Cancer Detection

Joann L. Ater, an assistant professor of pediatrics in the Department of Pediatrics, is the director of the Neuroblastoma Screening Program, one of 10 projects under the auspices of the Texas Outreach Program.

January-March, 1993
Volume 38, Number 1

The University of Texas MD Anderson Cancer Center

New test is provided at no cost to parents

Texas Outreach Program offers neuroblastoma screening in infants

Neuroblastoma is an aggressive cancer of the peripheral nervous system that is most commonly characterized by tumors in the abdomen, along the spine, on the skull, and behind the eyes. It affects one in every 6,000 children under five years of age and is the second most common solid tumor in children. Like many cancers, neuroblastoma is much more likely to be cured if detected early: although the cure rate is only 20% to 40% in children whose disease is diagnosed after the first birthday, it is over 80% in children less than one year of age. Unfortunately, because the disease is not usually detectable that early through normal well-baby physical examinations, few neuroblastomas are diagnosed in time to take advantage of these excellent odds. A new statewide screening program, however, may soon improve Texas children’s chances of cure.

The test is inexpensive, easy to perform, and accurate

Physicians at The University of Texas M. D. Anderson Cancer Center are taking advantage of a new test that can cheaply and accurately detect the levels of two catecholamine metabolites, homovanillic acid (HVA) and vanillylmandelic acid (VMA), in the urine. Elevated levels of these substances may indicate several different kinds of tumors, but none of these is known to occur in young children except neuroblastoma, essentially making the test specific for neuroblastoma in infants under one year old. The test, which uses monoclonal antibodies to identify HVA and VMA, is not easily contaminated, requires simple saturation of a filter paper with urine, and can be processed quickly in large numbers. The older tests were more laborious, could be contaminated by several normal dietary substances (such as vanilla) and medications, and in some cases required 24-hour urine collection.

The recently introduced program will screen six- to nine-month-old infants through much of the state.

The program, under the direction of Joann L. Ater, M.D., Department of Pediatrics, is one of 10 projects that compose the Texas Outreach Program, a cancer prevention initiative designed to provide new and expanded cancer screening and detection services in communities across the state. The overall goal of Texas Outreach is to make cancer resources more accessible to all Texans, especially those in rural and economically depressed areas and areas with higher-than-normal cancer incidence. The program attempts to enlist primary care physicians, nurses, allied health workers, and lay persons in practical cancer prevention and early detection programs. It is to be paid for not by state funds but by up to $15 million in fees earned by the physicians of M. D. Anderson.

Informal consortium established

The neuroblastoma screening program began when an informal consortium of Texas pediatric oncologists recognized the critical need for early detection of the disease in young children. “Our immediate goal,” Ater said, “is to detect neuroblastoma at a younger age and, therefore, reduce the population-based mortality rate from the disease. We want children who test positive to be seen by a pediatric oncologist before their first birthday.”

Oncologists who volunteered for the neuroblastoma screening program became “nodes” in a statewide network of screening sites. The network comprises major metropolitan areas in the state, a total of 32 counties, and accounts for nearly two-thirds of all the births in Texas, or about 300,000 per year. The actual screening began in August 1992. Names of newborn infants in the 32 counties were obtained from a Texas Department of Health data base. A test kit was sent to the parents of each child, along with a bilingual brochure explaining the purpose of the test and giving instructions for the collection and mailing of the sample.

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"We want children who test positive to be seen by a pediatric oncologist before their first birthday"

The procedure consists in saturating a filter paper with the child’s urine. The filter is dried and placed in a preaddressed, stamped plastic mailer. A technician at M.D. Anderson processes the samples, and parents of children whose tests are positive are contacted, usually within about a month. (Parents who do not receive a response can assume that the test was negative, although they are given a telephone number they may call to get their child’s results.) When the test is positive or inconclusive, the parents receive a second kit. If the child again tests positive, the parents are asked to take their child to the family doctor or pediatrician (who is named on the form returned with the specimen) for further evaluation. At the same time, Ater or one of the other physicians involved in the project contacts that physician with information on the test and the disease and provides guidelines for evaluating the child. If the follow-up liquid urine sample is also positive, the physician is asked to refer the child to one of several pediatric oncologists in their area who have agreed to see these children.

