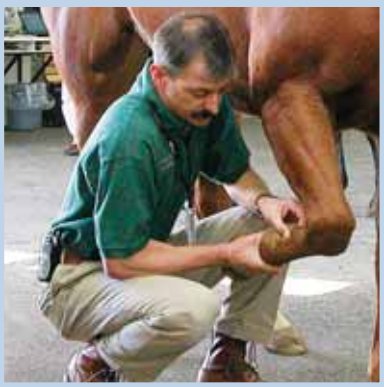
IN SIGHT

College of Veterinary Medicine and Biomedical Sciences

Fall 2004

RESEARCH



Colorado State University

Knowledge to Go Places

INSIGHT
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COLLEGE OF VETERINARY MEDICINE AND BIOMEDICAL SCIENCES

On the cover:
From left to right, Tina Daniels, and Drs. Joel Rovnak and Sandra Quackenbush review data from retroviral studies in fish that may offer clues to cancer regression. Insets (from left to right): Dr. Rob Callan brings clinical cases into the laboratory to enhance large animal medicine; a feline patient gets a quick check-up; Dr. Dean Hendrickson checks a patient.

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Welcome to *Insight*

Welcome to the Fall 2004 edition of *Insight.* In this edition, we focus on some of the many innovative research programs at the College of Veterinary Medicine and Biomedical Sciences. You'll read about new surgical techniques that enhance the health outcomes for horses and new nonsurgical techniques that help infants born with a devastating heart defect. We look at three projects focused on cancer research, including one funded by NASA to examine the long-term risks of radiation exposure to astronauts on extended space flights. You'll learn how researchers at CSU are making a difference in the world of veterinary medicine and pushing forward the boundaries in biomedical sciences.

We also honor several faculty members who recently have received prestigious awards for their work in teaching and research. These honors and awards reflect the overall excellence of the faculty at the College, and we congratulate the recipients – Drs. Stephen Withrow, Ian Orme, and Patrick Brennan – on their achievements.

Research is a strong component of our College mission. It helps us advance animal care, cure animal and human diseases, and protect public health. We hope you enjoy the articles in this special research edition of *Insight* and learn more about research at Colorado State University.

We welcome your questions and comments on *Insight* and its contents. If you'd like to get in touch with us, please send your correspondence to:

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You can e-mail *Insight* comments to Paul Maffey, Director of Development for the College, at rpmaffey@colostate.edu. We also invite you to visit us at our Web site at www.cvmbs.colostate.edu. ■

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Message from the Dean

Dear Friends,

In this special edition of *Insight*, we invite you to learn more about some of the many different research projects ongoing at the College of Veterinary Medicine and Biomedical Sciences. I'm sure you will be surprised by the diversity of subjects represented here and by the intriguing nature of the work of so many of our faculty members.

In past issues of the research edition of *Insight*, we have focused on our larger and more well-known research and teaching programs, including the Mycobacterium Research Laboratories, the Arthropod-Borne and Infectious Diseases Laboratory, the Flint Animal Cancer Center, the Animal Reproduction and Biotechnology Laboratory, and the Orthopaedic Research Center. These are but a part of the overall research picture here at the College, research that is evolving to meet the new needs of society as well as continuing to work on problems that have been around for a long time.

Dr. Sandra Quackenbush, a newcomer to CSU, is doing innovative work on a recurring fish tumor that may provide some answers to natural tumor regression. Dr. Dean Hendrickson continues to improve on equine surgical techniques, conducting studies that show how minimally invasive surgery can improve surgical outcomes. Dr. Janice Bright has been working with Children's Hospital in Denver on innovative heart surgeries that will help children with congenital heart defects live longer and healthier lives. These are just a few of the many research projects here at the College, and our programs continue to grow.

I'm very proud to report that 2003/2004 represented a phenomenal year in research for the College, including a $17 million grant from the National Institutes of Health to build a Regional Biocontainment Laboratory, a $9.7 million NASA grant for our Cancer Biology Group, new grants for our Mycobacterium Research Laboratories, and much more. This was the College's all-time best year for research grants. We lead all other schools and colleges at Colorado State University in terms of extramurally funded research, and we lead all other veterinary schools in the nation in research funding from the National Institutes of Health. This year, extramural research funding was $50,413,371, constituting 52 percent of our total budget and representing a 13 percent increase over research funding in the previous year.

Dr. Lance Perryman

"This was the College's all-time best year for research grants. We lead all other schools and colleges at Colorado State University in terms of extramurally funded research, and we lead all other veterinary schools in the nation in research funding from the National Institutes of Health."

This investment in research will help us advance animal care, cure animal and human diseases, and protect public health. In addition, research funding helps pay for buildings, new equipment, staff and faculty salaries, and overhead costs associated with our teaching, research, and outreach missions. Research funding provides unsurpassed learning opportunities for our graduate and undergraduate students who are able to work and learn in the laboratories of some of the world's leading scientific experts. Research funding helps us develop new knowledge that will benefit society as a whole.

I am very proud of our faculty members who work so hard to develop innovative and cooperative research programs at the cutting edge of their fields of study. In the year to come, we will continue to look at ways we can support our faculty, with particular attention to the upgrading of facilities to support our robust research mission. I hope you enjoy this edition of *Insight* and look forward to hearing your comments. ■

Best Regards,

Lance Perryman, DVM, PhD
Dean, College of Veterinary Medicine
and Biomedical Sciences

Unique Retroviral Tumor Offers Clues to Natural Cancer Regression

Walleye are most often thought of as a sport fish, but to cancer researchers at Colorado State University the fish is a great catch for the opportunities it offers to study a rarity in the world of cancer – naturally regressing tumors.

Dr. Sandra Quackenbush and her research team, graduate student Tina Daniels and special appointment faculty Dr. Joel Rovnak, recently arrived at Colorado State – by way of the University of Kansas – where they are continuing walleye studies originated at Cornell University. The team is studying the properties of a retrovirus that causes "stop-and-go" dermal sarcomas in the walleye.

