Bone Marrow Transplantation Supports Patients through High-Dose Chemotherapy

Karel A. Dicke, M.D., never tires of telling stories about patients whose lives were saved by bone marrow transplantation at The University of Texas M. D. Anderson Cancer Center, where he is a professor of medicine and pioneered the procedure.

There is the man who went through transplantation because he had recurrent Hodgkin's disease. A year later he started his own aircraft company. Today he is a pilot.

Then there is the young Netherlander, in transplantation for the same reason, who nearly landed in the Dutch army when he went home after recovering and finishing college in Houston. Only the scar from his lung operation, which provoked the army doctor to ask about the potential recruit's medical history—and a letter from Dicke confirming that history—kept him out of the draft.

“We are here,” Dicke said, “not to arrange the funeral, but to kick the door open to more treatment. Two things—improvement of the survival rate and a good quality of life for the patients—are what counts.”

The bone marrow transplantation program at M. D. Anderson, now in its fourteenth year with a record of more than 1000 of the procedures, has become a major way of supporting patients through high-dose chemotherapy.

The program expanded as autologous bone marrow transplantation was offered to new categories of patients, including those with recurrent solid tumors, and as the rates of long-term survival of leukemia and lymphoma patients rose. Autologous transplantation now far outnumbers the allogeneic procedure at M. D. Anderson because using the patient's own marrow avoids problems of unavailability or incompatibility of donors, who usually have to be siblings, and the risks of graft-versus-host disease. In leukemia and lymphoma, however, autologous bone marrow transplantation requires special care to assure that the patient's bone marrow is clear or almost clear of malignant cells.

Autologous transplantation now far outnumbers the allogeneic procedure at M. D. Anderson.

Allogeneic marrow transplantation is still done for patients with acute and chronic leukemia when a donor is available, for this therapy is curative, Albert B. Deisseroth, M.D., M. D. Anderson professor, chair of the Department of Hematology, and chief of the transplantation center, explained.

But perhaps transplantation should be done earlier in the course of the disease, he said, because nearly half of chronic myelogenous leukemia patients with donors can be cured by high-dose chemotherapy and bone marrow transplantation (cured meaning five years of freedom from disease). Unfortunately, not everyone has a donor. The first-line
treatment, interferon, controls the disease in 20% of patients, and another 25% of those whom interferon does not help are cured by allogeneic transplantation.

Although the risks of marrow donation itself are small, the procedure is “tough therapy,” with its own toxicity, Deisseroth said. Patients are never far from severe viral or fungal infections while their immunity is suppressed by high doses of drugs, a danger that has kept arguments about choosing high-dose chemotherapy and transplantation or treatment with conventional doses from being resolved. “But when cure is the outcome, we must take that chance,” he said.

“We still cannot tell at the beginning of therapy who will and will not benefit from interferon or from transplantation. A big problem for us is to know whom we should or shouldn’t subject to the risk of death from the treatment’s toxicity and to know who should receive interferon. We now have a new program at M. D. Anderson that is designed to fit the best therapy to each patient by using a combination of autologous bone marrow transplantation and biological therapy,” Deisseroth said.

Complete Remissions After Three to Six Years

Some of the M. D. Anderson physicians’ experience with leukemia treatment seems to argue for early autologous transplantation, during a patient’s first remission or early in the disease course, according to Dicke. Of 18 patients with acute myelogenous leukemia who underwent autologous transplantation during 1983-1985, the first group studied here, 10 are still in complete remission. The longest follow-up is 6 years and the briefest is 3, a dramatic change from the median disease-free survival of approximately 16 months after diagnosis for patients without transplantation.

These patients’ marrow, aspirated during remission, did not need to be treated in vitro, as is often done to destroy malignant stem cells, Dicke said, because “we gave basically thorough, aggressive chemotherapy, in this case with arabinoside and amsacrine. At the time of transplantation, therefore, the patient’s leukemic cell burden was very low.”

The process Dicke calls “in vivo purging” is usually done by exposing a patient repeatedly to standard-dose chemotherapy, which destroys the leukemic cells in the marrow. This type of therapy has low toxicity and can therefore be done without compromising hematopoiesis. This experience, too, argues for transplantation during an earlier stage of leukemia, when leukemic cells are more susceptible to eradication, and for extending studies of predictive markers like aberrant chromosomes, oncogenes, and, in the case of breast cancer, estrogen receptors, Dicke said.

