH 12/1/88-11/30/93	862,438	151,488
LOTHROP, C. D. *Animal Models of Human Gene Therapy*	Mathers Charitable Foundation 1/1/87-12/31/91	179,100	17,910

PROJECT DIRECTOR	SOURCE	TOTAL AMOUNT AWARDED	ESTIMATED EXPENDITURES 7-1-91/6-30-92
McDonald, T. P. Contract--*Development of Assays for Thrombopoietin*	Genentech 3/1/88-2/28/93	178,732	33,000
Performance of Assays for Thrombopoietin	3/1/88-7/31/93	112,700	20,808
McDonald, T. P. *Thrombopoietin: Immuno-assay & Characterization*	NIH 12/1/88-11/30/93	548,681	115,600
McDonald, T. P. Purchase of: *Cell Harvester System*	NHLBI Small Instrumentation Program 9/1/91-8/31/92	8,253	8,253
Munson, L. *Effects of Progestagen Contraceptives on the Uterus & Mammary Glands of Exotic Felids*	Nixon Griffis Fund (New York Zoological Soc.) 3/1/91-2/28/92	2,844	1,896
Oliver, J. W. *Toxic Fescue Alkoloid Effects on Catecholamine Receptors in Bovine*	USDA Special Grant 9/1/89-8/31/91	125,000	10,416
Oliver, S. P. *Mastitis Research*	Alcide Corporation 12/90-12/94	57,752	14,438
Oliver, S. P. *Mastitis Research*	Monsanto Agri Co. 11/90-12/92	25,576	12,788
Oliver, S. P. *Factors Influencing Bovine Mononuclear Cell Function during the Nonlactating Period*	USDA-SEA 9/90-9/92	98,388	49,194
Oliver, S. P. *Mastitis Research*	H. B. Fuller Co. 4/91-12/94	31,778	8,664
Oliver, S. P. *Mastitis Research*	Upjohn Company 10/91-12/94	6,293	1,992
Potgieter, L. *Development of Technology for use in the Discovery and Production of a Commercial BVD Vaccine and Diagnostic*	Upjohn Company 2/1/90-12/31/92	75,000	24,996
Potgieter, L. *Genetic Organization of a Pneumopathic Strain of Bovine Viral Diarrhea Virus*	USDA Special Grant 9/1/88-8/31/91	149,200	8,386

PROJECT DIRECTOR	SOURCE	TOTAL AMOUNT AWARDED	ESTIMATED EXPENDITURES 7-1-91/6-30-92
POTGIETER, L. *Cloning and Sequencing of BRSV G Glycoprotein and Detection of Strain Divergence*	USDA Special Grant 8/1/90-7/31/93	149,974	50,679
ROUSE, B. T. *Immunity Mechanisms in Herpesvirus Infections*	NIH 5/1/89-4/30/94	1,130,370	225,082
ROUSE, B. T. *Keratitis Treatment with Drug-containing Immunoliposomes*	National Eye Institute (NIH) 9/30/87-9/29/92	708,050	153,519
ROUSE, B. T. *Liposome Microencapsulation of Vaccine Antigens*	NIAID 6/1/90-5/1/95	828,289	156,833
ROUSE, B. T. *Herpes Zosterification*	SmithKline Biologicals 12/15/89-12/31/94	124,746	24,948
SCHULLER, H. M. *Transplacental Carcinogenicity of NNK*	NIH 9/1/89-11/30/92	491,219	161,316
SCHULLER, H. M. *Mechanisms of Neuroendocrine Lung Carcinogenesis by Nitrosamines*	Shannon Award (NIH) 9/1/91-8/31/93	100,000	41,670
SCHULLER, H. M. *Characterization of Induced Neuroendocrine Lung Cancer*	National Cancer Institute (NIH) 7/1/88-6/30/91 (Extension to 12/31/92)	437,299	1,653
Characterization of Induced Neuroendocrine Lung Cancer	National Cancer Institute (NIH) 2/7/92-1/31/95	409,781	75,380
SCHULLER, H. M. Contract--*Testing of Anti-carcinogenic Effects of Niguldipine*	Byk Gulden Pharmaceuticals 3/1/88-10/31/93	183,000	32,292
SCHULLER, H. M. *Air Pollutants and Neuroendocrine Lung Cancer*	EPA 1/1/89-6/30/90 (Extension to 8/31/91)	98,104	6,132
SCHULTZ, T. W. & **Kot, Mark,** Co-investigator *Chaos in Microbial Systems*	NSF 12/1/89-11/30/92	111,615	56,659
SHULL, R. *Molecular Study of MPS I: Gene Therapy in a Canine Model*	NIH 8/1/87-7/31/92	1,105,183	107,510