"The natural biology of the disease is somewhat unique in the world of cancer research," said Dr. Quackenbush, an Assistant Professor in the Department of Microbiology, Immunology and Pathology. "In the fall, the tumors first appear on the fish, popping up all over their bodies. The tumors grow through the winter and are at their peak in the spring when the walleye are spawning. This is also when the tumors are shedding substantial quantities of virus, quite understandable because the virus is spread through contact. After spawning, the tumors begin to regress, eventually falling off and leaving the fish perfectly normal. Come fall, the cycle starts again."

Tina Daniels, Joel Rovnak, and Sandra Quackenbush discuss their research on viruses that cause cancer using fish as a model.

Studying fish obtained from a hatchery on Oneida Lake, Syracuse, New York, where there is a high incidence of the disease, Dr. Quackenbush and Drs. Jim Casey and Paul Bowser of Cornell started working on a system to better understand the mechanisms of the retrovirus and what proteins might be causing the growth and regression of the dermal sarcomas, as well as to investigate fish tumor retroviruses as new models for oncogenesis (the formation and development of tumors).

"We have three goals in our current research," said Dr. Quackenbush. "We want to understand what viral proteins are responsible for oncogenesis, what viral proteins are associated with the regression of tumors, and how virus expression is regulated. What we do know is that around the time of spawning, something happens and we see a tremendous increase in viral gene expression. We want to learn more about that trigger."

> "What we do know is that around the time of spawning, something happens and we see a tremendous increase in viral gene expression. We want to learn more about that trigger."

To date, researchers have been able to reproduce the disease experimentally, but have not been able to replicate conditions for regression. They also have discovered that the virus encodes three novel proteins with functions that are uncertain. But Dr. Quackenbush and her team do have some theories. The first viral protein in the developing tumor seems to inhibit viral gene expression and also seems to affect cellular gene transcription. The second protein is expressed in the developing tumor and seems to be involved in cell signaling, most likely with oncogenesis. The third protein, and one of the most interesting, is expressed in the regressing tumor so is likely to be a key factor in tumor regression and also may be involved in up-regulating virus transcription associated with cells that will undergo apotosis (programmed cell death).

This walleye displays the tumors associated with a unique retrovirus.

In another fish cancer study, Dr. Quackenbush is investigating swim bladder sarcomas in Atlantic salmon. These tumors also are caused by a retrovirus, but the tumors do not regress and can be a significant problem for the salmon industry. Though the walleye is the significant portion of the laboratory's focus, Dr. Quackenbush believes there is much to be gained from knowledge acquired in both projects.

"We believe there is much to be learned by medical science in the development of these fish models as relates to cancer research," said Dr. Quackenbush. "In the future, it will be quite interesting to see where our studies lead us."

Dr. Quackenbush and her research team are supported in the walleye studies by a grant from the American Cancer Society. Work in the Atlantic salmon is supported with funding from the United States Department of Agriculture. ■

Vaccine Studies Raise Questions on Links to Kidney Disease in Cats

Veterinarians have long been stumped by the high prevalence of kidney disease in cats. While some cases are tied to specific illness such as arterial hypertension, pyelonephritis (infections), or toxicities, most causes of chronic renal failure in cats remain undetermined. So when feline vaccine research at Colorado State University showed some interesting anomalies in feline blood samples, researchers were intrigued and began to ask some questions that are in the process of being answered.

"Cats commonly go into chronic kidney failure, especially older cats, and we've been asking ourselves for a long time, what goes wrong, what kills these kidneys over time?" said Dr. Michael Lappin, Professor in the Department of Clinical Sciences and the Kenneth W. Smith Professor in Small Animal Clinical Medicine. "Most cats that die of kidney failure without a known cause have infiltrations of lymphocytes and plasma cells in the kidney tissues. These cells can indicate an immune reaction."

In the 1970s, it was discovered that a cell line derived from a cat kidney – the Crandall-Reese feline kidney (CRFK) cell line – could be used to grow feline viruses like feline herpesvirus1 (FHV-1), calicivirus, and panleukopenia. Some vaccine manufacturers began using the CRFK cell line to grow the viruses and

"Cats commonly go into chronic kidney failure, especially older cats, and we've been asking ourselves for a long time, what goes wrong, what kills these kidneys over time?"

Dr. Michael Lappin and Jennifer Hawley look at ELISA antibody test results.

then used them in a combined vaccine (FVRCP vaccine). In general, veterinarians administer the FVRCP vaccines to cats approximately three times as kittens with a booster at one year and, after that, boosters every one to three years. The use of the FVRCP vaccination program has helped save many feline lives by inducing great immunity to these three dangerous viruses.

During the course of a Colorado State University and Heska Corporation collaborative study to determine if blood tests could be used to assess the need for vaccines, researchers made an interesting discovery that related to the commonly used FVRCP vaccine.

"The vaccine companies are doing a great job making pure and efficacious vaccines," said Dr. Lappin. "However, when FVRCP vaccines are made, each dose is contaminated with just a little bit of cell culture. What we discovered recently was that cats not only develop antibodies to the viruses in the vaccine, which is our intent, but they also develop antibodies to the cell culture – a culture based on a feline kidney cell line. And that's where we have to begin to ask some very intriguing questions. In particular, is it possible that over-vaccination induces antibodies that are associated with immune-mediated feline kidney disease?"

An early proof concept study conducted in Dr. Lappin's laboratory as a collaboration between Colorado State University and the Heska Corporation showed the development of CRFK antibodies in cats after administration of injectable FVRCP vaccines. In some cats, these antibodies reacted with cat kidney cell extracts as well. But just because cats are producing antibodies to the CRFK proteins and cat kidney cell extracts does not mean those antibodies

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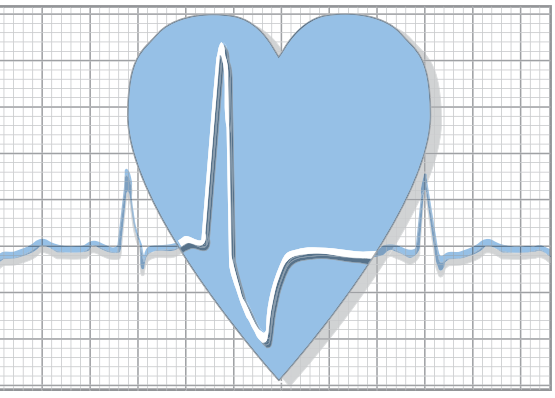
"Is it possible that over-vaccination induces antibodies that are associated with immune-mediated feline kidney disease?"

