EBR-II was not a power reactor, but an equivalently large and expensive reactor designed to test the effects of irradiation on a wide variety of components, but not those designed for any specific reactor. The project, named the fast flux test reactor (FFTF), has required at least as much money and effort as the prototype power stations in Europe. Officials defending the U.S. program argue that it will pay off in the advanced stages of breeder commercialization. But the FFTF is still not completed, 12 years after the previous big step in U.S. breeder development.

"If I had had the immense industrial resources of the United States, where you have two large corporations capable of the whole job," said one British official who has long been associated with nuclear power development, "I would simply have taken out my pen and written a check."

France and Britain found the need to develop a breeder more urgent than the United States did, because they have been more dependent on foreign oil and only have access to limited amounts of uranium. The situation is most acute for Great Britain, which has no domestic uranium reserves and had not discovered the North Sea oil fields when it made a national commitment to develop breeders. "We have long taken the attitude that only a foolish industry throws away 99 percent of its raw material," said T. N. Marsham, the deputy director of reactor development for the UKAEA, referring to the nonfissionable uranium left over from light water reactors. "In the United Kingdom we had a greater need," said Marsham, "and—let's face it—everyone does what he has to do."

British planners think that the country could just get by with 5 percent of the world's uranium supply, commensurate with the fraction of electricity it uses, if breeders are introduced quickly. Thus, Marsham comments, "I would hate to be a U.K. representative going into a conference to bargain for more than our fair share of uranium if I didn't have the capability of the breeder in my negotiating portfolio."

The French national commitment to develop breeders stems not so much from uranium impoverishment—since France has 2 to 3 percent of the world supply within her borders and has special arrangements with former colonies in Africa, such as Gabon and Niger, that control an additional 10 percent—but from a desire for energy independence. Officials at the CEA refer to the day when Phenix began commercial operation, which happened to be 14 July, as "our independence day." France is now in a position to export uranium, but breeders are absolutely essential for the country to become energy independent, which could occur by 2025 according to the CEA estimate. Short of total independence, French officials point out that the breeder can insulate their economy from the disruption that a geopolitical crisis in uranium distribution could cause.

Both France and Britain are planning to proceed quickly to build commercial-sized breeders based on their prototype designs. According to CEA officials, a contract for construction of the 1200-megawatt Superphenix is only being delayed by organizational changes in the energy authority, and should be completed within months. It will be built at Creys-Malville in southeast France by a combine of French government and industry, CIRNA, and paid for by Europe's three largest electrical utilities—EdF in France, RWE in Germany, and ENEL in Italy. The price will be slightly less than $1000 per kilowatt.

Before Superphenix is finished, which could be as early as 1982, the French national generating company, EdF, is planning to start two more 1200-megawatt breeders, to be ordered between 1978 and 1980. During the same period, Britain plans to start construction of a 1300-megawatt plant, already named the Commercial Fast Reactor (CFR). The designs of these plants are already in the final stages, and at least one of them could be completed before the U.S. prototype plant.

The leadership in breeder technology has clearly passed to Europe, and with their plans for early construction of commercial-sized reactors the British and French programs have enormous momentum. Public opposition to breeders is not nearly as strong in Europe as in the United States, and the economic imperative for their development is much stronger. The impressive record established so far indicates that Britain and France can probably meet their goals of installing a substantial number of breeders by the end of the century. If they are not limited by their industrial capacities, they will probably export breeders to other countries as well.

—WILLIAM D. METZ

Diabetes Therapy: Can New Techniques Halt Complications?

Insulin therapy has prolonged the life of diabetics by many years. But the quality of life for many diabetics, particularly those who develop the disease at a young age, is less than satisfactory. More than 60 percent of juvenile diabetics may have serious impairment of vision, kidney function, or peripheral blood flow. Many suffer from more than one such impairment.