Texas primary care physicians are key to program’s success

Informed primary care physicians are a cornerstone of the project. Because any primary care physician in Texas may see an infant who has had the test, nearly 10,000 physicians in the state received a mailing in the summer of 1992 outlining the importance of early detection, the details of the screening project, and the physician’s role in it. A second mailing is planned for this winter. Large, colorful posters explaining the program that are suitable for posting in waiting rooms have been prepared and will soon be distributed.

Of the 39,000 kits that have been mailed since August, about 3,000 have been returned. Three children have tested positive twice, but neuroblastoma has not been confirmed in any of them. Ater characterized compliance with the screening program as “improving,” although the initial response rate was very poor. One element of the project is a study of why parents would resist having their child tested, even though the test has been made both convenient and free. Statewide media releases have been targeted at educating the public about neuroblastoma and the need for screening.

Testing not yet mandatory

Such directed and repeated efforts to encourage testing are necessary because the project depends on voluntary compliance. Archie Bleyer, M.D., however, feels that the benefits of testing and the incidence of the disease will eventually call for mandatory testing, as is the case for phenylketonuria and galactosemia—two conditions that are rarer than neuroblastoma: “We see our screening program as a prototype or feasibility study for developing a proposal that may make neuroblastoma screening mandatory in Texas,” said Bleyer, who is head of the Division of Pediatrics at M.D. Anderson and chairman of the group that oversees the Texas Outreach Program. “Neuroblastoma screening of infants has been mandatory in Japan since 1985, and their data have shown a reduction in the death rate from the disease. An ongoing study in Quebec has been sufficiently rewarding that the province is considering requiring it. In the U.S., Maryland is also beginning neuroblastoma screening,” he said. Screening programs are also in place in Australia, Austria, Brazil, England, France, Germany, and Norway.

Whether neuroblastoma screening becomes state law or not, the program’s directive is to identify children with the disease and get them the medical attention they need. M.D. Anderson has devoted substantial resources to achieving this goal, but the program’s success will depend upon the support provided by primary care physicians.

—KATHRYN L. HALE

Physicians who desire additional information may write Dr. Ater, Department of Pediatrics, Box 84, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas, 77030, or call (713) 794-4620.
Sensitivity to carcinogens varies in the human population

Clinicians' ability to predict cancer risk may lie in new assay

If not for theft and revolution, T. C. Hsu, Ph.D., might have been a poet in mainland China instead of an eminent scientist. Hsu professes to have been a "not too diligent student," more interested in poetry and literature than in science, but his interests were redirected when, on a school day in the 1930s, Hsu opened his desk to learn that someone had stolen his prized stamp collection. He was heartbroken, so he vowed to collect something no one else would want: bugs. His interest in insects led to an interest in science, and in 1948 Hsu found himself in Austin, pursuing a Ph.D. in genetics at The University of Texas. He intended to rejoin his family after his studies and be a scientist in his homeland.

Simple plans, but they were complicated by Mao Tse-tung and the communist revolution. "This is a long, long story, a bloody story," Hsu said. Mao was purging geneticists and other scientists, so Hsu stayed in the United States and attempted to secure permission for his wife and daughter to immigrate. He finally succeeded in 1954, when his daughter was six years old. Because she was born shortly after he had left for Austin, it was the first time he saw her. During those years, he had been recruited by R. Lee Clark, M.D., founder of The University of Texas M. D. Anderson Cancer Center. Hsu came to the institution in 1955, where he is today.

New assay may help identify patients at risk

Hsu's achievements over the years are considerable (see box, p. 4). His latest discovery—an assay designed to identify patients at risk for environmentally caused cancer—may eventually prove to be an important component of cancer prevention programs. Hsu, professor emeritus in the Department of Cell Biology at M. D. Anderson Cancer Center, developed the assay in collaboration with Lorraine M. Cherry, Ph.D., now at The University of Texas Health Science Center at Houston.

The genesis of Hsu's assay began over 10 years ago, when he wondered, as had a few others in his field, whether carcinogen sensitivity varied in the human population. What distinguished Hsu from his colleagues was that he intended to develop a system to test this question formally. The task wasn't so easy. Fortunately, Hsu had one advantage other scientists didn't: cooperative clinical colleagues who would help him obtain human tissues and cells, both normal and tumorous. Hsu knew that if he was successful in developing the assay, access to such tissues would be essential to test the assay's validity.