Cardiology Program at VTH Helps Improve Treatment of Children with Congenital Heart Defect

The Cardiology and Cardiac Surgery program at the James L. Voss Veterinary Teaching Hospital has a number of firsts in veterinary medicine – creating the first open-heart surgery program for animals, pioneering surgical heart-valve repair and replacement in dogs, innovating pacemaker implantation in animals, and more. But what many don't realize is that the program also is at the cutting edge of helping to improve human heart health through a cooperative research program with Children's Hospital in Denver.

Specifically, the team of researchers at the Cardiology and Cardiac Surgery program have worked with Dr. Mark Boucek, head of the Heart Transplant Program at Children's, to develop a new nonsurgical technique to improve outcomes in children born with a congenital heart defect known as Hypoplastic Left Heart Syndrome (HLHS).

"Using studies in lambs, we helped Dr. Boucek develop a nonsurgical way of palliating children born with a serious congenital heart defect," said Dr. Jan Bright, a Professor in the Department of Clinical Sciences and member of the cardiology team. "The technique developed creates a connection between the pulmonary artery and aorta so the child can continue to get blood to the tissues of the body. At the same time, small, self-expanding, flow-limiting devices are placed into the left and right pulmonary arteries to protect the lungs from damage by high blood flow and high pressure. Done through a catheter, this nonsurgical approach is far less risky to the infant than surgery and gives them a better shot at successful ongoing care to correct their heart defect."



One of Dr. Boucek's patients successfully treated for hypoplastic heart using a device tested at CSU.

Congenital heart defects occur in approximately eight out of every 1,000 children born today, an estimated 35,000 to 40,000 cases each year. There are 35 recognized heart defects, including HLHS, which is diagnosed in about 1,000 neonates annually. In HLHS, the left side of the heart does not develop properly while the baby is in the mother's womb. The parts of the heart usually affected are the mitral valve, ventricle, aortic valve, and aorta. In a normal heart, red blood returning from the lungs flows from the heart's left upper chamber through the mitral valve to the left ventricle, where it is pumped through the aortic valve and out to the body. In babies with HLHS, the left side of the heart is underdeveloped and cannot pump enough blood to meet the body's needs.

Without treatment, 95 percent of babies with HLHS die within the first month of life. Treatment means either a three-stage heart surgery or a heart transplant. Dr. Boucek and Dr. Bright were interested in developing a nonsurgical, palliative (first-stage) procedure that would provide adequate blood flow to body tissues yet not compromise the long-term health of lung tissue. Their procedure has the additional advantage of facilitating and improving outcomes of the necessary additional surgeries used for long-term management of HLHS (second- and third-stage correction or heart transplant).

The new procedure takes advantage of a newborn's basic physiology. There is a fetal blood vessel joining the pulmonary artery and the aorta called the ductus arteriosus (DA). This vessel is present in all babies but normally closes within the first few days of life. The ductus arteriosus allows the blood to flow from the right ventricle out to the body, bypassing the nonfunctioning fetal lungs and left side of the heart. After birth, this fetal

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"The faculty and staff at the James L. Voss Veterinary Teaching Hospital made a revolutionary treatment for infants with lethal heart disease possible. I can say with certainty that, without the cardiac program at the CSU-VTH, we would not be successfully treating these kids today."

Thanks to NASA Grant, Cancer Biology Group Improving Basic Understanding of Leukemia

Almost a year ago, the Cancer Biology Group, housed within the Department of Environmental and Radiological Health Sciences, received a competitive grant from the National Aeronautics and Space Administration. The five-year, $9.7 million grant is helping researchers develop a better understanding of radiation risks to astronauts during deep-space travel and prolonged stays in space.

But the grant also is helping researchers understand the pathology of acute myelogenous leukemia (AML), one of the most common types of radiation-induced leukemia.

"Not many people are going to be venturing out into space, but the NASA grant gives us a real opportunity to study in depth the mechanisms for leukemia development, and that means improved diagnosis and treatment for people here on Earth," said Dr. Robert Ullrich, Director of the Cancer Biology Group and of research for the Flint Animal Cancer Center. "Over the long run, this research will have much wider applications, including the development of bio-markers for earlier leukemia diagnosis and a greater understanding of the molecular changes that occur during the development of leukemia, which in turn could lead us to develop unique therapies."

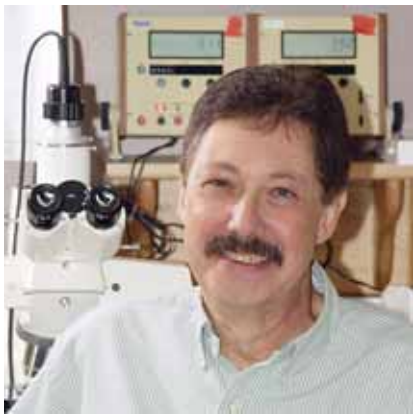
NASA's concern is first and foremost the safety of astronauts participating in the agency's space program, particularly those who may be traveling to Mars (a two- to three-year journey) or those staying for prolonged periods at the International Space Station. Though spacesuits and spacecraft keep astronauts alive and protect them from the near-zero gravity of space, they provide little protection from the unseen dangers of radiation.

"Space presents an unusual radiation environment, in which astronauts are exposed to energetic heavy ions that are more effective in causing lots of radiation effect compared to what we have here on Earth, where our atmosphere protects us from these particles," said Dr. Ullrich. "One concern of this exposure is the possibility of damaging cells and setting up the body for the development of leukemia in ensuing years. Astronauts have accepted the acute risks of space flights – accidents or equipment failure that may cost them their lives – but having a life-long risk, a time bomb of sorts, is unacceptable to them or the NASA program."