These complications are now often thought to result from the lack of continuous control of blood glucose concentrations. The healthy pancreas, in response to increases in the blood glucose concentration, releases small quantities of insulin throughout the day and thereby maintains the concentration within physiological limits (normoglycemia). But the diabetic generally receives only one large dose—or, at best, a few doses—daily. The diabetic's blood glucose concentration can thus fluctuate greatly during the interval between doses, and it has been suggested that the complications result from the periods of high concentrations of blood glucose (hyperglycemia). Many investigators thus believe that restoration of normoglycemia might halt the progression of such complications in severely debilitated patients and perhaps even reverse them.

There are three primary techniques that have been investigated for restoration of normoglycemia. They are: transplantation of healthy pancreases; transplantation of islets of Langerhans, that portion of the pancreas that actually secretes insulin; and implantation of artificial pancreases. Each of these techniques has been so publicly discussed that many diabetics have built up false hopes about the possibility of soon being "cured." There has, in fact, been a great deal of success in the development of these techniques and each seems, on the whole, promising. Nonetheless, it will undoubtedly be many years before any one of them is accepted as a treatment for diabetes.

To many people, the obvious approach would seem to be simply to transplant pancreases from cadavers in the same manner that kidneys and other organs are routinely transplanted. That was the rationale on 17 December 1966 when Richard C. Lillehei and his associates at the University of Minnesota Medical School performed the first recorded pancreas transplant. Since then, there have been 46 pancreas transplants in 45 other patients in the United States and five other countries. But only one of these patients is still alive with a

functioning graft, and surgeons have found that the procedure is not as simple as they once thought.

The surviving patient, whose pancreas transplant was performed by Marvin L. Gliedman and his associates at the Montefiore Hospital and Medical Center about 42 months ago, has required no insulin since then. Another of Gliedman's patients survived 638 days without requiring insulin. One patient who received a transplantation performed by John E. Connolly and his colleagues at the University of California at Irvine survived without insulin for 10 months before she was killed in an automobile accident. And one patient of Lillehei and Frederick C. Goetz of the University of Minnesota Medical School survived a transplantation for more than a year without insulin; he died when he chose not to take his immunosuppressive drugs. These results, though meager, suggest that the procedure has the potential for success.

The rest of the patients, however, either rejected the transplant or died within a much shorter period. There does not appear to be any technical problem with the procedure. Rather, most of the patients were already so severely debilitated by the complications of diabetes that they could not withstand the surgery and the immunosuppressive regimen required to prevent rejection. More than half the patients, furthermore, also required a kidney transplant. Most investigators now agree that the simultaneous transplantation of both organs is too great a shock to the patient and greatly increases the total risk. Kidney transplants are now generally performed well in advance of the pancreas transplant.

Exocrine Tissues a Problem

Another major problem is associated with the exocrine portion of the pancreas—those tissues that do not secrete hormones. Islets of Langerhans (endocrine tissues) comprise less than 2 percent of the mass of the pancreas; the remainder is composed of a fibrous superstructure and exocrine tissues that secrete various digestive enzymes. Disposal of these enzymes in the transplant recipient has been a problem. Some of the first investigators used ducts to shunt the enzymes into the bowel, but the bowel did not tolerate them well when the duct was installed at the same time as the transplant. Felix Largiadér of the University Surgical Clinic in Zurich, however, has demonstrated that better results can be obtained if the duct for connection to the bowel is prepared prior to the transplant. Gliedman has been successful with a somewhat similar procedure that shunts the enzymes to the ureters.

The greatest problem with pancreas transplants now, however, is that the early failures have made it impossible to assess the efficacy of the procedure. It is clear that the transplants can restore normoglycemia, but it is uncertain if they will affect the complications of diabetes. Despite some initial improvement, for example, Gliedman's surviving patient has not regained his vision and there is no evidence that his other complications have been affected. The pace of pancreas transplants in this country has thus slowed as the investigators have taken time to reassess the problems involved in the procedure and the types of patients that should be selected.