Assay identifies susceptibility to chromosome damage

It took Hsu and his colleagues two years to perfect what was to be called the bleomycin mutagen sensitivity assay; the assay quantitates the mutagenic effects (as determined by chromosome defects) in lymphocytes after bleomycin treatment. He had chosen the radiomimetic drug bleomycin because it induces DNA damage by a mechanism similar to that of ionizing radiation. With the help of his clinical colleagues, Hsu began collecting lymphocyte samples from healthy donors (including asymptomatic smokers) and patients who had tumors of the lung, colon, head and neck, or breast. It took years to collect enough samples, but in 1989 Hsu reported some promising results: Lymphocytes from patients with lung, colon, or head and neck cancer, generally considered to be environmentally continued on page 4
I was often told that the assay wouldn’t work.

caused diseases, showed a significantly higher sensitivity to bleomycin than did cells from normal donors, whereas patients with breast cancer, whose cause is considered hereditary and hormone related, showed no such sensitivity.

Hsu also compared “old smokers” (≥ age 50) and “young smokers” (< age 50). If sensitivity to bleomycin indeed was an indicator of susceptibility to cancer, he surmised that asymptomatic old smokers would be less sensitive, the rationale being that if they had smoked for a long time and yet showed no sign of disease, they may have some inherent resistance to carcinogens. Such was the case. Lymphocytes from old smokers were less sensitive to bleomycin than those from young smokers and normal controls, the latter two groups showing about the same level of sensitivity.

These results were encouraging. The difference in sensitivity between patients with environmentally caused and hereditary cancers and between old and young smokers suggested that inherent sensitivity played some role in cancer incidence, but Hsu and his coworkers realized that the study demonstrated only the plausibility of their hypothesis. First, the distinction between “environmentally caused” and “hereditary” cancers is essentially a working hypothesis. Although much evidence supports this general distinction, the subtypes of these cancers are biologically heterogeneous, so the “distinction” could not be confidently used as a basis for hard conclusions. Second, healthy donors were studied separately from cancer patients. A better method would be a prospective randomized trial of just one group monitored over time. Hsu’s objective, then, was to identify a population, test its members’ bleomycin sensitivity, and then monitor subsequent cancer incidence. These studies would help determine whether bleomycin sensitivity could be used as a predictor of cancer risk.

Hsu turned to Stimson P. Schantz, M.D., with his

Hsu’s first major discovery: the hypotonic solution*

There is one common thread in the 40-year career of T. C. Hsu (pronounced “Shoo”): the hypotonic solution. First discovered by Hsu in 1952, this solution is now routinely used by cytogeneticists to visualize and count mammalian chromosomes. In fact, the use of a hypotonic solution is a standard step in Hsu’s latest discovery, the bleomycin assay. The discovery of the hypotonic solution, however, is a classic example of how serendipity, followed by hard work, can lead to major advances. In 1952, Hsu was a postdoctoral fellow at The University of Texas Medical Branch in Galveston. Hsu had received his doctorate in fruit fly (Drosophila) genetics, but at Galveston he was studying human and mammalian cells. Hsu therefore spent his initial months learning new techniques and procedures. While doing so, he stumbled on “a miracle.”

When examining spleen cells under a microscope, Hsu noticed “beautifully scattered chromosomes... I could not believe my eyes,” he recalled. But he couldn’t repeat the effect. He spent the next four months modifying the cell preparation process. Finally, he duplicated the chromosome spread effect by using a hypotonic solution instead of the balanced salt solution that was typically used in his laboratory. Apparently, the earlier “miracle” was caused by a technician who had incorrectly prepared a batch of standard salt solution, inadvertently making it hypotonic. And who was that technician? According to Hsu, no one knows. “No one admitted to committing an error.”

*Quotes and background information were derived from Human and Mammalian Cytogenetics: An Historical Perspective, by T. C. Hsu. New York: Springer Verlag, 1979, pp. 15-19.
"Well, one idea begets another, and you want to see what happens\(^*\)

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idea. “If not for Dr. Schantz, if not for his enthusiasm and push, I probably would have published my paper and then let it go,” Hsu said. “He really took a personal interest in this and saw an opportunity to study second primary tumors in head and neck cancer patients. Typically, after removal of the primary tumor, about 20% of these patients develop another primary tumor within five years.” (Schantz, formerly of the Department of Head and Neck Surgery, now works at Memorial Sloan-Kettering Cancer Center; he and Hsu continue to collaborate.)