Long Remissions in Hodgkin’s Disease

For patients with lymphoma—Hodgkin’s disease and non-Hodgkin’s lymphoma—Dicke and his team are engaged in studies with researchers at the University of Nebraska and in Rotterdam, the Netherlands.

Patients with Hodgkin’s disease who have relapsed are given two courses of normal-dose chemotherapy. If they respond well to this, they may enter the high-dose program and undergo autologous transplantation. “We predict,” Dicke said, “that between 50% and 60% of the patients will be free of disease for a long, long time. I can’t say cured because in Hodgkin’s disease one can have a late relapse, maybe 10 years later.”

The record of bone marrow transplantation for non-Hodgkin’s lymphoma is different because, so far, standard therapies have brought high complete remission rates; for them, high-dose chemotherapy and transplantation have not proved better.

For Solid Tumors

As it became obvious that autologous transplantation supports many types of patients through intensive chemotherapy for blood and lymphatic-system malignancies, clinicians began about eight years ago to use the method for patients being treated for the solid tumors of, for example, breast cancer.

Fifty percent of breast cancer patients are cured by surgery and radiation—“good news and bad news,” said Deisseroth. “What can be done to circumvent the problem in the uncured half, in whom the disease is disseminated by the time it is diagnosed?”

Adjuvant therapy after surgery and radiation improves survival, he said, but it does not save everybody. “Here again, the problem is deciding who will do well with transplantation and who will not. It’s important not to wait six months when even people who will benefit from transplantation will be harder to treat.”

Some ways of assessing prognosis are known, Deisseroth said, including bulk and distribution of disease, type of estrogen receptors (positive being better), and the number of oncogenes present, particularly the recently identified new oncogene.

Transplantation Twice

Patients with recurrent breast cancer are offered autologous transplantation at several cancer centers—Dana Farber Cancer Center at Harvard and Duke University Cancer Center, among others—but only at M. D. Anderson is the chemotherapy regimen spread over two periods, and patients go through two transplantation procedures. These are usually a month apart, which means patients spend at least eight weeks in the hospital.

continued on page 7
Osteosarcoma: Expandable Prostheses and Allografts Reduce the Need for Amputation

“Osteosarcoma is an extremely virulent tumor. Without a multimodality approach to treatment, survival rates would average no more than 15% to 20%. Now, however, with a combination of surgery and chemotherapy, five-year survival rates average about 70% for adults and children,” said John A. Murray, M.D., chief of orthopedic services at the M.D. Anderson Cancer Center. Murray performs two procedures, prosthesis implantation and allografting, that are important adjuncts to therapy for osteosarcoma. These procedures are necessary not only for eradicating local disease, but also for limb preservation.

Indications for Prostheses
Expandable prostheses were developed about five years ago for the surgical treatment of children with osteosarcoma. “Expandable prostheses allow us to operate on children at an earlier age,” said Murray. “Nonexpandable prostheses can’t accommodate the child’s growth. The resultant discrepancy in leg length would be more of a burden than a help. In the past the only way to excise the tumor-bearing bone was to amputate the leg. Candidates for prostheses were limited to adults or to children who had no more than six centimeters to grow.”

Expandable prostheses allow us to operate on children at an earlier age.

Like other prosthetic devices, expandable prostheses have an articular surface and an intermediulary stem, but the expandable devices also have a machine screw attached to a ratchet. “The machine screw allows you to separate the two ends. The prosthesis can then be locked in that position. Depending on the growth rate, you could expand the prosthesis every six months or so to keep the leg length equilibrated,” Murray said.

The critical issue in determining whether an expandable prosthesis is indicated is the skeletal maturity of the child. “Females generally reach skeletal maturity between the ages of 13 and 15, whereas males do so a bit later, between 15 and 17,” Murray said. “Consequently, at the age of 15 children can be operated on as adults. These patients can receive nonexpandable devices, and any problems caused by growth can, in most cases, be easily corrected postoperatively; but younger patients need expandable prostheses to compensate for growth.”

