Marrow Transplants

The lives of some leukemia patients have been extended by bone marrow transplants, but problems with the technique must be solved before it becomes an accepted therapy

BY JOAN AREHART-TREICHEL

Researchers at the University of California at Los Angeles School of Medicine got into hot water with the school's Human Subject Protection Committee because they performed bone marrow transplants on dying leukemia patients without the committee's prior approval (SN: 1/3/81, p.5). The problem is that a marrow transplant, which consists of killing bone marrow (the source of leukemia white blood cells as well as of normal blood cells and cells of the immune system) with radiation then replacing the dead marrow with noncancerous bone marrow, can be just as life-threatening as terminal leukemia. However, for patients dying from certain types of leukemia — adult acute lymphocytic leukemia or adult or pediatric acute myeloblastic leukemia, for instance — a marrow transplant presents no more threat than terminal leukemia. As Sherman M. Mellinkoff, dean of the UCLA School of Medicine, told SCIENCE NEWS, "No patient at the UCLA Hospital died following bone marrow transplants who would not certainly have died rather swiftly without such treatment. . . ." And what's more, a transplant may be the patient's only hope of survival. "Many patients," Mellinkoff explains, "are alive and well today following bone marrow transplants. These patients would certainly have died or remained moribund without the bone marrow transplants." Thus it can be argued that a transplant is the best available, and hence accepted rather than experimental, therapy and should not need prior approval by a committee whose job is to ensure that the potential benefits of a human experiment outweigh the risks. To satisfy their medical school and the committee, though, the scientists are now obtaining approval from the committee before they perform the transplants.

But to better understand the investigators' line of reasoning, let's look at the experience at one of the nation's leading centers for marrow transplants for leukemia patients — the Fred Hutchinson Cancer Research Center in Washington. From 1970 to the present, E. Donnall Thomas of the center and his colleagues have given intensive radiation and chemotherapy followed by bone marrow transplants to more than 100 adult patients with acute lymphocytic leukemia or with acute nonlymphocytic (mostly acute myelogenous) leukemia. All patients were considered terminal. Although a number of these patients have died, 13 have survived five or even 10 years and are leading productive lives. "We are starting to use the term 'cure' for these long-term survivors," Thomas reported at the 1980 International Symposium on Cancer held in New York City. He and his team have also used the technique on 19 patients with acute myeloblastic leukemia, and 11 of them are now in remission and may even be cured.

Even with these promising survival figures, however, there are some serious problems associated with transplants that must be overcome if they are to save large numbers of leukemia patients.

For instance, HLA antigens are proteins on white blood cells, just as the A, B, AB and O blood type system describes proteins on red blood cells. If HLA antigens on a donor's white blood cells (called killer T cells) are not identical to those on killer T cells of a marrow recipient, the donor T cells recognize the recipient T cells as foreign objects and attack them. The result: graft-versus-host disease. A full-blown graft-versus-host disease strikes the skin, gut, liver and lymph tissues and can lead to death unless rapidly brought under control by immunosuppressive drugs. But this treatment can leave a transplant patient in danger of serious infections, especially cytomegalovirus-induced interstitial pneumonia. In fact, interstitial pneumonia is the major cause of death among marrow transplant patients because bone marrow hasn't reconstituted the immune system in time to fight it off. And even if patients aren't threatened with graft-versus-host disease or pneumonia, they may still experience recurrent leukemia after a transplant because radiation didn't totally wipe out the leukemic marrow cells.

But progress is being made toward solving these problems. For example, while Thomas and his team cannot predict which transplant patients will get graft-versus-host disease, they have identified some of the factors that predispose to it. Older recipients, for instance, are more susceptible than are younger ones, and marrow from female donors increases the risk over that from male donors. John Hansen and colleagues at the Fred Hutchinson Cancer Research Center are attempting to solve the graft-versus-host disease problem by eliminating killer T cells from donor marrow before it is injected into a recipient. During the past few months they have been incubating monoclonal (mass-produced) antibodies against killer T cells in bone marrow and have found that the antibodies can eradicate the killer T's. They are now getting a clinical trial underway to determine whether donor marrow that has had killer T cells removed fails to cause graft-versus-host disease.

Yet another way around the disease is being explored by George W. Santos and co-workers at Johns Hopkins University School of Medicine — reconstituting patients with their own bone marrow rather than with someone else's. This ploy is called autologous marrow transplantation. The researchers remove some of a patient's marrow and use antibodies or drugs against leukemic marrow to purge the marrow of any cancer cells it contains. Then they irradiate the whole patient (including the remaining bone marrow) and finally reinject the cancer-purged marrow. It is too soon to know, though, whether this technique can truly banish cancer cells from the transplanted marrow.

Progress toward preventing cytomegalovirus pneumonia is being made by Michel Oldstone, Frank Dutko and colleagues at the Scripps Clinic and Research Foundation in La Jolla, Calif. They are trying to find out whether the cytomegalovirus originates in donor marrow or in the patient's body by isolating cytomegalovirus DNA from infected patients and by using molecular hybridization techniques and restriction enzymes to identify its origin. In an effort to prevent recurrent leukemia after transplants, Thomas and his colleagues have, for the past few months, been exploring the value of giving interferon after a transplant in order to kill any residual leukemic cells missed by radiation. Monoclonal antibodies against leukemic cells, they contend, may also prove valuable in eradicating leukemic cells that escape radiation.

What is the future for bone marrow transplants as a form of leukemia treatment? Although Joseph Burchenal, director of clinical investigation at Memorial Sloan-Kettering Cancer Center in New York City, acknowledges that the transplants are greatly benefiting certain leukemic patients now, he believes that new drugs may eventually outpace the transplants. In Santos's view, "only time will tell." Thomas, on the other hand, asserts, "Anyone in the transplant field would be happy to see a drug which would cure leukemia. Until such a drug becomes available, however, we can only continue to apply the methods at hand." □