The only way to study these heavy ions on earth is to create them in large accelerators, as Dr. Ullrich and his team are doing at the Brookhaven National Laboratory on Long Island. Once the heavy ions are generated, researchers expose specially bred mice to the ions at varying doses. The researchers use mouse models to compare the effects of high-energy compounds, like the iron particles found in space, to the effects of the gamma rays most frequently associated with radiation-induced leukemia. These gamma ray studies come from patients with radiation exposure from cancer treatment, as well as older, existing data from survivors of the Nagasaki and Hiroshima atomic bombings at the end of World War II.

"We are exploring the cellular mechanisms affected by radiation exposure on a number of different levels so we can extrapolate animal studies to calculate human risk," said Dr. Ullrich. "We are looking at molecular changes in mouse models and comparing these to similar changes in people exposed to radiation during cancer treatment."

The Cancer Biology Group is partnering with research teams at the M.D. Anderson Cancer Center and the Baylor College of Medicine, both in Houston. One important part of the group's work is developing new mouse models to study radiation effect. This includes reconstituting an immune-compromised mouse's bone marrow using human cord blood so that living human blood cells can be studied in an animal model. Being able to study energetic heavy ion and gamma ray exposure on human blood cells in a living system will be invaluable, Dr. Ullrich said.



Dr. Robert Ullrich

"This grant will enable us to develop a better understanding of leukemia, especially in cancer patients where therapeutic radiation can lead to leukemia as a secondary cancer," said Dr. Ullrich. "We also will develop a clearer understanding of the long-term risks of radiation exposure. This wouldn't be happening without ambitious research programs, like those funded by NASA. What is true of NASA in general is that we as a society have reaped so much benefit from the space program because of the needs of NASA complementing the needs of expanding biomedical research."

Dr. Ullrich expects to see data coming out from the initial mouse studies in late winter or early spring. The Cancer Biology Group and its partners also will be meeting this fall to further plan the course of their investigations. The Cancer Biology Group is one of 14 Colorado State University Programs of Research and Scholarly Excellence, one of five such programs located within the College of Veterinary Medicine and Biomedical Sciences. ■

Researcher Uses Clinical Cases to Focus Investigative Work in the Laboratory

Malignant catarrhal fever was an illness Dr. Rob Callan had seen only once in 10 years while working as a large animal veterinarian. When he arrived at CSU, however, he saw several cases over a six-month period and became intrigued by the disease's seemingly greater prevalence in Colorado. There weren't many answers as to why or even basic information on transmission and viral properties, so Dr. Callan took the disease from clinic to laboratory with a variety of collaborative research projects.

In 2002, Dr. Callan was faced with a similar situation, though this time with a disease that had a worrisome impact on animals and humans and had gained national attention. West Nile virus was gaining a foothold in Colorado and, though alpacas and llamas originally were thought to have lower rates of infection and illness, the Large Animal Clinic soon began to see critically ill animals succumbing to the ravaging effects of the virus. Clinical work once again led to laboratory investigations and launched projects focusing on vaccine testing, transmission paths, and infection rates, particularly in alpacas for which very little information on WNV was available.

"I spend 26 weeks out of the year on hospital duty and get to see cattle, sheep, goats, bison, and llamas – even a baby moose – so my research focus stems from what I see in the clinics," said Dr. Callan, an Associate Professor in the Department of Clinical Sciences and faculty member in the Integrated Livestock Management (ILM) Program. "I enjoy being able to bridge the gap between clinicians and researchers, working both sides toward a common goal of improving animal health."

Dr. Rob Callan

Dr. Callan's initial research with malignant catarrhal fever (MCF) examined transmission of the virus, a form known as sheep-associated MCF in the United States (in Africa, the form is wildebeest-associated MCF). Sheep are asymptomatic carriers of the virus, infecting cattle or bison when they come in contact or herds are near each other. Epidemiological studies showed that cattle and bison appear to be dead-end hosts, developing a fatal illness but rarely if ever transmitting the virus. Dr. Callan's research team also showed that, in some circumstances, infected cows never develop signs of disease. Questions being examined now include why some animals develop symptoms and others don't; what triggers onset of the disease; and how does the virus disregulate the infected cells? The team also is in the process of developing cell culture systems for the virus to help identify and pick apart the virus/host interactions and how they cause disease. Successfully developing a cell culture system also will aid in vaccine development.

"MCF is generally a fatal disease when an animal becomes symptomatic," Dr. Callan said. "We have seen numerous outbreaks in dairy herds and on feedlots, and the disease is particularly devastating to bison populations, often wiping out an entire herd. We hope with continued progress at CSU, especially with the development of a cell culture system, we will be able to advance the prevention of MCF."

Dr. Callan works collaboratively on MCF with Dr. James DeMartini, a Professor in the Department of Microbiology,

"MCF is generally a fatal disease when an animal becomes symptomatic. We have seen numerous outbreaks in dairy herds and on feedlots, and the disease is particularly devastating to bison populations, often wiping out an entire herd."

Immunology and Pathology; and with Dr. Tshida Tsibane, a veterinarian from South Africa working toward her doctoral degree and supported with a joint fellowship from the USDA and South African government.

Another collaborative research project for Dr. Callan is his work with Dr. Richard Bowen, a Professor in the Department of Biomedical Sciences, on West Nile virus, one more case of clinical work focusing Dr. Callan's research programs.

"In 2002, West Nile virus just started to get into Colorado," said Dr. Callan. "States east of us had very few reports of WNV in llamas, alpacas, and even sheep and cattle. In 2003, we were getting calls from llama and alpaca owners concerned about WNV and their animals. At the time, we didn't recommend vaccinations because, one, vaccines had not been tested in these animals and, two, it didn't look like these animals were susceptible."

