antipollution budgets. But many business organizations concerned with water resources are appalled by what they see as a virtual stoppage of development if all projects must be self-supporting.

Furthermore, many observers have heavy reservations about returning so much authority for planning and execution of water projects to states and regions. They point out that many states have little competency in water matters, and the dangers of domination by special interests are great.

It will be some time before the thrust of future water legislation becomes clear. Right now, Congress is waiting to see what, if any, new legislative proposals are submitted by President Nixon along with the final report.—CONSTANCE HOLDEN

Restoring Immunity: Marrow and Thymus Transplants May Do It

This is the second of two articles exploring the basis for growing federal support of immunological research. The first (Science, *6 April*) *discussed current understanding of the nature of the immune system. This article looks at recent attempts to use the immune system as a therapeutic tool.*

A few months ago at University Hospital in Copenhagen, Bo Dupont transplanted bone marrow into a young boy who was born without an immune system. Dupont took the marrow from the child's uncle, even though he knew that the man and his nephew did not share any of the four genes that presumably matter when it comes to determining whether two individuals have genetically compatible tissues. Dupont went ahead with the marrow transplant anyway because the man and boy were matched with respect to what is being called the third gene locus of tissue compatibility.

Early indications are that Dupont's gamble paid off. The boy has accepted his uncle's bone marrow cells, and they are now making the immunologically competent lymphocytes that he needs to survive the everyday assaults of pathogens in his environment, but which he could not make for himself.

The premise that a transplant will take only if the tissues of the donor and recipient are genetically compatible has consistently been the guiding principle of organ transplantation—from bone marrow to kidneys and hearts—and nothing has happened to challenge that premise. But the tentatively held assumptions about what tissue compatibility really is at the cellular level and about how to identify it are being modified. The ground rules for deciding whether two people are genetically matched may be rewritten.

As far as is known, the Copenhagen case is the first one in which bone marrow was transplanted between individuals who are so thoroughly mismatched as far as the genes of the HL-A (human leukocyte—antigen) system are concerned. This is the genetically controlled system that researchers have closely associated with tissue compatibility for the last several years. A surgeon, looking for an ideal organ donor, asks an immunologist to find one whose tissues are "HL-A identical" with those of his patient.

Each individual inherits four genes—two from each parent—which control the HL-A system. Each of these genes produces a distinctive protein, or antigen, that sits on the surface of cells. Those four antigens together give tissues the special characteristics that a healthy immune system identifies as self or nonself. When lymphocytes come in contact with nonself, they react and graft rejection occurs. To date, at least 31 different HL-A antigens are known; tissue-typing techniques reveal whether two people share any of them and, if so, which ones. The chances of finding a four-antigen match are highest with identical twins. Siblings rank next; other relatives are third in order, but, by then, chances have dropped significantly. The chances of finding two people in the general population who are HL-A identical are even lower, but it can be done.

Dupont's deliberate experiment in HL-A mismatching lends support to the hypothesis that tissue compatibility is not under the sole control of the HL-A system, at least not as it is presently understood. Fritz Bach, of the University of Wisconsin, says it is possible that the HL-A system is not the main determinant of tissue compatibility after all. "It may be," he speculates with confidence, "that the HL-A antigens are simply markers for a histocompatibility gene that we have yet to find." Evidence that a third gene system is at work is circumstantial, but it has been accumulating at a fairly consistent rate since Bach and Bernard Amos of Duke University proposed the idea a few years ago.

(Nomenclature in this field, in which genes and their antigens are often identified by number, is confusing. The postulated "third gene locus" is so named because there are two gene loci on the chromosome where the four genes of the HL-A system are found, two genes at each locus. The number of genes that may be involved in this third locus is unknown.)

The possibility that it is this third gene that counts in tissue compatibility has opened the door to happy speculation that the pool of ideal donors may be expanded to include relatives other than just sisters and brothers. Thus, the impact of its discovery on the use of organ transplantation to treat disease could be substantial.

Dupont and Bach talked about their latest work at the Second International Workshop on the Primary Immunodeficiency Diseases in Man, held recently in St. Petersburg, Florida, under the sponsorship of the National Foundation–March of Dimes. Immunologist Robert A. Good, new director of the Sloan-Kettering Institute for Cancer Research in New York, organized the meeting, to which about 80 investigators were invited. Good also organized the first such workshop, which was held in 1967 on Sanibel Island off the west coast of Florida.

Immunology is going through a period of rapid growth that is both exciting and confusing. Investigators are

flush with new information but not quite sure just how it all fits into a comprehensive, and comprehensible, framework.

During the last few years, there have been some observations about the structure of the immune system that have significantly changed the course of immunological research. Of particular significance is the discovery that the immune system is divided into two parts. One, composed of lymphocytes that make antibodies, is known as the B cell system. The other, known as the T cell system, is made up of lymphocytes whose role is to ward off viral infections, protect against cancer, and recognize and reject foreign tissues. Recent advances in techniques for looking at these two types of cell populations have stimulated considerable research, and the nature of B and T cells is one of the hottest topics in contemporary immunology (see *Science*, 6 April).

