

1992

Oncolog, Volume 37, Issue 02, April-June 1992

Ralph S. Freedman MD, PhD

The University of Texas MD Anderson Cancer Center

Bartlett D. Moore III, PhD

The University of Texas MD Anderson Cancer Center

Nicholas H.A. Terry PhD

The University of Texas MD Anderson Cancer Center

Follow this and additional works at: <https://openworks.mdanderson.org/oncolog>



Part of the [History of Science, Technology, and Medicine Commons](#), and the [Oncology Commons](#)

Recommended Citation

Freedman, Ralph S. MD, PhD; Moore, Bartlett D. III, PhD; and Terry, Nicholas H.A. PhD, "Oncolog, Volume 37, Issue 02, April-June 1992" (1992). *OncoLog MD Anderson's Report to Physicians*. 40.
<https://openworks.mdanderson.org/oncolog/40>

This Newsletter is brought to you for free and open access by the Research Medical Library at OpenWorks @ MD Anderson. It has been accepted for inclusion in OncoLog MD Anderson's Report to Physicians by an authorized administrator of OpenWorks @ MD Anderson. For more information, please contact rml-help@mdanderson.org.

MD Anderson Oncolog

In any experimental protocol, the patient comes first, the research objective second.

The primacy of patient welfare

Ethics



Ralph S. Freedman is co-chairman of the M. D. Anderson Surveillance Committee

When physicians send patients to a research hospital, the referring physicians and patients alike may experience ambivalent feelings. On the one hand, a research hospital may offer the most sophisticated diagnostic techniques and therapies available. But on the other hand, the patient's relationship with the research physician can sometimes differ from his or her relationship with the referring physician. The research physician's invitation to some patients to participate in experimental protocols raises a singularly important question: what ensures the primacy of the patient's welfare?

Today, the responsibility for maintaining the primacy of the patient's welfare is firmly that of research institutions, but 30 years ago no firm rules or guidelines existed. In the absence of such guidelines, patients sometimes fell prey to unethical research practices. Stanley J. Reiser, M.D., Ph.D., and Griff T. Ross Professor of Humanities and Technology in Health Care at The University of Texas Health Science Center at Houston, observed: "In the era before the 1960s, the scientific community lacked an institutional forum that continually reemphasized, through a study of ethical questions posed by actual research protocols, the ethical underpinnings of human research. Research abuses widely publicized in the 1960s, such as one involving the injection of live cancer cells into 22 elderly cancer patients without adequately informing them, and a heightened sensitivity to civil and human rights in the United States became agents for change."

In 1966, the U. S. Public Health Service mandated that all institutions receiving federal funds must establish review boards to evaluate experimental protocols designed for human subjects. This mandate has helped protect the rights of the patient, but it is a duty that requires much time and emotional energy on the part of the members of such boards. The constant balance between the good of patients of tomorrow, who will benefit from today's research, and that of the patients of today, who often must choose between experimental protocols and quality-of-life issues, is never-ending.

At M. D. Anderson, this vigilance is the responsibility of the Surveillance Committee, which reviews each month about 20 proposals. These proposals are usually for experimental phase I protocols (in which the main objective is usually to determine the maximum tolerable dose of a drug or combination of drugs) and phase II protocols (in which the main objective is to determine the response rate of a single agent or combination of agents for which the dose and schedule have already been determined by phase I studies). This committee is composed of 27 voting members and seven non-

"The physician-friend and the physician-experimenter have different attitudes and interests, and when one doctor tries to combine the two parts there is a risk—quite a big risk sometimes—that the energy of the experimenter will prevail and that the patient will be deprived of the friend to whom he is absolutely entitled."

—T. F. Fox, *Medicolegal Journal*
(28:135, 1960)

voting, or ex-officio, members. Membership includes physicians from major clinical departments, which encompass medical, surgical, and pediatric specialties, representatives from the Division of Nursing, the Social Service, the Department of Chaplaincy and Pastoral Education, and a former patient. In addition, members also include people who are not employed by M. D. Anderson, such as lawyers, educators, and a representa-

“Informed consent must be voluntary. This is the key”



tive of an ethnic minority.

