Feature

Biotechnology:

A young industry with potential

In anticipation of the World Conference on Biotechnology for the Fats and Oils Industry, JAOCS *newswriter Anna Gillis interviewed leading biotechnology researchers to examine biotechnology's potential applications for fats and oils. Her findings are included in this article and in the three accompanying articles.*

By business standards, the biotechnology industry has not come of age, yet Wall Street and private financiers are investing with an enthusiasm and confidence that belies the industry's youth. The hope of profits from powerful new technologies translates into strength for young companies, according to Steven Burrill, chairman of the Arthur Young High Technology Group.

Burrill compares the agritechnology area to a 10-year-old, full of life and promise. "More and more, we'll see new money entering this sector. There will be more start-up companies and more public companies. Some studies say the biotechnology industry will be a $100-billion business by the year 2000," he said.

How much of that profit will come from altered oilseeds and oilseed products is difficult to determine. The investment and interest are there, however. When Calgene Inc. went public in July 1986, it sold 2.25 million shares and raised $29.3 million in one day during a time when other stocks on the New York Stock Exchange were vacillating. The Davis, California, company also has nearly one dozen agreements with other companies to use recombinant DNA technology to develop oilseeds and other crops with specific traits. Sungene Technologies Corp., which does research on oilseeds and grains, already has spent $10 million for research and development and field trials for corn hybrids which are not scheduled to enter the market until 1989. Other companies reportedly have spent between $50-$90 million on oilseed research.

Most plant biotechnology companies are using a wide range of techniques—transformation-regeneration, mutagenesis, protoplast fusion, classical plant breeding—to develop new products. "Depending on what trait is desired, the agricultural biotech industry must employ a combination of sophisticated techniques to successfully develop a crop," David McGee, vice president of operations for Sungene, said.

To date, no company has marketed an agronomically useful oilseed crop produced through transformation or tissue culture. However, many industry representatives expect products will be available within the next five to ten years.

Transformation (the process of introducing foreign genetic material into the genome of a target organism), combined with regeneration (the ability to grow whole plants from a single cell or a small piece of plant tissue), allows the most direct approach in changing plant materials, McGee said. "These molecular biology techniques allow the introduction of genes into plants that do not have a particular gene expressed or expressed well. These techniques provide a more direct approach to new genotypes compared with somaclonal variation which generates random genetic variation. Using these cell biology techniques becomes a numbers game. To create large numbers of variants increases the probability of creation and detection of a favorable genetic change," McGee said.

In somaclonal variation, large numbers of plants are regenerated from plant cells. To enhance genetic variability, mutagens are sometimes applied to tissue cultures. In both cases, the resultant plants are screened for desired traits.

"Spontaneous mutations (in nature) may occur once in a million times. What somaclonal variation does is increase genetic variability faster than the spontaneous mutation rate. It allows you to create more variations faster by turning on and shutting off certain genes, but it doesn't bring in genes that are not already there," McGee said.

Before new plant products can be developed through transformation, methods must be developed whereby the plant can be transformed and regenerated in the same system, i.e., plant cells that are transformed must be the ones regenerated in culture. Those cells also must eventually produce fertile, viable offspring with the desired added traits.

So far, the only oilseed in which this has occurred is rapeseed. In 1985, researchers at Calgene transformed and regenerated rapeseed and have since proven that the rapeseed progeny maintain the desired traits. Scientists at Monsanto Co. have done similar transformation and regeneration experiments on rapeseed.

In such experiments, a method of introducing new genetic material into a cell must be found; once the new material is incorporated into the host's genetic material, it must express itself, or "turn on," and do as expected. The cells which contain the new gene must be identified; those cells then must be regenerated or grown into a whole plant. "Until we find a system (that regularly allows for transformation and regeneration), we'll be looking at a vicious cycle," Robb Fraley, director of plant science technology at Monsanto Co., said, adding, "Once this technology is working, we can really begin modifying particular pieces of DNA to alter metabolic pathways."

In addition to Calgene's and Monsanto's success with the rapeseed system, there also are isolated reports that some researchers have regenerated certain transformed sunflowerseed cultivars, Fraley said. With soybeans, foreign genes can be inserted into the cells, but those cells can't be regenerated. Other soybean cell lines have been regenerated, but were not transformed.

