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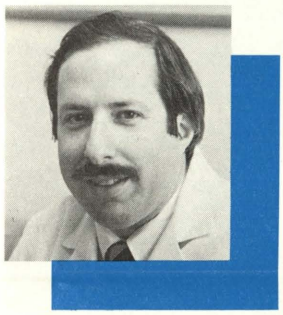
Neodymium:YAG Laser Therapy for Palliative Treatment of Penile Kaposi's Sarcoma



Kenneth I. Wishnow

Though laser therapy has had long-standing success in opthalmology and dermatology, its use in other fields is just beginning. Recently, two M. D. Anderson urologists, Kenneth I. Wishnow, M.D., and Douglas E. Johnson, M.D., were the first to treat penile Kaposi's sarcoma lesions with a neodymium:YAG (yttrium, aluminum, garnet) laser.

"The neodymium:YAG laser has a lot of potential, especially in regard to the palliative treatment of patients with AIDS (acquired immune deficiency syndrome). The patient we treated, like other AIDS patients, developed Kaposi's sarcoma. Though we could not cure his systemic disease, we successfully treated a local manifestation of it," said Wishnow.

Like all lasers, the neodymium: YAG laser precisely delivers high energy to a discrete area, removing diseased tissue while preserving normal tissue. But what distinguishes the neodymium: YAG from most other lasers, Wishnow said, is its versatility. The neodymium: YAG laser, unlike the more conventional CO_2 laser, has a wavelength suitable for endoscopic use, and thus can be used to treat internal tumors, such as those of the bladder. "It also has more tissue penetration and results in less bleeding," he said.

These advantages were important factors in deciding to use the neodymium:YAG laser for this patient, Wishnow said. "We could have used a CO_2 laser, but since we didn't know how deep the lesion was, we felt the better tissue penetration of the neodymium: YAG laser would result in a deeper surgical margin and therefore reduce the possibility of recurrence. And because the penis is a very vascular region, we were worried about bleeding. Though we could have used it for the topical lesion, the CO_2 laser cannot penetrate fluid as effectively. This makes it more difficult to cauterize underlying blood vessels."

In addition to reducing morbidity, the procedure is less expensive than surgery.

The patient had a topical lesion on the glans penis adjacent to the urethral meatus, which was easily photoablated, but the patient also had a second lesion in the fossa navicularis inside the urethra. To direct laser therapy to that lesion, Wishnow and Johnson used a gastrointestinal optic fiber passed through a panendoscope.

Though laser therapy was not the only possible form of treatment for this lesion, it clearly was superior in terms of morbidity, Wishnow said. "Radiation therapy might have resulted in a deformity of the penis, and open surgery—a total or partial penectomy—would have had a negative psychological impact on the patient."

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Alternative Treatments Sometimes Necessary

Wishnow emphasized that such treatments are sometimes necessary, as in the case of local disease that has the potential to metastasize. "If a potentially metastatic lesion is locally curable, then initial treatment must be aggressive, but in this case the patient had AIDS and thus a higher risk of developing infection as a result of open surgery. Moreover, the penile lesion was a local manifestation of a systemic disease, so we could 'undertreat' the patient in the sense that, if the lesion recurred, we could simply photoablate the lesion again."

The potential for metastasis was not a principal concern in this case, but if the lesion had been a local carcinoma with the potential to micrometastasize, then the patient's survival would have hinged on complete eradication of the disease. If this had been the case, then alternative treatments might have been necessary.

"Because the neodymium: YAG laser had never been used on a penile Kaposi's sarcoma lesion, we really didn't know how likely the lesions were to return," Wishnow said. However, to date, the lesions have not recurred in the treated area, though other penile lesions have appeared in untreated areas. If this form of therapy is as successful in other patients, then the neodymium: YAG laser may play an important role in palliative treatment for Kaposi's sarcoma, he said.

Reduced Morbidity

In this case, a local manifestation of systemic disease had compromised an organ's function. The Kaposi's sarcoma lesion had made urination painful and difficult. Treatment, therefore, was directed at preserving the organ's function at the least possible cost—both physically and psychologically—to the patient, Wishnow said. "After treatment, the patient reported no pain. Two or three days later he was able to urinate well. One week later, the treated areas showed tissue necrosis and minimal edema but no infection. The remarkable thing about laser therapy is that, even though there seems to be a lot of destruction on the surface, actual penetration is only a few millimeters. Though the epithelium is destroyed, the underlying tissue is preserved," Wishnow said.

