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Collaboration with College

Establishing collaborative research projects with a small private college might not be a top priority for every major research institution. But perhaps it should be.

An ongoing collaboration between the Institute and Harvey Mudd College (HMC) in Claremont, CA, has shown researchers just how valuable such a collaboration can be.



From left, J. Stuart Nelson, Bahman Anvari, and Sam Tanenbaum confer over results from tests of skin cooling during laser treatment.

Researchers at both institutions are cooperating on several mutually beneficial endeavors, including two scientific collaborations and research opportunities for HMC students.

The first collaborative project involves cooling devices for use in laser therapy. With Institute Associate Director J. Stuart Nelson, M.D., Ph.D., HMC researchers Sam Tanenbaum, Ph.D., and

Bahman Anvari, Ph.D., are working on methods to reduce possible damage to healthy tissue from heat released during laser removal of birthmarks and vascular skin lesions.

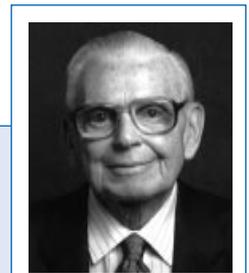
This project has special value for Dr. Tanenbaum. After 18 years as Dean of Faculty at HMC, working at the Institute has allowed him to return to his true love, engineering research. "This project has rehabilitated an old administrator," Dr. Tanenbaum remarks with a smile, "and for that I am grateful."

"His well-known modesty aside," Dr. Nelson responds, "Dr. Tanenbaum has brought extensive knowledge and invaluable experience to our work, not to mention good humor."

The second collaborative research project involves functional imaging of tissue. Institute Professor Bruce Tromberg, Ph.D., and Richard Haskell, Ph.D., of HMC are working to apply photon migration technology as a tool for non-invasive diagnostics.

For its part, the Institute has helped HMC start a bioengineering undergraduate program, one of the first in the nation. The Institute also participates in freshman engineering design projects at the college and hosts HMC students for summer research internships conducted at the Institute.

"This is our first collaboration with an undergraduate college," notes Institute Director Michael W. Berns, Ph.D., "and I think both institutions could not be more satisfied with the results achieved." ■



Tribute to Charley Hester

This issue is dedicated to a tireless supporter of the Institute. The Director paints a picture of Charley on page 2, and Institute friends remember him on page 6.

Remembering Charley Hester

by Michael W. Berns, Ph.D.

Arnold and Mabel Beckman Professor
President and CEO

It was with sadness and a deep sense of personal loss that I learned of the passing of the Chairman of our Board, Charles “Charley” Hester. Charley died on Thursday, February 29, following a short illness.

At the Institute, around UCI, and throughout Orange County, Charley was known as a generous patron and tireless supporter of many worthy causes (*please see our Tribute on page 6*).

And to his many friends, from fellow business leaders to the children and adults whose lives he touched in various ways, Charley was a source of warmth and inspiration.

Two Careers

After a fruitful career in real estate development, Charley, along with his wife Nora, began a second career in philanthropy.

Involving themselves extensively in Orange County charities, Charley and Nora became one of the area’s major philanthropic couples.

Their interests were broad, but they focused their work on children, medicine, and the arts.

One of their longest running interests was the Children’s Hospital of Orange County (CHOC). Charley was so beloved there that the hospital initiated the “Charley” Awards to recognize outstanding volunteers.

Charley was an important supporter of ours from the very beginning.

Our founding Chairman Arnold O. Beckman, Ph.D., enlisted Charley’s service on the Institute Board of Directors when both served on the board of Hoag Hospital.

Charley became Vice Chairman of the Board in 1991. Then, in 1994, board members unanimously elected Charley to succeed Dr. Beckman. Charley was also a founding member of the Institute’s Support Group.

Spontaneous Generosity

Even though he committed to do so much, Charley was always open to new ways to help that might just appear out of the blue. For instance, there is the story of how Charley helped an employee at CHOC, one of his most memorable and touching gestures.

Since birth, this employee, an insurance biller, had lived with a large port wine stain birthmark that extended from her face to her neck. One day Charley ran into her in the hallway at CHOC. He became interested in her situation, and later learned her story from her supervisor.

Charley knew that the Institute was an internationally known center for treating this kind of birthmark. He also knew that the cost of treatment would be beyond the employee’s means.