Other problems have also impeded the transplants. Frederick K. Merkel of Rush-Presbyterian–St. Luke's Medical Center in Chicago, for example, had to stop his program for lack of funds. And many patients who had planned to undergo the procedure changed their minds when press reports convinced them that islet grafts and artificial pancreases would be available soon. In the last 2 years, consequently, there have been no pancreas transplants in the United States—although there have been 11 in foreign countries during that period.

Many of the problems have been cleared up now and work is starting anew. Gliedman, for instance, is beginning a clinical study to attempt to stabilize the early stages of diabetes prior to the need for a kidney transplant. He has already performed preparatory procedures on two such patients. Connolly is also resuming his studies and has two patients in whom the bowel connections have already been made in anticipation of the transplant. Despite these efforts, however, there is little question that it will be many years before pancreas transplants can even approach the stage of becoming a routine procedure.

Because of the problems associated with the exocrine portion of the pancreas, some investigators have suggested that the best approach might be to transplant only the islets of Langerhans. Interest in this alternative was heightened by the observation that, in cases of rejected pancreases, the immune attack seemed to be directed at the exocrine tissue. It thus seemed that the islets might be immunologically privileged—that is, less likely to be rejected. Investigators have subsequently found that this is not the case and that the islets present an array of their own problems. Nonetheless, experiments in animals suggest that islet transplants show great potential for future therapy of diabetes.

Several investigators have shown that diabetes induced in rodents with chemicals or by removal of the pancreas can be reversed by injection of islets obtained from healthy, genetically identical (syngeneic) animals. Such injections restore normoglycemia for as long as 12 to 15 months, although the animals frequently show a slightly abnormal response to glucose tolerance tests. Healthy islets obtained from genetically nonidentical (allogeneic) rodents are generally rejected within 6 to 12 days unless the recipients are treated with immunosuppressive agents.

With the initial demonstrations of success, the investigators began to face a variety of problems, some of which are only now beginning to be investigated fully. These include obtaining sufficient quantities of islets and isolating them from exocrine tissue; determining the best place to inject the islets and the number required; preventing rejection of islets obtained from allogeneic donors; extending the work to species closer to man and to man himself; and assessing the ability of the islet grafts to reverse the complications of diabetes.

Islets Can Be Isolated

Paul E. Lacy and his associates at the Washington University School of Medicine were among the first to demonstrate that rat islets could be separated from exocrine tissues. The process is, however, difficult and inefficient. In his first experiments, Lacy was able to isolate only an average of about 151 islets from the roughly 15,000 in a healthy rat pancreas. More recently, he has been able to improve the procedure so that he can now obtain an average of 447 islets. Most investigators have been using 500 to 2400 islets per injection, so Lacy is getting closer to the point where one donor pancreas might suffice for one rat. He points out, though, that the rat pancreas is relatively easy to work with. Pancreases from higher species, including man, are generally much more compact and contain much more fibrous tissue, so that it is more difficult to remove the islets and smaller yields are obtained. In addition, islet grafts in humans will require from 50,000 to 100,000 islets; this larger requirement is partially compensated for by the fact that the human pancreas contains more than 1 million islets.

Because more than one pancreas might be necessary for each islet recipient—a condition difficult to fulfill for humans—some investigators have advocated the use of pancreases from fetuses. Among those who have adopted this approach are Josiah Brown and his associates at the University of California School of Medicine in Los Angeles and Robert Leonard and Orion B. Hegre of the University of Minnesota School of Medicine. Brown has observed that endocrine tissues of the fetal rat pancreas develop before the exocrine tissues. It is thus possible to isolate the rat pancreas at a time, about 18 days after conception, when the islets are almost fully developed but when the exocrine tissue has only just

begun to differentiate. If the fetal tissue is then transplanted or cultured, he finds, the islets will proliferate while the exocrine tissues atrophy.

Leonard and Hegre have obtained similar results with pancreases from 2- or 3-day-old rats, the age at which the relative volume of islets is largest. They find that maintenance of such pancreases in organ culture for 10 days produces as much as a 25-fold increase in the mass of the islet cells. Both groups have shown, furthermore, that it is possible to restore normoglycemia in adult rats with cultured islets from three to six fetuses. And with some adroit technical maneuvering, Brown has been able to restore normoglycemia in a significant proportion of adult rats with islets from only one or two rat fetuses.