The extent and location of metastasis may affect the decision to implant an expandable prosthesis, Murray said. “Metastases to the center of the parenchyma of the lung are usually most easily resectable. In such cases, if the pulmonary lesion and the primary lesion respond to preoperative chemotherapy, we wouldn’t hesitate in implanting the prosthesis. In other cases, however, the metastases are in locations in which the hazard of resection is lethal, in the vertebrae or skull, for example. These patients generally are not considered for an expandable prosthesis.”

No Diagnostic Symptoms
The diagnosis of osteosarcoma is often delayed because in its initial stages it has no distinctive symptoms, Murray
Identifying, isolating, and characterizing genes involved in carcinogenesis are important approaches for understanding cancer etiology, biology, and treatment. However, cancer is a heterogeneous disease, and for any one cancer many genes may be involved in the multistep process of carcinogenesis. As a result, the goal of understanding the role of genetic changes in carcinogenesis is made difficult. The study of familial cancers, however, serves to circumvent some of these complications.

Since the early part of this century, investigators have noted families in which individuals in multiple generations are affected with the same type of cancer. This observation has led investigators to believe that, though many genes may ultimately be involved, a single (mutant) gene may be responsible for the familial predisposition to a particular neoplasm. Because just one gene may be important for cancer susceptibility, it is feasible to identify, isolate, and characterize it. A knowledge of the identity and function of a predisposing gene, we reason, will be relevant not only to the familial form of that cancer but also to the more common, nonfamilial cancer. Furthermore, it is possible that the gene responsible for a familial predisposition to cancer likewise may play a role in other cancers seen in the population. On this premise we and other investigators are studying familial cancers for which only one or a few genes are believed to play a critical role in tumorigenesis. Wilms' tumor is one such cancer.

We are studying familial cancers for which only one or a few genes play a critical role in tumorigenesis.

Wilms' Tumor

Wilms' tumor is a pediatric renal neoplasm that affects approximately 1 in 10,000 children. In the United States, 300 to 400 cases are seen annually. Occasionally (5% to 7% of cases) aniridia, genitourinary anomalies, or mental retardation is also observed in Wilms' tumor patients. Tumors develop in both kidneys in 5% to 10% of patients. Most tumors (99%) occur sporadically, with no known affected relative. Of interest for this study, however, was the 1% of Wilms' tumor cases that are familial. In these cases siblings or cousins are most often affected. Based on epidemiologic observations of the age of onset and of the frequency of multiple tumors in familial and nonfamilial cases, Dr. Louise Strong, Department of Experimental Pediatrics, along with Dr. Alfred Knudson, who is currently with the Fox Chase Cancer Research Institute, proposed that at least two mutations are critical for the development of Wilms' tumor. In most sporadic unilateral cases, a tumor arises following two somatic mutations in the developing kidney, whereas in familial and bilateral tumors, the second mutation is somatic, the initial mutation is thought to be inherited via a germ cell.

Initial Studies Implicate Chromosome Band 11p13 in Wilms' Tumor

Cytogenetic studies of normal blood cells from Wilms' tumor patients with aniridia revealed the location of a gene important in Wilms' tumor. From these studies, investigators found that certain parts of the p13 band of chromosome 11 had been deleted, suggesting that in the genome of all cells of these individuals a portion of one chromosome 11 was deleted and that this germinal mutation predisposed the children to Wilms' tumor. Additionally, children with aniridia and a chromosome 11 deletion have a 50% risk of subsequently developing Wilms' tumor, providing still more evidence that germinal loss of genetic material at chromosome band 11p13 can predispose individuals to Wilms' tumor. Subsequently, cytogenetic studies revealed 11p13 deletions in a few tumors from patients who did not have a germinal chromosome deletion. These tumor-specific deletions suggested that somatic mutations at 11p13 were also important in tumorigenesis. In work done in our laboratory and in others worldwide, this observation has been extended by use of molecular genetic techniques. To date, we have demonstrated that approximately one-half of a large number of sporadic Wilms' tumors have detectable genetic changes at 11p13. From these data it appeared that one 11p13 gene mutation and a subsequent mutation or loss of the second 11p13 gene are necessary for tumorigenesis. By extension, we and others hypothesized...
that the inherited mutation in familial Wilms' tumor occurs at chromosome band 11p13.

