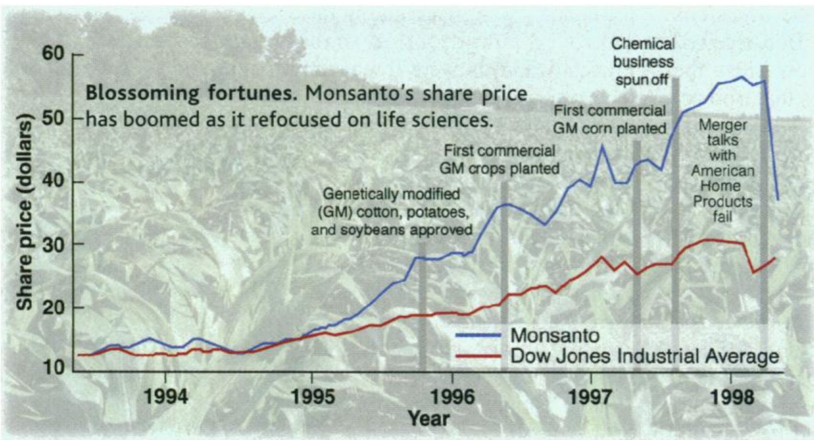
Big chemical firms are trading in their reactors and refineries for research labs and test plots. But will the bet on life sciences pay off?

Chemical Industry Rushes Toward Greener Pastures

When Howard Schneiderman joined the chemical giant Monsanto in 1979 as head of research, he took over a program focused on plastics and other petrochemicals. But he quickly began planting the seeds of the company's revolution. Trained as a geneticist, Schneiderman rapidly thrust Monsanto researchers into the burgeoning realm of genetic engineering. Within a few years company researchers had produced the world's first genetically modified plant—a petunia. It was just the first step on the road to engineering crops by adding genes that make them resistant to weed-killing herbicides or insect pests. The journey took more years, and sweat, than anyone had thought it would: Expressing herbicide-resistance genes in crops, showing that they worked, and then convincing regulators, farmers, and consumers that engineered plants were safe all became major hurdles.



Blossoming fortunes. Monsanto's share price has boomed as it refocused on life sciences.

Although Schneiderman died in 1990, his efforts are certainly bearing fruit now. In 1996, Monsanto began selling soybean seeds resistant to the company's leading herbicide, Roundup; farmers can apply the weed killer without fear of wiping out their budding crop. This year, U.S. farmers planted an estimated 25 million acres (10.1 million hectares) with the herbicide-resistant seeds, nearly one-third of the nation's soybean farmland. Herbicide-resistant corn and cotton and insect-resistant cotton and potatoes have followed. This year, of the nearly 70 million acres (28 million hectares) planted with genetically modified crops worldwide, Monsanto varieties account for over 70%. "We could have sold a lot more if we had the seed," says Gary Barton, a longtime Monsanto biotechnologist.

These new ventures are not just a sideline for Monsanto. In the mid-1980s Monsanto execs bet the farm: They began steering their entire $9 billion company toward engineered products for agriculture, as well as animal and human health and nutrition. They unceremoniously jettisoned slumping chemical manufacturing enterprises and plowed the cash into life sciences projects. Wall Street smiled on the move. The ratio of the company's stock price to its earnings per share shot up to around 100:1, although it dropped to around 65:1 last week with the announcement that merger talks with American Home Products had broken down. More traditional chemical companies continue to lag around 16:1.

With the scent of that kind of growth in the air, other lumbering chemical giants have begun retooling their business plans as well, creating a rush to the life sciences that DuPont research chief Joseph Miller calls "pervasive." Although the chemical industry has been edging this way for some time, "it's really starting to sprout now," says William Young, a chemical industry analyst with the Wall Street firm of Donaldson, Lufkin & Jenrette.