Poor results have been obtained when islets are injected at certain sites in rodents, such as under the skin or in muscles. The portal vein leading to the liver is the best site, according to Lacy, Clyde F. Barker and his colleagues at the University of Pennsylvania, and others. Islets injected in the portal vein accumulate in small pockets in the liver, establish a blood supply, and release insulin directly into the liver, which is believed to be the primary site of action of insulin. Injection of islets into the portal vein thus requires fewer islets for restoration of normoglycemia, they argue. They have also observed that allogeneic islets are not rejected as rapidly when they are injected into the portal vein, although the reason for this is not clear.

Not everyone agrees with them. John S. Najarian and his associates at the University of Minnesota Medical School, for example, have shown that restoration of normoglycemia can be achieved with only a few more islets if they are injected into the peritoneum. He argues, furthermore, that this approach eliminates the surgery that is required for injection of islets into the portal vein and that the islet preparation doesn't need to be quite so pure since the peritoneum is better able to tolerate the digestive enzymes produced by fragments of exocrine tissues. The situation may become even more complicated in other species. Najarian has shown, for example, that intramuscular injection of islets works fine in pigs, even though it is completely inadequate in rats. So it is not clear yet what site might be best in man.

The major problem with the potential therapeutic use of islet implantation is the rejection caused by use of allogeneic donors. Recent work by several investigators has demonstrated that allogeneic islets provoke an immune response that is perhaps even stronger than that provoked by heart transplants. It is thus necessary to find ways to reduce this response.

One approach is to vary the site of injection. Barker has found, for example, that if the donor and the recipient do not have grossly different transplantation antigens, the median survival of allogeneic islets injected into the portal vein is nearly three times as long as that of the same islets injected into the peritoneum. Another approach involves the age of the donor islets. Brown, Leonard, and Hegre have observed that fetal islets appear to be less antigenic than mature islets, so that allogeneic grafts of fetal islets are tolerated substantially longer than similar grafts of adult islets. Nonetheless, both allogeneic fetal islets and allogeneic islets injected into the portal vein are rejected much more quickly than are comparable syngeneic islets.

Isolate Islets from Immune System

Another alternative is to isolate the allogeneic islets from the recipient's immune system. William L. Chick and his associates at the Elliott P. Joslin Research Laboratory in Boston have shown that it is possible to culture functioning beta cells (the primary constituent of islets) from newborn rats on bundles of artificial capillaries through which tissue culture medium is passed. The capillaries are permeable to substances with masses smaller than 50,000 daltons, so nutrients, growth factors, and insulin can pass through them, but antibodies and lymphocytes cannot. It should thus be possible to use donor islets from species entirely different from the recipient. This artificial endocrine pancreas, Chick finds, responds to changing glucose concentrations in a manner similar to that of the pancreas. Beta cells cultured in this fashion proliferate and produce insulin for at least 3 months, he adds.

One major problem with this approach is finding biocompatible materials with which to construct the hollow fiber device. Most available materials are thrombogenic; that is, they tend to cause clotting of the blood that comes in contact with them, thereby clogging the fibers and rendering the device useless. Chick and Pierre M. Galletti of Brown University have been experimenting with new ways to construct the device to prevent clogging. They have developed a relatively nonthrombogenic prototype that they have successfully tested by linking it to a sheep's circulatory system. They hope to implant it in animals soon. But the problems of the biocompatibility of the device and the long-term survival of the cultured cells are sufficiently severe that much more work will be required before such a device could be used in humans.