PROJECT DIRECTOR	SOURCE	TOTAL AMOUNT AWARDED	ESTIMATED EXPENDITURES 7-1-91/6-30-92
SLAUSON, D. O. & **BOCHSLER, P. N.**, Co-investigator *Leukocyte Function and Host Defense in Developing Calves*	USDA Competitive 9/15/90-9/30/92	120,000	60,000
SLAUSON, D. O. *Equine Endotoxemia: An in vitro Model of Endotoxin-mediated Disease*	USDA Special 9/1/90-8/31/91 (Tranfer from Cornell)	64,175	10,695
WILKINSON, J. E. **MUNSON, L.**, Co-investigator *Role of TGF on Bovine Placental Growth and Development*	USDA Competitive 8/1/89-7/31/91	160,000	6,667
WILKINSON, J. E. **LOTHROP, C. D.**, Co-investigator *Development of Methods for Therapeutic Gene Transfer in Dogs*	AVMA Foundation 8/1/89-7/31/91 (Extension to 12/31/92)	13,895	4,068
WILKINSON, J. E. & **GODKIN, J.**, Co-investigator *Transforming Growth Factors in Early Pregnancy in the Cow*	USDA Special 7/1/89-6/30/92	149,653	49,884
GRAND TOTAL			**$1,991,358**

Plans For Next Year

III. PLANS FOR NEXT YEAR

With the acquisition of an Assistant Dean for Research and Graduate Programs, the college will be embarking on an era of renewed emphasis on scholarship. Responsibilities of the Assistant Dean will include coordinating all research and graduate study activities of the college. This position will enhance the college's visibility and strengthen its competitiveness in research and provide assistance in the day-to-day functioning of the Center.

More directed focus will be given the collaborative graduate program with UT Memphis under the direction of David M. Renquist, DVM, MS, Chairman, Department of Comparative Medicine, UT Memphis. Specific bylaws will be constituted, followed by a formal enactment by the Graduate Council. An adjunct appointment with veterinarians at St. Jude Children's Research Hospital will be activated relating to course work, teaching, and training requirements. As proposed, approximately one half of the trainee's time will be devoted to residency training in laboratory animal science and medicine consisting primarily of participation in clinical rotations, weekly pathology conferences, and participating in teaching programs and seminars on topics related to laboratory animal science and medicine. Trainees will be involved in all aspects of the clinical care program, and will learn to conduct all procedures carried out in the diagnostic laboratory. Another important aspect of the training program will be the study of animal models for medical research. The remaining half of the trainee's time will be devoted to research training offered through one of the basic medical science divisions. Students will attend research seminars sponsored by various university research departments.

Previously Biomedical Research Support Grant (BRSG) funds were received independently by the College of Veterinary Medicine and the Office of Research. The College of Veterinary Medicine and the Biomedical Science Departments in the College of Liberal Arts have agreed to cooperate in submitting a single proposal for BRSG funds. With this change in scope of "venture" applications, young and new faculty in the College of Veterinary Medicine will make application for BRSG funds through The University of Tennessee-Knoxville. Targeted areas most likely to receive funding are: (1) pilot research projects that show significant promise of leading to grant support from

NIH or some other funding agency; (2) new investigators will be given highest priority, but will be strongest when they show significant promise of achieving grant support from NIH or some other agency; and (3) unexpected needs for projects currently supported by NIH. These are proposals whereby funded investigators are experiencing unanticipated needs requiring urgent attention. The University of Tennessee will request a 1:1 match for BRSG funds.

The External Advisory Committee will arrive in late October or early November for a site visit. Suggestions from the November 8, 1990, site visit have been implemented. It was suggested by the committee to support a "limited number" of programs. While the college originally focused on three program groups: Growth Factors, Inflammation, and Oncology groups, the External Advisory Committee recommended the formation of a fourth group, to be "broadly labelled an Environmental Studies and Livestock Diseases Group." The Infectious Diseases and Population Medicine group was established. An Internal Advisory Committee, under the direction of the Assistant Director of COE, was also instituted and is now in its second year of "advising the Director on the Center's program coordination and planning (goals)." The External Advisory Committee has been instrumental in the implementation of major goals and objectives of the college. The external review process will continue. However, the review team will undergo a reorganization as Dr. Henry Baker and Dr. Peter Doherty will rotate off.

One of our major goals for next year is to strengthen research ties with ORNL. **Dr. David Slauson** will take the lead in these endeavors. **Dr. Erby Wilkinson's** two new grants from NIH will directly enhance our link with the Biology Division, ORNL. Drs. Virginia Godfrey and Laine Russell, of the Biology Division of ORNL, will be examining the role of the thymus and thymic cell components in scurfy induction in mice.

