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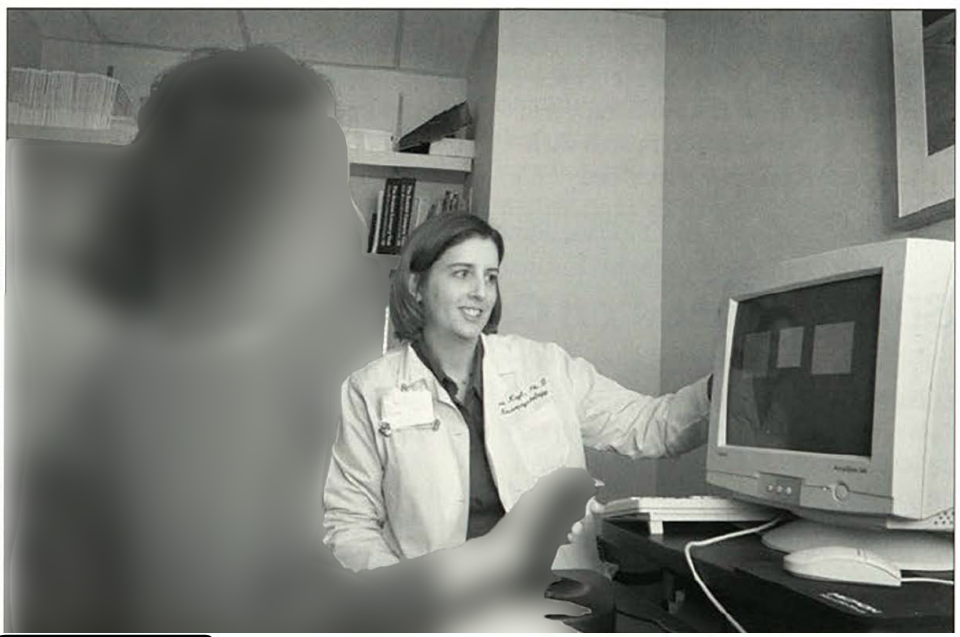
OncoLog

Multidisciplinary Team Helps Patients with Cancer Overcome Cognitive Problems

Researchers Work to Understand Cognitive Losses, Improve Function

by Karen Stuyck

Forgetting an important date or the name of a long-time associate, being unable to read an entire newspaper article in one sitting, suddenly finding it impossible to prepare the elaborate family dinners that were once second nature—many patients with cancer are surprised to discover that they have cognitive problems during and after cancer treatment. These problems, which can range from memory loss to difficulties in focusing attention, sustaining concentration, and performing multiple tasks, are common but often go undiagnosed and untreated by health care professionals.



[redacted] *uses a computer program to enhance her visual scanning and reaction-time skills under the guidance of* **Dr. Anne E. Kayl**, *assistant director of the Neuropsychology Service in the Department of Neuro-Oncology.*

"There are relatively few patients with cancer who don't experience some kind of cognitive problem," said Christina Meyers, Ph.D., a professor and director of the Neuropsychology Service in the Department of Neuro-Oncology at The University of Texas M. D. Anderson Cancer Center.

Dr. Meyers is part of a multidisciplinary team of neuro-oncologists, neuropsychologists, scientists, and psychiatrists in the Department of Neuro-Oncology. The team assesses patients' neurocognitive function and offers a cognitive rehabilitation program and other interventions to help them resume their normal activities. In addition, the neuro-oncology team

(Continued on **next page***)*

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Overcoming Cognitive Problems Related to Cancer

(Continued from **page 1***)*

conducts research aimed at reducing cognitive dysfunction.

Cognitive impairments may result from the cancer itself or from neurotoxic side effects of cancer treatments such as standard- and high-dose chemotherapy, immunotherapy, and radiation therapy. "Primary brain tumors, metastatic brain tumors, and leptomeningeal metastases all directly alter brain functioning at the site of the tumor," Dr. Meyers said. Between 20% and 40% of all patients with solid tumors develop brain metastases. Other types of cancers indirectly cause brain dysfunction, resulting in paraneoplastic brain disorders.