But Charley was determined to help, so he and Nora offered to personally underwrite the employee’s treatment at the Institute at a cost of over \$30,000.

On another occasion, Charley and Nora were visiting the Institute when Dr. Richard Keates, Chair of the UC Irvine Department of Ophthalmology, happened to remark how helpful it would be to have a new state-of-the-art ophthalmic surgery system located here.

Charley asked how much the system would cost. The next week he and Nora wrote a check for \$50,000.

Memories

Just two weeks before his death Charley was at the Institute to attend a baby shower for an employee of whom he was particularly fond.

He chatted casually with various employees. This was so typical of Charley—it didn’t matter whether he was speaking with a secretary, a physician, or a young student. He was equally interested in everyone.

Charley, we love you and we will miss you. You will always be an example and an inspiration to us. ■

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Laser Alternative to Hysterectomy

Institute researchers are working on a laser treatment for abnormal uterine bleeding that could make hysterectomies unnecessary in many cases.

The light-based treatment known as photodynamic therapy (PDT) has been used to treat cancer for over a decade. Oncologists value PDT for its ability to selectively target tumors without affecting surrounding healthy tissue.

Now, a team under Institute Medical Director Yona Tadir, M.D., and Professor Bruce Tromberg, Ph.D., in collaboration with the University of Zurich, is expanding the use of PDT to gynecologic medicine.

This laser technique would offer a minimally invasive approach to reduce or eliminate Dysfunctional Uterine Bleeding. Targeting the endometrium (the inner lining of the uterus) with laser light, PDT could become an alternative to removing the whole uterus or conventional endometrial surgery.

Targeting with Lasers

PDT relies on an interaction between a photosensitive drug and laser light to selectively remove tissue. When light of sufficient energy and wavelength interacts with the photosensitizing drug, highly reactive oxygen molecules are generated that irreversibly oxidize target cells and destroy target tissue.

Dr. Tadir and his team have recently patented a new intrauterine device (IUD) to diffuse light for endometrial PDT. When inserted into the uterus, the IUD emits a laser light that illuminates the whole uterine cavity. Harmless in itself, the light triggers the photosensitizer only in target tissue, leaving healthy tissue unaffected.

With their device patent in hand, Dr. Tadir's team is now proceeding to clinical tests of uterine PDT. They expect U.S. Food and Drug Administration (FDA) approval of plans for a clinical study soon. In the study, physicians will perform uterine PDT on women

suffering abnormal uterine bleeding that has not responded to conservative conventional treatments.

A solution of the photosensitizing drug will be applied to the uterus through a catheter. Four to seven hours later, the light IUD will be inserted into the uterus, and an argon-pumped dye laser will illuminate the uterine cavity with visible red light for 15-20 minutes or longer, depending on the thickness of diseased tissue.

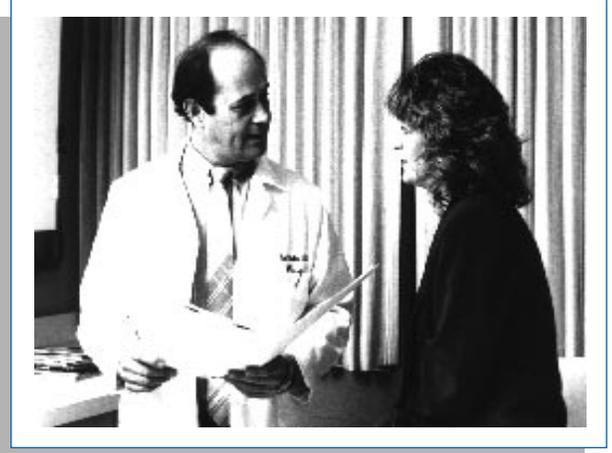
After the procedure, patients will be monitored for bleeding and pain as well as endometrial thickness for three months, and the outcome rated on a scale from "excellent" to "poor." An "excellent" result will involve no pain during treatment, little or no pain for a week afterwards, and the cessation of bleeding with complete destruction of the endometrium.

If tests prove the efficacy of endometrial PDT, the Institute team anticipates that the procedure will become common. "I am confident," Dr. Tadir explains, "that a significant number of hysterectomies can be avoided with the application of this new technique. Moreover, if successful, this procedure may be applied to make other gynecological treatments safer and less complicated."