In a second project, **Dr. Wilkinson**, along with Dr. Richard Woychik of the Biology Division of ORNL will be seeking to characterize the phenotype of the Tg737 mouse including the clinical, pathologic, and clinicopathologic changes associated with PKD.

A second major goal for next year is to broaden our oncology program. To that end, in an effort to strengthen ties with The Thompson Cancer Survival Center and in

collaboration with Dr. Donita Frazier, **Dr. Michael Breider** will make a transition from the Inflammation Group to the Oncology Group. Currently they are investigating the expression of angiogenic cytokines in several human tumor cell lines and have successfully demonstrated basic fibroblast growth factor in a squamous cell carcinoma line using Western blot techniques. They are also investigating photodynamic drug uptake by endothelial cells and methods to enhance drug uptake by the cells. Dr. Kevin Hahn has been brought into the group to provide the link between the clinical sciences and basic sciences.

In addition, we plan to strengthen our Growth Factors Group with the addition to the Center of Dr. Charmi Mendis-Handagama. Similarly, the Oncology and Toxicology Group will be broadened with the addition of Dr. Teresa Rowles and her expertise in neurotoxicity.

If **Dr. Hildegard Schüller's** Program Project Grant entitled "*Signal Transduction as a Target of Lung Cancer Therapy*" is awarded, it will enhance our status in expanding the Center's emphasis in Oncology and interinstitutional cooperative research. Project leaders from outside the UT system are:

- **Dr. Kenneth L. Becker**, project leader of the project "*Modulation of Neuroendocrine Markers in Lung Tumors*" will be directing the research effort from The George Washington University, Washington, D.C. (work will take place off-campus at the VA Medical Center).

- **Dr. André Castonguay**, project leader of the project "*Effects of B859-35 on Carcinogen Activation*" will be directing the research effort for Laval University, Quebec, Canada.

- **Dr. Paul Bunn**, project leader of the project "*Clinical Investigations*" will be directing the research effort for the University of Colorado, Denver, Colorado.

Projects carried out within the college will be:

- Regulation of Lung Cancer Mitrogenesis by Receptors, Project Leader Dr. Hildegard Schuller
- Second Messenger Pathways in Lung Cancer Cells, Project Leader Dr. David Slauson
- Molecular Biology of Lung Tumors, Project Leader Dr. Mark Miller
- Electron Microscopy of Lung Tumor Cells, Project Leader Dr. Don McGavin

The COE continues to be a strong influence and major support for many research programs in the CVM. The democratic manner in which funds are allocated for support of proposals underscores the spirit of cooperation and emphasizes the principle of shared resources. Funds for the COE are an example of a good investment in the future of Tennessee--*minimal funds with maximum benefits*.

Continued support for our expanding research endeavors is essential.

Budget Forms

SCHEDULE 1

CENTERS OF EXCELLENCE
ACTUAL, PROPOSED, AND REQUESTED BUDGET

Institution College of Veterinary Medicine

Center Livestock Diseases & Human Health

	1991-92 Actual Budget			1992-93 Proposed Budget			1993-94 Requested Budget		
	Matching	Appropriations	Total	Matching	Appropriations	Total	Matching	Appropriations	Total
Revenue									
New State Appropriation		517,900	517,900		506,500	506,500		532,000	532,000
Carryover State Appropriation		2,422	2,422						
New Matching Funds	258,950		258,950	253,250		253,250	266,000		266,000
Carryover from Previous Matching	821		821						
Total	259,771	520,322	780,093	253,250	506,500	759,750	266,000	532,000	798,000
Expenditures									
Salaries									
a. Faculty	51,085	102,323	153,408	36,877	73,865	110,742	33,400	66,600	100,000
b. Other Professional	54,891	109,947	164,838	55,250	110,670	165,920	55,417	110,503	165,920
c. Clerical/Supporting	25,307	50,691	75,998	22,568	45,203	67,771	22,712	45,288	68,000
d. Assistantships	7,999	16,022	24,021	1,340	2,687	4,027	6,430	12,820	19,250
e. Students	3,053	6,115	9,168	8,000	16,000	24,000	8,016	15,984	24,000
Total Salaries	142,335	285,098	427,433	124,035	248,425	372,460	125,975	251,195	377,170
Fringe Benefits	27,541	55,163	82,704	32,245	64,595	96,840	30,660	61,140	91,800
Total Personnel	169,876	340,261	510,137	156,280	313,020	469,300	156,635	312,335	468,970
Travel	242	488	730	1,665	3,335	5,000	300	700	1,000
Software	284	570	854						
Books and Journals									
Other Supplies	41,983	84,090	126,073	41,355	82,095	123,450	44,432	88,598	133,030
Equipment	41,546	83,213	124,759	49,950	100,050	150,000	58,450	116,550	175,000
Maintenance	5,840	11,700	17,540	4,000	8,000	12,000	6,183	13,817	20,000
Scholarships									
Consultants									
Renovation									
Other (Specify)									
Total Non-Personnel	89,895	180,061	269,956	96,970	193,480	290,450	109,365	219,665	329,030
GRAND TOTAL	259,771	520,322	780,093	253,250	506,500	759,750	266,000	532,000	798,000