Progress in understanding the fundamental aspects of the immune system has directly affected clinical experimentation in the field; that clinical work, in turn, has pointed the way to more basic observations.

The clinical studies that have contributed so much to an understanding of how the immune system is designed have been with patients suffering from primary immunodeficiency diseases. These genetic disorders occur with a variety of subtle manifestations but, generally speaking, involve a defect of the B cell system, the T cell system, or both.

One experimental approach to treating immunodeficient individuals, who are likely to die of overwhelming infection if their immune systems cannot be restored, is transplantation of bone marrow or thymus tissue. Bone marrow is the organ from which both B and T cells come. Therefore, bone marrow transplantation should be the answer for people with combined immunodeficiency disease, in which both B and T cells are missing, and for those with B cell defects.

Although bone marrow is the source of T cells also, these cells emerge from the marrow in an immature state and travel to the thymus gland, where they develop. Hence, thymus transplants could be the way to treat people who cannot produce mature T cells.

Marrow and thymus transplantation for the correction if immunodeficiency diseases has been, and is still being, tried. Each apparently works—some of the time. A few lucky patients have lived. Many have died. Bo Dupont's patient may be one of the lucky ones.

Attempts to correct immune deficiencies by bone marrow and thymus grafts began in earnest about 6 years ago, largely as a result of information about the two parts of the immune system and about tissue typing that fell into place at the Sanibel conference. Today, immunologists count at least 16 youngsters in the world whose immune systems have been reconstituted with apparent success by transplanted marrow. Two of them—one a patient of Good's, the other of Bach's—have been doing well since the summer of 1968.

Dupont's patient was suffering from combined immunodeficiency disease (CID), one of the most severe of the many forms of immunodeficiency that have been characterized. Approximately 200 cases of CID have been reported since it was first described in the early 1960's. Its victims often die of massive infection before they are 2 years old.

Dupont, of course, would have liked to use an HL-A identical sibling as the marrow donor for his patient, but there was none. So, he looked for a genetically compatible relative. In selecting the boy's HL-A mismatched uncle, Dupont apparently relied on the fact that the uncle was compatible by another measure—the mixed leukocyte culture (MCL) test, a technique developed by Bach and Amos. In MLC, cells from the patient and his potential organ donor are mixed together. If the patient's cells recognize foreign antigens on the surface of the donor's cells, they will react by enlarging and dividing. If they do not recognize the donor's cells as nonself, there is no reaction. Because some persons who are HL-A identical do react in the mixed cell culture, Bach and others have speculated that something other than HL-A antigens deter-

NAE Council Opts for Split

The governing council of the National Academy of Engineering has formally recommended to the NAE's 360 voting members that the academy dissolve its 9-year partnership with the National Academy of Sciences and reorganize itself under the aegis of a new and independent foundation. The council's decision requires the approval of NAE members at their next two meetings—scheduled for 3 May and 24 October—but establishment of the new foundation does not. NAE officials are expected to file incorporation papers in the District of Columbia shortly.

The council's decision was announced on 26 March in a spare, 150-word statement signed by NAE president Clarence H. Linder. It confirms in essence but adds no detail to an earlier report (*Science*, 30 March) that long negotiations between the NAE and NAS concerning joint operation of the National Research Council had come to naught.

"This action has been taken with much regret," Linder said in his statement. "It arises from the existence of apparently irreconcilable differences in arranging for the joint governance of the National Research Council."

Last November Linder announced that he would resign his post after this year's main meeting in October.

His statement went on to express the hope that the academy of engineering could "continue its cooperation" in study projects with the NAS. However, in a telephone interview from his home in Schenectady, New York, Linder was reluctant to speculate about the form that future relations with the NAS might take. "There is an infinite variety of ways we can work together," he said. "The council and I fully intend to find a way of working with the NAS that is both viable and highly visible."

As one example, Linder suggested that a "purely ad hoc" relationship might be arranged for each project of mutual interest to the two academies. (He did not rule out the possibility, however, that a standing liaison group might be established as a permanent link between the NAS and the NAE.) Linder was equally hesitant to talk about the proposed foundation, except to say that its organization would be "pretty standard" and that funds would probably come from NAE members and other private sources as well as from government contracts.—R.G.

mine reactivity in the MLC procedure.

In a very recent refinement on this idea, Bach, from experiments with inbred mice, supports the suggestion of Dutch researchers that there may actually be two populations of cells involved in the in vitro reaction between patient and donor. One population of lymphocytes recognizes the antigens of the other as foreign; a second population then attacks and kills the foreigners.

Although genetic compatibility is important to the success of any organ transplant, it is doubly important when the transplanted organs are those of the immune system itself. As is now well known, if a patient recognizes any transplanted tissue as being nonself, the cells of his immune system will reject it. In bone marrow and thymus transplants, one runs the added risk of the transplanted tissue rejecting the patient to whom it is given. Thus, donor marrow cells produce lymphocytes that recognize the patient's tissue as being foreign to themselves. The result, known as graft-versus-host (GVH) disease, is usually deadly unless the reaction is very mild.