Patients often have difficulty thinking and focusing their attention while on chemotherapy, Dr. Meyers said. She cited a recent study that assessed neurocognitive function in women with breast cancer who were given standard- or high-dose chemotherapy with stem cell rescue. The study showed that 32% of women receiving high-dose adjuvant chemotherapy had cognitive impairment, compared with 17% of the women who received standard doses. These problems were observed two years after treatment was completed.

Immunotherapy also can have a negative effect on brain function. More than half of the patients receiving cytokine treatment have documented cognitive impairments, according to Dr. Meyers. "Biologic therapies like interferon, for example, are extremely neurotoxic to the brain and cause all kinds of problems with the patient's mood as well as cognitive disturbances."

Other possible causes of cognitive disorders in patients with cancer include hormone ablation therapy for breast and prostate cancers, preexisting neurological conditions unrelated to the cancer, depression, stress, anxiety, fatigue, pain, and anemia.

Determining the cause of a patient's cognitive dysfunction is critically important to deciding what is the best treatment. "The type of intervention that is most helpful will differ dramatically, depending on the etiology," Dr. Meyers said. "The specific intervention plan not only needs to take into account the underlying cause of the complaint but also must be individualized, as the impact of a cognitive problem will vary in different people."

Neuropsychological evaluations assess all of the patient's cognitive functions, including general intellectual abilities, academic achievement, memory, language, visual-perceptual and visual-motor acuity, executive skills (the ability to plan and execute activities), motor skills, and personality. The tests also identify any emotional problems.

The Neuropsychology Service's Behavioral Intervention Clinic offers neuropsychological evaluations, along with individualized treatment and patient and family education. "Our goal is to provide comprehensive patient and family care," said Anne E. Kayl, Ph.D., assistant director of the Neuropsychology Service, who also directs the Behavioral Intervention Clinic. The clinic, she said, uses a multidisciplinary approach. "I work with the patient's primary doctor and also refer to other specialists as needed, such as social workers, speech therapists, or physical and occupational therapists," Dr. Kayl said.

PROTOCOLS

Studies Focus on Cognitive Effects of Cancer and Its Treatment

Clinical trials in progress at The University of Texas M. D. Anderson Cancer Center include the following for patients whose disease or its treatment may affect cognitive function.

- The effects of behavior and personality changes in adults with primary brain tumors (DM00-384). *Principal Investigator: Christina Meyers, Ph.D.*
- The effect of adjuvant tamoxifen on cognitive and emotional functioning in women with early breast cancer (ID00-425). *Principal Investigator: Christina Meyers, Ph.D.*
- Complementary and integrative therapy use in brain tumor patients and effect on outcomes (DM00-351). *Principal Investigator: Terri S. Armstrong, A.P.N.*
- Factors associated with depression and fatigue in adult brain tumor patients (ID01-281). *Principal Investigator: Christina Meyers, Ph.D.*
- Biological basis of cancer-related symptoms in acute myelogenous leukemia and myelodysplasia (ID01-574). *Principal Investigator: Christina Meyers, Ph.D.*
- Pilot study of total serum homocysteine and APOE genotype as potential markers of cancer treatment neurotoxicity (DMP99-311). *Principal Investigator: Christina Meyers, Ph.D.*
- Psychosocial functioning of children with chronic illness and their families (P00-067). *Principal Investigator: Bartlett D. Moore, Ph.D.*
- Neuroimaging and cognitive assessment of changes related to anemia: A pilot study (ID99-093). *Principal Investigator: Christina Meyers, Ph.D.*
- The neuropsychological assessment of long-term survivors of childhood cancer (P81-06). *Principal Investigator: Donna R. Copeland, Ph.D.*
- Neuropsychological assessment of children with cancer (P88-003). *Principal Investigator: Donna R. Copeland, Ph.D.* ●

