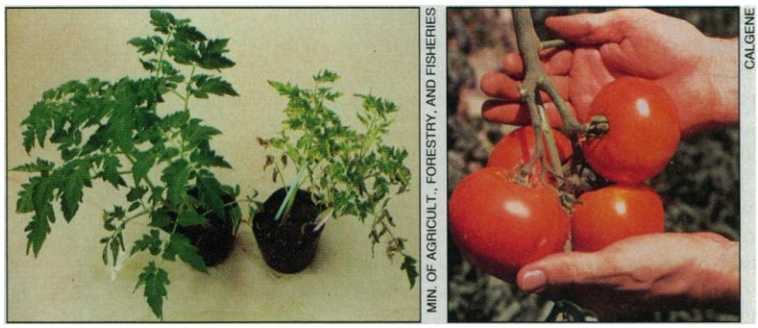
Agricultural Biotech Blooms Late

Government rules and tradition hamper research on transgenic crops, but the rice genome project and work on green technologies are flourishing

TOKYO—In a land where housewives fork over tens of dollars for a single melon and farmers spend $3 billion a year on pesticides, you might expect agricultural biotechnology to be a top priority. And if the domestic market were not incentive enough, surely the lure of potentially vast sales of high-yield, pest-proof crops throughout Asia would be irresistible. Yet Japan's agbiotech larder is nearly bare.



Not ripe. Virus-resistant tomato *(left)* is one of the few transgenic crops field-tested in Japan, while U.S. consumers can buy Calgene's Flavr Savr tomato *(right)*.

A mere 13 transgenic crop plants have so far been approved for field tests in Japan. Compare that with the United States, where the U.S. Department of Agriculture has authorized tests of more than a thousand genetically engineered fruits, vegetables, and grains. And the disparity is even greater for livestock and biopesticides, for which "research in Japan is not in the practical stage," says Toru Totani of the agriculture ministry's biotechnology division. "At present our ministry has no guidelines" for transgenic livestock and bioengineered micro-organisms for pesticides, he says.

The barriers to progress are formidable. For one thing, farming is a minor part of the national economy. "The entire seed business in Japan is worth only about 100 billion yen [$1 billion]," says Yoshiteru Yahiro, senior manager for business planning at Mitsubishi's Plantech Research Institute. "That's only a tenth the size of the U.S. market." Indeed, U.S. firms spend some $570 million a year on R&D for agbiotech alone, which is more than Japan spends on research into all food resources.

One result of this disparity is that foreign firms control the lion's share of important patents. To utilize such key technologies as virus-resistance genes and antisense technology, Japanese firms must pay substantial license fees to such companies as Monsanto and Calgene. "The lack of patents is our single biggest problem," Yahiro laments. "We need patents to make profits."

Japanese firms also complain that the system is dominated by government agricultural stations and the gargantuan national farmers' association. For example, seed developed by the national labs is sold to farmers at prices companies can't even match. And in the case of staple crops such as rice, there is an additional barrier—the Foodstuff Control Law, enacted in 1942 to prevent wartime black marketeering. The law regulates rice production from seeds to sales and serves to keep out newcomers. "You need a license for every step," explains Plantech's Yahiro. "We don't have a license, so we can't get directly involved in the business."

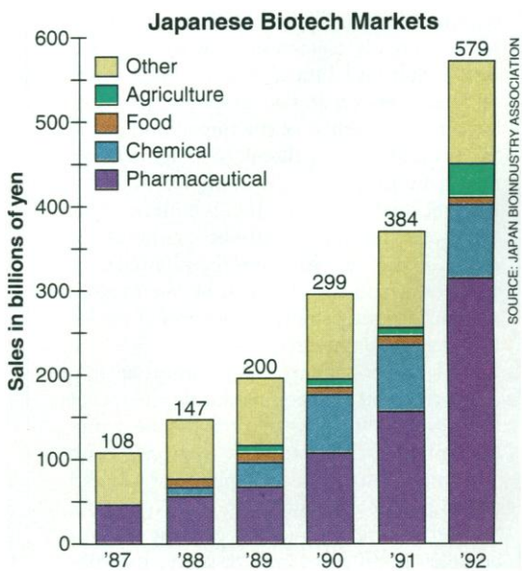
Japanese firms are also wary of customer hostility to unfamiliar products. In particular, agbiotech firms were shaken by last year's "rice shock," when a poor harvest led to a run on rice shops, sending the price of domestic rice through the roof. Consumers were willing to pay a premium for Japanese rice even though Thai rice was available for a pittance—a fact that was not lost on the biotech industry. "We wonder how consumers are going to accept recombinant rice," worries Koshi Koseki, a senior researcher in technology planning at Japan Tobacco. Delays by the Ministry of Health and Welfare in issuing safety guidelines for transgenic foods have also hobbled research into genetically engineered new strains.