Significance

About 600,000 hysterectomies are performed each year, making this the most common major operation in the United States. As an alternative to treat abnormal uterine bleeding, laser PDT removal of the endometrium could have significant economic benefit.

Dr. Tadir estimates that per-patient costs of uterine PDT will be about 90% lower than surgical methods: "If fully



Dr. Yona Tadir with a potential uterine PDT patient.

implemented in only the *minimum* target population (approximately 200,000 women per year), uterine PDT could potentially result in millions of dollars in health care cost savings annually."

Professor Philip J. DiSaia, M.D., the Dorothy Marsh Chair in Reproductive Biology in UC Irvine's Department of Obstetrics and Gynecology, sees great potential in PDT: "I really feel that this has the potential for making a major contribution to women's health care."

Interdisciplinary Team

This research is yet another example of interdisciplinary collaboration at the Institute. Researchers on this project come from several UC Irvine College of Medicine departments: Obstetrics and Gynecology, Biophysics and Physiology, Radiology, and the Institute's home department of Surgery. In addition, the collaboration of the department of Obstetrics and Gynecology at the University of Zurich under Professor Urs Haller makes the team international.

"It is very gratifying," comments Institute Director Michael Berns, Ph.D., "that our facility can bring together people with the diverse talents and problem-solving skills needed for creative research like this." ■

Institute Helps Veterinary Laser Programs Nationwide

An important part of the Institute's mission to advance the field of photomedicine is fostering innovative collaborations and providing advanced laser training. Since 1991, a grant from the Office of Naval Research (ONR) has enabled the Institute's Veterinary Outreach Program (VOP) to make a major contribution to this effort.

Under Veterinary Director George Peavy, D.V.M., the VOP has used funds awarded under the medical component of the Defense Department's "Star Wars" initiative, the Medical Free Electron Laser (MFEL) program, to host seminars in laser education for veterinary faculty from around the country. In addition, the Institute has distributed funds to eight different veterinary schools to stimulate and encourage research in photomedicine.

For example, the College of Veterinary Medicine at the University of Missouri-Columbia was awarded \$30,000 to conduct a study of photodynamic therapy (PDT) to treat cancer in dogs. Over twenty dogs have been successfully treated under this program.

Researchers have published several papers, and have begun new collaborations to study laser-tissue interactions.

"Our PDT program," comments Professor John Payne, D.V.M., "has led to strong collaboration here and with other universities. We are preparing to start an FEL project in orthopedics with projected applications for both animal and human patients."

In another example, the School of Veterinary Medicine at the University of Wisconsin at Madison was awarded \$25,000 to undertake a study to establish laser dosages to treat synovitis of the joints, a condition associated with rheumatoid arthritis in many animals. "The School of Veterinary Medicine," explains Professor Mark Markel, D.V.M., "has been able to leverage



From left, graduate student Matt West and Dr. John Payne in their laser lab at the University of Missouri.

MFEL research funding to obtain additional support from industry, private foundation, and government sources."

"The core support of this ONR grant," notes Dr. Peavy, "allows us to foster collaborations like these that advance Institute programs while promoting fruitful collaborations in photomedicine elsewhere, all for the benefit of animal and human health." ■

Industrial Associate Profile: NeXstar Pharmaceuticals, Inc.

Established to provide companies with a window into the evolving world of laser biotechnology, the Beckman Laser Institute's corporate relations program offers companies a formal affiliation with the Institute which allows these firms to conduct joint research projects and tap into the Institute's expertise in biomedicine.

In 1992, the Industrial Associates Program (IAP) was founded to offer start-up companies or divisions of larger corporations the opportunity to collaborate formally with the Institute.

NeXstar, Inc. (formerly Vestar) was one of the first companies to join this

program. There are now 13 active Industrial Affiliates.

"Our collaboration with NeXstar began when they were still Vestar," states Professor Bruce J. Tromberg. "We found that there were projects of mutual interest and our respective expertise really complemented each other."

Located in San Dimas, California, Vestar specializes in the development of new pharmaceuticals and drug delivery systems. Collaborative projects with the Institute have focused in the area of novel chemotherapeutics using liposome delivery systems.