**RFLP Analysis of a Wilms' Tumor Family**

To investigate this hypothesis, we studied a large family in which six children in three branches had Wilms' tumor. The clinical features of these patients—early age at diagnosis, bilateral tumors, kidney and tumor histology—were similar to those of Wilms' tumor patients who had 11p13 deletions and aniridia or genitourinary anomalies. However, this family did not have any of these congenital anomalies, and standard cytogenetic techniques detected no chromosome aberrations. Using another form of genetic analysis, we attempted to determine if the predisposition to Wilms' tumor was genetically linked to DNA markers that span the 11p13 region. The DNA markers we used were restriction-fragment length polymorphisms (RFLPs).

Researchers commonly employ DNA restriction endonucleases to analyze and manipulate segments of DNA. These enzymes recognize particular DNA sequences and cleave the DNA strand at or near the recognition site. Once the DNA is cleaved the resultant fragments can be separated based on size. In general, the size of a restriction fragment from a particular region of a chromosome is constant. Occasionally, however, the DNA sequence at the enzyme recognition site is altered. In this case, the enzyme will not cleave the DNA strand at that site, and the resulting DNA fragment will be longer than usual. Alternatively, the restriction fragment can be lengthened or shortened by insertions or deletions of DNA. This DNA variability, which occurs normally throughout the genome and usually has no known effect on the individual, results in RFLPs. Because one chromosome with different DNA polymorphisms is inherited from each parent, an individual's set of RFLPs can be used to discriminate between the chromosome 11 inherited from the father, for example, and that inherited from the mother. RFLP analysis allows us to trace in a pedigree a chromosome or a portion of a chromosome as it is passed from parent to offspring.

If the familial predisposition to Wilms' tumor resulted from a mutation at 11p13, all affected individuals in a family would have inherited the same 11p13 region from a common ancestor. The Wilms' tumor phenotype would cosegregate (i.e., be linked genetically) with 11p13 markers in the pedigree. However, if affected individuals inherited different 11p13 regions (no cosegregation), these data would indicate that the predisposition mutation is not located there.

**Lack of linkage of 11p13 markers to familial Wilms' tumor was unexpected.**

Researchers commonly employ DNA restriction endonucleases to analyze and manipulate segments of DNA. These enzymes recognize particular DNA sequences and cleave the DNA strand at or near the recognition site. Once the DNA is cleaved the resultant fragments can be separated based on size. In general, the size of a restriction fragment from a particular region of a chromosome is constant. Occasionally, however, the DNA sequence at the enzyme recognition site is altered. In this case, the enzyme will not cleave the DNA strand at that site, and the resulting DNA fragment will be longer than usual. Alternatively, the restriction fragment can be lengthened or shortened by insertions or deletions of DNA. This DNA variability, which occurs normally throughout the genome and usually has no known effect on the individual, results in RFLPs. Because one chromosome with different DNA polymorphisms is inherited from each parent, an individual's set of RFLPs can be used to discriminate between the chromosome 11 inherited from the father, for example, and that inherited from the mother. RFLP analysis allows us to trace in a pedigree a chromosome or a portion of a chromosome as it is passed from parent to offspring.

If the familial predisposition to Wilms' tumor resulted from a mutation at 11p13, all affected individuals in a family would have inherited the same 11p13 region from a common ancestor. The Wilms' tumor phenotype would cosegregate (i.e., be linked genetically) with 11p13 markers in the pedigree. However, if affected individuals inherited different 11p13 regions (no cosegregation), these data would indicate that the predisposition mutation is not located there.

**Chromosome Band 11p13 Not Linked to Familial Wilms' Tumor**

The pedigree of the Wilms' tumor family studied is shown in Figure 1. DNA from the individuals whose identification number is underlined in the pedigree was typed for RFLPs on chromosome 11, especially at 11p13. The data were analyzed using a maximum likelihood computer program that calculates the likelihood that genetic markers segregate with the disease (linkage) versus the likelihood that the genetic markers segregate randomly with respect to the disease (lack of linkage). These likelihoods are expressed as LOD (log of the odds ratio) scores. By convention, an LOD score of +3.0 or greater is considered statistically significant evidence supporting genetic linkage, whereas an LOD score of -2.0 or less is considered sufficient grounds for rejecting linkage. For the family we studied, linkage analysis of various 11p13 markers to Wilms' tumor revealed LOD scores of -5.17 to -2.84. Furthermore, by simple examination of the 11p13 marker data, we observed that the affected children had inherited three different 11p13 regions. Thus, these data indicated that the familial predisposition to Wilms' tumor in this pedigree was not due to a mutation at chromosome band 11p13. By a similar analysis, we also excluded another region of chromosome 11, 11p15, that has also been indirectly implicated in Wilms' tumor. Linkage of Wilms' tumor predisposition to 11p13 and 11p15 has also been excluded in another large Wilms' tumor family by other investigators, indicating that the lack of linkage to 11p13 was not unique to the family we studied. Lack of linkage of 11p13 markers to familial Wilms' tumor was unexpected in the face of considerable evidence continued on page 8.
Osteosarcoma continued from page 3

