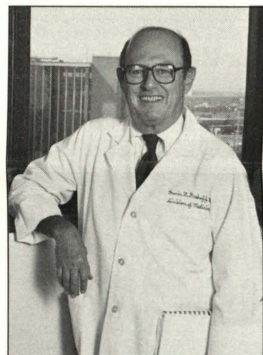


Learning How and Why Drugs Kill Cells Is Chemotherapy Researchers' Prime Goal

The Division of Medicine headed by Irwin H. Krakoff, M.D., includes the Department of Chemotherapy Research, in physical fact a row of crowded laboratories and tiny offices occupied by pharmacologists and chemists who have one unifying ambition: to replace the hit-or-miss nature of cancer chemotherapy with knowledge of how and why drugs kill cells.



Irwin Krakoff

One of Krakoff's interests in coming to Anderson from the University of Vermont Cancer Center three years ago was to extend the drug development program. Writing in the *Cancer Bulletin* of July-August 1985, he referred to the "tremendous intellectual and physical synergy" produced by "the interaction of chemists, pharmacologists, toxicologists, and clinicians."

The teams he assembled include those led by

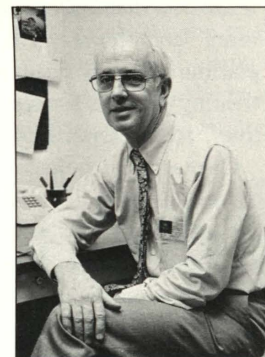
- Edward M. Acton, Ph.D., a chemist recently recruited from SRI International, who has made and is testing new doxorubicin-related compounds that, according to Krakoff, seem to be extraordinarily active;
- Abdul R. Khokhar, Ph.D., a medicinal chemist, who is developing a new line of platinum compounds;
- Leonard A. Zwelling, M.D., who works with DNA topoisomerase, an enzyme that alters DNA conformation and is a promising target for reacting with drugs that destroy malignant but not normal cells;
- Robert A. Newman, Ph.D., a pharmacologist, who investigates the antitumor activity of new drugs and attempts to reduce the ill effects of some drugs now in clinical use;
- Martin N. Raber, M.D., who works on the clinical side of Newman's projects, testing new drugs in patients for whom traditional therapies have failed;
- William Plunkett, Ph.D., a biochemical pharmacologist who studies new chemotherapies for leukemia.

Among other grants, Krakoff's division has a \$3 million contract with the National Cancer Institute to test drugs in

clinical trials. "Our own program," he said, "involves the synthesis of new chemotherapeutic agents, their study in animal systems, their characterization as to mechanism of action and toxicity, and finally their introduction into clinical trial."

Chemical Synthesis of New Drugs

Dr. Edward M. Acton came from California in February to continue his work in drug synthesis, attracted to Anderson because of its climate of interaction among scientists and physicians.



Edward Acton

Chemical synthesis of organic compounds, cancer drugs in particular, has been his work for 20 years. "But you find after some time that programs in chemical synthesis supposedly targeted to new drugs don't succeed very well unless you have a chance to interact with the people who will test the drugs, use them in the laboratory and ultimately in patients. That's the kind of interaction I believe is superior here," Acton said.

Four chemists have joined him meanwhile as part of Anderson's first organized program in chemical synthesis of new drugs, particularly analogues of doxorubicin.

Drug evaluation involves both cell culture and animal studies. Properly chosen, a complementary series can yield information about a drug's mechanism of action and tell whether a compound is active or not, Acton explained. "The state of the art is that tests against mouse tumors are at best only qualitatively rather than quantitatively predictive for human tumors—and that's another reason that understanding mechanisms of action and how the drugs work is important."

In talking about doxorubicin, "the most active single agent against cancer," Acton said that more active analogues of the drug are needed because, often, only about a third of the patients treated can respond to the drug. Doxorubicin therefore is usually given in combination with other drugs.

"One of our motivations," Acton said, "is that from a better understanding of how the drug works—of its advantages and limitations—ought to come better analogues and an improvement in chemotherapy. In theory you can triple the 30%

Learning How and Why Drugs Kill Cells . . .