Wishnow emphasized that in addition to reducing morbidity, the procedure is less expensive than other forms of surgery. "This patient was treated as an outpatient. The procedure was performed in less than an hour and the patient went home the same day. Use of the laser is expensive, but this cost is more than offset by eliminating the 5- to 7-day hospitalization. This is significant, considering that penile Kaposi's sarcoma, though once rare, is increasing in frequency as a result of AIDS."

Other Uses for Laser Therapy

Laser therapy is currently available in many community hospitals and can be used to treat noncancerous lesions as well, according to Wishnow. "Lesions of the external genitalia, such as condyloma acuminatum, can very easily be treated on an outpatient basis."

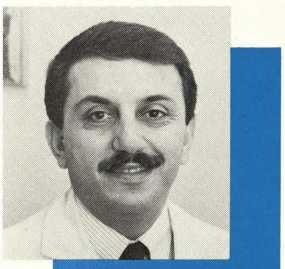
Wishnow cautioned, however, that a confirmed diagnosis is necessary before using laser therapy. "It is often necessary that a biopsy be performed so that histologic examination can confirm the diagnosis. If a lesion that is perceived to be benign is destroyed when in fact it was a carcinoma, you're putting the patient at risk for metastasis. If you eliminate the lesion before biopsy, obviously you're eliminating the only means of confirming the diagnosis."

The neodymium: YAG laser may play an important role in palliative treatment for Kaposi's sarcoma.

Aside from ophthalmologic and dermatologic applications, which have become well established, laser therapy is being explored for treating gynecologic, gastrointestinal, cardiac, neurologic, thoracic, orthopedic, and head-and-neck diseases, according to Wishnow. "If applications in other fields have analogous results, then laser therapy, in general, may end up costing the patient less. The irony of this treatment is that the laser itself is a very expensive piece of equipment, but the decreased morbidity from such treatment has other benefits, such as reducing—or eliminating—the need for inpatient care. In my field, whether laser therapy can effectively replace open surgery remains to be seen, but in terms of palliative treatment for local disease, its prospects are promising." ■

Physicians who desire additional information may write Kenneth I. Wishnow, M.D., Department of Urology, Box 110, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, or call (713) 792-3250.

New Range of Fungal Infections Seen in Cancer Patients



Elias J. Anaissie

Species of the fungi *Candida* and *Aspergillus* sometimes cause opportunistic fungal infections in cancer patients. Recently, however, severe infections of this type were traced to newly recognized fungi such as *Fusarium*, *Trichosporon*, *Bipolaris*, *Geotrichum candidum*, *Cunninghamella*, *Curvularia*, *Pseudalescheria boydii*, and others, according to Elias J. Anaissie, M.D., assistant professor in the Section of Infectious Diseases at The University of Texas M. D. Anderson Cancer Center.

Patients who are profoundly neutropenic and remain so for several weeks are most often affected—especially those with hematologic malignancies such as acute myelogenous leukemia and those receiving bone marrow transplants. The main predisposing factors for the development of these infections include bone marrow suppression, use of broad-spectrum antibiotics, disruption of the integrity of the skin and mucous membranes, and the use of immunosuppressive drugs. A few fungal infections have been related to the use of central venous catheters.

Neutropenic patients may not develop classic signs and symptoms of infection.

Infections Difficult to Diagnose

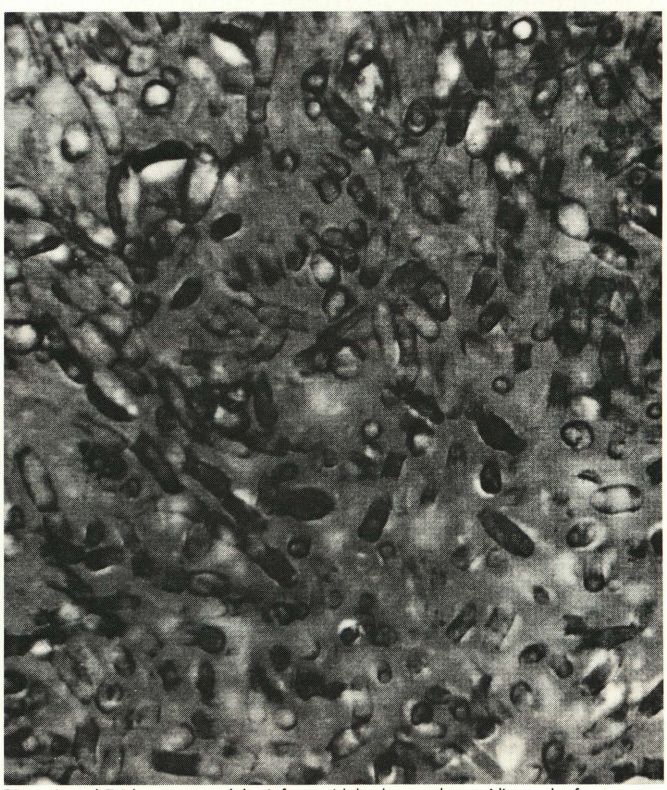
Ranging from minor to life-threatening ones involving multiple organs, these infections are usually disseminated, especially in severely neutropenic patients.