The Surveillance Committee is assisted in its review of the scientific issues of clinical protocols by a peer review committee (the prereview committee) that comprises experts from many fields. Once the protocol has been refined, it is submitted to the Surveillance Committee for final approval. The scientific merit of each protocol is independently evaluated by a minimum of two reviewers, whom the Surveillance Committee chairmen usually select from among physicians who have participated in the prereview discussions and who therefore have a good knowledge of the protocols. When this scientific assessment is complete, one of these initial reviewers presents the protocol to the entire committee, which then considers not only its scientific merit but also whether the protocol adequately protects the welfare of the people it proposes to involve.

Experimental phase I and phase II therapies involve complex interactions among medical investigators, pharmaceutical companies, the federal government, the research institution, and the patient. Martin Raber, M.D., a chemotherapy specialist in the Department of Medical Oncology who served on the Surveillance Committee for five years, explained that although this complexity of relations might seem to challenge the primacy of the patient, it in fact serves the patient, for what all parties share is a refusal to accept the incurability of disease. According to Raber, many patients express an interest in and are generally well informed about experimental therapies. “Patient interest is greater than the availability of experimental therapies,” said Raber.

Nonmedical factors often affect patient’s decision

Patients such as these know what they want and actively seek it out. Some patients, however, would not choose to participate in a study unless, or even if, asked by their attending physician. For them, potential benefits of experimental therapy may not outweigh the compromises they would have to make in other areas of their lives. As committee co-chairman Ralph S. Freedman, M.D., Ph.D., pointed out, many patients live long distances from the hospital, which means spending much time and money on transportation. In addition, a patient often must decide whether he or she can continue to hold a job while undergoing therapy and if not, what the emotional and economic consequences for

both the patient and the family might be. Some terminally ill patients would rather spend their last months at home with their families than in a hospital receiving experimental therapy. Any patient who may teeter on the edge of giving his or her consent is especially vulnerable. No matter what their enthusiasm for a new protocol, physicians should respect a patient’s choice to refuse experimental therapy based on nonmedical considerations.

To be voluntary, consent must be based on complete information

Besides posing emotional and economic concerns, experimental therapies also entail varying degrees of physical risk, and it is one of the Surveillance Committee’s most important duties to ensure that protocols sufficiently provide for obtaining the patient’s informed consent. The principal investigator or physician is responsible for gaining the patient’s informed consent and documenting it with a written form that the Surveillance Committee must approve. Freedman emphasized, “Informed consent must be voluntary. This is the key.” To promote genuine voluntariness, documents of informed consent must set forth the purpose of the therapy, describe its procedures, risks, side effects, and discomforts, and indicate potential benefits. In addition, the document must include a description of alternative procedures or treatments and their risks and benefits. Only when an investigator has communicated these details to the patient, allowing time for the patient to ask questions and think, is the principle of patient voluntariness respected.

Informed consent: theory versus practice

Although this process of informed consent is adequate in theory, Freedman acknowledged that the practice of securing a patient’s informed consent may be problematic. For example, despite the specificity of written documentation about the therapeutic regimen that the principal investigator must provide to patients, language that is medically accurate is not necessarily readily understandable to the patient.

Another problem is that the process of informed consent relies greatly upon the principal investigator’s or physician’s oral communication with a patient. Without necessarily being aware of it, a physician might subtly

“Deviations from the preferred treatment for a specific disease require review”

• • • • •

pressure the patient. Freedman said that, to address this problem, some medical departments at M. D. Anderson have begun to counsel physicians about oral communication with patients.

Stanley Reiser, an extramural member of the Surveillance Committee, concurs with Freedman that the process of informed consent is crucially important and raises problems that need more attention. “What happens after informed consent is obtained?” asks Reiser. “Does such consent for a proposed therapy raise false hopes?” Similarly, he thinks that assessments of a patient’s and the family’s observations on their actual experience of therapy compared with their expectations prior to therapy would provide useful information about the process of informed consent. Such questions not only warrant study by principal investigators, Reiser believes, but they also merit research by medical students in their courses in medical ethics, an area of study that both Reiser and Freedman find to be contributing significantly to the increased ethical awareness of medical investigators and practitioners.

Financial interest in the protocol is an important issue

In addition to ethical problems possibly posed during oral communication in the course of acquiring informed consent, another ethical problem is whether review boards should assess a principal investigator’s financial relationship to a pharmaceutical company. According to Reiser, interest in having physicians reveal their economic arrangements with pharmaceutical companies arises out of concern for how such arrangements affect both the scientific objectivity of a therapeutic regimen and the ethical treatment of patients. Presently, no federal or institutional regulations mandate scrutinizing investigators’ economic relations with a pharmaceutical company, but any protocol reviewer or any committee member may raise the issue for consideration, Freedman said.

