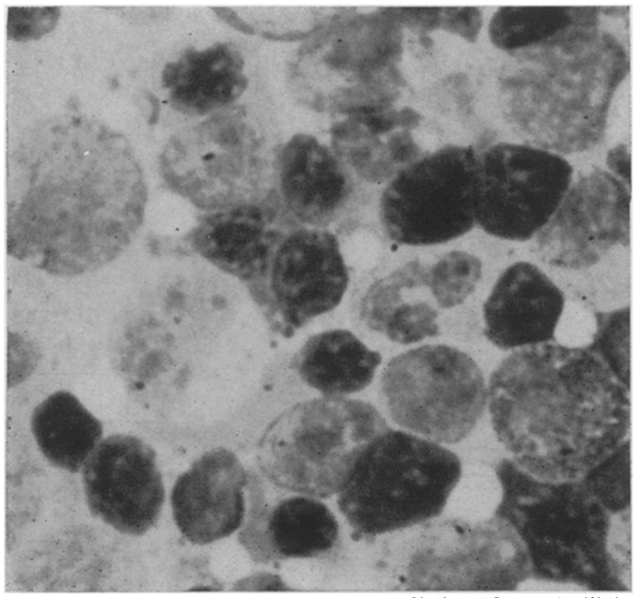
Marrow grafting holds promise

Cellular engineering is predicted for inherited diseases and leukemia



National Cancer Institute

Transplanted marrow cells in a leukemia patient.

by Barbara J. Culliton

David Camp was born without an immune system. His inherited defect had, over three generations, claimed the lives of 11 male relatives before they were a year old. In August 1968, Dr. Robert A. Good of the University of Minnesota in Minneapolis gave David a transplant of his sister's bone marrow which is now populating his body with healthy, immunologically active lymphocytes.

David Zeissett inherited an immune deficiency disease, Wiskott-Aldrich syndrome, that left him open to a host of infections during his first months of life. Though not completely immunologically deficient like David Camp, his immune system was too weak to protect him from even ordinary disease organisms. After destroying what immune cells the boy had, Dr. Fritz H. Bach of the University of Wisconsin in Madison transplanted his sister's bone marrow to David at virtually the same time Dr. Good was performing his marrow transplant. The graft took and, after 12 months of observation, the patient is still well.

Last July, at the National Cancer Institute in Bethesda, Md., Dr. Edward Henderson transplanted bone marrow to an eight-year-old boy dying from leukemia. For two years he had taken standard anticancer drugs (SN: 12/21, p. 626) that had destroyed much of his bone marrow while attacking the cancer. Though it is too soon to measure the results, there is evidence that the bone marrow transplanted from his sister is beginning to produce normal cells in the blood.

In Seattle and Durham and Baltimore, in France and in The Netherlands, scientists have lifted a long-standing moratorium against bone marrow transplants.

Recent developments in tissue typing, and in drug therapy, have given them tools for perfecting these transplants that, in the past, inevitably failed. Buoyed by recent successes, Dr. Good predicts that what he calls "cellular engineering" will become effective therapy for a host of disorders previously beyond the reach of medical control.

"In other words," he observes, "the sort of therapy that the molecular biologist would like to place on a molecular basis (manipulation of genes themselves) may actually be achievable through the manipulation of cells."

Genetic immune deficiency diseases, radiation sickness in which marrow cells are killed and cancers of the blood and lymph systems, may all be handled by bone marrow grafting. In fact, marrow grafting could become the first step in preparing individuals for other organ grafts because it offers at least a theoretical way around the threat of rejection. Because bone marrow produces the cells of the immune system if a patient first received donor marrow, his new immune cells would accept as self the other grafted organ.