This, then, was a suitable patient population in which to correlate sensitivity and incidence. Hsu, Schantz, and their team enrolled 84 patients in the study, all of whom were assessed for bleomycin sensitivity and lifestyle habits that exposed the subject to carcinogens (e.g., smoking). All received definitive therapy for the primary tumor. Of the 33 patients that the study team classified as “hypersensitive” to bleomycin, nine (27.3%) subsequently developed second primary tumors, whereas of the 51 less-sensitive patients, only four (7.8%) developed a second primary tumor.

**Assay attracts worldwide interest**

Ever the cautious scientist, Hsu is quick to say that the study sample was too small for definitive conclusions; nevertheless, his results have spurred considerable interest worldwide. The University of Pittsburgh is now conducting a similar study, and scientists from the University of Hawai‘i at Manoa, Free University Hospital (Amsterdam), and Institut Armand-Frappier (Quebec) have been sent to Hsu’s laboratory to learn the technique for the bleomycin assay. The current interest reminds him of the days when his idea wasn’t so eagerly received. “I was often told that the assay wouldn’t work,” Hsu said. “Fortunately, many of my clinical colleagues weren’t so negative. They gave me a great deal of encouragement and help.”

One of those colleagues was Margaret R Spitz, M.D., acting chairperson, Department of Epidemiology. She has used the bleomycin assay to study the risks of tobacco and alcohol use in head and neck cancer patients. “She has found that the risk estimate increases with increasing consumption of these two substances, but it escalates dramatically in individuals who are also bleomycin sensitive,” Hsu said. This assay is also being used in Spitz’s study of lung cancer in minority populations.

In other areas, Hsu has joined Waun Ki Hong, M.D., chairman, Department of Head, Neck, and Thoracic Medical Oncology, in a cancer prevention program, and Hsu is looking for a dermatologist to help him with his melanoma study. In the latter case, Hsu will attempt to develop a new assay using 4-nitroquinolone, which mimics the mutagenic properties of ultraviolet light.

This degree of collaboration is considerable for a man who ostensibly retired in 1977. “Well,” he said, “one idea begets another, and you want to see what happens.” Hsu is grateful to the institution and the University Cancer Foundation for continuing to fund some of his research and administrative support since 1977. He works six hours a day and does his reading and writing at home at night, except on Mondays during football season. “I like Monday night football,” he added. (His favorite team is the Houston Oilers, though he’s also a fan of Jim Kelly and the Buffalo Bills.)

At times, though, Hsu recognizes that time will eventually overtake him. Because many of these studies require long-term follow-up, Hsu thinks his melanoma studies will be his “swan song.” But he’s not complaining. “I’ve been a lucky guy,” he said. “All my life, wherever I went, people bent over backwards to help me. Since I came to this country, everyone has been nice to me—well, except once a cab driver in Boston called me a ‘damn confederate’—but that’s it.”

If the power of Hsu’s ideas and playful humor are evidence of the life force within him, one believes he will be around well into the next century, spending his nights with science, poetry, or football. —KEVIN FLYNN

Physicians who desire additional information may write Dr. Hsu at the Department of Cell Biology, Box 181, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, or call (713) 792-2582.
Cryosurgery  
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as effective as radiation therapy in achieving tumor response.

"The use of cryotherapy is not new," said Johnson. "What is new is freezing with minimal risk to the patient—using ultrasound and multiple small probes as opposed to one big one." The new technique was refined in 1991 by radiologist Gary Onik, M.D., and urologist Jeffrey Cohen, M.D., of Allegheny General Hospital in Pittsburgh, Pennsylvania. Using real-time transrectal ultrasound, they determined how to monitor the rate and location of prostate freezing. Last year Cohen, who had been a fellow at M. D. Anderson 10 years ago, presented the approach to his former colleagues.

"We were excited that this could represent a new local modality," said Andrew C. von Eschenbach, M.D., chairman of M. D. Anderson's Department of Urology. M. D. Anderson became the second institution in the country to obtain a prostate cryotherapy device.

M. D. Anderson urologists decided to begin offering ultrasound-guided cryosurgery to patients with recurrent disease in the prostatic or periprostatic area.