A social contribution. Such factors help to explain why only a handful of companies have ventured into agbiotech. And those pioneers—among them Mitsui Toatsu Chemicals, Japan Tobacco, Kirin Brewery, Mitsubishi, Suntory, and Sumitomo Chemical—have done so cautiously. "In the early days, Japanese companies were not sure about the commercial prospects of agbiotech," recalls Nam Hai Chua, a leading plant researcher at Rockefeller University. He suggests the skepticism ran so deep that companies chose to work on rice—a poor choice from a business standpoint given the 1942 law—because they figured it would at least be scientifically interesting.

These efforts have met with some scientific success. Plantech researchers managed to insert genes into rice using electrical pulses, and Japan Tobacco has done the same using agrobacterium as a vector. Mitsui Toatsu has created a low-allergen strain of rice by using antisense technology, and a government-sponsored collaboration has produced a low-protein rice for sake brewing. At the same time, a national rice genome–mapping effort has propelled Japan to world leadership in that field (see p. 1186).

Most of these efforts seem unlikely ever to turn a profit, however. Plantech's transgenic rice research fell under the budget-cutting scalpel this past spring after corporate executives decided it was unlikely to lead to a salable product. The estimated market for Mitsui Toatsu's low-allergen rice, still under development, is only 10,000 people. "We consider that we are doing this project as a social contribution," says company scientist Hiroaki Shimada.

Neither are consortium members likely to



Growing pains. The market for agricultural products is still a tiny share of overall biotech sales.

benefit monetarily from the low-protein rice, covered by a patent held by the national laboratory that sponsored the collaboration. (The six participating companies can license the technology.) Tatsuji Chuman, general manager for technology planning at Japan Tobacco, says the company has no regrets about its participation, however. "We can learn from this experience," he says. "So it's not such a wasteful thing for us to do."

Indeed, some Japanese agbiotech firms are already applying their expertise to crops other than rice, where the market barriers are less intimidating. Companies like Suntory and Kirin Brewery, for example, have made a strategic move into floriculture. "We think flowers will gain public acceptance sooner than foods," says Takeshi Ohtani, manager of Kirin Brewery's Central Laboratory for Key Technology. Suntory is collaborating with the Australian firm Florigene to create a blue rose, and Kirin is manipulating chrysanthemums to resist cold and disease.

To prepare for the day when its bioengineered mums might become big business, Kirin purchased the Dutch flower company Fides, the world's largest producer of chrysanthemums. "This alliance will give us a foothold in the global market," explains Ohtani. Also, he says, the technologies developed with mums "have a potential application in many plants." Japan Tobacco also has its sights set beyond Japan's borders. "We're developing cold-resistant corn, not just for within Japan, but for markets around the world," says Chuman. "Our thinking has been global from the start."

Ripening interest. All this activity suggests that, despite the hand wringing, Japanese agbiotech may yet blossom. One important factor is the government's grudging acceptance of rice imports. Last year's rice shock has also led to calls for reforming the 1942 law to lower trade barriers and shrink price supports that have benefited Japanese rice farmers for decades. Those changes could create more favorable market conditions for genetically engineered staple crops.

