Insulin Wars: New Advances May Throw Market into Turbulence

Genetically engineered insulin, insulin pumps, and the transplantation of pancreatic cells are expected to transform diabetic therapy by the end of the decade

Ever since insulin was first discovered in the early 1920's, the insulin market has been dominated by a single firm, the Eli Lilly company of Indianapolis. For six decades, no competitor has successfully challenged Lilly's control over the lucrative market, currently valued at more than $100 million a year.

Lilly's undisputed position is now about to be challenged from several directions. Diabetic therapy is entering a period of turbulence caused by new advances in medicine and technology, including those made possible by the recombinant DNA technique. For the million American diabetics who depend on insulin injections, the coming changes hold the promise of fewer side effects and easier treatment. The quality of insulin may soon improve and the price could perhaps decline.

Over the next 5 years, Lilly will be engaged in a tug-of-war with two established Danish firms, Novo Industri and Nordisk Insulin-laboratorium, for the insulin market both in the United States and abroad. The contest is evolving in two stages. The two Danish firms aim to wrest from Lilly a share of its home market. Their chief hope lies in a highly purified form of pork insulin, which they claim has certain clinical advantages over Lilly's standard brand of insulin. Lilly is not unprepared for the competition. Besides developing its own purified form of insulin, it has harnessed the new techniques of genetic engineering to develop a means of producing human insulin in bacteria. Lilly has developed its method in collaboration with Genentech, the biotechnology company now making waves on Wall Street.

All three makers of injectable insulin, however, are about to be challenged by new modes of delivering insulin which are likely to reshape the insulin market. Over the next decade, many diabetics will switch from injecting insulin daily to a far more sophisticated treatment, the use of a small, refillable pump that infuses the hormone in minute doses carefully calibrated to the body's exact needs. If widely used, the pumps will start a fierce race among insulin makers to satisfy the requirements of the new lords of the market, the pump manufacturers. About a dozen companies in the United States are developing pumps, Lilly included, and two companies already have models on the market.

But the pumps themselves may soon be superseded by yet another advance in diabetic therapy, one that may well constitute the ultimate treatment for diabetes: the transplantation of islets of Langerhans, the clusters of cells in the pancreas that are the body's natural source of insulin. Researchers have made notable progress in animal experiments to overcome immune rejection of foreign tissue. The first islet transplant in humans may be performed as soon as 1985. If the procedure becomes common, the market for both insulin and pumps can be expected to drop off dramatically.

Despite these coming shifts in market structure, executives and researchers at Lilly's Indianapolis headquarters express confidence that the company will maintain its position of dominance. But some observers believe that the foreign companies, Novo in particular, will give Lilly a hard run for its money. As one stock market analyst puts it, "Significant competition is developing in the insulin market." Just how much of the market Lilly might lose to Novo and Nordisk "cannot be clearly foreseen," according to the analyst.

The Danish companies' attempt to woo physicians and diabetics away from Lilly is a David and Goliath tale that began last spring when Novo and Nordisk started exporting their highly purified pork insulins to the United States. Lilly simultaneously came out with its own brand of purified pork insulin.

A few months later, Lilly announced its plans to produce recombinant DNA-made insulin of the same composition as the human hormone.

The two Danish companies are also exploring recombinant DNA methods of producing insulin, despite Lilly's apparently commanding lead. But Novo recently announced its development of an alternative method for making human insulin: a process for chemically converting pork insulin into the human variety. Both Novo and Lilly are expected to market their brands of human insulin within the next few years. Lilly has just begun clinical trials of its recombinant DNA-made insulin in Indianapolis: Novo is testing its pork-derived human insulin in Britain.