For more information *about these clinical trials, physicians or patients may call the M. D. Anderson Information Line. Those within the United States should call (800) 392-1611; those in Houston or outside the United States should call (713) 792-6161. Visit the M. D. Anderson Cancer Center clinical trials Web site at http://www.clinicaltrials.org for a broader listing of treatment research protocols.*

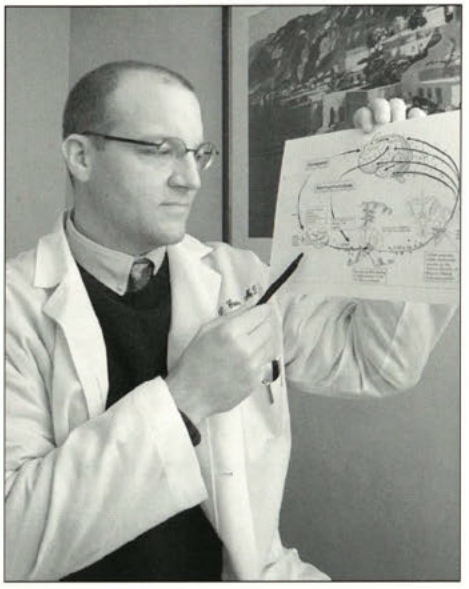
Treatment might focus on improving attention and concentration, speech and language, memory, or visual-spatial and hemispatial skills. The clinic also offers anger management training and relaxation training, as well as help in improving insight and awareness.

"We build on the results of the neuropsychological assessments and consider the individual patient's needs and goals," Dr. Kayl said. For instance, if a patient wants to return to work, the clinic can provide training in compensatory strategies that might include organizational and time-management skills to help the patient better deal with fatigue or attention problems. Computer-assisted training offers exercises for improving attention, memory, executive functions, and visual-spatial skills, while relaxation training can help the patient deal with anxiety.

Most of the people seen at the Behavioral Intervention Clinic are patients with brain tumors, Dr. Kayl said, but the clinic offers assistance to every patient with cognitive problems.

"We teach behavioral strategies, and if there are any lifestyle, workplace, or social adjustments that can be made, we recommend them. We're trying to treat these problems from every angle," Dr. Meyers said. "If there are any drugs that can help, we recommend them too." For instance, stimulants such as methylphenidate (Ritalin) can decrease fatigue in some patients with cancer and help them focus their attention.

Research studies in the Department of Neuro-Oncology focus on finding additional ways to mitigate the cognitive problems of patients with cancer. Morris Groves, M.D., J.D., an assistant professor in the Department of Neuro-Oncology, is working on pharmacological studies to understand the cognitive losses patients with cancer suffer and to find ways to improve cognitive function. He and Dr. Meyers are investigating the actions of donepezil, a drug used for Alzheimer's disease, and Ritalin, used alone or in combination, to improve neurocognitive functioning in patients with primary brain tumors who have had a decline in cognitive functioning following radiation therapy. Participants



Dr. Morris Groves, *an assistant professor in the Department of Neuro-Oncology, is conducting pharmacological studies to find ways of improving cognitive function in patients with cancer.*

are evaluated using neuropsychological tests and functional magnetic resonance imaging throughout the study.

"This should tell us what parts of the brain are not working properly and causing people to have these problems. We also should learn something about the ways these drugs work in the brain," Dr. Groves said. "The bottom line is, can these drugs help patients to become more functional, taking them from being unable to be home alone to independence? I think it's possible in some instances."

Two major goals of the department's research are protecting patients from the neurotoxicity of cancer treatment without compromising the efficacy of the treatment and identifying which patients are likely to develop the most severe cognitive problems from their chemotherapy or radiation treatment, Dr. Meyers said. "We're trying to discover if there are markers to determine who is likely to have these problems, because not everyone does," she said. When the patients who are most likely to develop cognitive problems are identified before treatment, clinicians can choose an alternative therapy or perhaps a lower-dose regimen. A long-term goal, Dr. Meyers said, is to develop drugs that protect the brain while the patient is receiving therapy.