A final question remains: What if, even after thorough review and conscientious assessment, a research idea proves wrong? Say 20 patients have been enrolled in a three-year study that is designed to enroll at least a 100, but six months into the study the data are overwhelmingly negative. Should the study continue, thus subjecting more patients to a protocol that increasingly seems

ineffective? To guard against this dilemma, the Surveillance Committee sometimes requests an early review of data after a predetermined number of patients have been entered on a protocol; this number could be six or fewer. Additionally, the committee has an innovative review process for pilot protocols that test the validity of research ideas, Freedman said. The pilot studies are implemented for therapies that do not put patients at any greater risk than they would experience under current practice for a particular disease; however, in contrast to most protocols, pilot studies include a maximum of 15 patients and fewer than three investigators. If data from these pilot studies prove promising, then more comprehensive studies can be planned, but if not, then the project can be terminated or modified, thus ensuring that additional patients are not enrolled in a protocol that shows no promise.

Research must show a potential for innovation

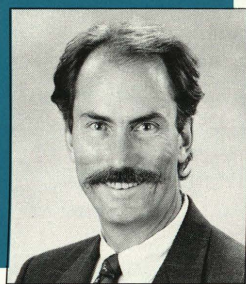
Ethical review committees like the Surveillance Committee necessarily educate reviewers and investigators directly involved in its deliberations. According to Freedman, this educational process inheres in rigorously addressing a single, crucial question: what constitutes research? “The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research,” which a presidential commission issued in 1978 to provide a basis for federal policy on research involving people, gave the question of what constitutes research its first official articulation. In contrast to “practice,” which “refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success,” “research” refers to “an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships)” and “is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.” Although not just any alteration of standard practice renders a treatment experimental, “radically new procedures . . . should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective.” Accordingly, it is the task of review committees like M. D. Anderson’s Surveillance Com-

continued on page 7

Prevention and control will depend on understanding brain activity.

Cognitive deficits in survivors of childhood cancers

Treatment Update



Bartlett D. Moore III is an assistant professor of pediatrics in the Department of Pediatrics.

The good news is that more and more children with cancer are surviving their disease. Twenty years ago, the five-year survival rate for children with cancer was about 50%; in 1990, it was projected to be about 80%. The bad news is that some of these survivors may be suffering long-term or permanent adverse effects, not of their cancers, but of the very treatments that are saving their lives. This is not a new idea; physicians and educators working with these survivors have long noticed their unusually high incidence of cognitive and intellectual impairments, such as learning disabilities, attention deficits, poor memory, slower-than-normal task performance, and perception problems. These cognitive difficulties have often been attributed to psychosocial factors associated with treatment of a chronic, life-threatening illness. However, these sequelae do not appear in all survivors, and often their appearance is delayed from a few to five years, leading some researchers to attribute them instead to gradual pathologic changes in the brain. The perplexing problem of identifying the causes and predicting the occurrence of these cognitive deficits has been undertaken by researchers at The University of Texas M. D. Anderson Cancer Center.

Bartlett D. Moore III, Ph.D., and his colleagues in the Department of Pediatrics are studying both survivors and children who are being treated for cancer in hopes of learning what factors contribute to these cognitive deficits. Moore, a neuropsychologist, is an assistant professor of pediatrics who specializes in assessing children's intellectual and cognitive abilities. He is extending the neuropsychological research effort in the department, initiated 10 years ago by his colleague Donna Copeland, Ph.D., into the area of neurophysiology, the study of brain function, through the use of electrophysiological measures. Copeland described it this way: "Neuropsychology measures behavior, whereas CT [computed tomography] and MRI [magnetic resonance imaging] measure the structure and anatomy of the brain. Dr. Moore's electrophysiological tests provide the bridge between the two. They tell us about the 'hard wiring' of the brain. His work will allow us to correlate structural and cognitive development." Moore used a similar metaphor when he compared cognitive development in these survivors to computer software that does not run properly because of problems in the computer hardware; his work aims to find the underlying

problem in the "hardware" of the brain. Using microcomputer technology, Moore conducts electrophysiological tests to study how brain activity in the cancer survivors with cognitive problems differs from that in the survivors who do not suffer these problems.