In late summer of 2003, however, the situation changed. The Veterinary Teaching Hospital admitted an alpaca with acute cranial neurological signs that died within 24 hours and subsequently tested positive for WNV. More cases showed up, and researchers quickly realized that the WNV situation was different in Colorado, possibly because one particular mosquito – *Culex tarsalus* – is more prevalent and particularly good at transmitting the West Nile virus. In December 2003, a vaccine study was initiated in alpacas and llamas. Drs. Callan and Bowen are now testing serum samples to determine seroconversion rates and are also looking for adverse effects of the vaccine in llamas and alpacas, including pregnant alpacas and their offspring (to date, none have been found). Further evaluation of vaccine efficacy, in collaboration with Dr. Michelle Kutzler from Oregon State University, is being planned for the future. Drs. Callan's and Bowen's WNV work is supported in part by donations from the Alpaca Breeders of the Rockies and individual private alpaca breeders.

"What we've learned during the past two years is that WNV can be devastating to alpaca herds – every one of our teaching llamas at CSU became infected, though interestingly none were symptomatic – so we are interested in vaccine studies," said Dr. Callan. "We also want to understand basic questions of why rates of infection are so high here, why some animals get sick, and why others show no symptoms. This work, and work on MCF, couldn't be done without the James L. Voss Veterinary Teaching Hospital, and it couldn't be done without the ties to basic researchers like Dr. Bowen and Dr. DeMartini. The hospital brings an immediacy to the research, and the research brings us closer to preventing and treating illnesses that are not only affecting animals, but humans as well." ■

Vaccine Studies Raise Questions on Links to Kidney Disease in Cats

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are causing illnesses or the deterioration of a cat's kidney health. Dr. Lappin said much work remains to be done before associations like that can be made. In a grant recently funded by the Heska Corporation, a more in-depth approach should begin to provide some answers. Dr. Lappin and Dr. Jacqueline Whittemore will study which feline tissues react with anti-CRFK antibodies; determine the concentrations of CRFK proteins in all commercially available FVRCP vaccines; and determine if the presence of CRFK or feline kidney cell antibodies are associated with the development of particular illnesses in cats including kidney failure, uveitis, pancreatitis, and hyperthyroidism.

Concerns regarding overvaccination have led the American Association of Feline Practitioners to adjust the vaccine schedule for FVRCP to once every three years after the kitten series and one year booster. However, it is very important for each cat to be treated as an individual. Owners should bring their cats to their veterinarian every year for a health check-up and to determine an optimal vaccination plan. In other studies, Dr. Lappin worked closely with the Heska Corporation to develop a veterinary-market blood test so veterinarians can test patients to see if vaccine boosters are necessary at the time of a cat's annual check-up rather than just arbitrarily vaccinating.

For additional information on these studies or if you are interested in finding out how you can support Dr. Lappin's work, contact Dr. Lappin at (970) 221-4535. ■

Minimally Invasive Surgical Techniques Lead to Better Outcomes

In the 1960's sci-fi flick, *Fantastic Voyage*, a group of scientists and their transport vehicle are shrunk to microscopic size and dispatched to repair a deadly blood clot in the brain of a brilliant scientist. This cinematic vision of minimally invasive surgery has not yet come to pass, but shrinking medical instruments and forays inside the body with specialized equipment are enabling surgical procedures that not so long ago seemed the stuff of movie fantasy.

Dr. Dean Hendrickson, an Associate Professor with the Department of Clinical Sciences, is a pioneer in such minimally invasive surgery, generally known as endoscopic surgery, specializing in equine laparoscopy, in which a viewing tube called a laparoscope is used to see inside the abdomen and pelvis. High-precision surgical instruments are used along with the laparoscope to perform specific procedures in the pelvic and abdominal areas, including corrections for cryptorchid horses (in which one or both testicles have not descended), ovariectomy (removal of the ovaries), and treatment of nephrosplenic ablation (one cause of colic in horses).

"The benefits of laparoscopy are smaller incisions, lower morbidity, and a faster return to function for our equine patients," Dr. Hendrickson said. "The downside is that laparoscopy requires specialized equipment and training and is a technically demanding field."

When Dr. Hendrickson arrived at CSU from the University of Wisconsin nine years ago, there was not a laparoscopy program in place. He had been trained on laparoscopic equipment and techniques while at the University of Wisconsin. As a large animal surgeon, he worked with small animal surgeons and human surgeons to develop new methods of treating conditions in horses that previously required large incision surgery and carried higher risk. After coming to CSU, Dr. Hendrickson dove in head first, ordering equipment and establishing a laparoscopy program for the Veterinary Teaching Hospital's equine patients.

"Laparoscopy has been around in veterinary medicine since the early 1970s, when it primarily was used in research," said Dr. Hendrickson. "In the early 1980s, it was starting to be used as a diagnostic tool, and in 1993, we started to see surgical applications. It quickly became appar-

> Two people typically work the equipment during a laparoscopy, one to move the camera and the other to do the actual procedure. Synchronicity between the two individuals is essential, as one provides the "eyes" and the other provides the "hands."

Surgeons at the James L. Voss Veterinary Teaching Hospital perform a laparoscopic procedure on an equine patient. The monitor in the background shows real-time images from the laparoscope.

ent that laparoscopy could dramatically improve the surgical outcomes for horses."

In standing laparoscopy, three or more small incisions are made in the horse's flank. One incision is for the laparoscope, with miniaturized camera and light, to provide images of the abdominal cavity, and the other incisions are for the surgical tools needed for the procedure. Two people typically work the equipment during a laparoscopy, one to move the camera and the other to do the actual procedure. Images from the camera are displayed on a monitor that the surgeon follows to complete delicate operations. Synchronicity between the two individuals is essential, as one provides the "eyes" and the other provides the "hands."

Cryptorchid castration was one of the first surgical procedures developed for equine laparoscopy. The standard surgery often was difficult at best, requiring general anesthesia, large incisions, and lengthy recovery times. In some cases, surgeons could not find the testicle in the abdominal cavity, and surgery had to be repeated. When Dr. Hendrickson developed the laparoscopy technique, standing horses could be operated on using local anesthetic and light sedation. Large incisions were replaced with three small ones, and rather than going in blind, the laparoscope enabled surgeons to locate and display on the viewing screen the testicle location in the abdominal cavity.

