Cancer in the cross hairs
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A registry to track tumors in pets may point to some of the environmental causes of cancer in both people and companion animals.

Most dogs and cats live simple lives. They share our homes and, whenever they can, the couch and the bed. But aside from a few table scraps and the exposure that some get to second-hand smoke, they don't share the consequences of the poor lifestyle choices that cause 40 percent of human cancers. When cats and dogs develop cancer, as many do, odds are that their disease is rooted in genetics or exposure to an environmental contaminant, or in the interplay of the two.

Rodney Page, professor of oncology and director of Cornell's Comparative Cancer Program, thinks that dogs and cats have a lot to tell us about the role that environmental toxins play in both animal and human cancers. "Any human epidemiologic study that looks at environmental contamination also has to account for tobacco use, diet, and alcohol consumption," he says. "Dogs and cats are not subject to all of the problems that humans inflict upon themselves. We're beginning to realize that cancer in companion animals may provide a vastly underutilized resource for cancer risk assessment in humans."

The Comparative Cancer Program recently received $20,000 from the State of New York to examine this possibility. The money will fund a pilot project to test the feasibility of establishing a statewide companion-animal tumor registry. The start-up funding was arranged by State Senator Michael Balboni (7th Dist.) and Nassau County Legislator Lisanne Altmann. Brian Rind, DVM '65, who practices veterinary medicine in Great Neck, New York, assisted in bringing the Cornell proposal to the attention of the legislators.

Researchers in the College and in the Program on Breast Cancer and Environmental Risk Factors (BCERF) within Cornell's Center for the Environment will use the funds to track geographic differences in the incidence of companion-animal cancers within two or perhaps three distinct areas, most likely in parts of Nassau and Tompkins Counties. "The goal is to choose sites within Long Island that complement the studies currently going on in people," explains Page. "We want to find a control site where the only difference in the incidence of cancer will be environmental, where there is some sort of carcinogenic exposure that can be studied."
The interest of the legislators and others stems from growing concern over the higher incidence of breast cancer in certain areas of Long Island relative to other parts of the state — which itself has a worse overall cancer mortality rate than 27 other states. "We know that the incidence of breast cancer is higher in parts of Long Island, but we don't know the causes," says Suzanne Snedeker, BCERF's associate director for translational research. "We suspect environmental chemicals because other studies have shown that environmental factors might explain up to 70 percent of breast cancer risk."

The task of identifying the source or sources of the problem on Long Island is complicated not just by lifestyle variables but also by the limited sample size and the long latency period — often 30 years or more — that can pass between exposure to a cancer-causing agent and the development of disease. The high mobility that has become a part of American life makes it even more difficult to tie location to incidence.

Comparing cancer data from dogs and cats to the information in the state's human cancer registry might help enormously in sorting out these confounding factors, Page believes. "The incidence of cancer in dogs is higher than in people," he says. "For some cancers, it's twice as high. Overall there are a lot fewer dogs than people, but if you add proportionately the amount of cancer that we estimate can occur in dogs to the cancer that occurs in people, then you may give additional meaning to the human data."

"There are a series of studies going on now to help us get answers about the higher incidence of breast cancer in parts of Long Island," explains Snedeker. "One is the Long Island Breast Cancer Study Project, a federal study of pesticides and other chemicals in breast cancer risk. Other efforts are going on through the New York State Department of Health. They have been doing a mapping project to look at breast cancer risk by zip code. They're also taking this several steps further to do environmental mapping using geographic information-systems technology to layer information. For example, what is the population? What are the locations of Super Fund sites and other

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**Most Common Cancer Sites for Estimated New Cancer Cases, U.S., 2002** *(Human data as reported by the American Cancer Society)*

<table>
<thead>
<tr>
<th>In Men</th>
<th>In Women</th>
<th>In Dogs</th>
<th>In Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Breast</td>
<td>Mammary</td>
<td>Lymphoma/Leukemia</td>
</tr>
<tr>
<td></td>
<td>30 %</td>
<td>50 %</td>
<td>30 %</td>
</tr>
<tr>
<td>Lung and Bronchus</td>
<td>Lung and Bronchus</td>
<td>Skin/Connective Tissue</td>
<td>Skin/Connective Tissue</td>
</tr>
<tr>
<td>14 %</td>
<td>12 %</td>
<td>30 %</td>
<td>30 %</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>Colon and Rectum</td>
<td>Testes</td>
<td>Testes</td>
</tr>
<tr>
<td>11 %</td>
<td>12 %</td>
<td>15 %</td>
<td>15 %</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>Uterine Corpus</td>
<td>Lymphoma</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>7 %</td>
<td>6 %</td>
<td>6-10 %</td>
<td>6-10 %</td>
</tr>
<tr>
<td>Melanoma of the Skin</td>
<td>Non-Hodgkin's Lymphoma</td>
<td>Hemangiosarcoma</td>
<td>Oral</td>
</tr>
<tr>
<td>5 %</td>
<td>4 %</td>
<td>7 %</td>
<td>3-5%</td>
</tr>
<tr>
<td>Non-Hodgkin's Lymphoma</td>
<td>Melanoma of the Skin</td>
<td>Oral</td>
<td>Bone</td>
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<tr>
<td>4 %</td>
<td>4 %</td>
<td></td>
<td>2-4%</td>
</tr>
<tr>
<td>Kidney</td>
<td>Ovary</td>
<td>Testes</td>
<td>Testes</td>
</tr>
<tr>
<td>3 %</td>
<td>4 %</td>
<td></td>
<td>15 %</td>
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<tr>
<td>Oral Cavity</td>
<td>Pancreas</td>
<td>Hemangiosarcoma</td>
<td>Hemangiosarcoma</td>
</tr>
<tr>
<td>3 %</td>
<td>2 %</td>
<td>7 %</td>
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<tr>
<td>Leukemia</td>
<td>Thyroid</td>
<td>Oral</td>
<td>Oral</td>
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<td>3 %</td>
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<td>3-5%</td>
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<tr>
<td>Pancreas</td>
<td>Urinary Bladder</td>
<td>Bone</td>
<td>Bone</td>
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<tr>
<td>2 %</td>
<td>2 %</td>
<td></td>
<td>2-4%</td>
</tr>
<tr>
<td>All Other Sites</td>
<td>All Other Sites</td>
<td>Mammary</td>
<td>Mammary</td>
</tr>
<tr>
<td>19 %</td>
<td>20 %</td>
<td>12 %</td>
<td>12 %</td>
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<td></td>
<td></td>
<td>Oral</td>
<td>Oral</td>
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<tr>
<td></td>
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<td>3-5%</td>
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places that might have had chemicals, like dry cleaning, old gas stations, old mechanic shops? Was the use of the land different in years past than it is now — was it used for agricultural purposes? What pesticides might they have used?"

"There's a lot of concern now, beyond pesticides, about the chemicals in our homes, gardens, workplaces, environment, in the air we breathe, that are risk factors for breast cancer," she continues. "If we can identify some of these chemicals through these types of mapping, that would give us clues to the environmental factors that we might be able to control, and we can reduce the risk of exposure. That's the ultimate goal, to reduce the risk of breast cancer and other cancers that are related to environmental chemicals."

Because cancer appears to develop more rapidly in animals than in humans, surveillance of tumor incidence in dogs and cats might provide earlier warning of environmental hazards — and a more rapid reading of the effectiveness of clean-up efforts. Furthermore, a dog's or cat's vulnerability to environmental carcinogens is potentially greater than ours. "Companion animals don't wear clothing," Page explains, "and they are in closer contact with chemicals applied to lawns or carpets, for example, or they are drinking contaminated water."

There are many computational and logistical complexities to be worked out in deciding where and how to proceed with the pilot study. Although federal law mandates the reporting of all human cancer cases to state-sponsored registries, cancer is not a reportable disease in companion animals. "It would be ideal," says Page, "to have certain assumptions made about how animals with cancer are going to be handled in a very strictly controlled region, so that every suspected lump gets biopsied, and that every biopsy gets sent to the same pathology laboratory, and we would have access to that pathology laboratory and to detailed information about the location of the animal."

"This animal tumor registry will be providing information that has not been developed in the past," he continues. "There have been other registries, but we have not been able to prospectively evaluate cancer risk related to environmental exposures. If we're successful in showing that animal cancers can be a sentinel for human cancers, we can expand this project to other parts of the state or other areas of the country that may be facing similar problems."