Appendices

CURRICULUM VITAE

S. M. LILITHA CHAMINDRANI MENDIS-HANDAGAMA

Education:	**Degree**	**Year**	**Field of Study**
Monash University Melbourne, Australia.	PhD.	1985	Reproductive Biology.
University of Sri Lanka, Peradeniya.	DVM.	1977	Vet. Med. & Surgery.
The Johns Hopkins University, Baltimore.	-postdoctoral training-		Reproductive Biology.

Career History: Assistant Professor, Department of Animal Science, The University of Tennessee, 1991-present; Research Associate, Department of Population Dynamics, The Johns Hopkins University, 1990-1991; Postdoctoral Fellow, The Johns Hopkins University, 1985-1989; Research Assistant, Monash University, Australia, 1984-1985; Doctoral Student, Monash University, Australia, 1980-1984; Lecturer, Department of Veterinary Pre-Clinical Studies, University of Srilanka, 1977-1980.

Honors and Awards: Recipient of 1992 Idea Grant, Awarded by the Institute of Agriculture, UT; recipient of Participation Award for 8ICSS awarded by the March of Dimes Organization, 1991; Institutional Scholarship, awarded by The Johns Hopkins University, 1985-1989; Postdoctoral Fellowship, awarded by the Mellon Foundation, 1986-1987; recipient of Hans Elias Award for Distinguished Young Stereologists, awarded by the International Society for Stereology, 1987; Trainee Travel Award, awarded by the Society for the Study of Reproduction, 1987; Postdoctoral Fellowship, awarded by the Hewlett Foundation, 1985-1988; Monash Graduate Scholarship, awarded by the Monash University, 1983-1984; Postgraduate Research Scholarship, awarded by the World Health Organization, Switzerland, 1980-1983; Commonwealth Bureau of Animal Health Award, awarded by the Commonwealth Bureau of Animal Health, England, 1975.

Invited Speaker in International Conferences: M.C. Chang Memorial Conference, Barcelona, Spain, 1992.

Journal Reviews: Journal of Andrology, Biology of Reproduction, Molecular & Cellular Endocrinology.

Publications (Last 5 years):

1. **Mendis, S.M.L.C.** (1985). Studies on Leydig cells: their development, heterogeneity and response to tubule damage. Ph.D. Thesis. Monash University, Melbourne, Australia.

2. **Mendis-Handagama, S.M.L.C.**, Risbridger, G.P., de Kretser, D.M. (1987). Morphometric analysis of the components of the neonatal and adult rat testis interstitium. Int. J. Androl. 10:525-534.

3. Hardy, M.P., **Mendis-Handagama, S.M.L.C.**, Zirkin, B.R., Ewing, L.L. (1987). Photoperiodic variation of Leydig cell numbers in the testis of the golden hamster: a possible mechanism for their renewal during recrudescence. J. Exp. Zool. 244:269-276.

4. **Mendis-Handagama, S.M.L.C.**, Zirkin, B.R., Ewing, L.L. (1988). Comparison of components of the testis interstitium with testosterone secretion in hamster, rat and guinea pig testes perfused *in vitro*. Am.J.Anat. 181:12-22.

5. Walters, J.R., Juniewicz, P.E., Oesterling, J., **Mendis-Handagama, S.M.L.C.**, Zirkin, B.R., Ewing, L.L. (1988). The effect of inhibition of aromatase enzyme activity on Leydig cell structure and function in beagles. Endocrinology 123:2223-2229

6. Keeney, D.S., **Mendis-Handagama, S.M.L.C.**, Zirkin, B.R., Ewing, L.L. (1988). Effect of long-term deprivation of luteinizing hormone on Leydig cell volume, Leydig cell number and steroidogenic capacity of the rat testis. Endocrinology 123:2906-2915

7. **Mendis-Handagama, S.M.L.C.**, Hardy, M.P., Keeney, D.S., Ewing, L.L. (1989). Application of the disector method to enumerate cells in the testis. In: Regulation of testicular function: signaling molecules and cell-cell communication, L.L. Ewing and B. Robaire (ed), The New York Academy of Sciences, NY (Publisher), 564:86-98.