Treatments implicated in long-term deficits

Supported by grants from the American Cancer Society, Moore is studying survivors of different types of childhood cancer (defined as any cancer diagnosed before the patient is 16 years old) and the effects of different kinds of treatments. Subjects for the study are recruited from the M. D. Anderson Long-Term Follow-Up Clinic, which is directed by Hubert L. Ried, M.D. Treatment of children with cancer depends on a number of factors, including the type and location of the cancer and the child's age. Treatments involving the central nervous system (CNS) are thought by many observers to be causal factors in these long-term cognitive effects. They suggest that the white matter of the brain, the myelin sheath that protects the nerve cells and increases the speed of brain processing, may be damaged by these treatments. Moore said, "we know that some of these long-term survivors have cognitive and intellectual deficits. Other researchers have studied the physical changes in the brains of these survivors. We're looking at brain function as a link between the cognitive deficits and the treatments these children receive."

Moore's study addresses the hypothesis that intensive CNS therapy that includes cranial radiation therapy (CRT) damages this white matter, disrupting normal patterns of cortical connectivity and slowing brain activity essential to normal cognitive functioning. CRT became one focus of Moore's study because it has been very widely used: in the past it was used prophylactically in most children with leukemia to prevent CNS metastases. It is still used to treat some patients who relapse and is also used extensively in children with brain tumors.

Moore studied three groups: those who had received no CNS therapy, those who had received systemic chemotherapy with or without CNS chemotherapy, and those who had received intensive CNS therapy, including chemotherapy and CRT. The groups received identical batteries of electrophysiological tests. "We're examining whether chemotherapy and radia-

tion therapy have any long-term physiological effects," Moore said. "There seems to be a consensus that therapies that include CRT do have some cognitive effects whose onset may be delayed for several years after therapy. The complication with this type of study is that very few patients get only one kind of treatment. One third of the subjects in this study received both CNS chemotherapy and radiation therapy, and there's evidence that the two have a synergistic effect. Some researchers are showing cognitive deficits in children after CNS chemotherapy [without CRT], but we haven't in our studies." What they have seen is corroboration of their hypothesis that intensive CNS therapies that include CRT, when used in children, can cause these deficits. Moore saw a significant performance deficit in the group of long-term survivors whose treatment included both CRT and CNS chemotherapy. The groups treated with only chemotherapy (systemic, CNS, or both) were within the average range of functioning.

Electrophysiological tests reveal deficits

Electrophysiological tests comprise a variety of techniques for determining the speed and organization of CNS processing, that is, how well the CNS is functioning. Most of the tests are performed by Bernadette Levy, a research assistant in Moore's laboratory, and include spectral analysis of electroencephalograms; brainstem, sensory, and cortical evoked potentials; and motor reaction time and dichotic listening tests. Most are measured on a microcomputer-based system: while electrodes attached to the scalp measure brain activity, the subject responds to automated stimuli, and the brain responses are amplified, digitized, recorded, and analyzed by the computer. When brainstem and simple sensory evoked potentials were recorded under resting conditions, there were no differences among the treatment groups; the group that received intensive therapy including combined CNS chemotherapy and CRT showed no impairment. However, when cortical evoked potentials were measured while the subject was involved in a mental task, definite differences were apparent among the treatment groups: those who had received no CNS therapy had the fastest cortical reactivity, and those who had received the most intensive CNS therapy, including CNS chemotherapy and CRT, had the slowest. Those who had received CNS chemotherapy alone had intermediate values. A similar gradient was found in the responses to a test of motor reaction time in which the subjects were required to push a key as quickly as possible in response to a visual stimulus after being presented with a warning stimulus several seconds earlier. In one condition, the interval between the stimuli was constant (4 seconds), whereas in another the inter-

val varied randomly (1 to 6 seconds). Those who had not received intensive CNS therapy were able to use their foreknowledge of the constant interval to increase their reaction times by about 20% over those in the random condition. The patients who received intensive CNS therapy, however, were not able to benefit from this knowledge to improve their speeds over patient in the random condition.