Dr. Hendrickson also has developed laparoscopic techniques for ovariectomy, decreasing pain and suffering, and the potential for complications in horses that must undergo this procedure. In addition, he has worked with new techniques to correct nephrosplenic entrapment of the large colon by performing nephrosplenic space ablation. In this condition, the large colon gets caught in a small trough between the spleen and the kidney and can cause the horse to colic. Traditional surgical corrections included a huge incision and removal of a rib. With laparoscopy, the colon is removed from the trough, and then the spleen is sutured to the peritoneum around the kidney to prevent a recurrence. Results so far show the procedure is 100 percent successful in preventing a recurrence of nephrosplenic entrapment.

> "We have owners come in who can't believe their horses have just had surgery – the horses look so good and have so much energy."

"It's just so amazing to be a part of this exciting work," said Dr. Hendrickson. "We have owners come in who can't believe their horses have just had surgery – the horses look so good and have so much energy. The availability of these techniques, and development of new laparoscopy protocols, means that we can continue to offer improved health care to our patients and help veterinarians bring these new technologies into their own practices."

When not treating his patients, Dr. Hendrickson works to advance the field of equine laparoscopy. He has ongoing research looking at ways to provide improved pain relief for cryptorchid horses during the laparoscopy procedure, as well as improved sedation techniques that will make it easier for veterinarians in private practice to administer; he has developed a knot-suture combination for laparoscopy; he uses laparoscopy extensively as a teaching tool so students can visualize anatomy when they are doing equine transrectal palpations; and he conducts regular continuing education courses in laparoscopy for practicing veterinarians. ■

Terminology for Minimally Invasive Surgery

- Endoscope: an endoscope is basically a camera mounted on a long thin lens with a cable and a light source. The first "endoscope" was thought to be used in the mid-900s A.D. by an Arab physician who used a short tube and a flame to examine the cervix of a patient.
- Endoscopy: the visual inspection of any cavity by means of an endoscope, allowing for surgery without having to make a large incision. Common forms of endoscopy include the following:
  - Laparoscopy: the visualization of the abdominal cavity. Laparoscopic surgery allows surgeons to use a laparoscope to see the surgical field and use specialized instruments to perform procedures in the abdominal and pelvic regions.
  - Thorascopy: the visualization of the chest cavity. Thorascopic surgery is used to assist in procedures of the heart and lungs.
  - Arthroscopy: the visualization of joints. Arthroscopic surgery typically is used to correct joint problems, particularly in the knees and shoulders, but also can be used in the wrists, ankles, and elbows. Arthroscopy is used commonly in the fetlocks, carpi, hocks, and stifles in horses. ■

Rare Disease Causes Researcher to Push Boundaries

Dr. Mike Weil doesn't treat patients. He doesn't develop drugs or new therapies. He doesn't diagnose illnesses or improve life expectancies. What he does is make many of these things possible. As a mouse geneticist, he is dedicated to developing mouse models that enable researchers to study diseased and normal systems, test drug and other therapies, and look at ways of improving diagnostic tools, including bio-markers for earlier detection and treatment of disease.

As a member of the faculty of the Department of Environmental and Radiological Health Sciences, a substantial portion of Dr. Weil's research work revolves around the Cancer Biology Group's NASA grant. But he is involved in other projects that may have a more immediate impact on breast cancer research and on those battling a rare disease known as ataxia-telangiectasia (A-T).

"A-T is a fatal disease that usually causes death in children by their early teens, mostly because of the neurodegeneration attributed to the disease," said Dr. Weil. "What we are working on now is the development of an animal model that will display neurodegeneration, a trait essential to our ability to test drugs that may be therapeutic for victims of A-T."

A-T is a "recessive" genetic disease because children must inherit a defective gene from each of their parents to develop the disease. Children with A-T appear normal at birth but begin to show the first signs of the disease in the second year of life, including poor balance and slurred speech caused by a lack of muscle control (ataxia). The cerebellum progressively degenerates, leading to a general lack of muscle control. Other symptoms include tiny red "spider" veins (telangiectasia), immunodeficiency with recurrent respiratory infections, a predisposition to cancer, and an extreme sensitivity to radiation (A-T children with cancer cannot tolerate therapeutic radiation). Currently in the United States, approximately 600 individuals are afflicted with A-T.

Part of Dr. Weil's work involves genetically engineering a mouse that has a lifespan long enough to develop the neurodegeneration that is a hallmark of the disease but to date has not been replicated in the mouse model. Dr. Weil and his colleagues currently are developing a "conditional knock-out" mouse model using specialized genetic engineering approaches that allow the mice to be completely normal, except for the brain (normal immune systems, normal physiological structure, etc.). These studies include three distinct populations: normal mice, mice that have one germline mutation (ATM heterozygosity), and mice with homozygous ATM mutations that will develop clinical A-T.

Dr. Weil and his colleagues wanted to know if women who carried a single defective A-T gene would be at a higher risk for breast cancer, especially given the susceptibility of A-T patients to radiation exposure.

"If we are successful in developing this model, we then will have the opportunity to test different therapeutic drugs that may help slow the progress of A-T or improve the quality of life for those suffering from A-T," said Dr. Weil. "While this is a rare disease, it is devastating to those families with children who are afflicted."

Dr. Weil notes that while A-T is not a public health issue because of the rarity of the disease, there is a connection between A-T and the risk of developing breast cancer that piqued his initial interest in the disease and definitely represents a public health issue. Mothers of children who have A-T have been reported to be at an increased risk for development of breast cancer. Dr. Weil and his colleagues wanted to know if women who carried a single defective A-T gene would be at a higher risk for breast cancer, especially given the susceptibility of A-T patients to radiation exposure. Previous studies by Dr. Weil's research group show that mice with a single defective copy of the A-T gene are susceptible to radiation-induced ductal dysplasia, a precursor to breast cancer.

"We began investigating this link, and our research showed that patients with breast carcinomas were more likely to have a variant in the ATM gene," Dr. Weil said. "We are just starting to explore the link between the ATM gene and relative risk of breast cancer, but it is an area that definitely needs additional studies."