Cancer is the number-one natural cause of death in dogs, while in humans it takes second place behind heart disease. According to Page, approximately 80,000 humans, 15,000 dogs, and 9,000 cats develop cancer each year in the State of New York. Mammary-gland tumors account for 50 percent of all cancer in dogs; in women, breast cancer accounts for 31 percent of new cancer cases.

"The types of cancers that pets get are similar to the types of cancers that people get," says Page. "For all of the animals that get cancer, as 50 percent of dogs and cats will during their later years, the biggest unknown is the frequency of certain types of cancers. The benefit for pets will be that we will be able to establish guidelines for early screening programs — similar to mammography, prostate screening, and colonoscopy for humans — that may allow us to pick up cancers at a stage when we can do more for the patient. And knowledge of where these animals lived when they developed cancer can improve our understanding of the causes of cancer in all kinds of animals, including humans, and help to prevent their occurrence."
SPECIAL FOCUS: CANCER

Responses to radiation and chemotherapy, between dogs and cats. Although the two species are subject to many of the same types of cancers, their prospects for a successful treatment outcome can be quite different, according to assistant professor Kenneth Rassnick, a medical oncologist in the Cornell University Hospital for Animals. For example:

- Half the mammary-gland tumors in dogs turn out to be benign, while mammary-gland tumors in cats are usually malignant. While mammary-gland tumors account for 50 percent of all primary cancer cases in dogs as opposed to only 12 percent of primary feline cancers, many of the canine malignancies are treatable. In cats, however, mammary cancer spreads very aggressively.

- Mast-cell tumors are typically benign in cats, while in dogs they are very unpredictable and run the gamut from benign skin tumors to very malignant tumors.

- Osteosarcoma also doesn’t have the metastatic potential in cats that it does in dogs. Amputation will usually stop the cancer in cats. A dog with osteosarcoma has no better than a five-percent chance of long-term survival.

Cancer in cats

Everybody knows that cats are not dogs. Dogs don’t purr and they’re just so...obvious. But on the other hand, dogs and cats are both mammals with four feet and a penchant for cohabiting with humans. Once we get past some admittedly significant differences in behavior, allergenic potential, and athletic abilities, we should find the same basic biology, right?

Not when it comes to cancer. There are striking differences in biological behavior of tumor types, and also in responses to radiation and chemotherapy, between dogs and cats. Although the two species are subject to many of the same types of cancers, their prospects for a successful treatment outcome can be quite different, according to assistant professor Kenneth Rassnick, a medical oncologist in the Cornell University Hospital for Animals. For example:

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When the diagnosis is cancer, cats should not be treated like dogs.

- Dogs with soft-tissue sarcomas respond very well to a combination of surgery and radiation. In cats, long-term survival is not very common, even with radical surgeries and radiation therapy.

- Primary lung tumors in dogs may not
cause symptoms for years, and when they do they can be treated. In cats, they are very aggressive and very malignant; survival time with surgery is generally around six months.

- Ocular melanomas in dogs are usually benign; in cats, they grow very rapidly and commonly metastasize to the lungs, brain, and other vital organs.
- Oral squamous-cell carcinoma in dogs responds well to radiation therapy. In cats, the disease is almost impossible to control with radiation alone.

Dogs and cats can also differ substantially in their responses to treatment. Dogs can sustain more severe reactions to radiation treatment than cats. Some chemotherapy drugs that are well tolerated in dogs can cause life-threatening side effects in cats, and vice versa.

For instance, Cisplatin, a chemotherapeutic agent used to treat solid tumors, works very well in dogs. Cisplatin must never be given to cats, however, because it can cause irreversible, even fatal lung damage. Carboplatin, a related drug, is safe to use systemically in cats and widely used, but almost no studies of its clinical activity in cats have been published.

That dearth of data is not limited to Carboplatin. “In terms of our knowledge of how to treat their cancers, dogs are probably ten years ahead of cats,” says Rassnick. “These drugs have all been tested in dogs, but for some reason the work hasn’t been done yet in cats.” Rassnick is working to fix that.

The oncologist has been evaluating a combination protocol of Carboplatin and Doxorubicin, which is a significant component of many chemotherapy protocols for cats, in order to establish the maximum safe and effective dosing schedule. Doxorubicin shows a broad spectrum of activity against a wide range of cancers including lymphoma, mammary and other carcinomas, and sarcomas, but high doses can cause cumulative, irreversible cardiac damage in dogs, especially boxers, Dobermans, and giant breeds. Cats are susceptible to kidney damage with large cumulative doses, but not heart failure.

Rassnick has also been studying Ifosfamide, a drug that has shown significant activity against soft-tissue sarcomas in humans. In humans it also has major anti-tumor activity against lymphoma, germ-cell tumors, and lung carcinomas. Rassnick has completed a two-year trial, focused on cats with vaccination-site sarcomas, to establish a safe dose. He has determined that cats can tolerate 900 mg/m², a much higher dose than the 375 mg/m² that can safely be given to dogs. It seems that cats can be safely treated every three weeks.

Although the phase-one safety trial was not intended to study efficacy, Rassnick saw some “dramatic” results among the 29 hospital patients he treated with Ifosfamide. Now that he has established the limits of safe use, he is evaluating the drug’s effectiveness in cats with measurable vaccination-site sarcomas. So far he has studied more than 50 cats. He has not evaluated all the results yet, but he says that this is “clearly an active drug.” He considers it likely that Ifosfamide will be added to the arsenal used to fight these devastating tumors in cats.

Rassnick thinks that these and other new drugs and combinations of drugs show very exciting promise in the treatment of feline cancers. More work must be done to evaluate their effectiveness, but he is certain that they will change the future of our ability to manage many types of cancers. Still, the best answer for cats, as for dogs and as for humans, will be to prevent cancer from developing, or at least from proliferating, in the first place.

“The future will be more about control, prevention, and early diagnosis. Hopefully our work will change from treating a cat with a terrible cancer burden to preventing that cancer or diagnosing it at an early stage when it will be possible to intervene effectively. The focus will be switched to defining cats that are at risk for cancer and getting them treated at a pre-malignant stage whenever possible.”
All cancers — whether slow-growing and localized or aggressively metastatic — get their start in the same way. Somewhere in the body, a single gene in a single cell mutates and malfunctions, and the now-cancerous cell begins inexorably to divide and multiply.

Other changes in other genes follow at different phases of tumor formation, with the result that a variety of abnormal proteins may be at work in one malignant tumor. For this reason, many have thought that trying to remedy any one gene defect would be too simplistic an approach to prove effective in eradicating a tumor. Alexander Nikitin, an assistant professor in the Department of Biomedical Sciences, takes a different view.

“It is becoming more and more clear,” he says, “that, despite many different effects on tumor formation, many tumors have a single driving force — a single gene alteration that really is important for all stages of tumor formation.”

Nikitin bases this assertion on his findings about Rb, the much-studied retinoblastoma gene, which is known to have a role in a variety of cancers, including osteosarcomas and tumors of the mammary gland and prostate. Rb expression is essential to preventing runaway cell proliferation and promoting normal cell differentiation. Nikitin demonstrated that mice having only one copy of the Rb gene instead of two uniformly develop a pronounced and fatal syndrome of multiple neuroendocrine neoplasia. Most ultimately develop metastatic lung cancer.

He has also shown that restoring the missing gene function not only prevents tumors from forming but dramatically suppresses existing metastases. More exciting still, he has demonstrated this effect not only through transgenic manipulation, but by delivering human Rb (denoted as RB) to the lungs of Rb-deficient mice via injection into their bloodstream, an approach with potential clinical applicability for humans and animals.

The intravenous gene replacement therapy has been accomplished through the use of a very new technique developed by Leaf Huang, a collaborator in the Laboratory of Drug Targeting at the University of Pittsburgh School of Medicine. LPD, which stands for lipid-entrapped, polycation-condensed DNA complex-mediated gene transfer, is a system for transporting genetic material to cells. The vehicle used is a liposome, a fluid-filled bubble of fatty material that is commonly found in some types of cells. The liposomes used in Huang’s work with Nikitin were chosen for their tendency to migrate from the blood-
stream to the lungs, where they were taken up into tumor cells at a much higher rate than into neighboring normal lung cells.

These findings, published in the Proceedings of the National Academy of Sciences in 1999, demonstrated for the first time that correction of a single gene defect could reverse the development of cancer. Nikitin estimates that perhaps a dozen scientific papers have been published since 1999 showing a primary role in tumor formation for one gene or another, but points out that all of them have been oncogenes — genes that cause cancer by activation and overexpression of their protein product. Rb, on the other hand, appears to be a genuine tumor suppressor.