Many of these electrophysiological measures correlate with cognitive ability, suggesting that they can be used to detect or predict cognitive deficits associated with cancer treatment. Moore believes that since evoked potentials measure the speed of information processing in the brain, they can be used to measure reductions in this speed in impaired patients, even if the damage to the brain cannot be detected on CT and MRI images. He further believes that his results support the idea that CRT and, to a lesser degree, CNS chemotherapy damage the white matter tracts of the brain, resulting in slowing and disorganization of cortical functions necessary for efficient cognitive activity.

First step to prevention

Moore's research is helping explain the physiological basis of cognitive deficits following cancer treatment, providing a rationale for designing new and effective therapies that minimize long-term cognitive effects. He is now planning to study children being treated for cancer to identify patterns or other clues of neurological damage that may allow prediction of future cognitive deficits. The ability to detect the damage as it is happening will allow clinicians to alter treatments and, Moore and his colleagues hope, either prevent the deficits or reduce their severity. It is also important to learn more about the nature of these deficits so that the survivors who suffer them can be successfully rehabilitated.

In light of these discoveries, what is the future of these intensive CNS therapies that cause the deficits? Moore was quick to note that a medical cure is necessary before the child can resume normal life, and that freedom from these deficits is irrelevant if the child does not survive the cancer. Neither he nor other researchers in the field advocate stopping these treatments. He does note that intensive CNS treatments are avoided in very young children at M. D. Anderson, and that, whenever possible, delaying these treatments until the CNS has matured can prevent or lessen their harmful effects. ■

Physicians who desire additional information may write Bartlett D. Moore III, Ph.D., The Department of Pediatrics, Box 87, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, or call (713) 794-4467.

Doubling Time

continued from page 8

response to therapy, particularly to radiation.

“The first thing we set out to do—and this was based on what I did with my colleagues in England before I came here in 1987—was to establish whether there is a spectrum of underlying potential doubling times in cell populations, even in a seemingly homogeneous population of tumors,” Terry said.

Potential doubling time varies widely

In preliminary studies of about 200 patients who had either head and neck cancer or rectal cancer, “we have found an enormous range in this parameter, irrespective of how quickly the tumor lump was growing. Tumor cells can be growing and proliferating very quickly, even though the lump is not, since existing cells can be dying just as quickly as new cells are proliferating,” Terry said. “For tumors that have fast-growing subpopulations with short potential doubling times, it might make sense to accelerate treatment; rather than give conventional radiotherapy of some 72 fractions in seven weeks, you might want to get the whole treatment in five weeks, for example. But it’s a trade-off. Accelerated treatment means a greater risk of normal tissue damage, and of course the whole balancing act is to sterilize the clonogenic cells in the tumor while sparing normal tissues.”

After the range in potential doubling times was confirmed, the next step was to obtain data on tumor response, local tumor control, and patient survival. In a small cohort of rectal cancer patients, Terry and his clinical colleagues have already noted a correlation between tumor response and potential doubling time. Patients with fast-growing tumors (which have short potential doubling times) do worse than patients with slow-growing tumors (which have long potential doubling times). Within a year, they hope to have specific data on local control and survival, not only for rectal cancer patients but also for those with head and neck cancer. “Our studies of both tumors are maturing at the the same time,” Terry said. “In head and neck studies, about 65 of 100 cases will have had at least two years of follow-up.”

Correlations of potential doubling time with patient survival would be encouraging, but not the final word. “We haven’t yet stuck our finger in the fire and prescribed treatment based on potential doubling time. We haven’t yet said, ‘Okay, because your tumor has such and such a doubling time, we think you should have accelerated radiotherapy and more intense chemotherapy,’” Terry explained. “There’s still a panoply of factors that need to be considered, not only the surgical

staging and other clinical parameters but also, perhaps, the intrinsic radiosensitivity of the tumor.”