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Accompanying this intricate web of market strategies by the three companies is a vigorous debate about the quality of the various forms of insulin. The position taken by each of the companies seems closely related to the market strategy each is pursuing. The focus of the debate is the allergic reactions experienced by some 5 percent of the diabetics who take insulin, a group that in the United States amounts to some 65,000 people. The reactions include skin rashes and lipoatrophy, an often unsightly condition in which the fat cells around the injection area deteriorate and form "dents" in the skin surface. The quality of insulin may also affect antibody buildup that may block insulin action in the patient. The

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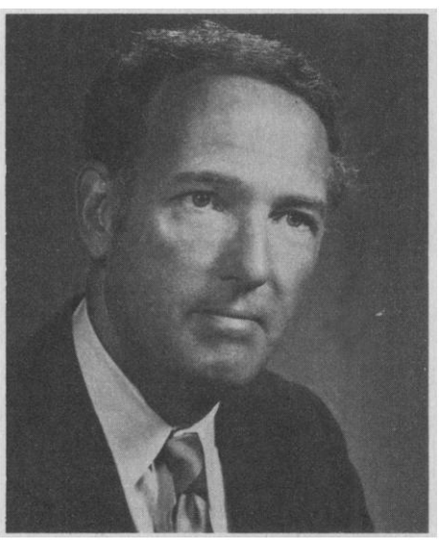
exact connection between the nature of the insulin and the allergic reactions is a matter on which the rival insulin makers have different views.

Lilly argues that its bacterially made human insulin will be better for patients than the present animal insulins. The reason is that pork insulin differs by one amino acid unit from the human variety. Fewer allergic reactions might therefore be expected with the human insulin. Novo, on the other hand, contends that the differences in amino acid structure are too slight to play a serious allergic role and that the reactions are due instead to the contaminants present in standard insulin preparations.

Novo claims that the purified insulin is suitable for many diabetics, not just those with insulin allergies. Novo Laboratories' medical director, Paul Haycock, says that the purified insulins, which have been marketed in Europe for 6 years, have helped pregnant women and young children just beginning insulin therapy.



Which insulin should go in pumps?

The human kind, says Lilly scientist John Galloway.

Other diabetics are buying the purified insulin too, Haycock states.

Novo is saying, in effect, that highly purified insulin is probably better for almost all diabetics, a claim which, if true, would hold enormous commercial significance. Lilly, while pushing ahead with its gene-spliced insulin, has hedged its bets by producing a purified insulin of its own. Lilly says its brand contains less than 10 parts per million of the chief contaminant, the proinsulin that is the precursor of the natural hormone. Novo says its highly purified pork insulin has less than one part per million of proinsulin.

Adding a further strand of complexity to the debate, however, is Lilly's contention that purified insulins should not be recommended for any but a few diabetics. Lilly argues that so much insulin is lost in the purification process that a serious shortage would develop if the demand for purified brands became widespread. Novo, not surprisingly, disputes this argument.

Both Novo and Lilly are conducting clinical trials of purified insulins in the United States. The results of the trials may clarify some of the issues in contention. Meanwhile researchers are generally skeptical about many aspects of the drug companies' arguments. Many diabetes experts believe that the highly purified pork insulins will benefit only the small percentage of diabetics who have allergic reactions to conventional insulins.

"Purity is a confusing issue," says Lester Salans, associate director of extramural diabetes research at the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD). "There's more smoke than fact."

Jesse Roth, chief of NIAMDD's intramural diabetes research, believes that for the vast majority of diabetics, purity is not going to make much difference. "Novo and Nordisk have made a big deal about it but patients and physicians were sold a bill of goods," Roth remarks.

Ubiquitous use of purified insulins would be like "using high octane gas in all vehicles. It seems inappropriate," says diabetes expert A. M. Albisser, director of biomedical research at Toronto's Hospital for Sick Children.

The question of whether newly diagnosed diabetics should be started on the highly purified insulins is harder to answer, because the data are not in, wrote J. Skyler in a recent editorial in *Diabetes Care*, the journal of the American Diabetes Association. "All things being equal, including price, one would opt for the purist form, but price is approximately double," Skyler says.

Haycock of Novo says that the increased cost of the purified insulins is small compared to the overall health care costs of the diabetic. To Lilly's criticism that promotions of purified insulins will cause a shortage, Novo claims that, by its estimation, no shortage of pork glands or pork insulin is in sight. Its high purification process results in an additional loss of insulin of only 10 percent, Novo says.