The past year alone has seen a flurry of activity (*Science*, 14 August, p. 925). Last week, Germany's Hoechst sold off its worldwide polyester business. In July, DuPont completed its buyout of Merck's portion of their joint pharmaceutical venture; in May, DuPont announced plans to begin selling off Conoco, its oil company, a move that's expected to give the company $20 billion to reinvest in the life sciences. Novartis has committed some $850 million to build a pair of new life sciences research facilities in La Jolla, California. Even the stately old Dow Chemical Co. recently spent nearly $1 billion to buy out Eli Lilly's 40% share of a joint venture to modify crops and formed a wide-ranging research alliance with France's Rhône-Poulenc Agro. "Virtually everybody is staking a claim," says Ed Wasserman, science adviser at DuPont and the president-elect of the American Chemical Society.

But the chemical industry's high-stakes bets could be risky. Monsanto's successful products are based on a simple change that adds a single gene; future crops may involve more complex genetic manipulation whose success is not yet demonstrated. Using plants as biological "factories" for other chemicals must get around problems of low yield and difficult extraction processes. Then there is the industry's image problem: Public opposition to genetically modified crops is strong in some parts of the world, particularly Europe, and governments are beginning to listen to popular concerns. Ultimately, Barton believes, genetically modified organisms will be universally accepted. But he adds, "In the short run there are bumps."

Manipulating margins

These industry-wide changes, say Young and others, are being driven by a powerful combination of economic and scientific forces. Increasing global competition is threatening to hit traditional chemical companies hard. The industrial chemicals business is a $340 billion a year venture in the United States and $1.4 trillion worldwide. With continued development around the globe, its growth is projected to be brisk. But it is also a mature industry with razor-thin profit margins, and it is notoriously prone to cycles of boom and bust—the economic crisis in Asia prompting the latest slump. Those trends are sending investors

PHOTO: OSBORN AND BARR COMMUNICATIONS; SOURCE: EXCITE INC.

looking for fatter returns and executives looking for other ways to boost their company's bottom line, says Young.

Meanwhile, the life sciences have all the hallmarks of a boom industry. Take agriculture, for example. This once sleepy, albeit profitable, sector has long relied on plant breeding programs to improve crop traits such as yield and pest resistance. "But it takes a long time to see improvements using this strategy," says Nordine Cheikh, a biotech researcher at Monsanto. "Biotech ... allows you to achieve those things much faster" by selecting just the genes you want. "It's a much more laserlike approach to improving traits."

That approach led to the success of pioneers such as Dekalb Genetics—a seed producer that has pushed its way into agricultural genomics—in producing crops such as a herbicide-resistant corn that have a single added gene that confers protection. Although these first-generation transgenics are successful, they are only the beginning. "These are Model T's," says Jerry Caulder, chief executive of Xyris, a San Diego–based agricultural genomics start-up. Now that researchers are gearing up to sequence entire genomes and decipher the function of entire families of genes, they hope to gain the ability to rewrite entire metabolic pathways, to improve numerous traits in tandem. Adds Michael Edgerton, director of genomics research at Dekalb: "Instead of gene by gene, you can look at the whole system. This means your chances of success are much greater."

CREDIT: DUPONT

"Biotech is a very sexy area, [but] there's a huge amount of science to be done."
—Joseph Miller

To companies, that potential could lead to a whole new array of products. Whether it is a new drug that prevents disease in people, a new animal feed that improves the health of livestock, or a drought-resistant corn crop, in each case companies foresee being able to charge more for their engineered products than standard commodities and possibly increase their market share.

With all the big chemical companies wanting a piece of this cake, some of the most active dealmaking has involved agricultural genomics. Last year DuPont paid \$1.7 billion for a 20% stake in Pioneer Hi-Bred International, the world's largest seed company, which already has at least some sequence data on 80% of the genes in corn. Monsanto agreed last year to pay genomics pioneer Millennium Pharmaceuticals \$118 million to help it set up Cereon Genomics, an agricultural genomics subsidiary, and the two partners intend to spend up to \$100 million over 5 years to fund research at the new company. For its part, Dow embarked last month on a 3-year alliance with Biosource Technologies of Vacaville, California, to use functional genomics to improve crop traits.

Engineering plants to be better food crops is not the only avenue open: Plants and microorganisms can also be modified to produce chemical feedstocks. This long-term goal, says Edgerton, raises the possibility of "breaking out of commodities and animal feeds and looking at new markets to replace petroleum products." Organisms, adds Caulder, "are the best chemists in the world. Why not use them to produce the chemical feedstocks you want rather than using petroleum?"