It still is not entirely clear why some patients experience radiation-induced brain injury and others do not, but it seems to disproportionally affect older people and patients who already have some disability in their thinking processes, Dr. Groves said. It is also "very likely that a person's prior cognitive reserve prepares some patients to better withstand cancer therapies," he added.

Recently, Dr. Groves' interest was piqued by studies of patients with Alzheimer's disease showing that the smaller the patient's corpus callosum (the bridge between the two sides of the brain), the more rapidly the Alzheimer's disease progressed. He did his own study of 20 patients with brain tumors who had received radiation therapy to the brain and chemotherapy and found that patients who had a very thick corpus callosum suffered significantly fewer cognitive problems than the patients who had a thin corpus callosum. "The cognitive reserve manifested by the thickness of the corpus callosum, which we think reflects neuronal density, seemed to prepare the patient to better withstand the toxicity of that brain-directed therapy," Dr. Groves said. "The preliminary data suggest that in patients who have this thin corpus callosum, one might want to delay, if possible, therapies that we know have some toxic effects on the brain."

As it is now well documented that patients with cancer experience a variety of cognitive problems, Dr. Meyers said, the focus in the field of neuro-oncology has shifted from identifying problems to correcting and preventing them.

As cancer treatment becomes more successful, she said, "increasing numbers of patients are living longer and will expect to return to their pre-illness level of functioning. The impact of treatment on the patient's ability to perform daily activities must be addressed more comprehensively." ●

FOR MORE INFORMATION, *contact Dr. Meyers at (713) 792-8296, Dr. Kayl at (713) 745-5051, or Dr. Groves at (713) 745-3806.*

Highly Selective Synthetic Binding Agent

Tools Are Now Available to Determine the Relati

by Kerry L. Wright

DNA in its most traditional form is called B-DNA, otherwise known as right-handed DNA, the kind of DNA that appears in textbooks and is by far the most prevalent in the body. On many occasions, books, newspapers, and even prominent scientific journals have mistakenly inverted images of B-DNA and reversed its twists, publishing illustrations of left-handed helices instead of the typical right-handed ones. While those images do not represent any actual DNA configuration, the image of left-handed DNA in this article (page 5) is not a mistake.

Collaboration among researchers at the University of Mississippi Medical Center, the James Graham Brown Cancer Center at the University of Louisville, and The University of Texas M. D. Anderson Cancer Center has led to the creation of the first compound that binds Z-DNA, a left-handed form of DNA, with selective affinity. The compound, called WP900, could lead to the development of a new class of anticancer agents that target Z-DNA. In turn, this effort is part of a broader program aimed at using small molecules to target and control expression, at the transcriptional level, of genes important to the development and progression of cancer.

For years, Z-DNA was an enigma. First visualized by researchers at the Massachusetts Institute of Technology in the 1970s, Z-DNA was thought by many at the time to be a fluke, an artifact of B-DNA rather than a biologically significant form of genetic material. Then, in 1999, the same persistent scientists showed that left-handed DNA was found inside living cells: It turned out that B-DNA could actually transform into Z-DNA, specifically during the transcription of genes.