Impressive evidence for a shortage of slaughterhouse insulin is hard to come by. The Food and Drug Administration (FDA) says predictions of a shortage are unsubstantiated. Two years ago, the FDA and the National Diabetes Advisory Board studied the question of gland and insulin supply and concluded that there would be adequate supplies for at least the next 20 years. "We haven't seen a shred of data about a shortage," says John Gueriguian, a supervising medical officer at the FDA. "We get the same letters (predicting shortages) ad nauseam but no data."

James Smart, president of Nordisk U.S.A., suggests that Lilly's emphasis of a shortage is self-serving: "It's very intelligent marketing until Lilly gets their recombinant DNA insulin."

While debate continues over the benefits and effects of highly purified pork insulin, the impact of human insulin is equally uncertain. Andrew J. Ferrara, director of corporate pharmaceutical new product planning at Lilly, says, "Lilly's enthusiasm for [the recombinant DNA] insulin is for what it promises to do, but we're unable to predict accurately what it will do."

Some researchers believe the human insulin may have problems of its own. Ronald Kahn, a diabetes specialist at NIAMDD, says that small amounts of damaged proteins may contaminate bacterially made insulin. "You get that even when you extract human pancreas and inject it," he notes. Irving Johnson, vice president of Lilly Research Laboratories, tends to scoff at the idea: "We don't anticipate problems with our ability to detect impurities," he says.

Since the clinical benefit of bacterially made human insulin has not yet been established, why has Lilly invested $40 million in research and development of the technique? "It was an easy decision," says Johnson. Among other reasons, the recombinant DNA production process makes an insulin identical with the body's natural hormone. It provides Lilly complete control over the source of supply, unperturbed by variations in the hog and cattle markets. And it opens up a new line of supply to offset the impending shortage foreseen by Lilly's experts, especially because the diabetic population is increasing by 5 percent a year.

Outside observers believe that Lilly may have a quite different reason for going into human insulin production, over and above those cited by Johnson. Human insulin would be Lilly's ticket into the European market where Novo and Nordisk insulins are big sellers. Lilly is setting up a production plant in Speke, near Liverpool, England.

Even if bacterial insulin proves no better than animal insulins, it may still sell well. "It's sexier than pork insulin. It

provides an entrée into the European market," notes a Wall Street analyst. Lilly's Ferrara does not deny the idea: "I think people would perceive that the recombinant DNA insulin would have more value compared to the pork insulins. Whether it becomes a marketing tool, we have yet to decide, pending the results of clinical trials."

Human insulin may also offer a means by which Lilly can protect its share of the U.S. market without getting into trouble with the federal government. Last spring, just as Novo and Nordisk began marketing their insulins in America, the Federal Trade Commission (FTC) ordered Lilly to desist from its monopolistic practices in the insulin market. Rather than fight the case in court, Lilly signed a consent decree in which, without admitting guilt, it agreed to a harsh condition laid down by the FTC: It had to license out its existing know-how in insulin manufacture to domestic and foreign companies. But Lilly won a significant compromise with respect to future technology. The FTC said that Lilly must make available future know-how to American companies but need not license it out to foreign firms.

Since then, no domestic competitor has apparently challenged Lilly in the insulin field. Lilly's only rivals on its own turf, the Danish companies, cannot gain access through the FTC ruling to the American company's recombinant DNA techniques. The exclusion "didn't address the issue of a monopoly," complains Novo's Douglas Johnson. "Only history will answer whether the FTC's order hindered our recombinant DNA research," he says.

But while Lilly and its competitors are still struggling for the multimillion dollar insulin market, they may all be overtaken by wider use of insulin pumps. The pumps are still mainly in the developmental stage but have the potential for displacing the insulin syringe.

Insulin therapy is much more rigorously controlled than a decade ago. Diabetics used to take a single big shot of insulin once a day, which is completely different from normal physiology. Physicians now recommend smaller shots at more frequent intervals, but this regimen also differs from the way the body normally functions. There is some reason to believe that the large swings in body insulin caused by the injection protocol may be responsible for many of the most serious complications of diabetes, such as blindness, vascular disease, and kidney failure.