It thus seems likely that the first clinical applications of islet grafts will require suppression of the recipient's immune system. There has been speculation that immune suppression might interfere with islet grafts because the corticosteroids used for such purposes are known to produce diabetes-like symptoms themselves. Najarian has recently demonstrated, however, that corticosteroids such as prednisolone do not interfere with the survival and functioning of transplanted syngeneic islets in rats. Other investigators have also shown that allogeneic islets can survive and restore normoglycemia in rodents given corticosteroids or serum containing antibodies directed against immune lymphocytes. In most cases, the allogeneic grafts have not survived as long as syngeneic grafts, but the period of survival is gradually being extended and it seems quite likely that this approach will ultimately be successful.

But immune suppression presents its own set of problems, particularly an increased susceptibility to infectious diseases and to cancer, and the side effects associated with long-term use of corticosteroids. To alleviate some of the risks, the National Institute of Arthritis, Metabolism, and Digestive Diseases—which sponsors much of the work on pancreas and islet transplants—and the American Diabetes Association last year released a position paper stressing that the first clinical studies of islet grafts in humans should be performed only on patients who have already had their immune systems suppressed. These would include, for example, patients who had already had kidney transplants. The statement also emphasized that both pancreas transplants and islet grafts should be considered only a highly experimental procedure and not a form of therapy for diabetes.

In any case, it will probably be some time before there is any substantial number of studies in humans. Only Najarian and Lacy have attempted to isolate quantities of human islets and only Najarian has transplanted them into a few humans. Most investigators agree that many more studies must be conducted with dogs, monkeys, and the like, before there can be any substantial progress with humans.

The hazards of islet transplants might be worth risking if the procedure could alleviate the complications of diabetes, and there is some evidence that this is the case. Najarian and his colleagues have shown that diabetic rats develop kidney lesions similar to those observed in human diabetics. These include thickening of the glomerular mesangium—a thin membrane that supports coils of capillaries extending into the tubules that carry away urine—and the deposition in the kidney of large quantities of antibodies (immunoglobulins) and complement (another factor that

participates in immune reactions). These effects eventually lead to a cessation of kidney function.

Najarian has demonstrated that both transplantation of a diseased kidney into healthy rats and injection of healthy islets into diseased rats reverse these symptoms. Within 3 months of either procedure, the immunoglobulins and complement completely disappear from the diseased kidneys and the mesangial thickening is reduced. If similar results can be achieved in humans, then the risks of the two procedures might be considered worth the effort.

The third alternative, and the oldest, is the use of a completely artificial pancreas. As long ago as 1962, Arnold H. Kadish of the Metabolic Dynamics Foundation in Los Angeles showed that normoglycemia could be achieved in diabetics by use of a Technicon AutoAnalyzer—an instrument for automatic, colorimetric determination of glucose concentrations—in association with devices to inject either glucose or insulin. This crude instrument suffered from a number of deficiencies, not the least of which were its bulk and the time required for measurement of glucose concentrations (15 minutes or more). But it proved that continuous monitoring of glucose concentrations could be useful in many situations.

Schism Has Developed

Although substantial progress has been made since then, a sharp schism now seems to have developed among those who have tried this approach. One group argues that there are technological limitations to artificial pancreases beyond which it will be quite difficult to progress in the near future. The second group contends that these limitations can be overcome soon and that a fully implantable artificial pancreas can be produced in the near future. This schism seems to have developed between those who have developed bulky, bedside machines and those who have worked only with miniaturized versions.

The first approach is perhaps best exemplified by the work of A. Michael Albisser of the Hospital for Sick Children in Toronto, Bernard S. Liebel of Mt. Sinai Hospital in Toronto, and their associates at other institutions in the area. They, like Kadish, use an AutoAnalyzer connected to devices for automatically injecting glucose and insulin into the patient. They also have developed an extensive set of mathematical formulas to allow the entire process to be controlled by a computer. In a variety of studies in both animals and man, the Toronto group and Ernst F. Pfeiffer and his associates at the University of Ulm in West Germany have shown that the machine can maintain normoglycemia far more successfully than can manual injection of insulin.