Dupont's patient has survived a mild bout of GVH. K. A. Dicke, of the Radiobiological Institute in the Netherlands, also talked about the problems of GVH and proposed a way to damp its strength. He calls it "sneak-in" therapy. The idea is to diminish GVH by administering marrow cells in small doses—as few as 1 million at a time. With this approach, Dicke and his colleagues managed to minimize GVH in ten patients with combined immunodeficiency disease, including a couple of cases in which the marrow donors were nonidentical at HL-A. Although the experimental use of sneak-in therapy was successful as far as GVH was concerned, many of the patients died from infections that set in before their deficient immune systems were fully reconstituted by the new marrow. Isolating such patients in a sterile environment, Dicke says, will be tried in future cases as one way of minimizing their exposure to microorganisms.

Obviously, as things stand now, bone marrow transplantation is not a ready solution to immunodeficiency diseases. Nonetheless, there is convincing evidence that it can work, and scientists are hopeful that eventually they will be able to use it to treat a variety of diseases of the blood as well.

As an experimental endeavor, marrow transplantation was first tried in the 1950's by French investigators who treated victims of a radiation accident in which their marrow had been destroyed. The experiment was a partial success. Persons suffering from radiation damage would, of course, still be candidates for a marrow transplant. Some people believe that, eventually, marrow cells could be transplanted to provide normal blood cells for persons with sickle cell anemia and Cooley's anemia. And many investigators hope that marrow transplantation can be used to help victims of leukemia and other blood and lymph cancers. This approach has been tried, but, so far, success has been marginal.

Although bone marrow transplantation, for all its limitations, remains a source of hope, immunologic bettors placed it way behind the thymus back in 1967, when odds were being set at the Sanibel conference. "As it turned out," recalls Richard Hong of the University of Wisconsin, "we were wrong. Thymus transplants just have not been very successful." However, no one, Hong included, has given the idea up for lost. One possible explanation for the thymus transplant failures, Hong suggests, is that the organ was given to a patient who was really not suitable. More precise characterization of the nature of a person's defect, now possible with new tools for distinguishing and quantitating B and T cells, may aid in the process of selecting the right patient. So far, thymus transplantation has perhaps been most successful in restoring immunity in individuals with the DiGeorge syndrome, a T cell deficiency disease.

The decision to try thymus transplants can be traced to the Sanibel meeting. At that workshop, Good and Max Cooper, who was then in Good's laboratory at the University of Minnesota, spoke about the two parts of the immune system. Angelo DiGeorge, an endocrinologist from Philadelphia, talked about four children he had in his care who had no thymus and no T cell system but who seemed to have a fairly normal B cell system. The idea of transplanting a thymus to produce mature T cells was obvious. It gained favor when it was suggested that one way to avoid graft-versus-host disease in a thymus recipient might be to use a fetal thymus, on the theory that its cells are not mature enough to mount an immune attack. London pathologist Humphrey Kay, who was at the workshop, could help out. He had a tissue bank of fetal organs.

The time to try a thymus transplant had come. It was just a matter of finding the right patient. William Cleveland, a pediatrician at the University of Miami, had that patient. He was treating a 6-month-old boy who, he concluded from a search of the literature, had the DiGeorge syndrome, and he called DiGeorge for consultation shortly after DiGeorge returned from Sanibel. The decision to try a transplant was made and Kay was asked to send a thymus. "The next thing we heard," Cleveland recounted at the St. Petersburg meeting, "was in the form of a telegram saying simply, 'Thymus arriving Miami BOAC flight 661.'" Within hours, the fetal thymus was implanted in muscle in the boy's abdomen. The boy is now 6 years old, 5½ years posttransplant, and his immune system is virtually normal.

Other Trials Less Encouraging

There have been a few other apparently successful thymus transplants. Charles Kirkpatrick of the National Institute of Allergy and Infectious Diseases, for example, reported that a fetal thymus recently transplanted in a 9-year-old boy is producing T cells. But it is too early to know how permanent that success will be. Generally, the experiences with thymus transplantation that workshop participants reported were rather disappointing. However, some are placing renewed hope in a procedure in which fetal liver cells and fetal thymus cells are transplanted in combination. (Fetal liver cells are precursors of the lymphoid cells of the immune system.) It is being tried in animal models and in man.

It is hard to say what the impact of this second workshop on immunodeficiency diseases will be. Certainly, the first proved to be a stimulus to a good deal of fairly dramatic experimentation in children with immune defects. In retrospect, many of the participants of the two conferences think, the first was a landmark meeting, although, as one of them put it, "It did not seem so to all of us at the time. Now, it is easy to see what happened and put things in perspective."

This time, there were few present who felt they were taking part in a meeting of equal magnitude. One spoke for many when he concluded, "The time is not right. We have a lot of valuable information but no new concepts. Now, we're going through a necessary historical stage. Perhaps in a year or two we'll have put it all together."—BARBARA J. CULLITON