Because other legumes, such as alfalfa, have been successfully transformed, Fraley thinks a viable method for soybeans is not far off once the right combination of vectors and regeneration media is found. "With a few tweaks, we'll get the right conditions," Fraley said.

Although no products are available, Robert Goodman, Calgene's executive vice-president in charge of research and product development, is confident that of all the biotechnological options, the best way to get specific products is through genetic engineering. But those techniques take time, Goodman said. "A misconception widely held is that there is a faster way to get to the marketplace. Many companies which started in the early 1980s went with tissue culture, saying it would lead to products faster, but those techniques still have not produced truly advanced products."

Calgene, like other plant genetics companies, plans to enter the marketplace by producing "specialty plant oils, processed plant products and agronomically superior plants." Most of the companies develop products through agreements with other firms seeking oils or oilseeds to meet particular in-house needs.

In a general sense, the fats and oils industry might like more oils with specific qualities at lower prices, a soybean oil with a reduced linolenic acid content which can be produced without a loss in yield, and high-value fats and oils, according to Vic Knauf, Calgene's principal scientist for the oilseed quality group. One example of a high-value oil development would be to use sunflowerseed to produce an oil similar to evening primrose, Knauf said, explaining that as the biosynthetic pathway goes most of the way to γ-linolenic acid, a few modifications might allow the production of an evening primrose oil substitute.

Calgene is particularly interested in improving oil yield, according to Knauf. However, certain biochemical information pertaining to lipid biosynthesis is missing. To improve oil yield, the rate-limiting factors in fatty acid synthesis must be determined. Certain enzymes such as acetyl-CoA carboxylase, ACP acetyl transferase, 3-oxoacyl ACP-synthase and ACP malonyl transferase are considered rate-limiting, but, Knauf said, Calgene believes that acyl carrier protein (ACP) availability also may be an important determinant of oil yield; ACP is involved in chain elongation in fatty acid synthesis.

Earlier this year, Calgene researchers took an ACP gene cloned from spinach leaves and reprogrammed it to express itself in rapeseed. Reprogramming took place by using the promoter—the segment of DNA which initiates gene expression—from a *Brassica napus* napin gene as a replacement for the ACP promoter. The napin gene, which expresses itself only during seed development, turns on 18 days after flowering. Fatty acid synthesis in the seed begins about 15 days after flowering. Because the timing of the two events is so close, the timing of the napin-ACP chimera's expression was considered—at least in theory—a suitable means to increase fatty acid synthesis. The napin/ACP gene then was inserted into Westar rapeseed varieties.

Calgene researcher Donna Scherer said it now must be determined whether the new gene controlling ACP levels is actually functioning in the plant. If it is, oil analyses will be done to see if oil production actually does increase. "If it does, homozygous plants would have to be produced and the new agronomic traits would have to be maintained in the line," she said.

"It's going to be two to three years before we'll get meaningful results from experiments on modifying vegetable oil characteristics.

Soybean work

One researcher who believes his group is close to putting transformation and regeneration together for soybeans is David Hildebrand, a biochemical geneticist at the University of Kentucky. Recent experimental data may indicate that the two necessary aspects for soybean genetic engineering have come together; however, this still needs to be verified, Hildebrand said.

"First, we need to see whether it was somatic tissue which was transformed. If it was, then desired traits may not have been passed on to the offspring. Germ line cells have to be transformed (to pass on traits). There is also the possibility that the Agrobacterium vector which carried the foreign gene into the soybeans may still be alive in the tissue, thus giving a false positive transformation indication," Hildebrand explained.

Initial cytological analyses and the use of probes specific for Agrobacterium indicate that no Agrobacterium cells were present in the plant tissue, but, Hildebrand said, the final proof of a viable transformation system for soybeans is transmission of the foreign gene to offspring. The research group currently is collecting that data.

Although other groups reportedly have been able to transform and regenerate soybeans, to date no one has developed a reproducible system.

We're just now starting to understand the biosynthesis of oil; this knowledge base is still behind the rapeseed technology base," William Scowcroft said. Scowcroft, vice president of research and development at Biotechnica Canada, added that researchers still don't know enough about the genes which control certain desired traits in rapeseed and other oilseeds. Researchers must determine how many genes are needed and how they regulate particular functions. Probably the first new oilseed products to be developed through recombinant DNA technology will be herbicide-tolerant rapeseed varieties, followed by varieties with modified fatty acid profiles, Scowcroft said. Finally, disease resistance, cold tolerance, drought tolerance and seed shattering problems will be addressed.