Already several hundred diabetics in the United States wear external pumps. These are basically battery-powered syringes that release insulin at a basal rate continuously. The insulin delivery can be increased by the patient by a press of a button whenever needed, such as after meals. As with the cardiac pacemaker, the next development is to make the pumps implantable in the body; they would be refilled with insulin by injection through a syringe. The first experimental internal pump was implanted recently by researchers at the University of Minnesota. Several other American groups have insulin pumps undergoing clinical trials.

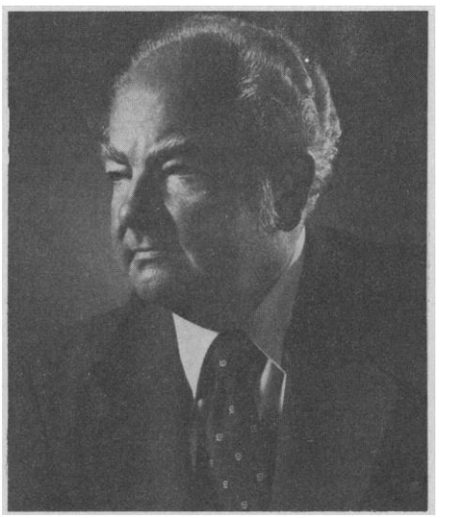
Many technical problems of pump design have yet to be overcome. One is that conventional insulin tends to clog the tubing. Another is that the internal pumps may require more concentrated forms of insulin so as to extend the time between refills. Most important is to devise a fail-safe means of controlling dose, since an excessive shot of insulin can be lethal.

But the major stumbling block with pumps is the lack of a portable sensor to detect glucose levels in the body that would then signal the pump to adjust its insulin output accordingly. A large version of a pump with a glucose monitor now exists, but it is the size of a 18-inch television and must be used in a clinical setting. The pump is expected to be approved shortly by the FDA for commercial sale, says the manufacturer, Life Science Instruments, a division of Miles Laboratories.

Until a portable sensor is designed, the interim solution is likely to be a system in which an implantable pump can be programmed from an electronic source outside the body.

The major insulin makers are working to keep abreast of the pump developments. Lilly is designing a programmable external pump, and Novo is collaborating with at least one university research team in the United States. The team is developing an implantable pump that will be controlled by a microcomputer.

The impact of the pumps upon the present insulin market is likely to be profound. For one thing, the potential control over dosage is likely to present an overwhelming clinical advantage. "On a scale of one to ten, the mode of delivery ranks ten; purity is worth two," says John Galloway, senior clinical pharmacologist at Lilly. For another, the influence over choice of insulin brand will probably pass from the insulin makers to the pump manufacturers, who will specify the formulations they require.



Developing a new source of insulin

Irving Johnson oversees Lilly's genetic engineering venture.

Some have little doubt what kind of insulin the pump makers will demand: It will be "the best insulin, and the best insulin will be human insulin, barring any surprises," suggests Lilly's Galloway.

Whatever the conclusion of pump development, the issue may be transcended by the advent of a radically different technique, the transplanting into the diabetic patient of living, insulin-producing cells. The procedure may afford the best possible treatment of diabetes.

Islet transplants are not so distant a notion as might be thought. One leading researcher in the field, Paul Lacy of Washington University, St. Louis, ventures that the first human transplant may be undertaken as soon as 1985. Lacy and his colleagues have recently succeeded in preventing immune rejection of islets in transplants from one species to another, such as from rat to mouse. The team is now working on transplants from pig to mouse and hamster to mouse. "If that can be done, we may be able to go from animals to humans," Lacy says.

Not everyone believes that islet trans-

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plants represent the ultimate solution. Experts at Lilly and elsewhere say they may go the way of heart and kidney transplants. As major surgery, islet transplants may be performed infrequently. However, the patient may opt for the transplant if it can halt the chronic complications of diabetes.

Perhaps the biggest question facing the insulin market in the immediate future is whether Lilly's recombinant DNA insulin will pan out. With Novo and Nordisk trying to grab part of the U.S. market, recombinant DNA insulin may be Lilly's saving grace. Bacterially made insulin may not only protect Lilly's share of the domestic market but also prove to be a product suitable for aggressive marketing in Europe. As Johnson of Lilly says, "The company has been the leader in insulin for decades. It was the first to produce insulin by recombinant DNA and it will be the first to bring it to market."