said. "Of the patients that enter a general practitioner's office, about 57% will have a musculoskeletal complaint, and often the description can be as vague as 'it hurts here.' Usually, the only symptom is pain. This is a real problem; osteosarcoma is detectable only by x-ray, but it's not feasible from a financial standpoint to x-ray everyone who has a complaint of some type of pain. But if the patient doesn't respond to the standard management quickly and significantly, it is critical that he or she undergo x-ray examination."

Osteosarcoma is distinctive on radiographs. "A typical case," Murray said, "would be a 14- or 15-year-old patient who has an epiphysis that is almost closed and a large destructive lesion in the bone just above the epiphysis. This is often accompanied by the production of new bone. Benign tumors, however, generally do not interrupt the cortex of the bone, and the margin between the normal bone and tumor is very sharp; the tumor may even appear to show some bone reaction around it. Ninety percent of osteosarcomas occur at the end of long bones. Of that 90%, 55% will occur at the distal femur, the proximal tibia, or the proximal fibula."

Allografts, Though Rare, Are an Option

About one in twelve osteosarcoma patients may be eligible for an allograft—the transplant of natural bone—instead of a prosthesis. "The first allograft technique was performed 35 years ago, so it's been around for a long time," Murray said. "But its application is limited to tumors that involve only the middle of the bone." M. D. Anderson once had its own bone bank, but recent federal regulations have required that all organs now be allocated through Organ Procurement Organizations (OPOs), Murray said. The M. D. Anderson bone bank has since been disbanded, replaced by an OPO that will now handle the dissemination of bone and other organs to medical facilities in the Gulf Coast area, he said. "There was some concern about the unfair distribution of organs, primarily regarding kidneys, hearts, and lungs, so the government mandated OPOs.

There generally was no shortage of bone—one donor can supply substantial amounts and any excess can be easily stored—but nevertheless the acquisition of bone is governed by the same guidelines as those for the acquisition of other organs.

The extent and location of metastasis may affect the decision to implant an expandable prosthesis.

The potential for infection is greater in patients receiving allografts than in those receiving prostheses, Murray said. "We were a little concerned that osteosarcoma patients receiving allografts were prone to infection because they receive heavy chemotherapy; fortunately, our experience has shown that bones are actually incorporated quite well. The advantage with allografts is that once the ends of the bone heal, the bone's function is essentially normal—a biological reconstruction that we don't have to worry about."

The body does not reject allografts as it does other transplants, but Murray said that some patients experience resorption. "This may be a rejection phenomenon, but we don't have any immunological parameters by which we can predict whether the graft-versus-host relationship is good or bad."

Research Continues

In combination with other modalities, prosthesis implantation and allografting will continue to be important components of the armamentarium against osteosarcoma, Murray said. "My colleagues Robert Benjamin, M.D., and Norman Jaffe, M.D., are continually exploring new chemotherapy protocols, and the new intraoperative radiation program of Tyvin Rich, M.D., has added some new dimensions to the treatment of tumors around the pelvis. With these modalities and local surgery, we hope to improve the existing 70% survival rate."

Physicians who desire additional information may write John A. Murray, M.D., Department of General Surgery, Box 106, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas, 77030, or call (713) 792-7210.
The trade-offs seem worth the added time, because drug dosages can be somewhat lower for each of the transplantation procedures and the total dosage higher, according to Gary Spitzer, M.D., professor of medicine, deputy director of the bone marrow transplantation section, and director of the solid tumor treatment program. The double method, he said, avoids non-bone marrow toxicity in such organs as liver, lung, and heart.