In 1994, Vestar merged with

NeXagen, a Boulder, Colorado-based biotechnology company. Using their own unique technology, SELEX, NeXagen develops efficient and cost-effective therapeutics and diagnostics for such conditions as cancer, cardiovascular disease, and AIDS.

"Our affiliation with the Beckman Laser Institute has been very beneficial," comments Eric Forssen, Pharm.D., Ph.D., NeXstar's Associate Director, Pharmaceuticals. "We appreciate the Institute's state-of-the-art facility as well as the ability to work with creative researchers like Bruce Tromberg and Tatiana Krasieva." ■

Optical Trap Provides New Insight into T-Cell Activation

T-cells are the cornerstone of the human immune system. A class of white blood cells necessary for mediating the immune response to infection, individual T-cells are activated by physical contact with antigen-presenting B-cells.

Although T-cell/B-cell contact is required for an immune response, little is known about the patterns of cellular interaction and their relation to activation.

Institute researchers are using the unique combination of sophisticated microscopy and laser resources at the Laser Microbeam and Medical Program (LAMMP) facility to crack some of the mysteries of T-cell activation.

LAMMP, a user resource sponsored by the National Institutes of Health's Division of Research Resources and located at the Institute, has made its powerful microscopes and lasers available to researchers from around the world for more than a decade. Now LAMMP is playing host to a project that could have profound consequences for understanding the human immune system and developing treatments for a wide range of diseases and immune conditions, from cancer and AIDS to the body's reaction to organ transplants.

Just the Tool for the Job

Paul Negulescu, Ph.D., became interested in T-cell research as a postdoctoral fellow in the lab of UC Irvine Professor of Physiology and Biophysics Michael Cahalan. Dr. Negulescu learned about LAMMP from Institute Professor Bruce Tromberg and LAMMP Resource Manager Tatiana Krasieva, Ph.D.

LAMMP's optical trapping capability was crucial to advance Dr. Negulescu's research: "The 'optical tweezers' offered just what we lacked—a way to grab and move individual cells and thereby investigate the physical nature of the immune response on a cell-by-cell basis."

Physically manipulating T- and B-cells is particularly important because successful triggering of an immune response depends on where the two cells connect.

Dr. Negulescu explains that "one side of the T-cell is far more sensitive than the other, and this is clearly where the two cells must meet for an immune response to occur."

In this project, the geometry of T-cell/B-cell pairs was manipulated on the stage of a confocal microscope using an optical trap produced by a near-infrared titanium-sapphire laser. One experiment involved placing B-cells at various locations along a single T-cell, which has a "head" and "tail" defined by shape and the direction of crawling.

A fluorescent readout of calcium signalling when the two cells touched indicated whether or not an immune response had been triggered. T-cells stimulated with a B-cell at the leading edge, or "head," were ten times more responsive than those contacting B-cells with their trailing end, or "tail."

These experiments reveal for the first time the relation between T-cell/B-cell orientation and T-cell activation, and the finding that the T-cell is polarized fundamentally changes our understanding of how the two types of cells interact in immune response.

More Progress Expected

Future experiments will use the optical trap to determine basic biophysical characteristics and requirements for stimulating T-cells *in*



From left, Tatiana Krasieva, Bruce Tromberg, and Paul Negulescu in the optical trapping lab.

vivo. Understanding how cells stick to each other is important because T-cell/B-cell pairs must be stable in order to properly activate. Improving our knowledge about the physical nature of T-cell activation will help in designing therapies to either promote or inhibit immune responses in humans.

After completing his postdoctoral fellowship at UCI, Dr. Negulescu has moved from academe into the biotechnology industry.

However, the project he brought to LAMMP has shown such promise that Institute researchers have decided to continue it, and Professor Tromberg has recruited graduate student Xunbin Wei to continue this work.

Everyone involved in this collaboration has found it to be very fruitful. "Paul has given us insight on new applications of the optical trap," Professor Tromberg observes.

And for his part, Dr. Negulescu feels that working at the Institute helped advance his research and his career. "The LAMMP facility," he feels, "is an invaluable resource for cell research, only matched by the brain power of my colleagues at the Institute." ■

Charley Hester: Leading by Example

Charles "Charley" Hester, Chairman of the Institute's Board of Directors, died on Thursday, February 29, 1996 in Newport Beach, California.