DuPont executives find this logic particularly enticing. "In the 20th century, chemical companies made most of their products with nonliving systems," said DuPont board chair Jack Krol in a speech last year. "In the next century, we will make many of them with living systems." The company already has efforts under way to use microbes and plants to manufacture everything from plastics to chiral compounds often used in drug synthesis. Working with researchers at Genencor International, for example, DuPont scientists have engineered a yeast strain to convert sugar into trimethylene glycol, a building block they plan to use to make a polymer for a wide variety of products, such as upholstery fabric and carpets in automobiles.

"The bigger dream is to do this in green plants," says Philip Meredith, DuPont's head of biochemical sciences and engineering. In addition to using less energy, and therefore cutting costs, growing chemicals in plants also hits on another theme of the push toward life sciences: sustainability. DuPont's Miller and others argue that by genetically manipulating crops to do some of the chemical synthesis, biotechnology may reduce the environmental "footprint" of the chemical industry. "Intrinsically, biological processes are sustainable at heart," says Michael Montague, Monsanto's current research chief.

An example is Dekalb's effort to commercialize low-phytate corn. Phytate is a naturally occurring compound that helps plants store phosphorus. But when corn is fed to animals such as pigs and chickens, phytate inhibits absorption of phosphorus by the animals, requiring farmers to add expensive phosphorus supplements. This helps the animals grow, but it also increases the amount of phosphorus in farm runoff, which collects in streams, bays, and estuaries, promoting fish-killing algae blooms. Low-phytate corn, developed as a hybrid by researchers at the U.S. Department of Agriculture, would both reduce the need for farmers to spend money on phosphorus supplements and reduce unwanted runoff as well, says Edgerton.

Risks and return

The effort required to develop such new products is dramatically boosting the chemical industry's R&D budgets. Chemical companies traditionally spend only about 3.5% of their revenues on R&D, while that number can be as high as 20% for pharmaceutical firms, says Stephen Dahms, who directs the molecular biology institute at San Diego State University and keeps close tabs on movements in biotechnology. Where will life sciences companies fall on this line? "I would say it's going to be on the pharmaceutical end of the spectrum," says Montague. The shift in the industry already seems to be changing the dynamics of the job market, adds Edgerton. "You're seeing a large increase in people with plant and molecular biology [backgrounds] being hired."

However, this transformation still faces major challenges, both scientific and societal. One of the biggest is that traits in agricultural products, such as yield and drought resistance, are complex and controlled by the action of many genes and their proteins. That can be both good and bad, notes Edgerton. Although there are lots of potential genes to which improvements can be made, understanding the interactions between all the genes can be difficult, he says.

Other parts of the strategy face potential difficulties as well. Even if plants can be engineered to produce useful chemicals, such as polymer precursors, there's no guarantee that this can be done economically. Plants normally produce only a small amount of any given product, points out Angelo Montagna, manager of external technologies at Exxon Chemicals in Baytown, Texas. As a result, "a lot of those monomers from plants will be expensive," he says. Making it profitable to grow chemicals requires boosting the yield of those compounds. But increase it too much and you kill the plant, says Montagna. Even if you overcome this problem and produce large amounts of a chemical, you still have to separate it from the rest of the plant, a task that itself may require capital-intensive extraction equipment. "Biotech is a very sexy area," says DuPont's Miller. "[But] there's a huge amount of science to be done."

By far the trickiest problem facing the new life sciences giants involves widespread public fears of genetically engineered products. Whereas such fears are only moderate in the United States, they resonate elsewhere, particularly in Europe, where much of the public remains skeptical of the safety of genetically modified organisms, particularly agricultural crops (*Science*, 7 August, p. 768). A Europe-wide poll published last year found that 53% of those surveyed said that current regulations are insufficient to protect people from the risks of biotechnology.

This public opposition is registering with politicians. Last week, the European Parliament's environment committee called on the European Commission to impose a moratorium on approvals to market genetically modified organisms. In July, the French government announced a temporary ban on commercial growing of genetically modified crops, and there has also been talk of a moratorium in the United Kingdom.