"Unfortunately, the diagnosis of these infections may be quite difficult," Anaissie said. "Neutropenic patients may not develop the classic signs and symptoms of infection because of the lack of inflammatory response. The only sign of infection may be a fever not responsive to adequate and broad-spectrum antibiotics."

Some of the isolates present as sinusitis, especially *Fusarium*, *Bipolaris*, and *Curvularia*; this suggests that the organisms are inhaled through the airways and "should alert us to the possibility that sinus infection in the immunocompromised patient could be caused by one of these organisms," he said.

Signs and Symptoms of Most Common Fungi

Most commonly encountered in recent experience are *Trichosporon beigelii* and *Fusarium* species (see photographs).



Disseminated *Trichosporon*: nodular infarct with hyphae, arthroconidia, and a few yeasts.

T. beigelii is a saphrophytic organism often found on the skin; it causes infection only if the host's defenses are severely altered. Its clinical presentation is similar to that

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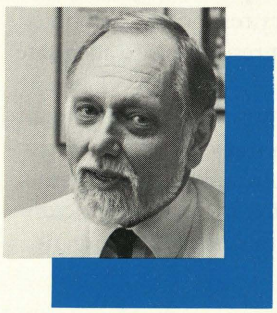
Knowing How Normal Cells Differentiate Will Add Rationality to Stopping Cancer Cells



William J. Lennarz

By what biologic principles is cancer connected to embryonic development?

William J. Lennarz, Ph.D., chairman of the Department of Biochemistry and Molecular Biology, speaks in questions and answers, which are the rhythm of his work, and he makes clear quickly that those who study basic cancer mechanisms are a long way from understanding them.

He explained the connection between cellular development of the embryo and cancer by describing the cellular process of the early stages of life, the predifferentiated stages during which identical cells replicate rapidly. During differentiation, the next stage, cells begin to "differentiate into specific subtypes," he said. "They become brain cells, liver cells, and so on, and then their fate is sealed, their schedule set. They can keep increasing—in the human being until adolescence—and then begin a slow rate of turnover but no longer rapid growth. But if cancer develops, the cells return to a dedifferentiated stage of rapid multiplication that eventually results in a tumor."

In cancer, cells return to a dedifferentiated stage of rapid multiplication.

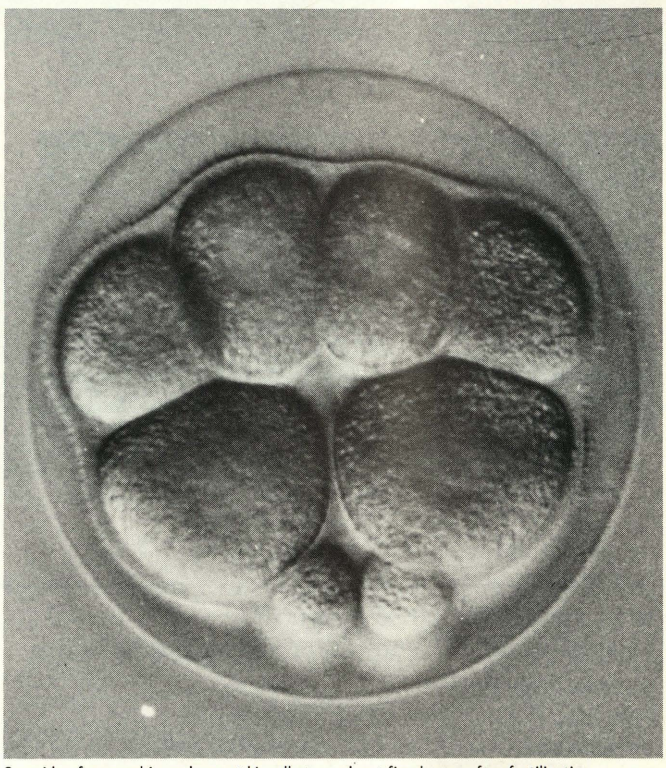
How Does a Cell Stop Differentiating?

What happens in cancer, he said, probably in several steps, is that the differentiation program of a skin or kidney or brain cell becomes perturbed, causing the cell to revert to its primitive form, to dedifferentiate. It starts losing some of its characteristic molecules.