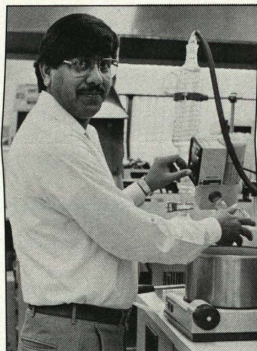
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response rate. That may not be realistic, but perhaps doubling it is.”

New Platinum Compounds

Dr. Abdul R. Khokhar came to Houston with Krakoff to continue working on a third generation of platinum-based antitumor drugs, specifically to synthesize and characterize new diaminocyclohexane platinum complexes. The prototype platinum drug is cisplatin, used for treating patients for testicular, lung, liver, and ovarian cancers.

Cisplatin, Khokhar explained, leaves much room for improvement because it produces toxic side effects in kidney, nervous system, and ears, causes nausea and vomiting, produces resistance in tumor cells, and suppresses bone marrow activity.



Abdul Khokhar

A Report to Physicians
OncoLog

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By next year, Khokhar and his co-investigator, Dr. Robert A. Newman, chief of the Section of Pharmacology, expect to have some new platinum complexes ready for clinical tests.

Cisplatin leaves much room for improvement.

Khokhar listed the goals as “a broader spectrum of antitumor activity, no cross-resistance with cisplatin, reduced myelosuppression and neurotoxicity, and less provocation of vomiting” than former drug versions.

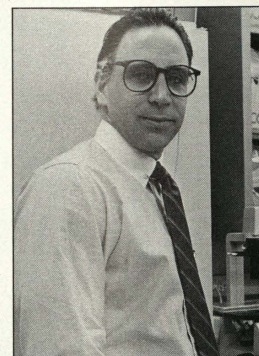
Cellular Research with a DNA Enzyme

Two steps down the hall but occupying a more distant spot on the research spectrum is Dr. Leonard A. Zwelling, who said, “Our research is focused on cells, not on drugs. The drugs are tools; the cells are the object of our work.”

His object is DNA topoisomerase, an enzyme that alters the three-dimensional structure of DNA “through concerted breaking of DNA strand-passing and strand-rejoining reactions. That’s what it does in the test tube—what it does in the cell is not clear,” Zwelling said.

The enzyme is an important research focus because some clinically effective antineoplastic agents seem to interact with DNA topoisomerase and disrupt its function. Whether that disruption is how the drugs work remains to be seen. The information is vital, Zwelling said, because the same drugs that disrupt topoisomerase can also kill malignant cells selectively—and “if you learn how the drugs kill malignant but not normal cells, you obviously have a handle on biochemical differences between malignant and normal cells.”

The drugs his group studies in relation to DNA topoisomerase include doxorubicin and the newer compounds amsacrine and etoposide.



Leonard Zwelling

Drugs are probes for malignant phenotype.

In the course of their work with human leukemia cells and amsacrine, Zwelling and his associates found that new leukemia cell generations are resistant to the compound. This

difference between parent and daughter cells raises the hope “that we might be able, in a sense, to test the drug sensitivity of leukemia cells in a patient,” he said. “Right now, much cancer therapy is empirical. If we had a specific biochemical reaction that is the critical determinant of a drug’s action, we could ask the biochemical rather than the more phenomenological question, which is whether the cells live or die.

“Since the drugs we work with can in a sense distinguish between malignant and normal cells, they become probes for the malignant phenotype. At least part of the system can now be studied.”

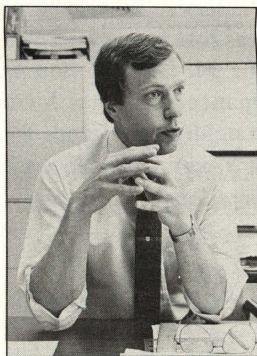
Bring Clinical Problems to Lab

Dr. Robert Newman’s pharmacology team, in addition to basic research with bleomycin, anthracycline, and platinum derivatives, works closely with physicians who administer investigational drugs in phase I clinical trials. This is the phase at which “we have only a limited idea of the drugs’ antitumor activity and the kinds of toxicity the drugs may produce in human beings,” he said. “We bring some of the clinical problems shown by these trials back to the laboratory to see if we can solve or at least understand them. We have some clues, of course, based on studies in mice and dogs, but human beings are different animals.”