"What are usually referred to as tumor-suppressor genes are really susceptibility genes," Nikitin explains. "These cause cancer by inactivation — failing to do their job, for example of repairing DNA. Inactivating these genes and then putting them back does not usually cure the cancer that develops, because they can only prevent the cancer from developing in the first place. But with Rb we have been able to demonstrate that, even at a late stage of metastasis, you can fix this one gene and have a dramatic effect."

P53, a gene that controls DNA damage and arrests cell growth and proliferation, is also under intense scrutiny in Nikitin's laboratory. As with Rb, p53 protein expression has been found to be abnormal in a majority of cancers. "Seventy percent is a very, very conservative estimate of the number of cancers in which at least one of these two genes plays a role," he says. "Some are now saying 90 percent." Many tumors, such as soft-tissue sarcomas, lack both Rb and p53, which Nikitin thinks might explain the notable aggressiveness of these tumors. According to Nikitin, the Rb and p53 genes also malfunction in about 95 percent of cases of small-cell lung cancer, a type that accounts for 15 to 20 percent of all lung cancers. Since coming to Cornell he has been developing mouse models in which to examine the effects of p53.

Nikitin says that LPD has been tried with some preliminary success in human trials with p53. Human trials with RB have also been contemplated. "The retinoblastoma gene both prevents and suppresses tumor formation. This is the promise of gene therapy," he says. "This really encourages us to seek more simple, straightforward approaches to gene therapy. And if you put this gene together with p53, you'll probably have an even better effect."

Stay tuned for further breakthroughs.

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**a model of inspired technique**

The key to studying the effects of Rb has been to devise methods to control expression of its associated protein with exact precision. Early transgenic studies of Rb showed that deleting the gene altogether from a mouse embryo caused fetal death. Creating mice with just one copy of the gene demonstrated that Rb deficiency had a role in cancer development, but a more sophisticated system was needed to pinpoint its effects in specific tissues and at specific ages and stages of malignancy. The techniques that Nikitin has used in designing his mouse models are as remarkable as the results he is achieving.

Nikitin began laying the groundwork for his present Rb studies nine years ago as a postdoctoral fellow at the University of Texas Health Science Center, working in the laboratory of pioneering Rb researcher Wen-Hwa Lee. By the time he arrived at Texas he had already earned a medical degree and a PhD in pathology in his native Russia and trained for an additional six years as a research associate in the West German Cancer Center at the University of Essen Medical School. He left Germany having established his expertise...
in developing advanced mouse models through the use of embryonic gene-transfer techniques.

A major technological advance that Nikitin adapted was the discovery by Gossen and Bujard, published in 1992, that the antibiotic tetracycline could be used to control gene expression in transgenic animals. This is done by inserting into a study embryo's DNA a custom-designed DNA construct that includes a tetracycline-responsive gene fragment fused to another gene sequence, called a promoter, that is selected for its ability to control activation of the gene of interest. When tetracycline is added to (or removed from, deletion in transgenic animals. This is done by inserting into a study embryo's DNA a custom-designed DNA construct that includes a tetracycline-responsive gene fragment fused to another gene sequence, thereby knocking out gene expression.

Nikitin was among the first to implement tetracycline regulation and show that it worked in mice. By administering tetracycline, he and his colleagues suppressed expression of the human RB gene, with the effect that the mice had only one functioning Rb gene instead of two. The animals developed cancer as expected. When the tetracycline was withdrawn, the human RB gene became operational and the tumors began to subside.

Another technical tool that is fundamental to Nikitin's transgenic work is the Cre-loxP recombination system. Since coming to Cornell, Nikitin and his colleagues have successfully applied his tetracycline and Cre/loxP combination system to the study of neuroendocrine neoplasias in mice. These mice carry one copy of the mouse Rb gene and one copy of loxP-flanked human RB that is linked to the tetracycline switch and a series of tissue-specific molecular switches controlling the scissor action of Cre recombinase.

In addition to the neuroendocrine cancer model, Nikitin has developed transgenic models for breast cancer and soft-tissue tumors. His laboratory is now preparing models that can be used to study ovarian and prostate cancer. Based on these models his group will characterize and compare the early stages of cancer development associated with inactivation of p53 and Rb in different cell lineages.

This work is aided by the use of extremely advanced technologies such as laser microdissection, which can cut out and collect a single cell from a microscope slide, and multiphoton fluorescence microscopy, an astounding development by Cornell physics professor Watt Webb that is allowing the researchers to image cancer progression at the cellular level, in real time, in living animals. The ultimate goal of this work will be to design molecules that can target tumor cells and interfere with their functioning.

In addition to this work, Nikitin is developing a refined version of the tetracycline switch-Cre/loxP mouse that he can offer to others in the cancer research community. This mouse can then be bred to others that carry whatever Cre/loxP-flanked gene inserts scientists wish to study by use of conditional knockout techniques.
Cancer research everywhere at Cornell can now benefit from an idea born in the Veterinary College: a new high-tech facility for recombinant protein expression.

In the molecular realm of biology, function follows form. The shape of a protein molecule — the way its amino-acid chain twists and loops — does as much to influence its biological activity as its amino-acid sequence. For a protein implicated in the development of cancer, determining its three-dimensional structure is critical to understanding how it interacts with other molecules — information that might suggest targets for molecular intervention.

Solving a protein's structure, however, is a very difficult and specialized process. Before the structural determination itself can be carried out, one must have a large quantity of pure protein — about 40 milligrams. The protein is obtained by inducing its expression, or synthesis, in an appropriate system of cultured cells. The expressed protein must then be purified — separated from the other 99 percent or more of polypeptides that the cells produce naturally. The expression and purification process poses a sizeable obstacle for the majority of laboratories that lack the equipment and skills to perform this kind of work.

For many cancer researchers across the Cornell campus, the solution has been to join forces and create a centralized resource for recombinant protein expression. Led by Richard Cerione, the Goldwin Smith Professor of Pharmacology and Chemical Biology; Danny Manor, an assistant professor in the Division of Nutritional Sciences; and Professor Rodney Page, director of the Cornell Comparative Cancer Program, the group has won a five-year, $986,000 grant from the National Cancer Institute to establish a facility to perform the high-level procedure for any laboratory that needs it. The facility's services will also be available to researchers from the Weill Medical College and its Tri-Institutional Collaboration partners, Rockefeller University and Memorial Sloan-Kettering Cancer Center.

The program is directed by Cerione, who holds joint appointments in the Veterinary College's Department of Molecular Medicine and in the Department of Chemistry and Chemical Biology in the College of Arts and Sciences. Manor, who implemented many of the methodologies for high-level recombinant protein expression as a postdoctoral fellow in the Cerione laboratory, directs the operation of the facility. A faculty advisory committee made up of core users from each of the major par-
ticipating research areas and departments — Molecular Medicine, Nutritional Sciences, Molecular Biology and Genetics, and Chemistry and Chemical Biology — will serve as gatekeepers for other researchers wishing to make use of the laboratory's services.

"The call is to go throughout the whole campus and draw in people from different departments and different disciplines to help them move faster towards getting to the molecular information that's cancer-relevant," says Cerione. "This facility is sort of a convergence point for that."

Of the 15 research scientists participating in the grant, 10 are working on different aspects of signal transduction and cell biology related to cell growth. Four are structural biologists who will use the proteins identified by those core users and others to perform structural determinations by means of X-ray crystallography or nuclear magnetic resonance spectroscopy. Cerione, with one laboratory in Molecular Medicine and another in Chemistry and Chemical Biology, has groups engaged in both ends of the process. In addition to Cerione and Page, five other faculty members from the College of Veterinary Medicine — Alex Brown, Jun-Lin Guan, Robert Oswald, Bendicht Pauli, and Andrew Yen — are signed on as core users of the facility.

The Recombinant Protein Expression Laboratory operates in close association with the Comparative Cancer Program, says Manor. "The Cancer Program provides the physical and conceptual framework for clinical testing of intervention strategies that originate from basic research," he explains. "For example, proteins that affect cell growth can be identified by cell biologists, purified by the protein facility, and their structures solved by structural biologists or chemists. Based on these structural insights, strategies to alter the protein's function may be devised and, in turn, tested in animal cancer models. In parallel, genetic aberrations in these proteins can be screened in mice and in the large number of cats and dogs seen as cancer patients by the oncology service of the Cornell University Hospital for Animals."