Lilly, however, may find that the pumps will change the face of the insulin market and see its dominance slip away. Within the next decade, Lilly's sales team, for the first time, may have to leave calling cards along with Novo and Nordisk. Whatever kind of shake-out occurs in the marketplace, diabetic patients will soon have a wider choice of drugs and therapies. The patient is thus one certain victor in the coming insulin wars.

—MARJORIE SUN

NRC Plans to Deregulate Biomedical Waste

Medical researchers may benefit; other producers of radioactive trash may be hit with higher costs

Few have the power to solve a problem by declaring it nonexistent, but that is what the Nuclear Regulatory Commission (NRC) hopes to do by proposing a new rule for the handling of radioactive biomedical waste. The problem is that no jurisdiction wants to accept garbage that the NRC has tagged as radioactive. For this reason, some laboratories are having trouble cleaning out their accumulated backlog. The NRC's solution is to remove the radioactive classification and hope that this will make it easier to dispose of the material.

The new rule, which could go into effect early next year if adopted by the Commission, would exempt certain kinds of biomedical waste from NRC regulations. The change could reduce by half the volume of low-level radioactive trash that must be shipped to federally approved burial sites. Many users of the sites will want to stop shipments if the rule is approved. One effect of the decline in traffic could be that fees may be doubled for those who cannot take advantage of the exemption. The cost of maintaining the sites will remain high, and dump operators may make up for lost business by charging the remaining clients more. The high cost of shipping the material ($250 a barrel from New York to the West Coast) will force laboratories and hospitals to find local solutions.

The NRC's proposal is simple; it would treat radioactive research materials in a couple of categories as though they were not radioactive at all. The categories to be exempted are animal carcasses and "scintillation media," the latter being most often a toluene-based organic solvent. In order to qualify, these wastes must contain only the standardized "tracer amounts" of hydrogen-3 or carbon-14, defined as less than 0.05 microcuries per gram.

If this rule change is approved, many large universities in the Northeast—where there are no waste burial sites now—will be able to reduce the amount of garbage they ship west for burial. Harvard and Columbia, for example, both send their low-level radioactive trash 3000 miles away to the only site that will accept it, in Washington State. This site, like the only other two in operation, one in South Carolina and one in Nevada, is scheduled to reduce the amount of material accepted from out of state. The NRC rule change would cut back on these interstate shipments, for it would encourage local disposal by such methods as incineration. The NRC estimates that the interstate traffic in scintillation wastes could be reduced by 200,000 to 400,000 gallons a year.

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In addition, the NRC proposes to allow research laboratories to pour more radioactive material down the drain into the sewers. Each licensee is now permitted to dispose of some liquids this way, provided that the liquid is water-soluble and carries no more than 1 curie of radiation out of the laboratory each year. The new rule would raise the limit from 1 to 7 curies per year, allocated as follows: 1 curie for undefined waste, 1 curie for carbon-14, and 5 curies for hydrogen-3. There would be no limit on sewer flushing of excreta from people undergoing medical diagnosis or therapy with radioactive material.

The proposal has attracted little attention, but those in biomedicine who know about it seem generally pleased. Radiation safety officials at several universities with large research facilities told *Science* that they were glad to see the NRC become more tolerant, but they wished the agency had gone further. Some suggested that certain radioactive isotopes of calcium, phosphorus, sulfur, and iodine should have been included in the general exemption. Some wanted the NRC to exempt laboratory gloves and wastepaper as well. Although the preponderance of comments received by the NRC favored the change, or regarded it as a "good first step," there was also some strong dissent.

Ralf Rahwan, an associate professor of toxicology at Ohio State University, wrote the NRC to protest the change. He argues that there is no evidence to support the agency's assumption that no harm will be done by releasing additional small amounts of radiation into the atmosphere and the sewers. "If they can provide figures showing that there is an increased risk that only 100 people a year will be affected then I think it would be

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