Newman’s group recently studied the molecular pharmacology, antitumor activity, and neurotoxicity of caracemide and nafidimide, investigational drugs from the National Cancer Institute. He, too, expressed the hope of “bringing to the clinic in the next couple of years some of the compounds developed by our system, drugs that will provide the best chemotherapy for the patients and yet not compromise their quality of life. We’re trying to do that by looking at toxicity associated with these drugs and reducing it without reducing the drugs’ efficacy,” he said.

Newman studies doxorubicin and bleomycin because, although these drugs work well against cancer, the first sometimes causes congestive heart failure and the second may contribute to pulmonary fibrosis. In both cases, the goal of his research is to come up with less toxic drug versions—Newman’s group is testing an improved bleomycin analogue—and, in the course of this, to find out how the drugs work.

“We all have some very naive assumptions of how drugs kill cells,” Newman said. “When it comes down to answering specifically how a drug kills cells, one can go to a textbook for some very trite answers. Drugs kill cells in many different ways, and defining which one is more important and which one we should concentrate on in terms of developing a better drug is difficult.



Robert Newman

“The only way to approach this is to go back to the subcellular level and ask specifically what a drug does to a malignant and to a normal cell—and then take advantage of what we find out in designing better drugs, drugs that affect malignant cells in a selective manner.”

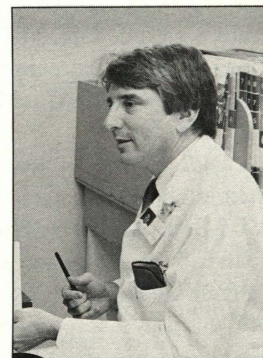
Try to reduce toxicity without lowering efficacy.

On Clinical Side

“Newman and I,” said Dr. Martin N. Raber, chief of the Section of New Drug Studies, “use the laboratory’s pharmacologic studies to design a clinical trial. As the trial goes along, if we see results and begin to understand the drug’s pharmacologic activity in the patient, we can modify the trial according to laboratory information on drug metabolism and toxicity.

“One has to understand clearly who the patient is and what we are doing,” Raber stressed. “The patient is one who has failed to respond to conventional treatments, and the drug has been used only in animals and laboratory trials.

“We ask the patient to take this drug at ever-increasing dosages until a toxic reaction occurs.” Patients who agree to do this, he said, understand that the treatment is “statistically unlikely to work.” Yet they consent to participate in the study because of the small chance that the treatment will be effective—and, Raber added, “because someone else is likely to benefit from it.”



Martin Raber

Patients easy to work with and staff committed to them.

These highly motivated patients are willing to undergo pharmacologic tests that go beyond treatment effectiveness to more basic information about drug action. Although some patients in phase I studies may experience serious side effects from new drugs, Raber said, “in the final analysis a drug’s activity and toxicity can only be tested in patients. The dog and the mouse can’t tell you that they feel confused or that the drug causes a burning sensation in the mouth. So, the final experiment is always the human experiment. This work is not

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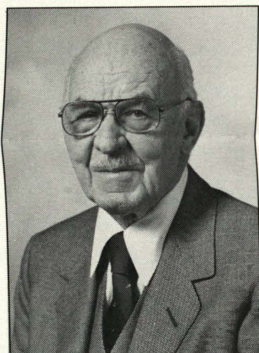
Grant Taylor Organized First Collaborative Drug Research Group in This Part of the Country

H. Grant Taylor, M.D., has a lecture series named for him, and his portrait hangs at the entrance to the sixth-floor pediatric unit of Anderson Hospital, the unit he directed from the first day, March 19, 1954, the hospital opened in the Texas Medical Center.