Recombinant proteins are typically expressed in bacterial cells (E. coli), an expression system that has been used for many years. The advantages of this method include the amount of recombinant protein that can be expressed in such a rapidly proliferating organism and the relative ease of separating a recombinant protein from the small number of other proteins naturally produced by the bacteria. The Recombinant Protein Expression Laboratory also has the capability to express proteins in insect cells, a new and more technologically demanding system that has the advantage of producing proteins with some of the modifications involved in cell signaling. Very few individual laboratory groups have the resources or expertise to employ this system.

Manor and Cerione also have a far more ambitious goal in mind. They intend to develop a system for expressing proteins in mammalian cells, a method that has not yet been applied in a successful structural determination. Manor, however, has been successful in using this method to produce milligram quantities of one protein to be used for structural analysis, and he and Cerione are confident that the scale-up to mammalian cell systems will be feasible within a few years. In addition to more closely replicating human or animal signaling proteins, mammalian cells offer the tantalizing opportunity to isolate these proteins as they go about their normal business in complex with other factors that might not exist in insect cells.

While the purpose of the facility is to further cancer research, Cerione sees the potential to create much broader connections. "Chances are that virtually anything molecular that most people are working on in the life sciences is going to be linked to cancer," he says. "Molecules are all linked in one way or another to what cells do; these things are all synchronized and coupled. This program provides a further mechanism to draw these disciplines together towards a common, important biomedical question. This is a concrete example of everything that the Life Sciences Initiative at Cornell is striving to do."

Richard Cerione knows a thing or two about G (or GTP-binding) proteins, a family of essential proteins that act as molecular switches to turn on and off cellular signaling pathways. His laboratories — one in the College's Department of Molecular Medicine and the other "down campus" in the Department of Chemistry and Chemical Biology — have been studying one such protein, Cdc42, for more than a dozen years. In that time they have gone from identifying, cloning, and sequencing it to mapping its three-dimensional atomic structure in complex with GDI, a key regulator of the protein, and are continuing their efforts to identify the cellular regulators and targets of this important protein.

Cerione has a particularly good reason to be interested in Cdc42 and other
G proteins. "When those switches are broken," he explains, "when a mutation occurs so that those switches aren't working properly, these pathways go awry, and often that ends up causing cancer."

Cerione, the recently named Goldwin Smith Professor of Pharmacology and Chemical Biology, got intrigued a few years ago by what appeared from its functioning to be another new G protein. "But when we purified the protein and obtained an amino acid sequence," he recalls, "we found out that it was actually a member of this family of enzymes called transglutaminases. I had no idea what these enzymes were. We were looking for a GTP-binding switch, and we ended up coming into a family of what seemed to me to be somewhat obscure enzymes."

G proteins tend to look a lot alike, says Cerione. " Virtually all G proteins that act as these switches have a very conserved amino-acid sequence. You can just look at the primary sequence and say, That's a G protein," he says. "Once you have the atomic structures, you can see how those amino acids are working just right to make them GTP-binding proteins."

So how do you make sense of a protein that behaves like a G protein but belongs to a very different family of enzymes? If you have the rare expertise and resources that Cerione has assembled in his two laboratories and in his collaborations with Jon Clardy, the Horace White Professor of Chemistry, you find out what it looks like by determining its three-dimensional atomic structure. Cerione, Clardy, and chemistry postdoctoral associate Shenping Liu have now done that, solving the molecular structure of TG, as the transglutaminase is called, in complex with GTP's molecular alter-ego, GDP. This considerable achievement, which was reported in the February 26, 2002 issue of the Proceedings of the National Academy of Sciences, is the culmination of a long and difficult process of expressing the protein, crystallizing it properly, and mapping its structure in Cornell's high-energy synchrotron source with the use of X-ray diffraction.

TG is so far the only transglutaminase that has been found to bind GTP and to have a role in pathway signaling. Transglutaminases had been studied in the past, but for very different reasons. They were known to be enzymes that catalyze the cross-linking of proteins in a process called transamidation.

"A search of the old literature revealed that GTP regulates this process of transamidation," says Cerione, "but typically TG has been attributed to biological activities that wouldn't be thought of as fundamental, but instead as rather specialized. Now we're beginning to suspect that this transglutaminase is involved in a fundamentally important process in cell differentiation."

Because TG had been observed to be present at higher levels in cells undergoing apoptosis, or programmed cell death, it was thought to have a direct role in causing that death. But Cerione has found, in research done over the past several years with postdoctoral fellows Jason Boehm and Marc Antonyak, graduate student Joe Washlag, and former laboratory members Carolyn Coombs and Ugra Singh, that quite the opposite is true: TG is apparently called up to protect cells from dying when they are under stress.

The researchers have found that TG is summoned to the aid of Rb, the retinoblastoma gene product, to protect it from attack when a cell stops growing and differentiates. In a process regulated by GTP binding, TG prevents the degradation of Rb by modifying it through transamidation.

"Rb is a cell-cycle checkpoint protein," Cerione explains. "When cells grow they go through a cycle of phases to tell them to keep growing. Rb typically ensures that cells are going through the cell cycle at just the right pace, and just when they're supposed to."

For cells to stop proliferating and become specialized, as brain cells, for instance, they have to undergo cell-cycle arrest. This is a perilous point in the life of a cell; along with the signals they get to stop growing, Cerione says it appears that they also get messages telling them to self-destruct. "And when cells are determined to die, one of the things they try to kill first is Rb."

So TG performs a very valuable service. But in the tangled web of protein synthesis, good proteins can be turned to bad purposes. "Where this starts to get interesting for cancer," says Cerione, "is that it appears now that there are cancer cells that upregulate TG. In some of these cancer cells, TG is being called up too much. So those cells then become especially hard to kill."

"Now that we have the structure of TG and can appreciate how guanine nucleotides binding to this part of TG influence the enzyme activity, we can start to make predictions about the kind of molecule that might inhibit this activity," says Cerione. "We would like to understand enough about how TG works to come up with an inhibitor that would keep TG silent in those cancer cells, or at least tone down its activity, and make those cancer cells susceptible to dying. Having this structure also tells us a lot about what other kinds of new switches might be out there and how we might have to intervene with those switches."

When asked about the relevance of such basic research to the eventual treatment of cancer in animals and...
The most powerful and sophisticated linear accelerator in any veterinary hospital east of the Rockies is up and running at the Cornell University Hospital for Animals. The brand-new and newly delivered Siemens Primus linear accelerator was unveiled before a throng of interested alumni and staff during Reunion Weekend in June. Associate professor Margaret McEntee, DVM, DACVIM, DACVR-RO, who directs the use of the equipment, was on hand to explain it to visitors touring the facility.

Guest of honor at the event was Jane M. Turrel, DVM, MS, DACVIM, DACVR, a veterinary oncologist and owner of Veterinary Oncology Specialties in Pacifica, California. Turrel's great generosity made acquisition of the linear accelerator a certainty. Turrel's parents, John and Eloise Turrel, who are both 1943 graduates of Cornell, then responded to her gift with one of their own, a charitable gift annuity to benefit the endowment that will fund maintenance of the linear accelerator.

The state-of-the-art equipment delivers six million photon volts and also has a range of six different electron energies from five million to 14 million electron volts. The electron capacity makes it possible to irradiate tumors at shallower depths while limiting the dose delivered to underlying vital organs. The machine also includes a multi-leaf collimator, which allows the outline of the beam to be shaped precisely to correspond to the area of an irregularly

radiation

THERAPY has arrived

Jane M. Turrel, DVM, MS, DACVIM, DACVR, a veterinary oncologist and owner of Veterinary Oncology Specialties in Pacifica, California, made acquisition of the linear accelerator a certainty.
The sub-specialty of radiation oncology is a relatively new one in veterinary medicine. The American College of Veterinary Radiology gave the first certifying examination for radiation oncology in 1994. According to McEntee (who passed the exam that year), there are currently only 38 board-certified veterinary radiation oncologists, 36 of whom practice in the United States. Including Cornell’s, there are now 10 approved radiation oncology residency training programs.
A veterinary dermatology conference, "Cutaneous Current Events and Controversies," will be held at the Punta Cana Resort and Club in Punta Cana, Dominican Republic, February 17 to 20, 2003.

Ellis Leonard, in the second volume of his indispensable history of Cornell's College of Veterinary Medicine, reproduces the text of a letter that then-dean Veranus A. Moore sent in the waning days of 1908 to all the veterinary practitioners in New York. Enclosed with the letter was the program for a Conference for Veterinarians to be held on January 12 and 13, 1909.