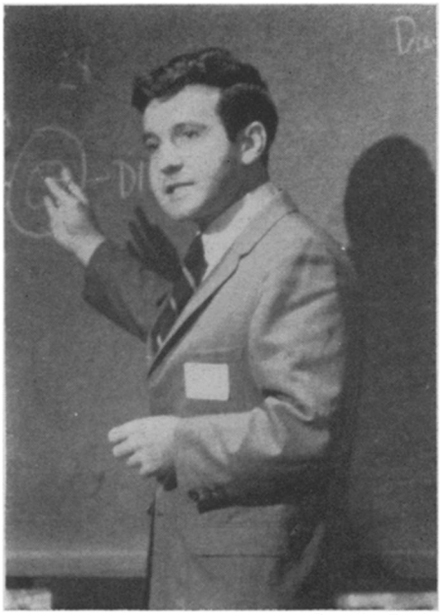
And yet, for all their enthusiasm sparked by encouraging results, immunologists recognize that the barriers that stand between marrow transplantation as an experimental treatment in desperately ill patients and its routine use are legion.

While heart transplanters worry that their patients will reject their borrowed hearts, marrow transplanters face a double-edged threat. On the one hand, the patient may reject the donor marrow. On the other, because bone marrow cells form the backbone of the immune system and are the guards that recognize foreigners in the body, healthy transplant marrow cells may reject the patient. In this phenomenon, called graft-versus-host disease (GVH), the transplanted cells attack and begin to destroy the patient's own body. Recent experience suggests that if donor and recipient have well-matched tissue, GVH disease will be mild and will subside of its own accord, but proof of this has yet to be established.

Among the pioneers in bone marrow transplantation is Dr. Georges Mathé of the Institut de Cancerologie et d'Immunogenetique in Villejuif, France. Since 1959, he and his colleagues have transplanted marrow in 24 leukemia victims with varying degrees of success. In 17 cases the graft took but the patients died of GVH. "However," said Dr. Mathé at a recent Minneapolis symposium on bone marrow sponsored by the National Foundation-March of Dimes, "we proved that marrow transplants could be done and dispelled doubt on that score, especially on this side of the Atlantic." The question was how to do it well.

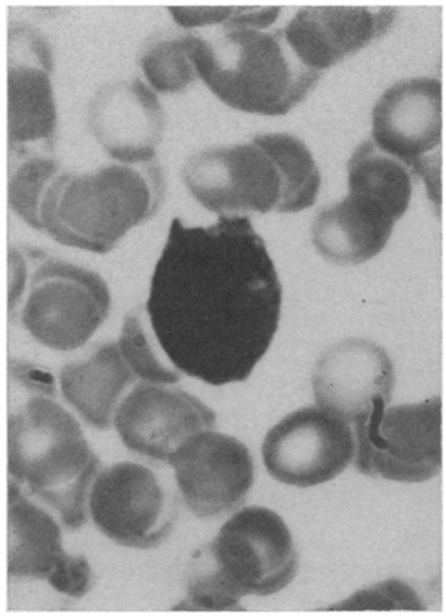
Answers began to emerge in the early 1960's when scientists gained new insights into problems of tissue matching. At this time they were slowly understanding what is called the HL-A system and its importance in transplantation. The HL stands for human lymphocyte.

Essentially a device for recognizing foreign tissue, HL-A system is a genetically determined mechanism that is controlled by several genes that all express themselves at a single position on a chromosome. In these genes is coded



Dorothy Davis

Dr. Bach describes lymphocytes.



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An active lymphocyte amid red cells.

Terasaki: HL-A indicates tissue type.

the information that results in the presence of the HL-A antigens on cells. As of now, 27 HL-A antigens are known, though scientists speculate that more will be found.

Two well-known tests permit researchers to measure tissue compatibility. Using a variety of antisera that will kill incompatible cells, Dr. Paul Terasaki of the University of California at Los Angeles measures HL-A identity between recipient and prospective donor at a facility that types tissue for hundreds of centers around the world. At present, the Cancer Institute is establishing what it hopes will be another major tissue typing center.

