BONE MARROW TRANSPLANTS

A GIFT OF HOPE

By MARGARET FRENCH

To a casual observer, the new Bone Marrow Transplant Unit at Oklahoma Memorial Hospital might be any typical critical-care ward. But make no mistake. This glistening, spacious area is the highly specialized home base for a revolutionary transplant procedure making medical progress daily.

Open since January, the facility is a joint project of the department of medicine in the College of Medicine at the OU Health Sciences Center and Oklahoma Memorial Hospital, one of the State of Oklahoma Teaching Hospitals. The unit is operated by HSC physicians Robert Epstein and R. Bradley Slease, 16 OMH nurses and BMTU coordinator Cynthia Watkins, a registered nurse whose position is funded by Presbyterian Hospital.

Before the advent of the unit, bone marrow transplants required the medical team literally to run all over the hospital; now almost everything takes place within this self-contained facility. A vacant 10th-floor area originally designed as an intensive care ward was remodeled for the unit, which accommodates eight patients with room for expansion to 12. Since the opening, only four patients have been treated at one time because of a shortage of nurses, but the physicians expect to be operating at capacity by June.

Each glassed-front room is equipped with special air flow to prevent entry of germs, and cardiac monitors feed information to the centrally located staff area, with its bird's-eye view of the semi-circle of suites. A laboratory within the unit allows the physicians to analyze the transplant recipient's laboratory studies and prepare both collected bone marrow to be stored for later use and that to be transplanted immediately.

The super-clean unit is fairly isolated, and multiple sets of double doors further insulate the area. Family members can take advantage of a roomy, comfortable waiting lounge nearby, and a separate "quiet room" offers more privacy when needed.

While the unit officially is but a few months into operation, Epstein and Slease offer impressive credentials in

immune-system research. Holder of the Eason Chair of Oncology, Epstein is also the chief of oncology (the study of tumors) at HSC; Slease, a professor of medicine, specializes in hematology, the study of blood. Both physicians had performed bone marrow transplants prior to coming to OU and actually pioneered the procedure at the OMH in 1982.

Epstein, who says the new unit represents "medicine circa early 1987 . . . with glimpses of what medicine in late 1987 looks like," came to OU from Chicago in 1982 to fill the Eason Chair. The chair was endowed by the late Oklahoma City oilman T. Winston Eason, his late wife Ada S. Eason, a leukemia victim, and their daughter Virginia Eason Weinmann.

When Epstein arrived, he brought with him 20 years of laboratory experimentation on animals, developing models and methods of treatment which only recently have been supplanted by newer technology.

Slease had performed similar bone marrow transplants at Bethesda Naval Hospital before being lured to OU by a medical colleague in 1980. He again became interested in the procedure upon the arrival of Epstein, a nationally prominent hematology and oncology specialist.

"The program really has arisen and flourished as a result of Bob's efforts," Slease notes, adding that he once had some doubts about his future in the often taxing specialty.

"I had remained interested in bone marrow transplantation, but I was not sure I was emotionally prepared to continue working in it clinically," he remembers.

However, everything came together, and in September 1982, with all preparations made and their crew standing ready, Slease and Epstein performed their first transplant at Oklahoma Memorial Hospital on a young leukemia victim who twice had been treated unsuccessfully. The patient was considered "end stage," and Slease believes he would have died in a few months without a transplant.

This time, however, the patient responded to treatment, went into remission and now is "getting close to the point where we feel really comfortable," Slease says, adding that 4½ years would be considered a long remission. "He probably is cured, but we don't want to use that term." With the exception of suffering a side effect of chronic sinusitis, he does quite well.

Bone marrow transplants, Slease points out, are performed for one of two reasons: to combat some kind of malignancy or to correct a bone marrow disorder or failure, as in leukemia or aplastic anemia. Chronologically, the lengthy transplant process begins with securing a donor.

A donor is often someone other than the patient—as in an *allogeneic* transplant, meaning "within species." However, the patient also can be his own donor in an *autologous* transplant, when his own marrow is removed, preserved and returned after treatment. Obviously, someone with a hematological malignancy involving the marrow or some marrow defect such as aplastic anemia usually will not qualify for an autologous transplant.

A new unit at Oklahoma Memorial Hospital is giving HSC physicians better odds for success with a high-risk but promising procedure.

For an allogeneic transplant, laboratory tests must be used to match as closely as possible tissues from donor and recipient. The best tissue matches usually occur between siblings, but even then only one in four will qualify. The first patient was given bone marrow from his 13-year-old sister.

With a donor at hand, the recipient is treated with two goals in mind: first to eliminate the neoplasm—or cancer—then to accept the graft. The deficient marrow is wiped out by eradicating all of the patient's marrow with very high doses of drugs and/or radiation. At this point, the recipient experiences a siege of general nausea and vomiting.