"It is the purpose of the Veterinary College to make this Institution of as much value to the veterinarians of the State as possible and reciprocally to receive the benefit that a closer relation between student and practitioner is sure to bring," wrote Moore about the rationale for the conference. Seventy-five veterinarians attended; James Law took time out from fighting a New York outbreak of foot-and-mouth disease to speak on the subject; other faculty members also took part; and the conference was declared a success.

This mention is just one of a great many details that Leonard included in his exhaustive chronicle, but one that holds particular significance for David Lee, the College's executive director of external relations and marketing. Lee, who graduated with the DVM class of 1994 and later earned an MBA from Cornell's Johnson Graduate School of Management, directs the College's continuing education activities as one part of a multi-faceted set of responsibilities he has held since September 2001.

"That was Cornell's first Annual Conference for Veterinarians," he notes with some pride. "So we are continuing a tradition that is almost 100 years old."

"Continuing," yes, but Lee is also taking a new look at all aspects of the College's approach to outreach education. "We're reinventing continuing education," he says. "It's not only important that Cornell maintain it; Cornell needs to be a leader in continuing education. We need to be looking at what people want from CE, push the boundaries of what has been offered in the past, and look at new models. If the College can't deliver information and education that is of interest to veterinarians in the real world, I will be concerned how well prepared our graduates are for such realities. Instead, leadership in continuing education allows us to hone our overall program to meet the current and future demands of the profession."

Lee concedes that the CE market is very competitive now. "It used to be that veterinary colleges were the sole source of cutting-edge information for practitioners," he says. "Now we have many new entrants, and they range from specialists and consultants addressing small groups of veterinarians to huge annual conferences that attract veterinarians by the thousands. There are almost no barriers to entry in this market and the lack of regulations governing veterinary CE creates a bit of a wild frontier. Fortunately, there is no shortage of information to be disseminated in our dynamic profession, and there is a growing appreciation among practice owners that providing access to CE opportunities is a good investment in the future of their practices."

Cornell has some unique advantages in the market that Lee is quick to point out. First is the quality of the
school's faculty. "Our faculty members are recognized worldwide in their respective fields. The fact that they contribute freely to CE events provided elsewhere generates even greater demand for their programs offered through Cornell," he says. And the College's instructional facilities are second to none. "In terms of our lecture halls and laboratory facilities, I've come to appreciate Cornell as the 'Taj Mahal' of veterinary colleges. Furthermore, no amount of money can transform a Holiday Inn ballroom into a surgical suite that would rival our newest wet-lab facilities."

Lee intends to leverage Cornell University's vast resources at the university level to create new competitive advantages for the College. "It was a comment from one of our alumni, Dr. Doug Aspros [DVM '75], that really opened my eyes to the potential that resides at the other end of Tower Road," says Lee. "Doug was likening veterinary practice to the hospitality industry, and we began kicking around the idea of getting Cornell's top-ranked hotel school involved with the Veterinary College to address some critical needs of the profession. Step even farther back and you begin to recognize how valuable Cornell's leadership in industrial and labor relations, business management, law, hospital administration, and agriculture and life sciences might be to the College. Needless to say, we are working quickly to forge some of these collaborations," assures Lee.

If Cornell has a disadvantage in the CE market, it might be its "centrally isolated" location in a region renowned for its bad weather. "For decades, Cornell's Annual Conference was held in January. I still hear patrons of those past events speak proudly and somewhat nostalgically about their weather-related misadventures while en route to Ithaca," recalls Lee. The conference was moved to March several years ago to make travel more predictable and to reduce competition from larger conferences that were luring veterinarians to more attractive mid-winter climes. "Ithaca is a well kept secret as a tourist destination. Three seasons out of four are simply gorgeous here, and there is a good blend of outdoor activities, cultural events, and family-oriented opportunities. It's an easy day's drive from almost anywhere in the Northeast and accommodations are relatively inexpensive. And some of the restaurants and entertainment offerings — including Cornell hockey — are world-class," says Lee.

Still, he is quick to admit that growth of the college's CE programs isn't likely to derive from a sudden boom in tourism in the Finger Lakes region or from population expansion in the surrounding communities, many of which have been in economic decline for several years. The real growth opportunities, he insists, will come from entering new markets — finding unique niches, providing new services, leveraging technology, and moving beyond the limits of Central New York.

While some of Lee's innovations are still in the planning stage for introduction later next year, one new tradition is ready for launching in February 2003: the College's first-ever international continuing education conference. A veterinary dermatology conference, "Cutaneous Current Events and Controversies", will be held at the Punta Cana Resort and Club in Punta Cana, Dominican Republic from February 17 to 20. If this conference succeeds as expected, Lee and his CE colleagues, Dee Brothers and Donna Green, plan to offer one meeting every year in a foreign venue, each of them focusing on a different specialized area of clinical practice. "We wanted to test the waters in providing CE programs off-site, and the warm Caribbean Sea seemed the most inviting to test," he grins. "We will soon be applying the same expertise to programs offered in the New York metropolitan area and in the northeast United States."

One growth area that Lee has identified is that of certification. His concept for certification courses is less formal than board certification, which requires a lengthy clinical residency and success on a rigorous specialty examination. But he does envision offering advanced training in certain niches that would be delivered on-site at regular intervals scheduled to accommodate busy professional and personal lives. At the end of the course, participants would receive a certificate to display with their other credentials. "Cornell has great brand recognition with clients as well as with veterinarians," says Lee with a marketer's enthusiasm. "To the extent that we can help our clients use the Cornell name in promoting the quality of their practices, I think that's a good thing, too."

Lee sees additional opportunities in distance learning, but he's quick to point out that what was once viewed as the next gold rush has not really panned out. While distance learning would help compensate for the College's geographic shortcomings, Lee believes that the technology required to make such programs truly effective for most people still resides in the future. "Social interaction between colleagues is still a major component of CE events, and I honestly don't expect that to change much in my lifetime," he says. "In the meantime, I'm more interested in finding ways that distance learning can complement traditional educational forums."

As for the venerable Annual Conference, Lee admits that he had some difficulty creating a nimble new strategy. "The concept of being all things to
all people is a bit dated. It's difficult for a conference of this scale to offer a full range of programs that will appeal to all practice types. But it's a nearly one-hundred-year institution, and we wanted to do what we could to keep it relevant,” says Lee.

Lee and his team thoroughly researched the market and made changes to increase customer satisfaction. “We’ve changed our definition of ‘customer’ to include corporate partners and presenters, as well as attendees,” states Lee. “Without sponsors and exhibitors, there would be no conference, and naturally, we want to keep our lecturers happy, too.”

Corporate partners are primarily interested in attendance levels and exposure. Because Lee’s office is also responsible for corporate affairs for the college, he remains acutely aware of their budget constraints and marketing needs. “It’s not in anyone’s long-term interests for us to simply run the well dry. I’m committed to helping companies find new, meaningful relationships with the college, and ‘meaningful’ should ultimately show itself in a positive way on their financial reports,” he states emphatically.

To increase attendance, Lee targeted a wider market this year. “Somehow Annual Conference has come to be viewed as an alumni event,” he says. “We want our educational offerings to serve the entire field of veterinary medicine, not just Cornell graduates.” That said, he has also started building the alumni base for the future by ensuring that students could participate this year. In the past, the conference was timed to take place during college recesses, when facilities and faculty would be available. Unfortunately, this approach also ensured that the vast majority of students graduated without any direct knowledge of what the Annual Conference could offer.

This year the conference was moved to a date more accommodating to the students. The College offered students a greatly discounted fee, and CE coordinator Dee Brothers worked hard to solve the multitude of little problems these changes created. Over forty students participated in the conference, a number they expect to increase significantly next year.

Lee sees benefits in this interaction for both the students and the clinicians who attend the conference. “From a job-seeking perspective, students really want to know what the real world is like. As great as our faculty are, relatively few of them have recent work experience in a private clinical setting. Here’s a wonderful opportunity for students to interact with veterinarians in private practice, and for veterinarians to see what the school is about — to find out about the problem-based curriculum, for instance. The best jobs are found through networking, which is something I teach in Practice Management. Here’s an opportunity for the students to use it.”

“In our veterinary curriculum we teach students how to learn throughout a lifetime,” he continues. “If Cornell continuing education is a part of that, we build the program from the inside. It’s a very strong strategy, because it benefits everybody.”