Dr. Weil's breast cancer work – in conjunction with researchers at the University of Texas M.D. Anderson Cancer Center and the Center for Genome Information, Department of Environmental Health, University of Cincinnati – is sponsored by the Department of Defense Breast Cancer Research Program, the Cleberg Fund for New and Innovative Research, and the American Cancer Society. The most recent findings on the link between A-T and increased breast cancer risk were published in *Cancer 2004*; (100:1345-51 2004 American Cancer Society). His work on A-T is funded by the Ataxia-Telangiectasia Children's Project. You can learn more about A-T at the organization's Web site, www.atcp.org. ■

New Combined DVM/PhD Program Launched

The College of Veterinary Medicine and Biomedical Sciences has introduced a revised DVM/PhD program, designed to increase student success through a more structured curriculum, stronger administrative presence, and enhanced student support.

"There has been a combined DVM/PhD program for several years, but it was much less structured and therefore much harder for a student to navigate," said Dr. Jeffrey Wilusz, new Director of the DVM/PhD Program, and head of the Department of Microbiology, Immunology and Pathology. "My previous experience with an MD/PhD program showed the importance of a planned curriculum for these students and ongoing student support. What we've been able to do here is incorporate changes to optimize numerous aspects of the program. These changes include formalizing many aspects of the program, setting clear standards and expectations, and giving participating students better guidance."

In the first year of the seven-year program, students take PhD-related courses and participate in laboratory rotations so that they are able to select their research lab by the end of the first year. Students also are able to establish in-state residency during that first year. In years two and three of the program, students complete the first and second years of the Professional Veterinary Medical Program. Students then spend years four and five working on and completing their PhD, before returning to the PVM program to complete their final two years of veterinary school. During all the PhD and PVM years, students continue to maintain ties with their research laboratories.

In addition to their course and lab work, students also participate in group sessions every other week with Dr. Wilusz to discuss research, explore topics related to their course work, provide support to each other, and address concerns. These "journal club sessions" continue throughout the seven years and provide an important touchstone for students participating in the program.

"One of the goals of the College is to increase the number of veterinary students going into research and public health," said Dr. Lance Perryman, Dean of the College. "The new DVM/PhD program is a part of that effort, and we are very excited to see our first new students get on board this fall."

Two students, Tim Kurt and Katrina Easton, are starting the DVM/PhD program this fall. In addition, six students who were in the original program will be grandfathered in under the structure of the previous program while being able to take advantage of new features from the revised DVM/PhD program. Those students are Laura Austgen, Jennifer Mackler, Martha Shearin, April Davis, Julita Ramirez, and Jim Perry. ■

Cardiology Program at VTH Helps Improve Treatment of Children with Congenital Heart Defect

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vessel closes to separate the left and right sides of the circulation. Unfortunately, children with HLHS develop severe, fatal effects of inadequate perfusion to body tissues when the DA closes. Lamb studies showed that pediatric cardiologists could use a catheter to place a stent in the fetal vessel so that it cannot close. This, however, is not sufficient to prevent damage to the lungs from overcirculation.

"Dr. Boucek had us test a novel idea," said Dr. Bright. "We protected the lungs from overcirculation by placing flow-limiting devices Dr. Boucek had designed in both main pulmonary arteries. Because of the success of the lamb studies and follow-up work to further refine the novel flow-limiting devices, Dr. Boucek was able to begin to use this nonsurgical palliative approach on his patients at Children's Hospital, and since then, five other medical centers have adopted the procedure."

While the catheter approach does not repair the heart defect over the long term, it does buy time for infants who are on a wait list for heart transplantation and for those who will get a surgical repair for their heart defect, rather than transplantation.

"The surgery used in the first week of life prior to the development of this procedure was very high risk in neonates," said Dr. Bright. "I think we can say that it is also a very difficult and brutal surgery. The catheter approach minimizes the trauma to the child, while achieving the goal of sustaining blood flow and maintaining healthy lung tissue. I know transplant surgeons love this approach because they have more success with these patients in heart transplants."

For Dr. Boucek, the clinical dividends provided by the cardiology research team at CSU have been incalculable.

"The faculty and staff at the James L. Voss Veterinary Teaching Hospital made a revolutionary treatment for infants with lethal heart disease possible," said Dr. Boucek. "I can say with certainty that, without the cardiac program at the CSU-VTH, we would not be successfully treating these kids today." ■

VMBS Faculty Members Receive Honors

Dr. Stephen Withrow Named as University Distinguished Professor and Recipient of the Bonfils-Stanton Foundation Award

Colorado State University has named Dr. Stephen Withrow a University Distinguished Professor, the highest academic recognition awarded by the University. President Larry Edward Penley made the announcement in April during a special ceremony at the annual Celebrate Colorado State awards. Dr. Withrow also was named the recipient of the Bonfils-Stanton Foundation Award in May.

Dr. Stephen Withrow

A maximum of 12 current faculty members at the University may hold the rank of University Distinguished Professor, which is a permanent designation. To obtain the rank, faculty members are nominated through an extensive review process and must be approved by the current University Distinguished Professors.

Dr. Withrow, Director of the Flint Animal Cancer Center at the James L. Voss Veterinary Teaching Hospital, was named a University Distinguished Professor because of his impressive career in animal cancer research, including ground-breaking discoveries benefiting companion animals as well as humans. Among his many contributions to cancer research and treatment, Dr. Withrow developed a limb-sparing technique to treat osteosarcoma, a malignant bone tumor in dogs. The technique revolutionized treatment of the disease and has been widely adopted in human cancer centers.

The Bonfils-Stanton Awards, often described as the Colorado version of the Nobel Prize, are given annually to Colorado citizens for lifetime achievements in the arts and humanities, community service, and science and medicine. The award recognizes Dr. Withrow's work in developing pioneering cancer treatments for animals.

Twenty-five years ago, Dr. Withrow and Dr. Ed Gillete established the Animal Cancer Center, now the largest animal cancer center in the world. The center has trained more veterinary surgical, medical, and radiation oncologists than any other veterinary institution and is the only veterinary cancer group to have more than 25 consecutive years of funding from the National Cancer Institute.