Japanese agbiotech companies are also closely watching U.S. public reaction to Calgene's Flavr Savr tomato, the genetically engineered squish-proof fruit that landed on U.S. supermarket shelves this past spring. Reports that the tomato is finding favor with shoppers may prod companies into plowing more into R&D, some researchers suggest. "If Flavr Savr is popular," says a leading young plant scientist in Japan, "maybe we can be more optimistic."

Some experts outside Japan already are. "Here are 120 million people who can afford to spend a lot of money for food," says Ganesh Kishore, head of agbiotech research at Monsanto Corp. in St. Louis. "In Japan alone, rice is big enough for two or three major players. Japan also has the opportunity to be a very strong player in Asia," he asserts. "Because the Japanese are closer to Asia, they are more aware of what crops are consumed in that region—things that are not on our radar screen."

One sign that Japan could soon be a serious contender, says Kishore, is the rapid improvement in the quality of its basic research. "Where Japan lags is in discovering useful genes," he predicts. "But I think that's likely to change over the next 3 to 5 years. For Japan, national prestige and economy are at stake. I don't think they'll walk away from this technology."

–June Kinoshita

PROFILE

Biologist on the Fas(t) Track

When Shigekazu Nagata is not working in his lab at the Osaka Bioscience Institute (OBI), he can often be found cruising the open road in his espresso-colored Toyota Sprinter. "I like to drive very fast," he impishly admits. Nagata's love of speed carries over into his science. For the past several years, he and his OBI coworkers have raced into print every few months with pathbreaking papers that have attracted the notice of researchers around the world working on cellular signaling proteins called cytokines. "He is really fast," says James Wells of Genentech, who has collaborated with Nagata. "You don't want to end up competing with Shiggy."

OSAKA BIOSCIENCE INSTITUTE

Highly cited. Shigekazu Nagata of the Osaka Bioscience Institute.

Nagata, age 45, has the disheveled air and energy level of a man half his age. Bounding around his lab, he explains his latest experiments on the fas antigen and its receptor—a system that appears to play a primary role in apoptosis, or programmed cell death. His earnest expression often breaks into grins of delight, as though he feels extremely lucky to be doing what he's doing. His publication record, however, suggests that luck has little to do with his achievements. More likely, his success derives from his keen nose for important problems, his tenacity, and his willingness to take risks. Also, as one close friend remarks, "He's very nice, very modest—and he's very competitive."

Nagata took his first big leap in 1977 by taking his newly minted Ph.D. in biochemistry from the University of Tokyo Institute of Medicine to the Swiss laboratory of University of Zurich professor Charles Weissmann. His goal was to learn the then-new recombinant DNA technology. "I thought this must be so powerful," he explains, "but at the time no one at Tokyo was doing it." Nagata proved an able student. In 1980, he beat out formidable competitors, including Genentech's David Goeddel, in the race to clone the human interferon gene.

Two years later, Nagata was back at the University of Tokyo as a research associate in the lab of Yoshito Kaziro, where he proceeded to isolate and clone granulocyte colony-stimulating factor (G-CSF). Unlike many young Japanese scientists, who often toil anonymously under a senior professor, "I could do what I wanted," he recalls, "perhaps because Dr. Kaziro is so kind."

Still, that wasn't the same as running his own show. In 1987, when OBI asked him to head its molecular biology department, he jumped at the chance. With typical understatement, he describes his decision to leave the prestige and security of Tokyo as "a nice challenge." OBI was then a small, brand-new research center, funded by the city of Osaka and local companies and without precedent in Japan. Once there, Nagata quickly discovered that building a department from scratch consumed much of his time. "Recruiting the staff to come to a new institute was hard," recalls a colleague. "He had to train them himself."

But having assembled his team, a dozen people in their 20s and early 30s, Nagata has never looked back. Unencumbered by academic hierarchies and administrative chores, the lab has made seminal contributions to the understanding of the G-CSF and fas systems. And mindful of how the Japanese system assigns minor roles to young scientists, Nagata tries to give his protégés plenty of leeway. "They are all independent," he says matter-of-factly. And like their mentor, they enjoy going at top speed.

–J.K.