Next, in the operating room under a general, or occasionally a spinal anesthetic, multiple samples of marrow are drawn from the donor's pelvis, the easiest site from which to harvest. The doctors make only five or six skin punctures on each side, maneuvering the needle for approximately 100 aspirations of the marrow. Three-quarters of an hour is required to collect one or two pints of a thick liquid that resembles a bag of donated blood.

The gift marrow is filtered to remove impurities and fat particles and then administered to the recipient intravenously, exactly as in a blood transfusion. The donor, meanwhile, is up and around the same day, going home that evening or the following day with only a dull pain and complaints chiefly of stiffness. Epstein explains that the pain associated with the donating process occurs because nerve fibers deep within the marrow cavity cannot be anesthetized locally.

"The donating procedure itself has gone well," he says. "We have done it about 120 times; it's gone fine, and the donor doesn't have any pain during the actual procedure."

He likens what happens next to the recipient to sowing a lawn.

"We get billions of marrow cells, but the stem cells represent a very small fraction of the total. These are the grass seeds; they implant as they travel through the bones, and end up finding the micro environment suitable for their proliferation."

In 7 to 10 days, he says, a biopsy reveals "little islands" of growing marrow cells busily replacing the former marrow cells which have been eradicated. From 10 days to 4 weeks later, newly manufactured blood cells are visible in the bloodstream. By this time, the doctors note, the patient's disease should have been stamped out, his unhealthy marrow has been replaced by brand-new, non-diseased marrow, and he may be homeward bound in 21 to 28 days.

This is the ideal scenario. Unfortunately, the process is not always perfect. There are problems, the most obvious arising in cases in which the disease was not completely eliminated—similar, Epstein says, to spraying for insects in the home and missing a few. By presently available means, all of the problem cells cannot be killed. Somehow, some survive.

Another worry—and a leading reason for creation of the specially equipped transplant unit—is the danger of infection. Slease and Epstein estimate that approximately 10 percent of the transplant recipients

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Drs. Robert Epstein, left, and Bradley Slease extract a bag of cryopreserved bone marrow from a liquid nitrogen freezer in Epstein's laboratory in Oklahoma City.

are at a higher risk immediately following transplantation.

"From the time we give the drugs until the marrow begins working properly, there essentially is no marrow function," Epstein explains. "Susceptibility to infection is extremely high during that time, because there are no white cells to defend against infection."

"The white cells come back in about 2 to 2½ weeks, and the platelets come back about a week later," Slease adds. "That first 30-day period is really the critical period."

With low platelet counts, the physicians must administer platelets to prevent bleeding. Also, body tissues damaged from the intensity of the radiation and chemotherapy leave the patient vulnerable to many vital organ problems.

The patients are at their lowest point when their white counts drop to zero. They usually contract an infection, their fevers shoot up, and until the white cells begin to come back, they are very sick.

The last looming problem in allogeneic transplants is graft versus host (GVH) disease. Unique to marrow transplantation, this side effect does not occur in liver, kidney or other transplants, Epstein points out.

"The cells that are responsible for growing the marrow also are responsible for growing the immune system. So you can repopulate the immune system, which is the good thing. However, because no two people are exactly identical—these new cells that the graft has produced can recognize that the body tissues are not their own, and they attack them.

"The interesting thing is that these cells learn, and they adapt. Although most patients have some evidence of GVH reaction—usually skin rash and some abnormal lab tests—they get through it. The cells gradually feel comfortable, if you will, in the new hosts, and the disease subsides on its own."

However, the physician hastens to add, as with all other illnesses, patients with GVH disease run the gamut of mild to severe cases, which usually are fatal. Again the special unit, in which the transplant recipients stay from day one until they leave the hospital, plays a vital role by diminishing all the risks facing the patients.

Slease claims that caring for a patient in the transplant unit reduces the incidence of certain infections. There is even some scientific evidence that being in such a protective environment reduces the risk and severity of GVH disease.

Epstein agrees. "The unit provides optimal monitoring of these patients during the critical period of marrow aplasia, care for the normal tissue damage that is done by these intense treatment regimens and the best possible prevention—state-of-the-art prevention—of infection from environmental sources. The unit basically represents a high intensity nursing care capability."

Nurse Watkins, who trained most of the BMTU personnel from nurses to laboratory technicians, shares Epstein's philosophy that the difference makers are nurses trained to deal with the transplant patients on a constant basis, not just occasionally, as would be the case on a regular floor.

"These nurses are not 'stuck' with the patients," she emphasizes. "They are here because they want to be."

Also a big factor, she says, is the "clean unit," isolated from the rest of the hospital, minimizing infections that before could have been lethal.