A long-time Institute board member and supporter, Charley was only the second Chairman in the Institute's history, having succeeded Dr. Arnold O. Beckman in 1994.

Born in 1913, Charley was raised in a small town 100 miles from St. Louis. After his marriage to Nora in 1936, they moved to Orange County, California for his health.

Settling in Santa Ana, then the commercial center of the county, they bought a motel and started the Hester Development Company, which began building apartments and homes. Charley was one of the first to see the true value of beachfront property, which led him to develop several important coastal sites.

In the mid-seventies, he and Nora began to support local charities. These included the Children's Hospital of Orange County, Hoag Hospital, the Orange County Performing Arts Center, the Boy Scouts of America, Chapman University, and, of course, the Institute.

"Charley supported the Institute in so many ways," comments Dr. Beckman. "When I asked him to join the Board," he continues, "I had no idea how generous he would be with both his commitment of financial support and, more importantly, his time."

"Charles Hester exemplified the very best philanthropic ideal: leading by example," comments UC Irvine Chancellor Laurel Wilkening.

In addition to wife Nora, Charley is survived by three daughters: Marilyn Gianulias, Charlene Immel and Janet Hamilton. ■



Nora and Charley Hester.

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PRESENTATIONS

Yona Tadir, M.D., spoke on "Photodynamic Therapy in Gynecology: New Trends" at the third annual Immunological Approach to Tumor Therapy Meeting in Bonn. In conjunction with Institute Industrial Associate Cell Robotics, Inc., Dr. Tadir gave a presentation to the Food and Drug Administration on optical trapping applications in assisted reproduction.

J. Stuart Nelson, M.D., Ph.D., presented a talk entitled "Recent Advances in the Clinical Management of Hypervascular Skin Abnormalities" at the International Laser Update in Plastic, Cosmetic Surgery and Dermatology Meeting in Tokyo. He addressed the UC Irvine Department of Pediatrics Grand Rounds on "Laser Treatment of Selected Dermatoses in Children."

Joseph Neev, Ph.D., presented four papers at the annual SPIE meeting in San Jose, California: "Applications of Ultrashort Pulse Lasers for Hard Tissue Surgery"; "Thermal and Noise Level Characteristics of Hard Dental Tissue Ablation with 350 fs Pulse Laser"; "Ultrashort Pulse Laser System for Hard Dental Tissue Procedures"; and "Scanning Electron Microscopy and Ablation Rates of Hard Dental Tissue with 350 fs and 1 ns Tunable Pulse Duration Laser System."

George Peavy, D.V.M., addressed both the Alameda County and the Santa Barbara/Ventura County Veterinary Medical Associations on "Photodynamic Therapy for the Treatment of Cancer in Animals."

Dr. Petra Wilder-Smith spoke to the German Society for Lasers in Dentistry in Frankfurt on "The CO₂ Laser at 9.3 μ m: a New Tool for Hard and Soft Tissue Applications in Dentistry?" She also addressed the annual SPIE meeting on "Histological Events Resulting from Soft Tissue Incisions Using a CO₂ Laser Emitting at 9.3 μ m."

Olivier Coquoz, Ph.D., spoke on "Optical Monitoring of Cellular Physiology Using Frequency-Domain Photon Migration" at the OSA Annual Meeting in Portland, Oregon.

PUBLICATIONS

Yona Tadir, M.D., published "Laser Technology in Reproductive Medicine" in the book *Reproductive Endocrinology, Surgery and Technology*.

Bruce Tromberg, Ph.D., published "A Mathematical Model for Light Dosimetry in Photodynamic Destruction of Human Endometrium" in *Physics in Medicine and Biology*.

Hong Liang, Ph.D., published "Wavelength Dependence of Cell Cloning Efficiency after Optical Trapping" in *Biophysics Journal*.

Dr. Petra Wilder-Smith published "Thermal Microstructural Effects of Nd:YAG Laser Irradiation and Root Planing on Root Surface" in *The Journal of Periodontology and Biomedical Optics*. She also published "Incision Properties and Thermal Effects of Two CO₂ Laser in Soft Tissue" in *Biomedical Optics*.