Taylor is also the founder of this area's first collaborative drug study program, the Southwest Cancer Chemotherapy Study Group, a bridge between scientists who until then tended to work competitively and in isolation.

Luckily, in this year of historical reminders, Taylor is present in pictures *and* in person because he is 83, not 150 years old. One can't celebrate a sesquicentennial of cancer research or of treatment of children for cancer because the history of these endeavors does not go back that far.

Taylor is one of this cancer center's early activists and theoreticians. His work spans nearly the entire history of the UT M. D. Anderson Hospital. Now an emeritus professor of pediatrics at Anderson and still working in the UT Health Science Center Division of Continuing Education—he headed the division's forerunner, the UT Postgraduate School of Medicine—his so-called retirement consists of writing and teaching and seeing patients one day a week in a City of Houston pediatric clinic. His definition of "part time" leans toward everyone else's "full time."



H. Grant Taylor

He is one of cancer center's activists and theoreticians.

Taylor is loved for his comforting and confident professional care, his willingness to try new methods of cancer treatment, and his efforts to broaden the world's knowledge of cancer by extending learning opportunities to physicians and researchers from other countries. Now he has the joy of seeing one son as head of the oncology service of Walter Reed Army Medical Center and the other as administrator of the Air Force hospital at Wichita Falls.

Talent for Connecting People

Taylor earned degrees in engineering and education before he graduated from medical school at age 37. Perhaps this broad

education, after growing up in a pioneer farming family on the Canadian prairie, nurtured his talent for building links. He managed to do this among solo researchers and doctors in private practice, and between Japanese research fellows and Houston citizens with World War II memories and anti-Japanese prejudices.

In the early 1950s, when Taylor was recruited from the National Academy of Sciences to become chief of pediatrics at Anderson, he says "I was warned not to come here because I was told the place was a medical intellectual desert. Yet here the M. D. Anderson Foundation had the foresight to help finance the Texas Medical Center and make it possible, by matching state funds with private money, for The University of Texas to establish a cancer hospital. So in this state there were lots of enlightened forces."

Lesson of war: work on teams and forget self.

Taylor believes it was his war experience as an Army physician and his later service with the Atomic Bomb Casualty Commission in Hiroshima that brought him home with the idea that cancer research should be done collaboratively. "After the war," he says, "everybody was working alone, with no cooperation. And yet I think one of the biggest lessons of that time was that people had to work on teams and forget self."

Preaching and Recruiting

In 1958, he organized the Southwest Cancer Chemotherapy Study Group with a grant from the U.S. Public Health Service (PHS), the first collaborative research group in this part of the country. Taylor was making rounds preaching and recruiting—"talking about getting together because we had to have a volume of patients to learn more about treatment, and we had to have collaborative laboratory research to back it up," he says.

Early members of the research group were teams at UT sister institutions in Galveston and Dallas, at Baylor College of Medicine, the Veterans Administration Hospital in Houston, the University of Arkansas Medical School, and Tulane University. Ten years later, the Southwest group had spread north to Chicago, Detroit, and Minneapolis, and east to Atlanta and Memphis, until it involved 20 institutions and some 80 researchers.

As Taylor recalls with some glee, the idealistic research

cooperative worked on a hard-nosed principle: "I got the grant for the cooperative chemotherapy study group from PHS, and the grant stated that researchers who became members could then apply for a grant to cooperate with us. We were the umbrella organization for 'A Cooperative Study in the Comparative Evaluation of Hydrocortisone Used Alone and in Combination with a Mercaptopurine in the Treatment of Acute Leukemia.' "

The drugs were two of many to follow that would produce complete remissions in some leukemic children.

Texas Nonwelcome

Wataru W. Sutow, M.D., who died in 1982, is seldom absent from Taylor's conversation. He is the Japanese-American physician—interned with his family during the war even though he was born in this country—with whom Taylor worked in Japan and later recruited to head Anderson's research with children. Well remembered, too, are the Japanese research fellows whom Taylor and Sutow trained and who now head major Japanese medical institutions.

Led by Sutow, research with children moved forward fast.