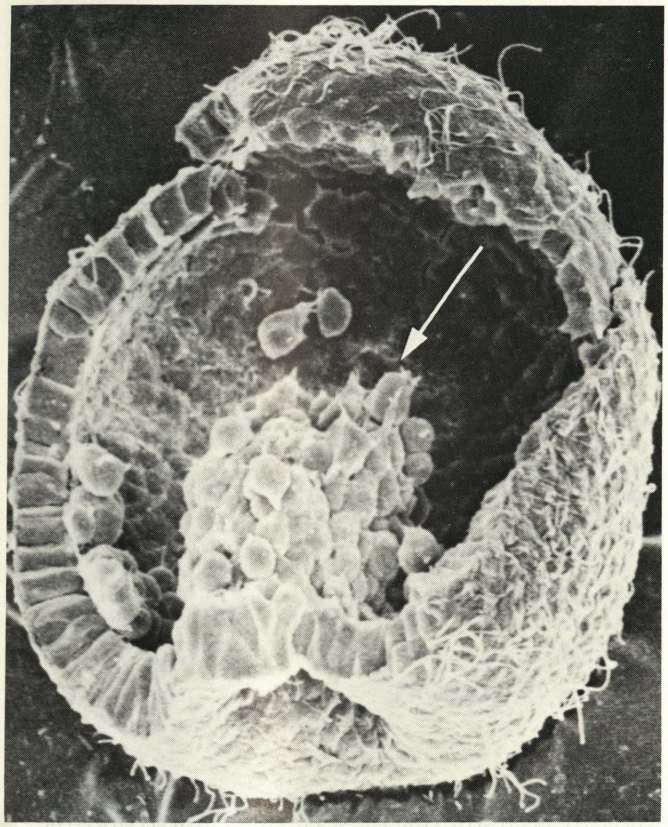
"We ask," Lennarz said, "why and how does that cell now lose its ability to maintain differentiation, its specific characteristics? And the bottom line is that if you put my back to the wall and ask me to describe the events, I can't do it because I don't understand normal growth nor does anybody else. Basically, then, we need to understand how growth is controlled before we can answer the question, What causes this cell to dedifferentiate and grow like crazy to form a tumor?"

Sea Urchin a Useful Model

An accessible model for studying these basic processes is the sea urchin embryo, Lennarz said, "because you can produce these embryos in very large numbers by mixing sperm and eggs in the test tube; you can have millions of them growing in synchrony—and perhaps even more important, you can benefit by the knowledge of people who have been studying the sea urchin embryo since the discovery of the microscope."



One side of sea urchin embryo at 16-cell stage about five hours after fertilization.



Gastrula-stage sea urchin embryo about 48 hours after fertilization, dry-fractured to expose differentiating cells (arrow) that form the primitive gut. Cells inside wall at left will form the skeleton. The embryo now consists of about 1000 cells.

Flattened pluteus-stage embryo about 96 hours after fertilization, showing terminally differentiated cells that form the skeleton.

For hundreds of years, he said, "people have been peering at this organism, so we know which cell gives rise to which tissue. And it's simpler and cheaper and everything happens a lot faster than in the mammal. Some basic biologic processes, for instance the formation of the intestine and the skeleton, have analogues in mammals, so this is a reasonable model system" (see photographs).

In describing the process of differentiation, he said each kind of cell in the body has a sort of "fingerprint collection of molecules it makes." The liver cell produces serum albumin to be pumped into the serum to carry lipids and other components, and it produces transferrin, which picks up iron to be returned to the cells. "So the liver cell has a pattern of molecules it makes, controlled by a set of genes—which are the same in all the cells of the whole organism, but the genes turned on in the liver cell are different from those in, say, the skin cell." During this process the cell involved in cancer reverts back to the earlier stage of rapid, seemingly uncontrolled multiplication.

How cells know where they are "is becoming a fundamental issue."

Muscle to Mouse

Lennarz is the first chairman of his department, having come here five years ago from Johns Hopkins University School of Medicine where he was a professor in the department of biological chemistry. At the M. D. Anderson Cancer Center, he is the Robert A. Welch professor of chemistry. His department has 110 staff members, including 11 faculty members, 25 graduate students, and 35 postdoctoral trainees. All are engaged in studying one or another aspect of cell differentiation because what Lennarz calls the shotgun approach to cancer, to stopping abnormal growth, will not be totally replaced by more rational methods until the normal processes are known.

