FALL 2007

Point of View
THE EYE RESEARCH INSTITUTE UNIVERSITY OF WISCONSIN–MADISON

Coming Full Circle

During his sophomore year in high school, Daniel Albert's father was diagnosed with bladder cancer and was treated at New York's Memorial Hospital (now part of Memorial Sloan-Kettering Cancer Center). Albert, who found the cancer wards to be places filled with people in great pain, resolved that he would someday contribute to alleviating the sort of suffering he witnessed.

Now, over fifty years later, Daniel Albert, MD, MS, is the Retina Research Foundation Emmett A. Humble Distinguished Director of the UW Eye Research Institute. His academic career began at Yale, where he served on the faculty for seven years; he then spent seventeen years as professor at Harvard University. In 1992, he was recruited to the University of Wisconsin to serve as chair of the department of Ophthalmology and Visual Sciences, where he continues as professor and chair emeritus.

During that half-century span, Albert became a world expert in cancer and ophthalmology, and has written over 600 peer-reviewed research publications and 25 textbooks. He is the recipient of numerous national awards, including the prestigious Lucien Howe Medal of the American Ophthalmological Society, the Fight for Sight/Mildred Weisenfeld Award for Lifetime Achievement in Vision Research, and the American Academy of Ophthalmology's Distinguished Service Award for his service as editor of the premier journal, *Archives of Ophthalmology*. Each facet of Albert's career has been shaped by educational experiences and his years of research in the laboratory.

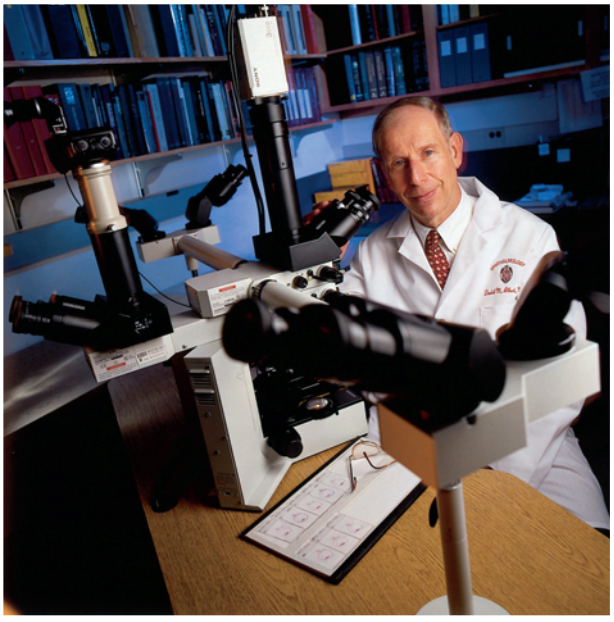
Early laboratory exposure during his undergraduate years at Franklin and Marshall College introduced Albert to tissue culture techniques. "These techniques were advancing in the 1950's and I was fascinated with the process. We drove to West Chester to get fertilized eggs from a farm, and then dissected the embryos to obtain the cells we needed. We applied nerve growth factors to the cells and learned about the mechanisms that control cell growth.

"We also used HeLa cells, which were cells derived from cervical cancer tissue; these were special in that they divided an unlimited number of times in a laboratory cell culture plate. We put varying doses of cyanide on the cells to learn how toxic compounds affected cells. In very small doses, the cyanide actually caused cells to grow faster, and increasing the dose then inhibited their growth."

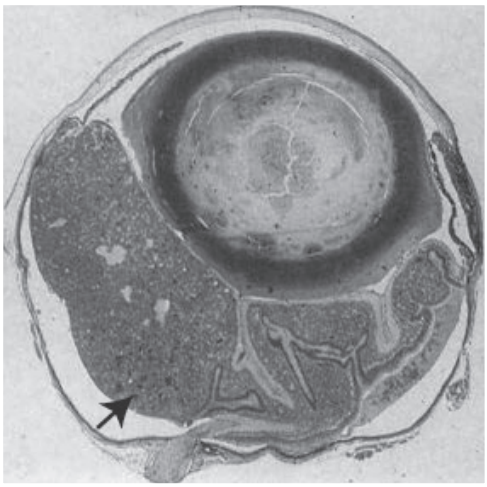
It wasn't until his senior year in medical school at the University of Pennsylvania that Albert fell in love with the eye. He had been preparing for advanced training in pathology, but the late renowned ophthalmologist Dr. Harold Scheie convinced Albert that he could do nearly anything related to pathology by pursuing ophthalmology training, as ophthalmic pathology comprised all the diseases of the eye and also required substantial knowledge of cell mechanisms in diseases of the nervous system, neuromuscular system, and other body systems.