8. **Mendis-Handagama, S.M.L.C.**, Ewing, L.L. (1990). Sources of error in the estimation of Leydig cell numbers in control and atrophied mammalian testes. J. Microscop. (Oxford) 159:73-82.

9. **Mendis-Handagama, S.M.L.C.**, Zirkin, B.R., Scallen, T. J., Ewing L.L. (1990). Studies on peroxisomes of the adult rat Leydig cell. J. Andrology 11:270-278.

10. **Mendis-Handagama, S.M.L.C.**, Kerr, J.B., de Kretser, D.M. (1990). Experimental cryptorchidism in the adult mouse I. Qualitative and quantitative light microscopic morphology. J.Andrology 11:539-547.

11. **Mendis-Handagama, S.M.L.C.**, Kerr, J.B., de Kretser, D.M. (1990). Experimental cryptorchidism in the adult mouse II. A hormonal study. J. Andrology 11:548-554.

12. **Mendis-Handagama, S.M.L.C.**, Watkins, P.A, Gelber, S.J, Scallen, T.J., Ewing L.L. (1990). Luteinizing hormone causes rapid and transient increase in Leydig cell peroxisome volume and its sterol carrier protein-2 content. Endocrinology 127:2947-2954.

13. **Mendis-Handagama, S.M.L.C.** (1991). Mitosis in normal adult guinea pig Leydig cells. J. Androl. 12:240-243.

14. **Mendis-Handagama, S.M.L.C.**, Kerr, J.B., de Kretser, D.M. (1991). Experimental cryptorchidism in the adult mouse III. Qualitative and quantitative electron microscopic morphology of Leydig cells. J. Andrology 12:335-343.

15. Gelber, S.J., Hardy, M.P., **Mendis-Handagama, S.M.L.C.**, Casella, S.J. (1992). Effects of IGF-1 on androgen production by highly purified pubertal and adult rat Leydig cells. J. Androl. 13:125-130.

16. **Mendis-Handagama, S.M.L.C.**, de Kretser, D.M. Heterogeneity of adult mouse Leydig

cells with different buoyant densities. (1992). J. Andrology 13:274-282.

17. **Mendis-Handagama, S.M.L.C.** (1992). The assumption of nuclear roundness causes an overestimation of Leydig cell number in atrophied rat testes. Acta Stereol. 11(Suppl.1):495-500.

18. **Mendis-Handagama, S.M.L.C.** (1992). Error estimation in Leydig cell numbers of atrophied rat testes due to the assumption of spherical nuclei. J. Microscop. (Oxford). (*in press*).

Abstracts:

1. **Mendis, S.M.L.C.**, Kerr, J.B., Robertson, D.M. and de Kretser, D.M. (1981). Leydig cell hyperplasia and gonadotrophin responsiveness following cryptorchidism in the mouse. Proc. Aust. Soc. Reprod. Biol. Abstract 73.

2. Kerr, J.B., Robertson, D.M., Muir, J., **Mendis, C.** and de Kretser, D.M. (1982). Purification and characterization of Leydig cells from mouse testes. Proc. Aust. Soc. Reprod Biol. Abstract 50.

3. **Mendis, Chamindrani,** Kerr, Jeffrey B., Robertson, David M., Muir, Julie. and de Kretser, David, M. (1983). Morphological observations of normal adult mouse Leydig cells in different Percoll fractions. Proc. Endocr. Soc. Australia. Abstract 31.

4. **Mendis-Handagama, S.M.L.C.**, Risbridger, G.P. and de Kretser, D.M. (1983). Morphometric analysis of the neonatal and adult rat testis. Proc. Aust. Soc. Reprod. Biol. Abstract 1.

5. **Mendis-Handagama, S.M.L.C.**, Risbridger, G.P. and de Kretser, D.M. (1986). Fetal and adult Leydig cells in the rat testis. Soc. Study of Reprod. Abstract 141.

6. Walters, J.R., Juniewicz, P.E., Oesterling, J., **Mendis-Handagama, S.M.L.C.**, Zirkin, B.R. and Ewing, L.L. (1987). The effect of inhibition of endogenous aromatase activity on beagle Leydig cells. Am. Assoc. Anat. 100 Annual meeting. Published in the Anat. Rec. 218 (1): 145A.

7. **Mendis-Handagama, S.M.L.C.** and Ewing L.L. (1987). Are peroxisomes involved in Leydig cell steroidogenesis? Soc. Study of Reprod. Abstract 333.