Bahman Anvari, Ph.D., published "A Theoretical Study of the Thermal Response of Skin to Cryogen Spray Cooling and Pulsed Laser Irradiation: Implications for Treatment of Port Wine Stain Birthmarks" in *Physics in Medicine and Biology*. He also published "Dynamic Epidermal Cooling in Conjunction with Laser Treatment of Port Wine Stains: Theoretical and Preliminary Clinical Evaluations" in *Lasers in Medical Science*.

Josh Fishkin, Ph.D., published "Gigahertz Photon Density Waves in a Turbid Medium: Theory and Experiments" in *Physical Review E*.

NOTABLES

Martin J.C. van Gemert, Ph.D., is a Visiting Professor from the University of Amsterdam, where he is director of the Laser Center, located at the Academic Medical Center. Dr. van Gemert is researching non-invasive thermal and optical sensing of port wine stain birthmarks with J. Stuart Nelson, M.D., Ph.D.

Mark A. Anton, M.D., Assistant Clinical Professor of Plastic Surgery, has joined the staff of the Surgery Laser Clinic. He also practices in Newport Beach, California.

Hugh M. Bailey, M.D., Assistant Clinical Professor of Plastic Surgery, has joined the staff of the Surgery Laser Clinic. He also practices in Newport Beach, California.

Malcolm Paul, M.D., Assistant Clinical Professor of Plastic Surgery, has joined the staff of the Surgery Laser Clinic. He also practices in Fountain Valley, California.

Johanna Stewart has joined the clinic as Billing Manager. She comes to us from Lifeline Homecare where she was Director of Reimbursement.

Jo Bowman has joined our staff as an Administrative Assistant. She provides secretarial support to faculty. Jo comes to us from Sweek Connolly and Company, a CPA firm.

Cecilia Young is a new Administrative Assistant. Cecilia's responsibilities include administrative support for Director Michael Berns, Ph.D., and other Institute faculty.

Jill Monti has been hired as Resource Coordinator for the LAMMP program. She also serves as Animal Care Assistant, responsible for assisting in the operation and maintenance of the Animal Treatment Suite. ■

NEWSBRIEFS

SKIN RESURFACING

The Institute has recently acquired a new Coherent UltraPulse laser for skin resurfacing. This means that we now have two state-of-the-art lasers to provide the most comprehensive and up-to-date skin resurfacing procedures available, including wrinkle and acne scar removal.

Please contact our clinic at (714) 824-7997 for more information, or to arrange for a consultation appointment.

UPDATED WEB SITE

If you haven't seen the Institute's Internet site on the World Wide Web recently, then you haven't seen it at all!

Now, Internet visitors to the Institute can learn about clinical procedures, access our current research report, browse faculty and staff profiles, skim electronic versions of this newsletter and other publications, and even fill-out an application to use the Institute's NIH-sponsored Laser Microbeam and Medical Program (LAMMP).

We have also been working to make the site easier to use and more visually attractive. You can find us on the web at <http://www.bli.uci.edu>.

Since our site is still in progress, we welcome your comments and suggestions.

NEW PATENTS

Several new patents have recently been issued to Institute researchers. Among these are a medical device to deliver light into the uterine cavity to treat gynecological disorders (see "Laser Alternative to Hysterectomy on page 3), and a promising method for non-invasive diagnostics.

Professor Bruce J. Tromberg, the lead inventor of the diagnostic method, comments, "It's gratifying to see our research result in a patent."

"I see these inventions," explains Institute Director Michael Berns, Ph.D., "as the by-product of our increased efforts to spin-out new medical procedures and devices into the marketplace to benefit patients."

SHOW HONORS VET

"The Pet Place" television show recently honored the Institute and Veterinary Director Dr. George Peavy at its Fourth Annual Special Recognition Awards Luncheon held December 10 in Huntington Beach, CA.

Dr. Peavy was recognized for the Institute's on-going Veterinary Outreach Program, which offers laser treatment to animals and advanced laser training to local veterinarians.



"Pet Place" host Fred Bergendorff presents a Recognition Award to Dr. George Peavy.

Dr. Peavy was among the area celebrities, animal activists, volunteers, and animal rescue heroes who were nominated by either colleagues, clients, or community leaders for extraordinary acts on behalf of animals.

Southern California viewers can watch "The Pet Place" Saturdays at 6:00 p.m. and Sundays at 6:00 a.m. on KDOC-TV, Channel 56. The show features pets available for adoption along with discussions of animal welfare issues. ■



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