The procedure will be much safer than it is now, Spitzer said, when the duration of low white-cell and platelet counts produced by chemotherapy is shorter. "Wider application is held back by the procedure's toxicity and potential mortality," he said. "We are constantly researching ways of reducing these. One method may turn out to be with granulocyte-macrophage colony-stimulating factor, which stimulates recovery of the white blood cells and makes possible the use of more mature marrow stem cells from blood in autologous transplantation."

Frank Dunphy, M.D., an instructor in medicine in the bone marrow transplantation section, explained drug combinations used in the program, the usual one being cyclophosphamide-etoposide-cisplatin. Among new ones being tried, he said, is the combination of mitoxantrone and thio-TEPA (triethylene-phosphoramide). Since last September, 50 patients have received the second combination, and in 25% the cancer is gone, but how durable these patients' remissions turn out to be remains to be seen, Dunphy said. The physicians are devising a new system of giving one drug combination before the first transplantation, the other before the second, to see possible differences in drug effectiveness and safety.

In the last three years, some 100 patients have been treated for recurrent breast cancer with high-dose chemotherapy and autologous bone marrow transplantation. About 60% achieved complete remissions, Spitzer said, and he estimated that 25% to 35% will be free of disease after two years or more. "We need longer follow-up to assess relapse rates," he said. "The experience of conventional methods of treating breast cancer patients who have relapsed is that about 10% to 15% of patients are free of disease two to three years later. We have to be sure that the differences in results of the conventional and high-dose therapies are real and not the result of patient selection."

At M. D. Anderson, the overall mortality resulting from transplantation is 7%, mainly from infectious complications. Spitzer expressed the physicians' hopes for improving the procedure's safety and results and for easing some of the emotional load. "When the mortality is low and the patients are mobile and able to exercise," he said, "transplantation will not be so terrifying."

Physicians who desire additional information may write Albert B. Deisseroth, M.D., Department of Hematology, Box 24, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, 77030, or call (713) 792-8750.
Genetic Analysis continued from page 5

(as described above) that genetic alterations at 11p13 are important in the development of Wilms' tumor. Our data, however, indicate that the predisposing gene in this family is different from the 11p13 gene. The nature of the interaction, if any, between these two types of genes in the development of tumors in predisposed individuals is unknown. The predisposing gene may lead to tumorigenesis independently of a gene at 11p13. Alternatively, tumor-specific genetic alterations at 11p13 may be required in addition to the predisposing mutation. Analysis of tumors from familial cases might be informative in this regard. To date, tumor-specific 11p13 alterations have been observed in only half of all examined (sporadic) tumors. We previously thought this was due to our inability to detect subtle changes in 11p13 in these tumors. However, in light of the familial linkage data, it is possible that some sporadic tumors arise independently of an 11p13 mutation and are a consequence of a mutation at the familial predisposition gene.

A broader question with regard to the 11p13 Wilms' tumor gene and the familial predisposition gene is their possible role in the development of cancers other than Wilms' tumor. Genetic alterations of chromosome 11 have been observed in some cancers. Whether or not the 11p13 Wilms' tumor gene is involved in these cases, either as a primary or secondary event during tumorigenesis, is still unclear. Additionally, investigators have noted that a chromosome 11 from a normal cell can suppress the expression of some transformed characteristics of a tumor cell line. Though the possible role of the 11p13 Wilms' tumor gene in tumor suppression is unknown, further work will clarify the part, if any, the 11p13 Wilms' tumor gene plays in cancers other than Wilms' tumor.

For Wilms' tumor, we know that a gene located at chromosome band 11p13 is important in at least some cases. Now, however, we must also focus our efforts on identifying the gene (or genes) directly linked to the familial predisposition to Wilms' tumor. A knowledge of the nature and function of both genes will be instrumental in furthering our understanding of the biology of Wilms' tumor. This may, in turn, serve as a useful paradigm for understanding the normal and abnormal functions of multiple genes that interact in carcinogenesis. ■

Physicians who desire additional information may write Vicki Huff, Ph.D., or Grady F. Saunders, Ph.D., Ashbel Smith Professor of Biochemistry and Molecular Biology, Department of Biochemistry and Molecular Biology, Box 117, 1515 Holcombe Boulevard, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, 77030, or call (713) 792-2690. Physicians may also write Louise C. Strong, M.D., Department of Experimental Pediatrics, Box 209, or call (713) 792-2589.