So, for example, Eric N. Olson, Ph.D., works on differentiation of muscle and other cells; Daniel D. Carson, Ph.D., on how the mouse embryo becomes attached to

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Fungal Infections continued from page 3

of disseminated candidiasis, which frequently causes metastatic skin lesions. These lesions may be diagnosed by biopsy examination. "For diagnosis and therapy, it is useful to know that *Trichsporon* shares common antigenic determinants with *Cryptococcus neoformans*. If you get a positive antigen for *Cryptococcus* in a cancer patient with unexplained fever and without evidence of cryptococcal infection, it is likely that the patient is infected with *Trichosporon*," said Anaissie.

Acute branching septate hyphae of *Fusarium* in lungs.

Fusarium species, fungal organisms commonly present in nature, were responsible in World War II for intoxicating millions of people who ingested contaminated food. But infections are rare and have been noted only recently, primarily in cancer patients. *Fusarium* tends to cause skin lesions similar to those of aspergillus infections and, unlike *Aspergillus*, *Fusarium* can be cultured from blood, Anaissie explained.

Profoundly neutropenic patients are most often affected by these fungal infections.

"Several of the newly recognized fungi look like *Aspergillus* or *Candida* in tissue. The only way to distinguish them from commonly encountered fungi is to obtain a culture," he said. Culture specimens should be obtained from any site of potential infection, including blood, sputum, urine, and bone marrow, but blood culture will not yield the fungus in the majority of cases. Serum blood tests for detecting fungal antigens are currently being developed but are not yet clinically applicable.

Amphotericin B remains the treatment of choice for these infections.

Drug Resistance and Susceptibility

Cunninghamella, *Trichosporon*, and *Pseudalescheria boydii* tend to resist amphotericin B, the drug most commonly used to treat candidiasis and aspergillosis, making identification of the pathogen and establishment of drug sensitivity critical for the management of these patients.

Amphotericin B remains the treatment of choice unless the offending organism has been shown to be resistant to this drug and susceptible to other drugs or drug combinations.

A new approach to preventing aspergillus pneumonitis may be the use of aerosolized intranasal amphotericin B, which has been shown in a limited series to prevent the development of this life-threatening infection.

Use of the drug 5-flucytosine, in combination with amphotericin B, has been advocated for treatment of disseminated candida infections, "but studies to support its use are lacking," said Anaissie. Other possible drugs for treating these fungal infections are miconazole and some other newly described azoles such as itraconazole or fluconazole. But these drugs are fungistatic only and have not been adequately studied in cancer patients.

Neutrophil Count Most Important

"The patients' neutrophil count is the most important factor in their recovery from fungal infections," said Anaissie. "By using granulocyte-macrophage colony-stimulating factor (GM-CSF), we try to shorten the duration of neutropenia in patients and thus either prevent or treat some of these infections."

In addition, said Anaissie, other newly developed antifungal drugs are under investigation for their potential as prophylactic agents for fungal infections. ■

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Cell Differentiation continued from page 5

uterine epithelial cells and invades that tissue, a process similar to cancer metastasis; and Barry D. Shur, Ph.D., on how cell surface molecules provide information to the nucleus.

This last question, how cells know where they are, "is becoming a fundamental issue," Lennarz said, "boiled down to: cells know where they are in response to the environment because on the surface their binding molecules interact with molecules on nearby cells, or with molecules in the fluid around them. That binding process sends molecular signals into the cells, which end up turning genes on or off. A lot of the molecular details on how this works are not totally clear, but that seems to be the general strategy."

How Are Genes Regulated?

The other theme of their work, perhaps broader and overlapping, Lennarz said, is, "How are genes turned on and off, how are they regulated? Again, we're approaching this using mainly normal, not cancer, cells. What are the factors that cause a cell to become a muscle cell? That's a terminal differentiation event; after that the cell will proliferate no more. It fuses with another cell, and they start making a structure that we would eventually recognize as muscle tissue. It's a program, and if the cell doesn't follow that program, it may become a cancer cell."

Cell growth is the focus of much basic research around the world, most of it unrelated to cancer, he said. "Some cancer centers support research, some don't, and I think our institution deserves credit for the fact that, in addition to being known for the best possible cancer treatment, it recognizes that the future of cancer treatment is in basic research."

And since scientists are wishful thinkers by profession, Lennarz would like to believe, he said, that the principles of growth control will be clarified in some great discovery, and that this will open the door to a whole new way of treating cancer. "No one has seen any direct sign of this yet," he said, "and anyway if I saw it, I hope I would be smart enough to make the discovery myself." ■

Physicians who desire additional information may write William J. Lennarz, Ph.D., Department of Biochemistry and Molecular Biology, Box 117, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, or call (713) 792-8602.