8. **Mendis-Handagama, S.M.L.C.** and Ewing, L.L. (1988). Comparison of disector and Floderus methods to determine Leydig cell number in control and atrophied mammalian testes. J. Histochem. Cytochem.36:(7a) Abstract no.299

9. **Mendis-Handagama, S.M.L.C.** and Ewing, L.L. (1989). Leydig cell peroxisomal volume depends on luteinizing hormone. Proc. Am. Soc. Cell Biol. Abstract 689.

10. **Mendis-Handagama, S.M.L.C.**, Zirkin, B.R., Scallen, T.J. and Ewing, L.L. (1990)

Luteinizing hormone (LH) regulation of sterol carrier protein-2 (SCP_2) in rat Leydig cells. Soc. Study of Reprod. Abstract 199.

11. Gelber, S.J., Hardy, M.P., **Mendis-Handagama, S.M.L.C.**, Casella, S.J. (1991). IGF-1 Effects on steroidogenesis in cultures of purified rat Leydig cells. International Symposium on Insulin-like Growth Factors/Somatomedins. Abstract A58.

12. **Mendis-Handagama, S.M.L.C.**, Krisans, S.K., Ewing, L.L. (1991). Adult rat Leydig cell peroxisomes contain 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoAR). Proc. Am. Soc. Androl. Abstract 22.

13. **Mendis-Handagama, S.M.L.C.**, Sourdaine, P., Garnier, D.H., Jegou, B. (1991). Peroxisomes play a significant role in testicular steroidogenesis: further evidence from Sertoli cells in the dogfish testis (*Scyliorhinus canicula*). Dedicated to Larry L. Ewing. Proc. XIth North American Testis Workshop. Abstract 82.

14. Gelber, S.J., Hardy, M.P., **Mendis-Handagama, S.M.L.C.**, and Ewing L.L. (in memorium; 1991). Effects of IGF-1 on steroidogenesis in highly purified pubertal rat Leydig cells. Proc. XIth North American Testis Workshop. Abstract 74.

15. **Mendis-Handagama, S.M.L.C.**, Aten, R.F., Scallen, T.J. (1991). Sterol carrier protein-2 distribution in luteal cells of control and treated rats for acute luteotrophic and luteolytic activity. Soc. Study of Reprod. Abstract 554.

16. **Mendis-Handagama, S.M.L.C.**, Zirkin, B.R. Peroxisomes in Leydig cell steroidogenesis. Fifteenth In-House Cell Biology Symposium, The Johns Hopkins University, Baltimore, Maryland. Abstract 10.

17. **Mendis-Handagama, S.M.L.C.** (1991). The assumption of nuclear roundness causes an overestimation of Leydig cell number in atrophied rat testes. Eighth International Congress for Stereology. Abstract 7.202.

18. **Mendis-Handagama, S.M.L.C.**, Aten, R.F., Berhman, H.R., Scallen, T.J. (1991). Peroxisomes are responsible for the transport of cholesterol from lipid droplets into mitochondria by sterol carrier protein-2 during luteal cell steroidogenesis. Proc. Am. Soc. Cell Biol. Abstract 1356.

19. Handagama, N.B., **Mendis-Handagama, S.M.L.C.** (1992). A mathematical model for shrinkage of testis tissue as a function of the volume density of seminiferous tubules. Soc. Study of Reprod. Abstract 16.

NAME: Teresa K. Rowles

TITLE: Assistant Professor

NATURE OF APPOINTMENT: (100% CVM)

EDUCATIONAL BACKGROUND: (Most recent degree last)

Degree	Year	University	Major
PhD	1989	Texas A&M University	Toxicology/Anatomy
DVM	1980	University of Tennessee	Veterinary Medicine
BA	1976	University of Tennessee	Zoology

CAREER HISTORY: (Professional experience only - most recent first)

Interval	Title	Employer
1992-Present	Assistant Professor	University of Tennessee
1988-91	Assistant Professor	Virginia Tech
1983-88	Vet. Clinical Associate	Texas A&M University
1982-83	Instructor	University of Tennessee

PROFESSIONAL SOCIETIES:

American Association of Veterinary Anatomists, IAAAM, Ph Zeta, Sigma Xi, American Association Anatomists, Tissue Culture Association.