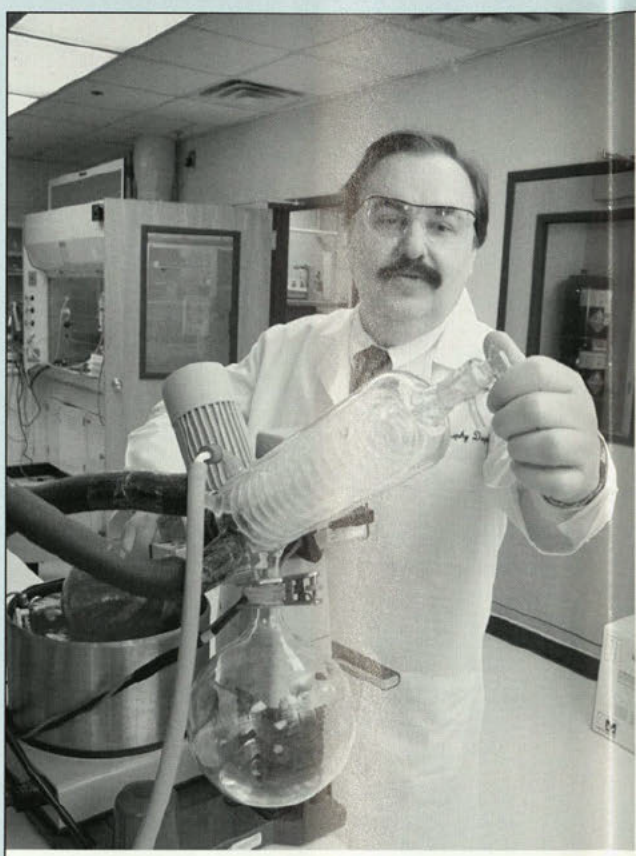
Though only present for a short time before it coils back into the right-handed form, Z-DNA is the target of an RNA-editing enzyme called adenosine deaminase that uses the left-handed genetic material as an anchor while it slides along newly transcribed RNA, making small changes that eventually create modified proteins. This activity provided the first inkling that although Z-DNA most likely makes up only a tiny percentage of the DNA in cells, it might have a very important biological function.

But how could scientists selectively study Z-DNA? Waldemar Priebe, Ph.D., a professor in the Department of Bioimmunotherapy at M. D. Anderson, was asking the same question. Although compounds were available that could bind B-DNA alone or both B-DNA and Z-DNA, there weren't any that selectively bound Z-DNA—until WP900.

After several years of collaboration between Dr. Priebe, Jonathan B. Chaires, Ph.D. (University of Mississippi Medical Center), and, more recently, John O. Trent, Ph.D. (University of Louisville), WP900 was synthesized through an arduous 32-step process and then molecularly modeled. The rationale: WP900 was designed as a mirror image (or an enantiomer, in chemical terms) of naturally occurring daunorubicin, a common anticancer drug that selectively binds right-handed DNA. Although B-DNA and Z-DNA are not exact mirror images of each other, WP900 still bound, with great selectivity, to Z-DNA but not to B-DNA in vitro, and it even caused the allosteric conversion of B-DNA oligomers into the left-handed form.

"For a long time, it was speculated that Z-DNA was important, but there were no good tools to investigate its biological role. WP900 provided the initial opening into this area," said Dr. Priebe.

Now that compounds (and, even



(Left) **Dr. Waldemar Priebe**, *a professor in the Departm to separate a compound from the reaction mixture—a step agent such as WP900.*

(Top right) Shown with **Dr. Priebe** *(third from the left) are of DNA-binding agents. Pictured in the M. D. Anderson W from the right), a research associate in the Department of Bi right)* **Joanna Dziewiszek**, **Sangkyou Lee**, **Slawo**

(Bottom right) WP900 is a synthetic enantiomer of daunom a left-handed form of DNA that may one day be a target fo B-DNA is shown at left.

s Target Different DNA Conformations
onship between Enigmatic Z-DNA and Cancer

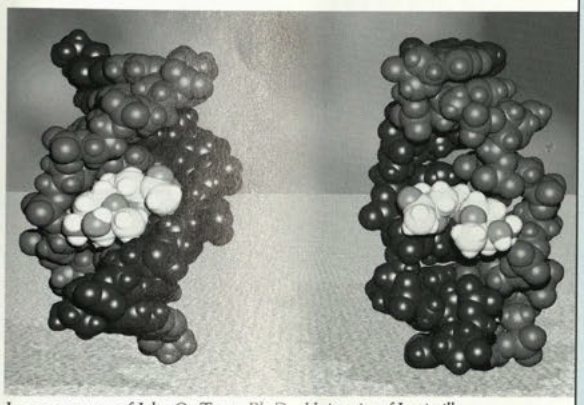


Image courtesy of John O. Trent, Ph.D., University of Louisville.