When they were first invited to Houston in the 1950s, these young Japanese physicians were welcome only where they worked. They found it difficult to find a place to live until a church congregation got involved in helping them become more accepted by the community. Sutow and his family also would have been homeless at first, Taylor says, if a realtor had not moved out of his house so that the Sutows could live there.

Under Sutow's leadership, research with children moved forward faster than research with adults because, as Taylor says, "Pediatrics was really the leading edge. Research with children is easier because the disease is more clearcut in children and not complicated by problems of aging. Furthermore, we had some drugs for leukemia—methotrexate among them—and a response that could be measured."

Taylor is particularly proud of the 34 Japanese physicians trained at Anderson during those years, despite the problems. "In a way," he says, "one of our hospital's major international contributions was the training of people and their going home. The Japanese did much with what they learned here. Their society was moving forward fast, and so they went right ahead with what they learned."

Hard Lesson

Among the new drugs barely tested at that time was vincristine. As Taylor tells it, "I had gone to a meeting in Indianapolis where I was given some vincristine, and I gave the first dose to a child who had a tumor. It was a brand-new drug, tested in animals, but the dosage I gave the child was too high, and he went into convulsions that lasted seven days. The day after the convulsions stopped, the child's X ray showed that the tumor had disappeared. That was our first time that vincristine was a success, despite that horrible blunder."

Light from Sixth Floor

Taylor describes the accomplishments of his career with a fresh memory and sense of drama. The heroes of his stories are associates and students and, above all, the parents of his young patients. When his two sons were children, he used to tell them that the glow at night from the pediatric unit sixth-floor windows was made by the mothers' and fathers' care for their children.

"I think today of those mothers and fathers, who gave us permission to try new drugs we knew so little about," Taylor says.

"That was perhaps the most magnanimous gesture I have ever witnessed in my life, for a mother to say: 'Doctor, I understand you can't help our little boy, but if you can learn something that might help somebody else, go ahead and do it.' It was expensive for families to stay here, they were upset, and yet they did that.

"If they hadn't done it then, the mothers and fathers today would be right in their place. We were partners."

Taylor describes his career with a fresh memory and sense of drama. His heroes are associates and students and, above all, the parents of his young patients.

Learning How and Why Drugs Kill Cells . . .

continued from page 3

for the faint-hearted, neither patient nor doctor.”

Raber talked about the strong support among nurses, social workers, physicians, chaplains, and psychiatrists. Staff members carry a tough emotional load because the majority of patients taking new drugs are very ill and may soon die, despite every therapeutic effort. Nevertheless, the patients are easy to work with, he said, because they take such an active part in their own care.

“The staff at Anderson is very committed to the patients. And I find that patients, particularly young ones, like it here because here they’re not thought of as freaks. In the general hospital, the 26-year-old woman with lung cancer is an anomaly. She’s lost her hair, she’s very thin, everyone looks at her strangely and thinks how tragic she is. But when she walks into the Anderson hospital, people treat her as just another patient. She fits in,” he said.

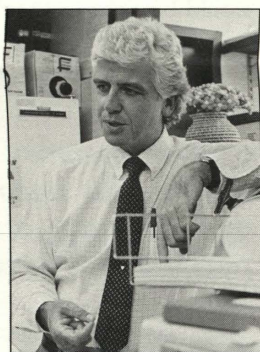
Raber is proud of his section’s “compulsive” record-keeping and complete computerization, which improve the reliability of drug trial data, and he is well acquainted with the fact that researchers’ and drug companies’ goals may be different: the company wants to prove a drug is worthwhile and should be approved by the Food and Drug Administration, whereas the researcher may have a more objective view. Both want to find “the most efficacious way to use the drug, the best dosage, best schedule, and most responsive tumor to use it on. The design of trials,” he said, “is a complicated problem.”

And, he added almost seriously, testing drug analogues is like “digging oil wells in Texas today. You know there’s oil down there—you just want to come up with it in an easier way.”

Testing Leukemia Treatments

Dr. William Plunkett, who conducts studies of new drugs and new treatment regimens in leukemic patients who can no longer benefit from other therapies, sums up his work as “trying to target effective treatment at susceptible disease.”