HONORS AND AWARDS:

Faculty Wives Graduate Student Award
Boehringera Engelheim Graduate Student Award

TEACHING RESPONSIBILITIES:

Course Number	Course Title	Frequency Offered
VM821	Basic & Clinical Veterinary Anatomy	Fall
VM822	Basic & Clinical Veterinary Anatomy	Spring

RESEARCH RESPONSIBILITIES:

Project Number	Title
Current:	
1	*In Vitro* Systems for assessment of neurotoxicity and cytotoxicity and for transfer of toxicants to the nervous system. CAAT, 1992-93. Principle Investigator.
2.	Development of an *in vitro* assay for preeclampsia. COE, 1992-93. Principle Investigator.
3.	An *in vitro* model of hypoxia/reperfusion injury in the central nervous system. Venture grant
4.	Metabolism and neurotoxicity studies on MTPT analogs, NIH, 1989-1995, consultant.

5. Metabolism and neurotoxicity studies on MPTP analogs. Consultant, performing *in vitro* work. $768,998.00, 7 years, NIH.

Past:

10. Development of an *in vitro* model of the blood-brain barrier for neurotoxicity testing. Principle Investigator, $15,000, 1990-1001. The Johns Hopkins University Center for Alternatives to Animal Testing.
11. Effects of ridogrel on maternal fetal homeostasis and neonatal coagulationin an ovine model of preeclampsia. Co-I. $148,848.00, 2 years, 1990-1992. Janssen Research Foundation.
12. Effects of ridogrel on the synthesis of eicosanoids and endothelial derived relaxong factor (EDRF) by placentae and umbilical arteries from normal and preeclamptic women: an *ex vivo* study. Co-I. Janssen Research Foundation. $74,783.00, direct. 1 year, 1991.
13. Development of *in vitro* techniques of assessing neurotoxicants by affects on neurite outgrowth or maintenance of neurites. Principle Investigator. NIH BRSG, $4,855.00, 1989.
14. Devlopment of an *in vitro* model of the blood-brain barrier. Principle investigator. New Initiative, $4,000.00, 1989.
15. Quantitation of the synthesis of eicosanoids and endothelial dependent relaxing factor (EDRF) by umbilical arteries and placentae from normal and pre-eclamptic women: an ex vivo study. Co-I, NIH BRSG. $4,950.00, 1989.
16. Morphological and toxicological assessment of reproductive system of cetaceans. Co-I, New Initiative, $4,000.00, 1989.
17. Effects of a 48 hour intravenous infusionof primagrel in the third trimester of pregnancy in guinea pigs. Co-I, Ciba-Geigy, $36,952.00, 1990.
18. Neurochemical effects of prenatal lead exposure in guinea pigs, Principle investigator, NIH BRSG, $3,500.00, 1988.
19. Cellular effects of carbamates in neuroglia and neuronal cultures. Principle investigator. Creative Match Grant. $5,000.00, 1988.
20. Endothelial Cell cytotoxicity of serum from preeclamptic patients, New Initiative, Principle investigator, $3,727.00, 1988.
21. Evaluation of cardiovascular adaptations to divine in ringed seal and Bowhead whale, Co-I, North Slope Burrough, $9,900.00, 1989.

COMMITTEE ASSIGNMENTS:

1. Corresponding secretary of American Association of Veterinary Anatomists.
2. Committee of National Marine Fisheries Service, Northeast Regional Stranding Network Meeting, 1992.

PRESENTATIONS AT STATE, REGIONAL, AND NATIONAL MEETINGS: (Last Five Years)

1. T.K. Rowles, et al. *In vitro* Evaluation of neural function. 1992 World Congress on Cell and Tissue Culture. Invited speaker and session chair.
2. T.K. Rowles. Applied anatomy of marine mammals. 1992 Aquamed '92, Galveston, Texas.
3. D. Taylor, T.K. Rowles, A.C. Nostrandt and M. Ehrich. Early morphological changes in SH-SY5Y neuroblastoma cells after exposure to a neuropathy-inducing organophosphorus compound, mipafox. 1992 CAAT 10th anniversary symposium. Baltimore, Maryland.
4. A.C. Nostrandt, T.K. Rowles, and M. Ehrich. 1992 CAAT 10th anniversary symposium. Baltimore, Maryland.