ient of Bioimmunotherapy, uses a rotary evaporator sed repeatedly in the preparation of a DNA-binding

colleagues who have participated in the development Woodlands facility are **Dr. Izabela Fokt** *(second oimmunotherapy, and postdoctoral fellows (left to* **nir Szymanski**, *and* **Szymon Kosinski**.

bicin that selectively binds Z-DNA (shown at right), anticancer agents. A complex of daunorubicin with

better, an enantiomeric pair of compounds) are available that selectively bind B-DNA and Z-DNA, further therapeutic questions can be addressed. Said Dr. Priebe, "So here we are back at the fundamental question, 'Can we design small molecules that can target specific sequences and forms of DNA and that can control the expression of pathogenic genes or other genes whose expression it is important for us to control?'"

Before they developed WP900, Dr. Priebe and his colleagues sought to answer that question by creating a method of developing small molecules that bind targeted DNA sequences, such as gene promoters, with extremely high affinity and sequence specificity. Their concept involves identifying small molecular fragments of naturally occurring DNA-binding agents or designing small novel DNA-binding molecular fragments to create building blocks (similar in concept to interconnecting toy LEGO blocks) that can be assembled to produce new compounds with much higher affinity and extended-sequence specificity than any of the parent compounds.

The first proof of this concept was WP631, a six-base-pair–binding agent that was synthesized by linking several small subunits of daunorubicin. When compared with doxorubicin, an anticancer agent similar to daunorubicin, WP631 was more cytotoxic against MCF-7 breast cancer cell lines. A later in vitro transcription assay showed that WP631 was very effective at inhibiting transcription from an adenovirus promoter containing an Sp1 protein–binding site, which the new compound was designed to bind.

"So we can assemble these 'LEGO blocks' into DNA-binding agents using structure-based design and molecular modeling," explained Dr. Priebe, "or we can use a combinatorial chemistry approach, such that we create a library of random DNA-binding agents and then identify the agent with the highest affinity for a desired sequence."

The combinatorial approach has been used to identify another new DNA-binding compound with unique anticancer properties, called WP760. Dr. Priebe and his colleagues Izabela Fokt, Ph.D., a research associate in the Department of Bioimmunotherapy, Teresa Przewloka, Ph.D., a postdoctoral fellow, and others created a small library of at least 80 randomly assembled molecules that were recently sent to the National Cancer Institute to be tested for their activity against 60 different disease-oriented cell lines. The results showed that WP760 was selectively cytotoxic against melanoma cell lines and two non–small cell lung cancer cell lines.

Libraries are also being created using both the structure-based, rational design method and the combinatorial chemistry approach to identify molecules that specifically control the transcription of genes related to breast cancer. The first structure-based design will target the promoter of HER2/neu, a gene that is commonly overexpressed in breast cancers.

The hope of Dr. Priebe and his colleagues is that these B-DNA–binding compounds will be developed into small-molecule therapeutic agents that will treat cancer more effectively than do some of the agents now available. And the new "LEGO-block" strategy will also make it easier to define the biological importance of Z-DNA as well as identify any involvement that Z-DNA has in the development and progression of cancer. The new strategy can also be used to increase the base pair specificity of WP900 and allow it to bind even more tightly to its Z-DNA target.

"So for all practical reasons, this is just the beginning of the story, which could lead to the creation of new anticancer agents using the molecular LEGO concept and to the creation of a new class of therapeutics based on the targeting of Z-DNA," said Dr. Priebe. "How practical it will be, no one can tell. However, this approach opens new areas of research that can be investigated in more detail than ever before." ●

FOR MORE INFORMATION, *contact Dr. Priebe at (281) 363-9072 or (713) 792-3777 or by e-mail at wpriebe@mdanderson.org.*

HOUSE•CALL

Simple Steps Can Put Patients on the Road to Well-Being

Whether receiving treatments or undergoing follow-up examinations, the patient with cancer's measure of well-being is "feeling better." "When patients feel well, their strength returns, their outlook improves, and they are better able to cope with their diagnosis," says Margaret Harle, R.N., a senior research nurse in the Pain Research Group at M. D. Anderson Cancer Center. Harle encourages patients to practice restorative activities during treatment and follow-up care to help them achieve a feeling of well-being and improve their quality of life. Here are some of her suggestions:

Four Essential STOPS on the Road to Well-Being

Above all, taking care of yourself means following your doctor's advice during and after treatment and adhering to the practical guidelines listed below.