The Animal Cancer Center has pioneered numerous surgical, radiation, and chemotherapy procedures for animals with cancer. The center treats up to 2,000 pets per year with cancer and handles a volume of 10,000 appointments. A 1998 campaign successfully raised $9.3 million to fund a new wing on the Veterinary Teaching Hospital, which became the new home of the Flint Animal Cancer Center.

In addition to directing the Animal Cancer Center at Colorado State, Dr. Withrow has maintained a commitment to work in the clinic, seeing patients as a surgical oncologist 50 percent of the time. This commitment provides a hands-on, personal involvement with the center. Dr. Withrow holds the Stuart Endowed Chair for Oncology and is the only veterinary fellow of the Musculoskeletal Tumor Society, a prestigious international society of elite orthopedic physician oncologists. He founded the Veterinary Cooperative Oncology Group, an association of 20 private practices and universities that cooperate in clinical trials. He is a charter member of the American College of Veterinary Internal Medicine Oncology board and is a board-certified member of the American College of Veterinary Surgeons, one of only three people in the nation to be board certified in both disciplines.

During his tenure at Colorado State, Dr. Withrow has established two endowed chairs and raised more than $20 million in private funds. His career has been recognized with the Gains award, the highest honor a clinical veterinarian can receive, from the national veterinary associations of two countries, Canada in 1978 and the United States in 1990.

In addition to his many commitments at Colorado State, Dr. Withrow has volunteered for 23 years as a counselor and fund raiser for the Sky High Hope Camp for children with cancer, earning him the Ronald McDonald House Volunteer of the Year award in 2003.

Expert in TB Research Receives Scholarship Impact Award

Dr. Ian Orme, a Professor in the Department of Microbiology, Immunology and Pathology and a world-leading expert in tuberculosis research, has received the 2004 Scholarship Impact Award, one of the University's highest awards and its honor for accomplishment in research. The award, given annually by Colorado State's Office of the Vice President for Research and Information Technology, recognizes one top faculty member whose scholarship has had major national and international impact.

Dr. Ian Orme

The award was presented in April at the all-University Celebrate Colorado State awards luncheon. The Scholarship Impact Award includes $10,000 to support Dr. Orme's research.

"Dr. Orme's vital research continues to have significant impacts at Colorado State and throughout the world. We are proud to present him with the 2004 Scholarship Impact Award," said Dr. Anthony Frank, Vice President for Research and Information Technology. "To say that Ian is a key member of our University would be a great understatement. Colorado State is fortunate to have such an intelligent, dedicated individual on our faculty, and millions of people throughout the world are fortunate that Dr. Orme is directing his impressive talents toward controlling, delaying and even preventing the development of TB."

Tuberculosis is the leading bacterial killer in the world, with 10 million new cases and three million deaths each year. It is resurgent in developing countries and, in America, in prison populations, among the homeless, and in HIV/AIDS-infected patients. A factor in its return, and one of particular concern to Dr. Orme, is that some strains are resistant to several anti-TB drugs. The Mycobacterium Research Laboratories, which are unique given the amount of expertise focusing on one problem, are part of the Infectious Diseases Program at Colorado State, a Program of Research and Scholarly Excellence.

Dr. Orme, previous director of the Infectious Diseases Program and the Mycobacterium Research Laboratories, is known internationally for his TB research and has made major contributions to understanding the mechanisms at work in immunity to tuberculosis. In recent years, Dr. Orme has developed various models for the study of TB that now are widely used in vaccine and drug screening, work for which he was appointed a Fellow of the American Academy of Microbiologists in 2002. In addition to TB vaccine development, Dr. Orme also heads a research team working on a separate seven-year, $3.4 million National Institutes of Health contract to screen the most promising TB treatment drugs.

Dr. Orme's TB-related work has generated more than $50 million in research support at Colorado State and led to several breakthroughs in the field. Additionally, he has published more than 200 papers in leading medical and science journals that have been cited more than 6,400 times. Last year, Dr. Orme and his colleagues were awarded a five-year, $3 million NIH grant to conduct a pioneering study to examine the long-term effectiveness and safety of tuberculosis vaccines. Dr. Orme and his team also have led groundbreaking studies examining broad-spectrum antibiotics to discover a drug that is effective in fighting latent tuberculosis without creating drug resistance.

Dr. Orme joined Colorado State University in 1986, after receiving his doctorate from the University of London and a postdoctoral fellowship at the Trudeau Institute.

Distinguished Professor Elected to American Academy of Microbiology

Dr. Patrick J. Brennan, a Colorado State University Distinguished Professor, has been elected as a Fellow of the prestigious American Academy of Microbiology. Dr. Brennan, a Professor in the Department of Microbiology, Immunology and Pathology, was honored for his important contributions to the fields of microbial physiology, infectious diseases, and molecular biology.

Dr. Brennan's primary research involves two bacterial diseases, leprosy and tuberculosis; he is renowned as a world leader in research related to both diseases. Dr. Brennan founded the Mycobacterium Research Laboratories at Colorado State in 1980 as one of the few basic research programs on leprosy and tuberculosis worldwide. The laboratories focus on immunology, synthetic and analytical chemistry, molecular biology, and genetics to develop new vaccines, diagnostic reagents, and drug targets for the diseases.

Dr. Patrick J. Brennan

Dr. Brennan's research focuses on the biochemical characterization of cell wall constituents and their assembly in mycobacterium. Understanding the structure of the complex mycobacterial cell wall, including the genes governing its construction and the enzymes synthesizing the wall components, has key implications for developing improved means of diagnosing and treating diseases caused by mycobacterium.

Fellows of the American Academy of Microbiology are elected annually through a highly selective, peer-reviewed process, based on their records of scientific achievement and original contributions that have advanced microbiology. There are now more than 2,000 Fellows representing 37 countries and all subspecialties of microbiology, including basic and applied research, teaching, public health, industry, and government service.

The mission of the American Academy of Microbiology is to recognize scientific excellence and foster knowledge and understanding in the microbiological sciences. The Academy is the honorific leadership group within the American Society for Microbiology, the world's oldest life science organization with more than 43,000 members. ■

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