Lee maintains a close connection to the students and is passionate about helping them succeed in veterinary practice. In addition to carrying broad responsibilities as head of external relations and marketing, he is also a part-time lecturer in the DVM program. He teaches Practice Management, an elective, or "distribution", course in the veterinary curriculum, and has also tutored students in Block I, a cluster of required courses collectively termed “the Animal Body”, and helped teach in various other areas of the curriculum. Although his recent assumption of responsibility for the College communications office is forcing him to reduce his teaching load to some extent, Lee has no intention of simplifying his life at the expense of his favorite classes. “If I were just an administrator and not involved in teaching,” he says, “I might as well be working in industry.”
Alfonso Torres, director of the New York State Animal Health Diagnostic Laboratory and associate dean for veterinary public policy, testified July 17 before the U.S. Senate's Committee on Agriculture, Nutrition, and Forestry, which is conducting hearings to examine proposals for creation of a new Department of Homeland Security. His comments focused on the proposed transfer to the new department of all U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) activities as well as the Plum Island Animal Disease Center.

In his remarks, Torres recommended that all APHIS laboratories and science centers involved in animal and plant health protection continue to be administered under USDA. He argued that parallel units involved in human health protection were to remain independent of the new Department of Homeland Security but would get federal funding for laboratory support, diagnosis, and research related to homeland security. APHIS units involved in animal and plant health protection were no different in mission and activities than the human-related variety, he said. However, he agreed that some of the APHIS inspection activities at ports of entry could appropriately fall under the new department.

The following day Homeland Security Director Tom Ridge, under pressure from Congress, announced that only USDA border inspectors would move from APHIS to the Department of Homeland Security.

Torres came to Cornell in February 2002. Previously he was deputy administrator for veterinary services at APHIS, and from 1991–1996 served as director of the Animal Disease Center at Plum Island, where he also was chief of the foreign animal disease diagnostic laboratory (1995–96) and head of diagnostic services (1991–95). The full text of his remarks is available at http://www.news.cornell.edu/releases/July02/TorresComments.dhs.html. Below are excerpts from his prepared testimony.

"In general I support the president's proposal for the creation of a Department of Homeland Security to increase our border security and be better prepared and coordinated in dealing with potential bioterrorist and agroterrorists attacks. ...

"The president's proposal ... reflects the recognition and general understanding of the importance of APHIS activities in safeguarding animal and plant health for more than 150 years. APHIS's contributions to the well-being of society have been well demonstrated in its success in keeping serious animal diseases and plant pests from entering our country. However, it is important to keep in mind that APHIS has many functions that are not totally related to the exclusion of animal diseases and plant pests. Three out of five APHIS main programs do not have functions that are directly associated to the proposed mission of the new Department of Homeland Security. They are International Services, Wildlife Services, and Animal Care. The other two, Veterinary Services and Plant Protection and Quarantine, have some activities compatible with the new department. These activities are related to the actual inspections at ports of entry and the issuing of import permits for agricultural commodities and for restricted animal or plant pathogens. ...

"Based on my experiences at USDA and my knowledge of APHIS ... missions and activities, I respectfully

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Lisa Fortier, DVM, PhD, DACVS, assistant professor of clinical sciences and of molecular medicine, received a New Investigator Award for the work she presented at the meeting in February of the Orthopaedic Research Society. Fortier presented “Cdc42 and Rac activation are down-regulated by insulin-like growth factor-I in articular chondrocytes.”

Fortier’s research interests include the use of embryonic stem cells for articular cartilage repair and the role of Rho proteins in chondrocyte differentiation.

Nikolaus (Klaus) Osterrieder, Dr.med.-vet., Dr.med.vet.habil. joined the Department of Microbiology and Immunology in August as an associate professor of virology. Osterrieder’s research is focused on determining the genomic basis for the virulence and pathogenesis of two alphaherpesviruses, Marek’s disease virus, a virus of chickens that can cause T-cell cancer, and equine herpesvirus type 1, which causes respiratory disease, abortion, and neurological symptoms in the horse.

Osterrieder received his veterinary degree and five years of graduate training as an independent researcher in virology, which culminated in the degree of Dr.med.vet.habil., at Ludwig-Maximilians-University in Munich, Germany. He became a member of that university’s faculty in February, 1998.

Jerome Van Biervliet, DVM, senior resident in large-animal internal medicine, won a Resident Abstract Award at the annual meeting in June of the American College of Veterinary Internal Medicine. His presentation was entitled “Evaluation of a diagnostic criterion for spinal cord compression during cervical myelography in horses”. Co-authors were faculty members Peter Sivigliani, Thomas Divers, Hollis Erb, Alexander de Lahunta, and Alan Nixon.
William E. Hornbuckle, a professor of medicine in the Department of Clinical Sciences, is the new Rudolph J. and Katharine L. Steffen Professor of Veterinary Medicine. He was appointed by Provost Carolyn Martin following a review of faculty nominations by the College’s 11 other named professors. He was appointed for a term of seven years, subject to reappointment.

In nominating Hornbuckle, Associate Professor Stephen Barr cited his establishment in 1990 of the Community Practice Service (CPS), the first university-based service of its kind to be run, with close faculty supervision, by senior veterinary students. According to Barr, “Professor Hornbuckle’s vision for CPS was to incorporate the rigor of an academic environment with the pragmatic demands of private practice to provide an experience for veterinary students that would best prepare them for future clinical careers. There is no other academic teaching hospital in the country that operates in quite the way that CPS does, nor are others as successful in achieving their mission.” In forwarding the College’s nomination to the provost, Dean Smith added, “The program affords a major advance in medical care at the interface of academia and private practice.”

Hornbuckle received a DVM from Oklahoma State University in 1967 and is board-certified in veterinary internal medicine. He joined the Cornell faculty in 1977 after spending ten years in specialty clinical practice. He achieved tenure as an associate professor of small-animal medicine in 1984 and was made a full professor in 1995. From 1986 to 1988 he directed Cornell’s Small Animal Clinic. He has received many recognitions for outstanding teaching, including the Student Chapter of the American Veterinary Medical Association Award for Teaching Excellence and the Norden Distinguished Teacher Award, an honor he received in both 1979 and 1992. Hornbuckle has also authored or co-authored 38 articles and 20 book chapters.

The Steffen Professorship is intended for “distinguished faculty who have advanced the scholarship of veterinary medicine in any of the domains of research, or clinical or diagnostic practice, while maintaining a distinguished record of teaching.” It was first awarded in 1993 to Bruce W. Calnek, now emeritus, a former professor and chairman of the Department of Avian and Aquatic Animal Medicine. Rudolph Steffen, DVM '34 practiced veterinary medicine in Horseheads, New York and was a longtime supporter of the College before his death in 1995.

Alicia Bertone, DVM '82, PhD, DACVS, a professor of veterinary clinical sciences at the Ohio State University, has been appointed to the True Family Chair in Equine Clinical Medicine and Surgery. The chair's focus is the creation of new knowledge through comparative biomedical research in human and veterinary orthopedics. Bertone recently completed a year's sabbatical leave at the Center for Molecular Orthopedics at the Brigham and Women's Hospital in the Harvard Medical Complex in Boston and the Genetics Institute in Cambridge, Massachusetts. She is investigating the use of biological pharmaceuticals for gene therapy.

Rudolph Tass Dueland, DVM '56, MS, DACVS is this year's recipient of the American Kennel Club Career Achievement Award in Canine Research. The award, consisting of a Tiffany crystal sculpture and $5000, was presented at the annual meeting of the American Veterinary Medical Association in July.

A professor of orthopedic surgery, emeritus at the University of Wisconsin, Dueland was recognized for his 30 years of leadership in developing innovative treatments for hip dysplasia and other orthopedic problems. He was one of the earliest researchers to study design requirements and clinical outcome of total hip replacement in dogs.

Howard B. Gelberg, DVM '71, PhD '80, DACVP is the dean of Oregon State University's College of Veterinary Medicine. Gelberg, a pathologist, was associate dean for research at the University of Illinois before assuming the Oregon State post in July 2001. He has also worked in private practice, at Plum Island Animal Disease Center, and as a consultant to private industry. His research interests center around host-pathogen interactions in gastrointestinal infections and the role of sialic acid in glomerular function.

Sandra Manfra Marretta, DVM '77, DACVS, DAVDC received the Innovative Veterinary Diets Award at this
year's annual meeting of the American Animal Hospital Association. The award is given in recognition of significant contributions to small-animal veterinary medicine and surgery.

Following specialty training and ten years in practice as a staff surgeon at the Animal Medical Center, Manfra Marretta joined the veterinary faculty of the University of Illinois, where she is an associate professor of small-animal surgery and dentistry. She is also a recent recipient of the American Veterinary Dental Society Education and Research Award and a Campus Award for Excellence in Graduate and Professional Teaching.