1. Eat a healthy diet. (With some treatments, patients will receive a special diet plan.)
2. Follow your medication schedule.
3. Go to all clinic appointments.
4. Report any problems to the appropriate treatment team member.

Whatever your preference—jazz, gospel, show tunes, classical, big band, country and western, rock 'n' roll—music can be uplifting. There is only one rule: if you like it, it is good for you. Or, relaxation tapes, which simulate such sounds as a seashore, a thunderstorm, or a forest, can help patients achieve whole-body relaxation. Try using earphones for a sense of "getting away."

Is there a place where you feel peaceful and happy? Maybe it is your backyard, a park or wooded area, a bench in a museum gallery across from a favorite painting, or even the fountain in the mall. Go there, and go often.

As often as possible, visit with family, friends, church members, those with whom you share similar hobbies or interests, or a cancer support group. Not feeling up to a visit? Record a message on a cassette tape or video or send a letter or an e-mail.

If your treatment plan permits, pets can provide a healthy dose of fulfillment. If large pets are not practical, consider a small aquarium of fish.

Write down your thoughts in a letter (to yourself or someone else), a poem, or a descriptive paragraph—however they come to you. If writing is not your preferred form of expression, you could draw, paint, make craft items, or create a collage or scrapbook of treasured photos, cards, and gifts.

Practicing one or more of these or other restorative activities and following doctor's orders may help you feel better and get you started on the road to well-being. ●

For more information, contact your physician or contact the M. D. Anderson Information Line:

(800) 392-1611 *within the United States, or*

(713) 792-6161 *in Houston and outside the United States.*

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OncoLog

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DiaLog

Bedside Manner

Ziya L. Gokaslan, M.D.
Associate Professor,
Department of Neurosurgery

"We must be calm, approachable, comforting, and accessible."

Despite the advances made in treatment and rehabilitation over the past 30 years, a cancer diagnosis still evokes fear and helplessness in almost everyone. Patients are afraid of the pain that the disease could inflict and of the disfigurement that surgery or other treatments might cause. Above all, they are afraid that they will die of the disease. As physicians treating our fellow human beings, it is our obligation to be sensitive to the emotions of our patients. We must be calm, approachable, comforting, and accessible. Patients need to feel that we are available for them to talk to about their illness and the effects of the treatment they will be receiving.

Greeting a patient by name is always the first step. Touching the patient, shaking hands, hugging, or even giving them a kiss on the cheek demonstrates that you care about them and maintains the warmth and human contact that is so needed while removing the formality that so often limits real interaction.

It is important to convey that burdens such as bad news, decision making, and social, personal, and economic problems can be shared. A good example is to tell the patient that "we" instead of "you" have a problem that needs to be addressed. Including ourselves in the process helps to dilute the fear and anxiety the news can create and allows us to offer solutions to the problem and help our patients make a decision.

I work at a wonderful institution with a staff that has an incredible array of talents coupled with tremendous caring—from the person greeting you at the door all the way to our president. Our patients show remarkable courage and strength, endure sometimes painful treatments, and demonstrate an unmatched determination to continue with their lives. I have been humbled many times by the dignity and composure our patients maintain, even in the face of the most dreadful situations, and I have always felt that it is a privilege for me to care for them.

The least that we as physicians can do is to respect our fellow human beings in need and offer our kindness in the most expressive way possible. We may have the most advanced technology or science or offer the most promising new treatments, but unless we provide the human side of healing, our efforts will never be truly successful.

Dr. Gokaslan received the 2001 Faculty Achievement Award in Patient Care at M. D. Anderson Cancer Center.

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