Plunkett’s recent investigations have focused on effective dosage, therapeutic efficacy, and pharmacologic correlates of arabinosylcytosine (ara-C) in patients with refractory acute leukemia. These patients differ greatly in their ability to metabolize ara-C, he explained. His research group’s finding of a relationship between the ability to achieve remission and the inhibition of DNA synthesis by ara-CTP, an ara-C metabolite, has been a clue to knowing the metabolic characteristics of the leukemia likely to improve with this drug.



William Plunkett

Optimistic and Impatient

One characteristic of the Department of Chemotherapy Research is a mixture of optimism and impatience. Krakoff pointed to “enormous improvements” in the ability to cure neoplasms like acute lymphoblastic leukemia, testicular cancer, and Hodgkin’s disease, “marked advances” in treating head and neck cancer, and “some progress” in treating breast and ovarian cancer. But the successes highlight the failures, he said, because “we still do very little for many of the common cancers—for example, those of colon, lung, pancreas, and others. Perhaps those tumors must be approached by different principles, but it is more likely that the principles shown to be successful for treating some tumors would be successful in others if we had better or more specific drugs.”

Successes highlight failures.

Bleomycin, doxorubicin, and cisplatin “have been around for a decade or more, which means that new ones are needed,” he said.

(Physicians who desire additional information may write Irwin H. Krakoff, M.D., Division of Medicine, Box 15, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas, 77030.)

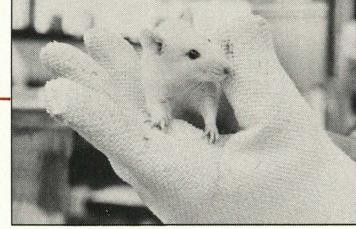
Thirty-ninth Annual Symposium
on Fundamental Cancer Research

Critical Molecular Determinants in Carcinogenesis

September 16-19, 1986
Stouffer’s Greenway Plaza Hotel
Houston

For registration information, contact Shirley Roy, Office of Conference Services, HMB Box 131, The University of Texas M. D. Anderson Hospital and Tumor Institute, 6723 Bertner Avenue, Houston, Texas 77030, (713) 792-2222.

Science Park Hosts First Texas Carcinogenesis Meeting



The Texas Carcinogenesis Meeting at UT System Cancer Center Science Park-Research Division in April was the first of what are to be twice-yearly meetings for Texas scientists to discuss research in carcinogenesis, the biology of cancer, genetic toxicology, and mutagenesis. Financial support for the all-day conference, attended by 103 professionals and students from 14 institutions, came from the Texas Division of the American Cancer Society.

In the keynote address, J. Carl Barrett, Ph.D., National Institute of Environmental Health Science at Research Triangle Park, N.C., reported his work on the molecular action of tumor promotion. Barrett and his colleagues are the only researchers currently doing *in vitro* studies of the genes that suppress tumor growth.

Milton Marshall, Ph.D., Southwest Foundation for Biomedical Research at San Antonio, described his research with baboons on smoking and cancer. Marshall has been able to train primates to duplicate human cigarette smoking, and he is beginning to quantitate his data on the presence of mutagens in the animals' blood, urine, and other specimens.

Rebecca Morris, Ph.D., Science Park-Research Division, reported on the retention by epidermal cells of benzo(a)pyrene, a ubiquitous carcinogen formed by combustion of hydrocarbons.

Morris has used radiolabeling techniques to determine that benzo(a)pyrene may remain in the skin for up to one month after exposure.

Jonathan Ward, Ph.D., UT Medical Branch at Galveston, discussed his study of risks of contact with pollutants along the Gulf Coast. Ward exposes mice to the most common pollutants and then assesses their effects on the animals' organ systems.

Organizers of the Texas Carcinogenesis Meeting want to hold these sessions at different institutions in the state and to encourage a lively exchange of information in an informal setting. They invite postdoctoral fellows and graduate students to attend and submit abstracts for the poster sessions.