**Tracey McNamara**, DVM '82, DACVP was honored in July with the President's Award of the American Veterinary Medical Association. The award is given to individuals or groups who have made a positive impact on animal, human, or public health, veterinary organizations, and the profession.

It was McNamara who, as head of pathology for the Wildlife Conservation Society, headquartered at the Bronx Zoo, made the connection between the unusual deaths of crows and various species of zoo animals and the outbreak of an unidentified encephalitic disease of humans in the New York City area. By noting the zoo species that did and did not fall ill or seroconvert, she was able to rule out St. Louis encephalitis, the diagnosis that had been made by public-health officials. She alerted officials at the federal disease laboratory at Ames, Iowa to the presence of a virus.

**McNamara, DVM '82**, Zweighaft learned that Kiyonaga had made a very generous gift in order to place his name on the **Harold M. Zweighaft Examination Room for Oncology** in the Cornell University Hospital for Animals.

Zweighaft, who lists his Boston terriers by name and age on his *curriculum vitae*, has many other noteworthy credits as well. From 1992 to 1998 he served on the Executive Board of the American Veterinary Medical Association, the last year as chairman; he currently chairs the AVMA's Judicial Council. He is also a member of the College Advisory Council, the Cornell University Council, and the AVMA's Task Force for a Model Practice Act. He is a 42-year member of the Dog Show Committee of the Veterinary Medical Association of New York City and a fixture at the Westminster Kennel Club Dog Show. He has received the city association's award for Outstanding Service to Veterinary Medicine, the College's Daniel Elmer Salmon Award, the Baker Institute's Founders' Award, the New York State Veterinary Medical Society's Veterinarian of the Year and Distinguished Life Service Awards, and the Distinguished Service Award of the New York State Education Department.

**Mary Kiyonaga**

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**Harold Zweighaft Honored**

June 8, 2002 will surely rank right up there as one of the best days of Harold Zweighaft's very enjoyable life. On that Saturday morning of Reunion Weekend, Zweighaft, a member of the DVM class of 1956 and venerable director of the West Parc Veterinary Clinic in New York City, was the surprised recipient of a very special tribute conceived and executed by his client and friend **Mary Kiyonaga**. Before family, friends, and a roomful of fellow alumni who had gathered in the John D. Murray Lecture Hall to hear featured speaker Tracey

**Dorothy and Hal Zweighaft**
never before seen in the United States. They confirmed the diagnosis of West Nile virus that was first made from McNamara's samples in the laboratory of George Ludwig at the U.S. Army Medical Research Institute of Infectious Diseases in Frederick, Maryland.

McNamara has since been active in advocating for improved communication between veterinary and public health officials and in raising awareness of the value of the health surveillance routinely done in zoos across the nation. Her vision has resulted in the formation of the National Zoological West Nile Virus Surveillance Working Group, with more than 35 zoos participating and with funding from the Centers for Disease Control and Prevention. The surveillance group also includes Cornell's Animal Health Diagnostic Laboratory, where the zoos send samples for testing, and various public health departments.

Karyn A. Havas, Jodi K. Sangster, Kelly M. Still, and Ryan D. Taggart have been awarded U.S. Army Health Professionals Scholarships. All are members of the DVM Class of 2005.

The Cornell students won four of the eight scholarships awarded in veterinary medicine this year in the United States. Each will receive funds to cover full tuition and academic fees, required books, and equipment, as well as a monthly stipend for living expenses. In return, they will graduate as commissioned officers with a service obligation of one year for each year of their scholarships.

Commenting on the scholarship awards, Dean Donald F. Smith said, "It is gratifying to learn that the Army shares our confidence in these outstanding students. For Cornell to receive half of the scholarships awarded to all veterinary students this year is a powerful testament to the quality of our students. It is our privilege and responsibility to provide them with a superb educational experience so that they may fulfill the public-health and animal-health needs of their country."

**Mastitis Program Wins Grant From Vitamin Settlement**

A Cornell study aimed at offering new methods for prevention and treatment of recurrent *Escherichia coli* infections in dairy cows has won a grant of $235,000 from New York's share of a $225-million nationwide consumer settlement against six of the world's largest vitamin manufacturers.

The goals of the research are to evaluate the presence of adhesion and invasion of *E. coli* organisms in recurrent vs. one-time infections, and to understand the mechanisms involved in adhesion and invasion of the microorganisms in udder epithelial cells. The project will be administered through the Quality Milk Promotion Services, a program of the New York State Animal Health Diagnostic Laboratory. Principal Cornell investigators are Ynte Schukken, an associate professor in the Department of Population Medicine and Diagnostic Sciences and director of the Quality Milk Promotion Services, and epidemiology professor and department chairman Yrjö Gröhn.

In October 2000 New York was the lead state in antitrust negotiations to recover damages from six companies accused of price-fixing in overcharging food manufacturers for vitamins used in a wide variety of products including bread, milk, cereal, baby food, and pet food. State Attorney General Eliot Spitzer had announced that New York's $18.5-million share of the settlement would be used to fund programs studying prenatal care, livestock, and nutrition and hunger prevention aimed at children, the elderly, and underserved or needy populations.

**On to Greener Pastures**

Ellie the Fistulated Cow, whose fistula (the portal in her side) was a window to the mysteries of ruminant digestion, died June 2 of old age. Born in May of 1988, Ellie was a perennial favorite for thousands of visitors to the College's annual open house and an esteemed "instructor" for hundreds of veterinary students. The removable cap on the fistula fitting also let Ellie serve as a rumen donor to less healthy cows whose digestive juices needed a boost. Remembered by Farm Animal Hospital staffers as a gentle and patient animal who craved love and attention, Ellie outlived most Holsteins.
USDA to Fund Cornell Biosecurity Efforts

by Roger Segelken, Cornell News Service

Cornell's expertise in plant and animal diseases has been enlisted in the war on bioterrorism, with funding from the U.S. Department of Agriculture (USDA) program to bolster food and agricultural homeland-security protections.

Part of the $2.1 million channeled through New York state by the USDA will help establish facilities in Cornell's College of Agriculture and Life Sciences and College of Veterinary Medicine. The facilities will join a network of laboratories sited strategically throughout the nation to permit rapid and accurate diagnosis of animal-disease threats and to assist states in improving their capabilities to detect plant pests and diseases, according to the USDA announcement of the $43.5 million appropriation to the states.

The USDA allocation to New York state was announced May 30 in Albany by U.S. Agriculture Undersecretary for Food Safety Elsa Murano, who said that $1.65 million was for New York's part of the rapid detection and diagnostics network, $200,000 for plant pest and disease detection, $176,596 for animal disease response and $77,771 for animal disease surveillance. Not all of the New York state allocation will come to Cornell.

Also participating in the Albany announcement were state Agriculture Commissioner Nathan L. Rudgers and Cornell College of Veterinary Medicine Dean Donald F. Smith.

In Cornell's New York State Animal Health Diagnostic Laboratory, Director Alfonso Torres said the animal-health diagnostic program here would become a satellite laboratory to a USDA-designated core laboratory. But exactly what role the Cornell veterinary laboratory will play will not be determined, Torres said, until the completion of a 90-day planning process among the federal, state, and university units in the network.

Speaking at the Albany announcement of the USDA funding, Dean Smith said veterinary public-health endeavors are a crucial component of the human public-health infrastructure.

"More effective integration of existing components of the public-health infrastructure with the veterinary diagnostic, surveillance, and response infrastructure is not only sensible," he said, "it is essential to the creation of an effective overall defense against bioterrorism."

Torres testifies

Continued from page 17

suggest that you consider the following suggestions...

"All agricultural port inspection could be transferred to the Border and Transportation Security Division of the Department of Homeland Security. Their duties are quite integrated [with] the Customs Service of the Department of Justice, and they are already co-located at sea, land and air ports of entry. ..."

There is a need to have Emergency Management veterinarians co-located with FEMA [Federal Emergency Management Agency] to coordinate their assistance in disasters of any origin where animals are involved. ...

"All APHIS Veterinary Services laboratories and science centers involved in animal health ... should be kept under the current administrative arrangements within USDA. The same recommendation applies to APHIS Plant Protection and Quarantine plant health laboratories in several locations in the United States ..."