"With these patients, for example," Epstein points out, "one has to act very quickly on the evidence of infection. You can't come in at eight o'clock in the morning and find out the patient has had a fever ten hours before. Patients who get into trouble get into trouble quickly and require high intensity nursing care. I think the unit at OMH now provides such a facility in Oklahoma for our people."

The alternative to the risky allogeneic transplant is the autologous transplant, in which the patient receives his own marrow. The greatest advantage, of course, is the absence of graft versus host disease. Because statistics indicate that only one in three transplant candidates will have a tissue-matched sibling donor, the impetus for autologous transplants is clear. Progress now is about equal to that attained with the allogeneic method several years ago.

"This actually is the oldest method. It's very straightforward, very clear," Epstein says. "The autologous transplant was the first thing I did in the early '60s. The idea behind this is to store some marrow and give the patient with a tumor a lot of chemotherapy, destroy his tumor and give him his marrow back."

During a remission or just at the onset of relapse, the patient's marrow is extracted and cryopreserved, or frozen. In the meantime, with very high doses of chemotherapy or radiation, the tumor is attacked. Then the frozen, healthy marrow—the patient's own—is thawed and readministered to the patient, ready to grow new, healthy marrow.

The doctors say the process, as it is applied to acute leukemia, is designed to grant patients a second remission at least as long as the first, reversing the trend of diminishing remission durations. The theory is that the body's normal defense mechanisms can handle small numbers of malignant cells.

While autologous transplants offer the advantages of eliminating GVH disease, new cells actually "growing" better and presenting fewer biological challenges, transplant candidates still present their own problems, not the least of which can be high odds further complicating chances of success. Among others, two common problems the doctors confront are difficult-to-treat solid tumors and, in the case of older patient populations, pre-existing health complications.

Today, the research focus at OMH is on the autologous transplant, addressing the very patients of which Slease speaks: those with acute leukemias, breast cancers and other patients with solid tumors who are not expected to survive. In an effort to determine the role of the autologous transplant in the oncologists' therapeutic regimen, Slease and his colleagues have treated a number of patients with a variety of malignancies, and the majority have responded.

Response in this case means being able to measure objective reduction in the size of the tumor. Some patients have experienced complete remission, in which all evidence of a tumor disappears—remarkable results, considering that these patients already have failed standard treatment.

Epstein estimates the temporary response rate with autologous transplants is approximately 50 percent worldwide. The HSC group has achieved comparable results treating a variety of incurable solid tumors.

"Studies are continuing," Epstein says. "There is a good scientific base; preliminary data is encouraging."

Slease believes the bone marrow transplants offer some patients hope. "Certainly there are patients whose lives are extended by this transplantation procedure in a variety of diseases—malignant lymphomas, acute leukemias, breast cancers, certain kinds of childhood sarcomas. Unquestionably, some people are living a long time where they otherwise wouldn't. How many people are being cured? It's too early to say," he cautions.

While the treatment options are clearer for allogeneic transplants, part of the work at the HSC has included the establishment of protocols to aid in making decisions, particularly in determining which patients are candidates for autologous transplants.

"For autologous transplants, it's not nearly as clear, and those are many of the studies that we're involved in now—lymphomas, leukemias, breast cancers," Slease says. "In autologous transplants, many of the questions remain unanswered, and while we know that in certain patients, certain situations, they can certainly be helpful, we don't know exactly when to apply them in given diseases."

Epstein says, "We wrestle with the problem: it's too late to do this on this particular patient, and it's too early to do it on that particular patient. At an international conference we just attended, the questions were really 'where and when and how do you do it best?' "

The scenario has a definite pattern, Slease says. "Someone with breast cancer has it surgically removed. If the patient is a high risk for recurrence, a period of chemotherapy is conducted for six or so months after the breast has been removed.

"Then at some later point the disease comes back; the patient develops metastases in the lung, liver, brain or bone. At that point, the patient's private oncologist has utilized standard chemotherapy again. After the patient fails one or two tries at different kinds of chemotherapy for metastatic disease, I get a telephone call."

Now that bone marrow transplants are gaining recognition as viable alter-

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The high-intensity care required for patients in Oklahoma Memorial Hospital's new bone marrow transplant unit is provided by a specially trained staff, which includes nurses Teresa Madrid, left foreground, Donna McLauchlin and Debra Owen.

natives to standard malignancy treatments that produce significant results, many physicians are beginning to back away from "last-ditch stands" in favor of transplant implementation earlier in the course of the disease. At Duke University, physicians are transplanting high-risk women immediately following breast cancer surgery instead of playing the "wait-and-see" game with endless rounds of chemotherapy.

The OU physicians are splitting the difference and intervening after the first round of chemotherapy, but before the "last stand." They feel that such late intervention does little more than prolong the time to relapse in a terminal patient.