The meetings are open to all interested persons, including specialists in other fields who wish to extend their knowledge of the biology of cancer and related phenomena.

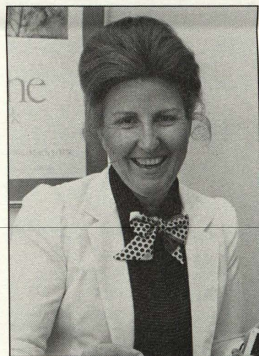
The next Texas Carcinogenesis Meeting, Nov. 11 at the Hotel Inter-Continental in Houston, will coincide with the 30th Annual Clinical Conference on Cancer, "Current Approaches to the Diagnosis and Treatment of Gastrointestinal Cancer."

(For more information contact the Office of Conference Services-HMB Box 131, UT M. D. Anderson Hospital and Tumor Institute, 6723 Bertner Avenue, Houston, Texas 77030; 713-792-2222.)

Cancer Prevention Begins at Home: With MDA Screening and Detection Clinic

Helping M. D. Anderson staff members apply principles of prevention and early detection of cancer to their own lives is the goal of the employee screening program directed by Linda N. White, R.N., with medical direction by J. Taylor Wharton, M.D., professor of gynecology.

According to its *Ten Year Report*, the Cancer Screening and Detection Program aims "to increase the accessibility, availability, and quality of cancer prevention and detection services by training nurses to assume a direct and collaborative role with physicians in all health care settings, and to reduce the impact and costs of cancer by lowering the risk of developing it."



Linda White

A worthwhile goal—and it is working, according to White and clinic coordinator Judy Faulkenberry, R.N. The full-fledged cancer screening program was established in June 1981 after a pilot program tried in 1980 turned out to be overwhelmingly popular. Today, cancer screening for employees is a full-time operation, run by nurses and supervised by an advisory board of physicians with specialties in gynecologic, gastrointestinal, and breast cancers, and in mammography and diagnostic radiology.

The physicians helped establish the examination protocols, which include a thorough examination of skin, head and neck, breasts, lungs, abdomen, female genitalia, rectum, male genitalia, and lymph nodes. An assessment of cancer risk is based on a detailed medical and family history questionnaire staff members fill out. They are taught self-examination techniques and given cancer education booklets. When appropriate, employees are referred for additional tests.

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Cancer Prevention Begins at Home . . .

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As of last March, 3,199 Anderson staff members who were asymptomatic for cancer had been examined; 874 were found to have noncancerous abnormalities that required medical attention, and 49 had premalignant conditions. Twelve cancers were detected.

Asked for their reactions to the clinic's services, the staff's helpfulness, and the thoroughness of the examination in written evaluations six months after their clinic visits, Anderson employees gave the program a close to excellent rating, 6.5 on a scale of 1 to 7. One of the most encouraging results is that 86.4% of the women and 90.3% of the men shared the information they had received with friends and family members. Most of the screened employees, both men and women, did self-examinations more often.

The staff of the Cancer Prevention and Detection Clinic, White says, continues to train nurse specialists from other Texas institutions and to help companies—Johnson & Johnson, for example—to start cancer screening programs for their own employees.



Cancer detection specialist Alice Judkins with client.

(Physicians who desire additional information may write Linda N. White, R.N., Cancer Prevention and Detection Program, Box 133, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030.)

The University of Texas
 M. D. Anderson Hospital and Tumor Institute
 at Houston

Thirtieth Annual Clinical Conference on Cancer
**Current Approaches to the Diagnosis
 and Treatment of Gastrointestinal Cancer**

November 11-15, 1986

Hotel Inter-Continental · Houston

Chaired by Bernard Levin, M.D.
 Chief, Section of Gastrointestinal Oncology
 and Digestive Diseases
 and Robert Herring Professor in Clinical Research

In eight sessions and 45 lectures and panel discussions, the conference will provide information on the best in diagnosis and treatment for this type of disease. It will be a forum for sharing new ideas and learning about advances.

Registration fees are \$285 (advance)
 and \$325 (after Oct. 20).

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