Obtaining an accurate prognosis depends on sophisticated models

Sorting out those factors will require sophisticated experimental models. In the realm of mouse tumor systems, such models already exist, but for human tumors the task has been more difficult. In mouse models, multiple samples can be taken both from within individuals and from across a large homogeneous population. Any assumptions about prognostic parameters can therefore be verified by the use of such “multiple replicates.” But for humans, it is essential that any type of prognostic test be reliable using one surgical sample or biopsy. Development of such models, which has already begun at M. D. Anderson Cancer Center, is “a very interactive project” involving four departments, Terry said. Some of Terry’s collaborators are R. Allen White, Ph.D., Department of Biomathematics, who conceptualizes mathematical models that are then tested in cell culture or mouse systems; William A. Brock, Ph.D., Department of Experimental Radiotherapy, who is currently devising studies to assess patient and tumor radiosensitivity; and Lester J. Peters, M.D., head of the Division of Radiotherapy. Peters, together with his colleagues Helmuth Goepfert, M.D., chairman, Department of Head and Neck Surgery, and David M. Ota, M.D., deputy chairman of Department of General Surgery, directs the clinical arms of the studies. In addition, cooperation with the Division of Pathology is vital for obtaining specimens in a timely fashion.

Complicated logistics necessitates clockwork coordination

At this stage in Terry’s studies, his collaboration with his clinical colleagues is especially important, for the data they are gathering now, as mentioned above, will determine whether potential doubling time correlates with local tumor control and patient survival. The task, however, is logistically daunting. The study population extends across two services; furthermore, some patients may undergo one of several possible types of biopsy, whereas others may undergo one of several types of surgery. Many of these procedures are performed by different specialists in different locations of the hospital. For example, surgery patients are often perfused with bromodeoxyuridine by the anesthesiologist, whereas biopsy patients may be perfused in the ambulatory infusion clinic. The result: many people in a variety of departments need to know precisely what to do and when to do it.

“It’s a big deal when we’ve got patients undergoing

the procedure. We have fingers all over the place making sure everyone knows what is happening," Terry said. Since the accuracy of the bromodeoxyuridine perfusion technique is highly time dependent, "we need to know precisely when the patient is perfused and when the biopsy or specimen was taken."

M. D. Anderson collaborates with European research facility

Such collaboration requires extensive dialogue within M. D. Anderson, but Terry is also in another dialogue of sorts with other research facilities. Three other institutions are researching aspects of potential doubling time as determined by bromodeoxyuridine perfusion. All share a desire to standardize the methodological and analytical techniques of the bromodeoxyuridine techniques, but they are going about it differently.

"We've published a lot of data on cell kinetic theory and analytical models. The University of Wisconsin group is working very hard along the same lines we are, trying to gain fundamental insight into cell kinetics," Terry said. "The group at the Gray Laboratory (London) is collecting an enormous spread of clinical data, but they're not focusing on theory. Adrian Begg's group at the Netherlands Cancer Institute is somewhere in between. Begg has great insight into the analytical

methodology, which he is sharing with us, but his group isn't building the models."

Almost certainly, the academic aspect of this type of research will proceed as it has for the past 40 years or so, with radiation biologists like Terry elucidating the fundamental questions of cell kinetics. The unresolved question, though, is the utility of such research for clinical use. "If all we're doing is measuring a parameter that is closely correlated with other variables such as staging or something like that, then our technique probably won't be useful," he said. "It's quite an investment in lab time and machine time. But if—and this is something that Allen White and I are particularly concerned about—if we can create a reliable, independent prognostic technique, then it might be possible to make it relatively inexpensive. The question is, does the technique give any benefit to a significant cohort of patients? That's where we are right now, and that's what we hope our clinical studies will show. The next two years should be very exciting." ■

Physicians who desire additional information may write Nicholas H. A. Terry, Ph.D., Department of Experimental Radiotherapy, Box 66, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, or call (713) 792-3424.

Patient Welfare

continued from page 3

mittee to ensure that "a major innovation be incorporated into a formal research project," for "the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects."

Freedman emphasized the necessity of maintaining the crucial distinction between practice and research and thinks that relentlessly pursuing the question, "What constitutes research?" rightfully compels research physicians to continuously assess their motivations. "Taking the best care of patients means that a physician sometimes has to be innovative," Freedman said, "and a research protocol may offer patients an opportunity to receive the best therapy. Treating breast cancer with taxol is an example of such an opportunity." Yet Freedman cautioned that "physicians must know that deviations from the preferred treatment for a specific disease require review." Intellectual excitement over possible discovery and publication of a research report should never take primacy over patient welfare. The single most important educational role of the process of ethical

review, Freedman thinks, is that it exists to force the question of motives.