Patients eligible for the pilot study, which began last July, had received radiation therapy as primary or definitive treatment, had no evidence of metastatic disease, and gave informed consent.

In 1992, 31 such patients underwent ultrasound-guided cryosurgery at M. D. Anderson. Because no major complications have occurred in them or in the more than 100 patients who have been treated at Allegheny General Hospital, the procedure is now a standard option for M. D. Anderson patients with recurrent disease. (Medicare, however, still considers cryosurgery for treatment of prostatic carcinoma investigational.)

M. D. Anderson chose this patient population for its pilot study because the traditional treatment options for them either do not remove the tumor or have undesirable side effects. Because the tissue is already damaged from radiation therapy, salvage prostatectomy involves excessive risk of complications, and surgeons often are not able to remove all the tumorous tissue. "And further radiation therapy is usually out of the question because patients have had about as much as the body can tolerate in that area," Johnson said. Until now these patients have had only two choices: no therapy until symptoms appear or hormonal therapy.

Hormonal therapy involves castration or costly in-
Contrasted cryosurgery is one-time therapy, and patients aren’t freezing. After about 10 to 15 minutes, the ice ball with liquid nitrogen, to -175°C to -200°C. Johnson said. "You can see an ice ball forming." When all the cryoprobes are in place, the surgeon lowers the temperature of the probes, which are filled with liquid nitrogen, to -175°C to -200°C. As the tissue freezes and hardens, its acoustic properties change, so the progress can be monitored by ultrasound (Figure 1). "The tissue turns dark black," Johnson said. "There really has been very little work published on what happens at the tissue level." He hopes to determine the answers to several questions. If the cryoprobe temperature is -200°C, what is the temperature in the surrounding tissue? Are malignant cells more sensitive to freezing than normal cells? Which elements of the prostate are more apt to be destroyed? Is the connective tissue component more resistant to freezing than the glandular element? How does the body "absorb" the dead tissue after cryosurgery? Follow-up of the patients being treated now for recurrent disease will demonstrate how effectively cryosurgery eradicates prostatic carcinoma. "If it works in this situation, and we can prove that over the next two or three years, then we can consider it in selected patients for primary therapy, instead of surgery or radiation," Johnson said. Taking into account the operation time, length of hospitalization (about seven days), and length of recovery (four to five weeks) for radical prostatectomy, cryosurgery is cheaper. "It certainly would have a significant impact on the cost of care in this country if it can be proven to be useful," Johnson said.

—SUNITA PATTERSON

Physicians who desire additional information may write Drs. Johnson or von Eschenbach at Box 110, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, or call (713) 792-3250.
Cryosurgery for prostate cancer shows promise in pilot study

With traditional therapies, prostate cancer patients face two depressing prospects: a long treatment or recovery period and a high risk of severe complications such as impotence and incontinence. But with a new experimental technique—ultrasound-guided cryosurgery—patients are hospitalized for only two days, and the risk of complications is low, according to urologists at The University of Texas M. D. Anderson Cancer Center.

Prostatic carcinoma is the most common cancer in American men; 132,000 cases are diagnosed a year. New screening procedures, such as prostate-specific antigen (PSA) tests and ultrasound-guided biopsies, are detecting an increasing number of cases.

“From 1972 to 1988, we averaged six radical prostatectomies a year,” said M. D. Anderson Cancer Center urologist Douglas E. Johnson, M.D. “We’re doing 150 this year.”

Given this increase, the development of an effective yet minimally traumatic treatment has become all the more important. To achieve this goal, two common technologies, ultrasound and cryosurgery, have been combined in a new way.

New technique makes old idea feasible

When Johnson joined the M. D. Anderson faculty 25 years ago, hormonal therapy was used as primary treatment for most patients with prostatic carcinoma, and radiation therapy was just beginning to be used. Around this time, investigators first conceived that cryosurgery, which was commonly employed for malignancies in the skin, eyes, and cervix, could be applied in the prostate.

In early attempts, the cryoprobe was inserted through the penis, freezing and destroying the urethra, which resulted in patients passing blood and tissue for weeks or months. Even after an open perineal approach was developed, urethra damage and urethrocutaneous or urethrectal fistula formation often occurred because the freezing could not be monitored. Nevertheless, researchers were encouraged because cryosurgery appeared to be as effective as prostatectomy and almost continued on page 6