5. T.K. Rowles, K. DiLorenzo, and J. Kalnitsky-Aliff. 1991. The assessment of a supravital stain as an indicator of mitochondrial damage in neuroblastoma cells exposed to specific neurotoxicants.
6. M. Farage and T.K. Rowles. 1990. Toxicity of carbaryl and aldicarb on brain and limb cultures of chick embryos. The Toxicologyist 10:1366.
7. T.K. Rowles, K. DiLorenzo, and J. Kalnitsky-Aliff. 1990. A comparison of the effects of specific enurotoxicants on mitochondrial morphology and function in neuronal cells. AAVA.
8. L.E. Freeman, and T.K. Rowles. 1990. Forelimb duplication malformation in a lamb. AAVA.
9. L.E. Freeman, T.K. Rowles, T. Caceci, and L.A. Eng. 1990. Male reproductive system anatomy in cetaceans. AAVA.
10. C.J. Pfeiffer, L.E. Freeman, T.K. Rowles, and T. Caceci. 1990. Comparative ultrastructure of cetacean retia mirabliia. AAVA.
11. K. DiLorenzo, T.K. Rowles, J.C. Keith Jr., J. Kalnitsky-Aliff, R. Gogal, C. Davis, W. Isenhour, D. Meincke, D. Armour, M. Langebeck. 1990. Measurement of cytoxicity caused by serum from normal women and women with PIH using a bovine pulmonary artery endothelial cell culture system. International Society for the Study of Hypertension in Pregnancy, Perugia, Italy.
12. T.K. Rowles, W.D. Blaker, an dE. Tiffany-Castiglioni. 1989. Neurochemical effects of prenatal lead exposure in guinea pigs. Neuroscience 15:1022.
13. J.C. Keith Jr, T.K. Rowles, J. Kalnitsky-Aliff, M.K. Eggleston, S. Fortunato, and S. Welt. 1989. Effects of primagrel, a thromboxane synthetase inhibitor, on the cytotoxicity of serum from women with pregnancy-induced hypertension: a preliminary study. National perinatal association annual clinical conference.
14. T.K. Rowles, L.E. Freeman, J. Burns, T. Caceci, C.J. Pfeiffer, and T. Albert. 1989. Cardiovascular adaptations to diving in the ringed seal. AAVA published Anatomia Histologia Embyrologia 19(1):90.
15. L.E. Freeman, T.K. Rowles, J. Burns, and T. Albert. 1989. Musculoskeletal system of the ringed seal. AAVA, published Anatomia Histologia Embryologia 19(1):83.
16. T.K. Rowles, and M. Farage-Elawar. 1989. In vitro toxicity of aldicarb an dcarbaryl in neuroglia. The Toxicologist, 9:220.
17. T.K. Rowles, C. Womac, G. Miller, A.J. Castiglioni Jr, G.R. Bratton and E. Tiffany-Castiglioni. 1988. Zinc and lead interactions in immature guinea pigs. Neuroscience.

PUBLICATIONS: (Last Five Years)

1. TK Rowles, C Womac, GR Bratton, E Tiffany-Castiglioni, 1988. Interaction of lead and zinc in cultured atroglia. In: Biochemical Pathology of Astrocytes (MD Norenberg, ed), AR Liss, New York, pp. 235-236.
2. Rowles TK, C Womac, GR Bratton, and E Tiffany-Castiglioni. 1989. Interaction of lead and zinc in cultured astroglia. Metabolic Brain Disease 4:187-201.
3. Sierra EM, TK Rowles, J Martin, GR Bratton, C Womac and E Tiffany-Castiglioni. 1989. Low level lead neurotoxicity in fetal and maternal guinea pigs: reduction of astroglial and oligodendroglial enzyme activities and alterations of trace metal concentrations. Toxicology 59:81-96.
4. Farage-Elawar M, and TK Rowles. 1992. Toxicity of aldicarb and carbaryl in brain and limb cultures of chick embryos. in press.
5. Keith JC Jr, TK Rowles, K Warwick, E Yau. 1992. The effects of a continuous intravenous infusion of CGS 13080 on the perinatal and early postnatal period in the Guinea pig. Teratology, in press.
6. Keith JC Jr, TK Rowles, K Warwick, and E Yau. 1992. Gastric Torsion and Dilation in a pregnant guinea pig. Laboratory Animal Science, in press.

7. Rowles TK, JC Keith Jr, G. Saunders, K Warwick and E Yau. 1992. Imperforate anus, colo-colic intussusception and bowel rupture in a neonatal guinea pig. Laboratory Animal Science, in press.
8. Moon M, and TK Rowles. 1992. The Cardiovascular System. In: Applied Anatomy of the Cat. WB Saunders, in press.
9. Nostrandt AC, TK Rowles, and M Ehrich. 1992. Cytotoxic effects of organophosphorus esters and other neurotoxic chemicals on cultured cells. accepted.
10. Legare ME, AJ Castiglioni Jr, TK Rowles, JA Calvin, C Snyder-Armstrong, and E Tiffany-Castiglioni. 1992. Morphological alterations of neurons and astrocytes in guinea pigs exposed to low levels of inorganic lead. Neurotoxicology, submitted.
11. Rowles TK, JC Keith Jr, J. Kalnitsky-Aliff, and K. diLorenzo. 1992. A simple assay to evaluate the cytotoxicity of sera from pregnant women. submitted.

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