Complementing the Terasaki technique is the mixed leukocyte culture method designed by Dr. Bach who, with Dr. Bernard Amos of Duke University in Durham, N.C., demonstrated the correlation between the two techniques (SN: 9/28/68, p. 319). The MLC yields quantitative information about the degree of compatibility or incompatibility between donor and recipient. With this method, scientists can spot incompatability that might go unrecognized by the Terasaki technique and may eventually have a system for matching individuals who are not HL-A identical but who appear to be sufficiently compatible to risk trying a transplant.

The best guess is that among the population at large, the chances are probably less than one in 1,000, and certainly less than one in 200, obviously limiting the possibility of transplants in individuals without matched brothers or sisters, among whom the chances of HL-A identity is one in four. Therefore, investigators are trying to determine what, if any, degree of incompatibility can be tolerated. The MLC may eventually answer that question.

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Drs. Good and Mathé discuss approaches to bone marrow transplantation.

If authorities now agree that tissue matching is essential in marrow transplantation, they have yet to settle on methods of handling GVH in close but not identical recipients and donors, and they show considerable disagreement over procedures for handling patients in either situation.

One palliative to the GVH threat was proposed at the Minneapolis symposium by Drs. D. W. van Bekkum and K. A. Dicke, Dutch researchers from the Radiobiological Institute, Rijswijk, The Netherlands. Generally, marrow transplants have involved the transfer of two types of cells—active lymphocytes and stem cells. The latter are the undifferentiated or infant marrow cells that divide and become either antibody-producing lymphocytes circulating in the blood or lymphocytes that attach themselves to cells. The latter produce no antibodies but by some unknown mechanism destroy foreign tissue directly.

"It is possible," Dr. van Bekkum suggests, "that if we gave only stem cells, they would develop tolerance to the recipient as they differentiated in his body and therefore no severe graft-versus-host disease would develop." This theory has yet to be tried in slightly mismatched patients.

On the other edge of the rejection sword is the still present threat that

. . . marrow grafts

the patient will reject his grafted marrow. In the case of a patient like David Camp, who had no immune system, this was no problem. But in most other cases it is. To cope with this situation, immunologists rely on a variety of drugs that wipe out the patient's immune system before the transplant. Which of these drugs to use, when, and in what sequence is still a matter of debate.

Dr. George Santos of Johns Hopkins University favors a program using cyclophosphamide, an antitumor drug that also destroys the bone marrow. First, an injection of peripheral blood cells from the donor is given to stimulate an immune response in the recipient. Then cyclophosphamide is given to wipe out marrow cells in general, but most specifically, those which could react to the donor's marrow, damaging its protecting potential.

Dr. Bach followed this procedure in treating David Zeissett. So did Dr. Henderson, using even lower doses of drug than Dr. Santos recommends, while injecting his patient with another drug, methotrexate, following transplant. Methotrexate therapy (the drug is a known antileukemia agent that hits dividing marrow cells as well) is favored by Dr. E. Donnall Thomas and his colleagues working at the University of Washington in Seattle, Wash.

Dr. Henderson says it will be a while before he can tell whether the graft in his patient is having an antileukemia effect. But he declares that the successful take of the donor marrow opens the door to further experimentation. It knocks down the theory that a marrow graft would be rejected in a patient such as his, who, in the course of two years' treatment, received more than 100 blood transfusions from different donors.

"However," Dr. Henderson reports, "in spite of his exposure, our patient accepted the marrow from his HL-A identical sister. We find this very encouraging." At this point, he and his colleagues, as well as Drs. Bach, Mathé and others, are planning to try marrow grafts in other leukemia victims. Ultimate success remains to be proved.

As Dr. Richard Hong of the University of Wisconsin, formerly with Dr. Good's team, said in Minneapolis, "We may have opened a Pandora's box. There is no way we can tell at this stage how long these grafts will survive or whether they will be rejected in a matter of years." Nevertheless, at present there is every reason to be optomistic and no sign that a transplant moratorium will be reinstated. □