The atmosphere has grown so tense that last month a U.K. printer pulped the entire run of the September/October issue of the campaigning *Ecologist* magazine—a special issue focusing on Monsanto—reportedly fearing a libel suit by the company. (The issue has since been reprinted elsewhere.) Environmental organizations also continue to raise concerns that modified crops could cause unforeseen turmoil, such as invading new territory, passing on key genes to weeds, and contributing to the degradation of valuable ecosystems such as salt marshes by allowing farmers to grow salt-resistant crops and therefore plow up the land.

Gary Jacob of Monsanto says that "the fate of this technology has to be made by society in general." But such concerns raise questions about the wisdom of the chemical companies' bet on the life sciences. "They increase the risk," says Montague. Faced with these risks, DuPont, unlike Hoechst, Monsanto, and others, has decided to retain some of its chemicals business. "It's a matter of hedging our bets," says Miller. "We need a strong and healthy chemicals and materials business. But at the same time we're going to develop our capability in the biological sciences." But Montague argues that at this critical time, some boldness is necessary: "Unless you begin on the road, you'll never get anywhere."

–ROBERT F. SERVICE

NOBEL PRIZES

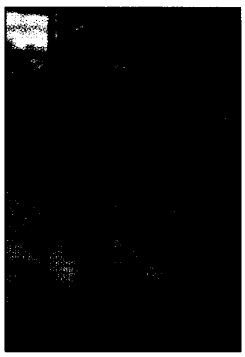
Nine Scientists Get the Call to Stockholm

The work honored by this year's crop of Nobel Prizes was done years ago but shows no sign of dating. The physiology prize went for the identification of a signaling molecule whose roles are still being explored; the chemistry prize for work enabling chemists to exploit quantum mechanics; the physics prize for a still-mysterious quantum "fluid"; and the economics prize for studies of poverty that remain all too relevant.

NO News Is Good News—But Only for Three Americans

The surprising discovery that the simple gas nitric oxide (NO) is a powerful messenger molecule in the body—a find that *Science* honored six years ago as "Molecule of the Year" and that helped spawn the impotence drug Viagra—has earned three U.S. researchers this year's physiology or medicine prize. The $975,000 prize was divided equally among pharmacologists Robert Furchgott at the State University of New York, New York City, Louis Ignarro at the the University of California, Los Angeles, and Ferid Murad at the University of Texas Medical School in Houston for identifying the first known gaseous signaling molecule and triggering a surge of further work on NO's diverse roles in the body. But the Nobel committee's omission of a fourth researcher, pharmacologist Salvador Moncada of University College London, drew fire from several senior scientists, including Furchgott himself.

"I'm delighted for the nitric oxide field, which Furchgott created, but I'm very disappointed Moncada has not been included," says pharmacologist John Vane of the William Harvey Research Centre at the University of London, a 1982 Nobelist for work on prostaglandins. Strict rules allow the Nobel committee to divide a prize between no more than three researchers. But Vane (who once worked with Moncada) and others say that this was the year for an exception, because Moncada carried out some of the key work showing that NO is released by cells.



Many researchers agree that Furchgott founded the nitric oxide field in the 1980s by recognizing that a mysterious signaling factor was at work in blood vessels. He wondered why drugs acting on blood vessels often gave contradictory and confusing results, sometimes causing a contraction and sometimes a dilation. He went on to show that the endothelial cells lining the inside of the vessels must be intact in order to receive a signal from compounds such as acetylcholine, which causes vessels to dilate. He concluded that the endothelial cells produce some unknown factor that relaxes smooth muscle and causes dilation. He called this factor endothelium-derived relaxing factor (EDRF).

Then, in 1986 Furchgott and Ignarro independently reported at a conference that EDRF is NO. The finding startled scientists because it showed that a simple gas—one best known at the time as a component of smog—can carry important informa-

Winners' circle. Ignarro *(below)*, Furchgott *(top)*, and Murad *(far right)* shared the prize.

CREDITS: (CLOCKWISE FROM TOP) A. NADEL; P. SULLIVAN; F. CASTANO/AP