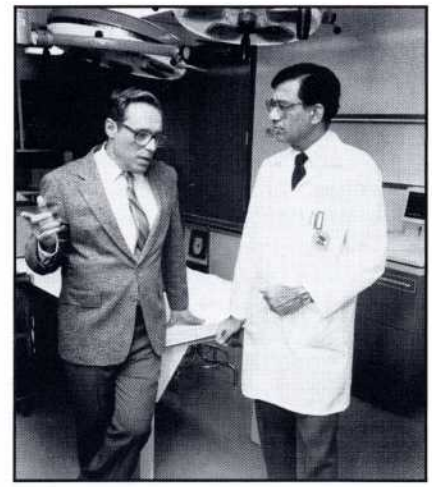
"We're very conservative people here in Oklahoma—and that includes physicians," Epstein explains. "But hopefully we're seeing patients a little earlier." Slease and Epstein have had all too much experience making initial visits to hospitalized patients so desperately ill that they don't have the remotest chance of survival.

The results of bone marrow transplants so far are promising, and the physicians are encouraged. However, a paradox still exists, and time is still the enemy.

Epstein illustrates the dilemma with the case of a chronic myologenous leukemia patient. The patient often can be managed for years with drugs but eventually will enter an accelerated, uncontrollable, fatal phase of the disease. The onset of the phase cannot be predicted, yet a marrow transplant can cure approximately one-half of the patients if administered before the final stage. Still, the physicians encounter mixed reactions when presenting patients with their alternatives.

"Patient X says, 'I'm not going to wait for this to explode. I'll take the transplant. If there's a chance to be cured, I want it now,' " Epstein says. "Another will say, 'I'm feeling good, and as long as I'm feeling good, you can forget it.' So there's this spectrum of responses, and who's to judge? Someone can walk into the hospital for the transplant feeling well. Then GVH disease, infection and so forth occur, and that patient doesn't make it. You know that he could have had more time with his family."

Watkins, the first person patients



Drs. Epstein and D. L. Solanki confer at the opening of the transplant unit.

meet upon entering the unit, remains close to them and their families during their entire confinement. She says that nurses, too, have great problems during this period. When patients become ill and in some cases die, the nurses must deal with the emotions. For that reason, Watkins believes, nurses in this specialty experience a higher-than-usual susceptibility to burnout.

"The problem is we see them when they come in, and usually, they look fine. Then we administer the drugs to them, and their conditions do worsen. Sometimes it's almost as if we do it to them," she says.

"But at least we should give our patients the best possible chance," Epstein maintains. "The bone marrow transplant unit gives us a vehicle to treat patients under what is considered the best of circumstances and an opportunity to try and utilize new initiatives and to train people."

The training program is another benefit of the new transplant unit. HSC medical residents have an opportunity to serve a rotation in the transplant unit with Slease, Epstein and other faculty members in the sections of hematology and oncology.

"Four years ago, folks didn't know about histocompatibility typing, what kind of problems these patients get into, what physicians should do. These are the problems they're going to be confronted with when they go out into practice," notes Epstein.

But Slease insists that the teaching goal is not to churn out specialists. "We're not going to train these people to become bone marrow transplanters in small towns in Oklahoma, but we are going to train them to be able to recognize quickly which patients would best be treated with this kind of technique."

An important aspect of the physicians' work—and lifeblood of medical progress—continues to be ongoing research. With an OU College of Medicine Alumni Association grant, Slease is working on laboratory studies of GVH reaction; lab work continues on patients with marrow graft failure; and efforts continue to develop a test to predict how fast a patient's marrow will repopulate. Another HSC faculty member, Dr. Ron Greenfield, is working to diagnose fungal infectious complications earlier. Epstein, Slease and Dr. Brian Geister, one of the hematology-oncology fellows, are working with an animal model to hasten marrow engraftment with peripheral blood white cells.

"When you talk about research," Slease says, "I view it as clinical research—the testing of knowledge that has evolved. We're trying to become precise about the best way to use it."

Epstein sees the bone marrow transplant unit developing in three ways. He views the first priority as the proper care of people in Oklahoma.

"Everything aside, we're here to help people. We don't see the work of this unit as administrators, and we don't see it as budget heads."

The patient care, Slease agrees, "is the bottom line for us."

The remaining priorities for the development of the unit lie in increasing knowledge and teaching its application. The research and training arms of the medical profession go hand in hand, and Epstein believes the HSC physicians have a responsibility to explore new treatments in bone marrow transplantation and to pass the results along.

Despite vast progress achieved thus far, Epstein concedes that, "It's still a high-risk procedure, and there's no doubt about it. Many patients cannot be transplanted; we cannot accept some patients, and we do not help certain patients that we do accept. So I think it's incumbent upon everyone working in that unit to be better next year than we are this year."