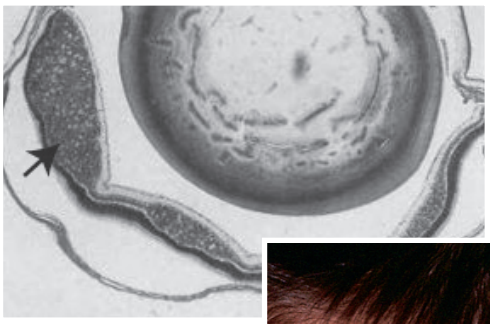
These early experiences combined to greatly influence Albert's research career of nearly 40 years, which has produced significant contributions to the treatment and understanding of eye cancers, and in particular, has spurred his investigations of the use of vitamin D and other natural compounds to reduce tumor size.

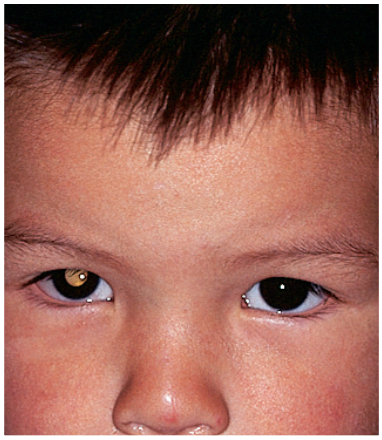
His many achievements have included participation in the team that first cloned the gene for *retinoblastoma*, a childhood eye tumor, and—harkening back to his Franklin and Marshall experiences—the development of the first "immortalized" line of retinoblastoma cells which could be grown indefinitely in a dish. Albert was also part of the group that designed the first lab mouse with retinoblastoma. By studying these genetically-modified mice, Albert and his colleagues can simulate the develop-



Daniel M. Albert, MD, MS, reviews and classifies the microscopic changes in tumor cells treated with natural chemotherapeutic compounds.







Above: The tumor fills the back of the eye in the top photo of a mouse model of retinoblastoma; in the bottom image, the tumor size is greatly reduced after treatment with vitamin D compounds. The arrows point to the tumors.

Right: The appearance of a "white pupil" reflection in one or both eyes is a characteristic of retinoblastoma.

ment and progression of human disease and can create new treatment methods.

"Our research has found that a type of vitamin D helps to shrink tumors in mice," says Albert. "Vitamin D also may prevent the spread of the tumor cells in retinoblastoma with a less toxic effect than traditional chemotherapy or radiation treatment." These results are sufficiently promising that Albert is now initiating clinical studies in children with eye tumors at M.D. Anderson Cancer Center and, bringing his work full circle, at Memorial Sloan-Kettering. As is often the case in science, Albert's research has implications for other types of cancer. The clinical trials in retinoblastoma are being extended to the treatment of children with ***neuroblastoma***, a devastating tumor prevalent among infants and young children that carries a high mortality in its advanced form.

Vitamin D is a naturally-occurring vitamin, produced by the body and found in foods such as fish, liver, and egg yolks. Albert and Arthur Polans, PhD, Associate Director of the Eye Research Institute and professor of Ophthalmology and Visual Sciences, now collaborate on studies of another natural product for the treatment of an adult eye cancer, *uveal melanoma*. Albert was the first investigator to generate immortalized melanoma cell lines derived from this type of cancer.

Resveratrol, a non-toxic plant product with chemopreventive and chemotherapeutic potential, holds promise for the inhibition of the growth of melanoma and other cancer cells. Resveratrol is found in the skins of red grapes and in some berries and nuts.

Albert explains, "The addition of resveratrol to tumor cells in culture inhibits their proliferation. In addition to these effects, resveratrol also encourages tumor cell death in animal models of eye and other types of cancer. Our next steps are to learn exactly how the drug works within the cells, and in what ways we can add resveratrol to the treatment options for eye and skin melanoma patients and those with other cancers."

Critical to this work was funding provided by David Mandelbaum, an attorney and real estate developer in New Jersey, and his brother, Nathan Mandelbaum, also an attorney. Known as the *Mandelbaum Cancer Therapeutics Initiative*, the project supported the testing of resveratrol derivatives in varying formulations and dosages to learn which might be most effective in therapy. These experiments provide the necessary data to prepare compounds that can then be given to human patients in clinical trials, and eventually, to secure FDA approval for commercial therapeutics.

"The support from the Mandelbaums allowed this project to move ahead much more quickly than otherwise possible," says Albert. "Funding from the National Institutes of Health doesn't arrive in an investigator's account for at least nine months after a grant proposal is submitted. In that amount of time, the Mandelbaum funding allowed us to complete the dose-response testing, studies of the mechanism of drug action, and brought us to the point of deriving a purified compound ready for clinical trials. And every minute we save brings the possibility of a useful treatment closer to delivery to a cancer patient."

And for Albert—whose career was shaped by his father's encounter with cancer, reinforced by his early work and educational experiences in the laboratory, and accelerated by funding provided at a critical juncture—seeing his research come to fruition is extraordinarily gratifying. "I'm hopeful that my years of work in the laboratory will make a significant contribution to cancer research and treatment. And I like to think that my father would have been proud of the work he helped to inspire."

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