The machine has a variety of potential uses. Pfeiffer, for instance, has shown that it can bring a patient out of a diabetic coma more quickly and safely than other methods of therapy. Both groups have also found that it is useful for controlling diabetics during and after surgery, pancreatectomies, labor, and dialysis. It is also useful for the study of metabolism in diabetics. Because of the many potential uses, the Life Science Instruments division of Miles Laboratories in Elkhart, Indiana, will shortly begin clinical trials of a production model at several hospitals. This model, which has been reduced to about the size of a television set, will incorporate a new enzyme electrode that should reduce the lag time in measurement of glucose concentrations.

Such sensors have been the focal point of the investigators who have attempted to construct a miniaturized artificial pancreas. There are at least three different types of sensors that are under development. The Miles sensor, according to Anton H. Clemens of that company, is composed of a hydrogen peroxide–sensitive electrode sandwiched between membranes containing the enzyme glucose oxidase. The enzyme oxidizes glucose and, in the process, liberates hydrogen peroxide; the concentration of peroxide is thus proportional to the concentration of glucose.

The second sensor, developed by Samuel P. Bessman, Ennis C. Layne, and Robert Schultz at the University of Southern California School of Medicine, incorporates two oxygen-sensitive electrodes. One is surrounded by a membrane that contains covalently bonded glucose oxidase. This enzyme removes oxygen from the immediately adjacent solution in proportion to the amount of glucose in the solution. The difference in oxygen concentrations between the two electrodes is thus proportional to the concentration of glucose in the blood.

The third sensor was developed jointly by J. Stuart Soeldner and his associates at the Joslin Laboratory and by Kuo Wei Chang and Sol Aisenberg of the Space Sciences Division of Whittaker Corporation in Waltham, Massachusetts. This electrode is essentially a fuel cell that oxidizes glucose at a platinum electrode and produces a signal proportional to glucose concentration. It is surrounded by a semipermeable membrane which filters out many substances that might interfere with the measurement. The Bessman sensor is about the size of a nickel, the Soeldner sensor is about the size of a quarter, and the Miles sensor is slightly bigger.

Soeldner has tested prototypes of his sensor in more than 80 animals for as long as 117 days and finds that it responds satisfactorily. He has recently spent most of his time refining the electrode and studying its electrochemistry—defining its specificity and ascertaining that it produces no toxic by-products. He finds that the electrode responds to a few antibiotics, but that the "noise" produced by metabolites in the blood is less than 15 percent of the response produced by normal concentrations of glucose. Soeldner says that next year he will conduct 90-day bench studies of his newest sensor to determine its stability. After that, he will proceed to animal trials and clinical trials. He suggests that the first use of the sensor might be to monitor a patient's blood glucose concentration and produce a warning when the concentration varies beyond predetermined limits.

A Miniaturized Pump

Bessman has found that his sensor performs adequately in animals and he has just begun tests in humans. Furthermore, he and Lyle J. Thomas of the University of Southern California School of Medicine have developed a miniaturized pump that can deliver a total of 10 units of standard insulin in 1000 strokes. They have combined the sensor, the pump, a simple computer circuit to translate sensor output to pump signal, and a battery into an implantable apparatus that has a volume of about 50 milliliters. They are modifying the electronic circuits to obtain the best possible response to varying blood glucose concentrations, and they hope to have a prototype of the apparatus implanted in an animal within a year. They are already using a nonimplantable version of the device to control diabetes in rabbits.

Critics such as Kadish argue that there are a number of severe technological problems that must be worked out before there can be any substantial use of such devices. These include the long-term stability of the electrode, resistance of the metals in the apparatus to conditions in the body, and, especially, the biocompatibility of the sensor. Soeldner replies that these problems are comparable to those that were encountered in the development of such devices as the heart pacemaker and are soluble with current technology. Bessman argues that none of these are problems with his device. He says that the major impediment now is the lack of knowledge about the response of the pancreas in various species to changing glucose concentrations. This lack makes it difficult to design computer circuits to mimic pancreas function, he adds, but even this problem will just require some extra time to work out pragmatic solutions.

—THOMAS H. MAUGH II