"It is important to point out that the Plum Island Animal Disease Center was created ... in 1954 as the only laboratory in the U.S. where foot-and-mouth disease and other highly contagious diseases could be studied. ... APHIS conducts diagnostic [tests] on highly contagious diseases of livestock at Plum Island [and] conducts training of veterinarians from the U.S. and abroad, in the recognition and diagnosis of most foreign animal diseases. This is an activity outside the main scope of the proposed Department of Homeland Security. ...

"The president's proposal would keep the Centers for Disease Control and the National Institutes of Health under their current department but would provide additional funding and programs for assisting the new Department of Homeland Security with laboratory support in the areas of diagnosis and research to enhance the capabilities of the U.S. in deterring, preventing, and responding to bioterrorist attacks. Exactly the same arguments could be made regarding the USDA's laboratory facilities and program at Ames, Iowa and Plum Island, New York. There is no difference in mission and activities between the CDC/NIH laboratories for human health and the [Ames, Iowa] and Plum Island Animal Disease Center laboratories of APHIS for animal health. They both provide the scientific basis for surveillance, early detection, and responses for either human or animal diseases... Thus the integration of the diagnostic laboratories from the state Departments of Agriculture with USDA will more than justify keeping the critical animal and plant federal laboratories under the USDA."

CORNELL VETERINARY MEDICINE
The English mastiff has been revealed as a key animal model to help explain retinitis pigmentosa (RP) in humans. The dogs, which sometimes carry a gene defect that can cause canine progressive retinal atrophy (PRA), can be used to test possible therapies for the human disease, according to researchers at Cornell University's Baker Institute for Animal Health and the University of Pennsylvania's Scheie Eye Institute. At least 100,000 people in the United States currently suffer vision loss and blindness from RP.

The determination, which follows the recent Cornell discovery of the genetic mutation leading to PRA blindness in the English mastiff, is reported in the April 30, 2002, Proceedings of the National Academy of Sciences.

Both the canine and human inherited vision disorders involve the loss of rod cells, the photoreceptors in the eye's retina responsible for black-and-white and night vision, and a defect in rhodopsin, the light-sensitive pigment in the rods. Light particles, called photons, striking rhodopsin in the rods cause the rhodopsin protein to change shape, starting a chemical-signaling cascade that enables the brain to detect light and perceive a visual image. Then the rhodopsin molecules must regenerate to their original form in the dark. The genetic defect blamed for some forms of RP and PRA produces a mutated form of rhodopsin that appears unable to regenerate properly.

"Most of us have a little trouble seeing in a darkened theater when we first come inside from the bright light," explains Gustavo Aguirre, the Caspary Professor of Ophthalmology. "Then rods and the rhodopsin in our eyes begin to adapt to the dim light. But in people with this form of RP and mastiffs with PRA, the rhodopsin protein is defective and rods gradually lose the ability to recover — first in small areas, then throughout the retina — and they lose vision altogether."

Gregory Acland, another Cornell ophthalmologist/geneticist in the vision studies, explains that in one form, human RP is an early-onset disorder with rapid loss of rods throughout the retina soon after birth, whereas in another form of RP, the loss of rods begins later in life and is more gradual. This is puzzling to researchers, but also gives them hope of finding a treatment that at least will slow the course of the disease.

Not only does the mastiff PRA — one of several forms of PRA seen in various dog breeds — parallel the progression of the gradual form of human RP, but the genes responsible for the disorders are located in similar parts of the human and canine genomes, Acland says. He credits Cornell researcher James W. Kijas with the lengthy and difficult task of cloning the mutant canine RHO gene.

University of Pennsylvania researchers Artur Cideciyan, Tomas Aleman, Michael Pianta, and Samuel Jacobson found the critical similarities in retinal function between the mastiff disease and humans with RP that led to the decision that this was a major discovery for the field. Also contributing to the study at Cornell were Baker Institute researchers Susan Pearce-Kelling and Brian Miller.

Gene therapy is one possible treatment, replacing the defective genes with functional ones, as a Cornell-Pennsylvania-University of Florida team did recently to cure another type of blindness in briard dogs. Now the vision researchers hope to learn what environmental factors set the disease in motion in dogs and humans with the genetic predisposition. They anticipate that dogs will be perfect candidates to test therapies as they are developed.
endnote

We closed the books on the 2001–02 academic year on June 30. Like most institutions of higher learning, we had a challenging year financially, principally due to decreased state support in several critical areas and increased program expectations, some of which are in response to September 11th. In addition, the university’s belt-tightening has passed down increased financial expectations for individual colleges at Cornell.

Lean years, however, are part of an up-and-down cycle, and we had several robust years in the late 1990s in which to prepare for this downward phase. Starting in 1997, our preparation focused on defining strategic areas worth major investment in faculty and infrastructure, reorganizing and consolidating departments to reflect contemporary veterinary medicine and biomedicine, and recruiting department chairs and other faculty whose programs would complement and expand the areas of greatest strength among our faculty and meet most effectively the emerging needs of the profession.

In addition, we became more aligned with the university’s academic and administrative priorities, forging new or solidifying existing relationships with faculty in departments in agriculture, biology, engineering, the physical sciences, and nutrition.

These changes have not been easy, but they have positioned the College to take advantage of several strategic opportunities in research and education, and in clinical practice and diagnostic medicine.

For example, the bold introduction of a major oncology initiative not only provides crucial clinical service in an area of great need, but it also complements the cancer biology research program already established at Cornell University. The installation of an advanced linear accelerator with the support of the Kresge Foundation and of Dr. Jane Turrel and other private donors gives Cornell the capacity to provide radiation therapy for cancer patients using the most sophisticated machine currently available in veterinary medicine. Moreover, the recent funding of a companion-animal tumor registry by the State of New York, and of the protein expression facility by the federal government, demonstrates the responsibility of the public sector to good ideas presented by our faculty.

The College of Veterinary Medicine has also been a major force in the university’s genomics program, providing leadership in the areas of mammalian and microbial genomics, and at the interface of the physical and life sciences. The College has added core facilities in pathology and microarray analysis as well as a barrier facility for transgenic mice. Most of the cost of these facilities, as well as the start-up costs associated with several new faculty hires, have been borne by the university in an unprecedented recognition of the enormous potential that veterinary medicine provides in supporting biology and the physical sciences.

The recruitment of Dr. Alfonso Torres as director of the Animal Health Diagnostic Laboratory and as associate dean for veterinary public policy has catapulted Cornell to a new leadership plateau in animal health management. Despite our proximity to the federal laboratory at Plum Island, we were selected in June by Secretary of Agriculture Ann Veneman to serve as a regional satellite laboratory for animal disease surveillance and control.

Whenever I report on the fiscal status of the College to my superiors in the university, I mention three things that mark our success: reorganization of the College’s infrastructure, with considerable administrative savings; strategic investment in existing and new initiatives; and the generosity and support of alumni and friends. In this year of extraordinary challenge, you have demonstrated enormous support. Our annual fund has expanded, and the total gifts and commitments for the past year have remained very strong.

Gifts for designated programs, such as scholarships, oncology, the Feline Health Center, and the Baker Institute, have enabled these programs to continue to grow and meet ongoing needs. Unrestricted gifts have been especially welcome this year, as they can most flexibly be applied to areas of highest priority and greatest need. In 2001–02, the bulk of this support has been directed to clinical programs, including the oncology effort, intensive and critical care, equine programs, neurology, and cardiology. As always, student scholarships have also benefited from unrestricted giving this year.

I deeply appreciate your support and encouragement and, as always, I welcome your comments and suggestions.

[Signed]
coming events

SEPTEMBER
23  “Black Tie & Tails” benefit, New York City
26–28  American Association of Bovine Practitioners Conference, Madison, Wisconsin
27–28  Homecoming Weekend

OCTOBER
11  Welfare of Zoo Animals Forum (AVMA), Milwaukee, Wisconsin
31–11/2  Trustee/Council Weekend

NOVEMBER
1–3  American Association of Veterinary Medical Colleges Biodefense Conference, Washington, DC
2–3  Endoscopy Laboratory, Cornell
9  Cornell Symposium for Dog Enthusiasts, Old Greenwich, Connecticut

DECEMBER
14–15  Equine Practitioners Conference, Cornell
14–17  NY2K Annual Conference (NYSVMS), Kerhonkson, New York
16–17  19th Annual Farriers Conference, Cornell

JANUARY
18–22  North American Veterinary Conference, Orlando, Florida

FEBRUARY
17–20  75th Annual Western Veterinary Conference, Las Vegas, Nevada
17–20  Dermatology 2003, Punta Cana, Dominican Republic

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