Reiser, too, affirmed the educational value of the review process but believes that the educational role warrants expansion. He pointed out that since the work load of reviewing proposed protocols prohibits most review committees as they are presently structured from assuming a more active part in education, a review committee might create a separate arm to realize more of its educational potential. ■

Physicians who desire additional information may write Ralph S. Freedman, M.D., Ph.D., Department of Gynecology, Box 67, or Martin Raber, M.D., Department of Medical Oncology, Box 92, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030; or Stanley J. Reiser, M.D., Ph.D., Office of the Program on Humanities and Technology in Health Care, The University of Texas Health Science Center, P.O. Box 20708, Houston, Texas 77225. Physicians may also call Drs. Freedman, Raber, and Reiser at (713) 792-2770 (Freedman), (713) 792-7765 (Raber), or (713) 792-5140 (Reiser).

MD Anderson Oncolog

The University of Texas
M. D. Anderson Cancer Center

President,
Charles A. LeMaistre, M.D.

**Vice President for
Academic Affairs**
James M. Bowen, Ph.D.

**Associate Vice President
for Academic Affairs**
Robin R. Sandefur, Ph.D.

**Director, Department
of Scientific Publications**
Walter J. Pagel

Editor
Kevin Flynn

Contributing Editors
Kathryn L. Hale
Pamela Walker

Production
K. Patrick

Photographs
Donald G. Kelley

Editorial Board
David M. Gershenson, M.D.
Frankie A. Holmes, M.D.
Raymond E. Meyn, Jr., Ph.D.
William Plunkett, Ph.D.
Tyvin A. Rich, M.D.
S. Eva Singletary, M.D.
Michael J. Wargovich, Ph.D.

Published quarterly by the
Department of Scientific
Publications, Division of Academic
Affairs, The University of Texas
M. D. Anderson Cancer Center,
1515 Holcombe Boulevard,
Houston, Texas 77030.

Made possible by a gift from
the late Mrs. Harry C. Wiess
and by grants from The University
Cancer Foundation.

MD Anderson Oncolog
Scientific Publications, Box 234
M. D. Anderson Cancer Center
1515 Holcombe Boulevard
Houston, Texas 77030

Address correction requested

Inside

Ethics of experimentation
Cognitive deficits after therapy
Tumor biology and prognosis

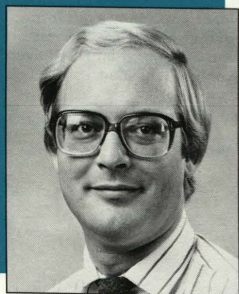
Oncolog

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Nonprofit Org.
U. S. Postage
PAID
Permit No. 1
Austin, Texas

Potential doubling time of tumors may be the key to accurate prognosis, appropriate treatment

Lab to Clinic



Nicholas H. A. Terry is an assistant professor in the Department of Experimental Radiotherapy

"I've been known to make a bloody nuisance of myself, but when we have a surgery patient scheduled for bromodeoxyuridine perfusion, we're very jealous of making sure everything works," said Nicholas H. A. Terry, Ph.D., an assistant professor in the Department of Experimental Radiotherapy at The University of Texas M. D. Anderson Cancer Center.

The operating room is not the typical habitat of a radiation biologist like Terry, who has devoted almost a decade to analyzing cell cycle kinetics in mice and in cell culture. His location of choice is the research wing, in a room that he shares with a flow cytometer. But Terry's current basic research requires occasional forays into the world of the surgeon. The prognostic capabilities of his bromodeoxyuridine perfusion technique have already proved promising in experimental systems. If current human studies progress as Terry hopes, the test may be useful in determining the most effective radiotherapy for patients with certain tumors.

Tumor growth rate may be prognostic

The key aspect of the bromodeoxyuridine technique is that it allows one to estimate the growth rate of cells within tumors. Patients are first infused with nontoxic levels of bromodeoxyuridine. Several hours later, a surgical biopsy is taken and manipulated such that total DNA and bromodeoxyuridine-labeled DNA can be visualized and quantitated using a flow cytometer, a device that measures cellular constituents based on the amount of incorporated fluorochromes. Because bromodeoxyuridine binds only to cells in the DNA synthesis (S) phase, it can be used to distinguish S-phase cells from those in other phases of the cell cycle. Why are S-phase cells important? By knowing the fraction of S-phase cells in the total population and their rate of progression, one can estimate the time it would take, theoretically, for the population to double. This parameter is called the "tumor potential doubling time," and Terry expects that it may correlate with a tumor's

continued on page 6