In May, Calgene began field trials in Manitoba, Canada, with a phenmedipham-tolerant variety of Westar developed through a cell selection program. It also is conducting field tests in the U.S. on tobacco plants containing its patented glyphosate-tolerant gene.

Scowcroft doubts that herbicide tolerance will ever be the flagship at his company or others; it would instead be of add-on value to varieties such as hybrids. He noted that in Canada, for example, an atrazine-tolerant canola variety is available, but is needed for less than 1% of Canadian canola area. "Herbicide tolerance is certainly not the most important trait we'd want," he said. "Development of hybrid varieties is a far more important objective for Biotechnica Canada."

An agronomic trait worth developing in rapeseed for Canada is early maturity, Scowcroft said. He speculated that a variety which reached maturity even three days earlier would have a tremendous added value, perhaps as much as higher-yielding varieties. Early varieties which maintained high yields might be able to take over in the market the way the Westar variety did, Scowcroft said. The Westar variety, developed by Keith Downey of Agriculture Canada, was introduced in 1982; within three years, it had taken over 50% of the 6.5 million-acre canola seed market, Scowcroft said.

Allelix Inc., based in Mississauga Ontario, also wants to develop rapeseed hybrids. "We'd like to turn rapeseed into a crop like corn. Hybrids would give us a chance to recoup our investment because farmers would have to buy seed every year," Wallace Beversdorf of Allelix said.

Allelix's largest efforts are in developing pollination control systems which would allow hybrid production from single crosses. "We'd like to exploit heterosis to increase production yields by 20 to 40%," Beversdorf added.

Most of the plant-altering work at Allelix is done through classical plant breeding. "Biotechnological methods are just refined modern techniques which allow us to improve crops faster," Beversdorf said. "They will not replace classical methods, only augment them.

"We're working on transformation but in general, it's unpredictable. It will probably be 10 years before any significant products produced by transformation will be available commercially," Beversdorf said.

The company also uses protoplast fusion and isolated microspore techniques to get desired traits. "Protoplast fusion techniques are better than classical techniques when we want traits found in the cell's cytoplasm which can only be passed through the female line," he said, explaining that the company currently is using this cytoplasmic technique to obtain seed which will eventually be tested in Canada. "The microspore techniques allow us to develop in-bred plant lines in four months, instead of five years," Beversdorf said.

In protoplast fusion, cell walls are dissolved to allow the mixing of the cytoplasmic contents of two plants. This method is used to obtain traits which may not be obtained through direct sexual crosses, and can be used to cross plants of two different species. Microspore (immature pollen) techniques, meanwhile, can be used to develop traits in the male line. These techniques produce large numbers of plants which, being haploid in nature, allow recessive traits to be identified.

Those involved in manipulating soybean genes believe that soybean hybrids also would be profitable. Soybeans now are sold as varieties. Once genetic improvements are made in soybean varieties, nothing would prevent a farmer from buying only once and using seed produced from the crop the following year, Paul Kiefer, manager of business development for the Monsanto Agricultural Co., said. "With the millions that have been, and will be, spent on research, hybridized crops provide a good means for cash flow year-to-year."

However, one major obstacle is cost. Currently, soybean hybrids are produced by cross-pollinating plants by hand, McGee said. The plants have small flowers which make cross pollination difficult. Modifying the flower would not be the best way to address the problem since flower development is controlled by more than one gene. Instead, it would be better to target changes controlled by one gene, McGee said.

Because a soybean transformation-regeneration system has not been established, some researchers have said soybeans will be at a disadvantage relative to rapeseed when it comes to making controlled changes to produce specific products. Despite this, some companies plan to release soybeans altered through other means. Sungene reportedly will have new varieties developed through tissue culture in two to three years.

In other soybean-related work, Biotechnica International is working on a *Rhizobium*-alfalfa model to determine the feasibility of eventually using altered *Rhizobium* to increase soybean yields through enhanced nitrogen fixation. The company has genetically altered three strains of *Rhizobium meliloti*; according to Ashley Stevens, company vice-president of marketing and sales, those strains have improved alfalfa yields by 15-20% in greenhouse tests.

Earlier this year, the Massachusetts-based company applied for Environmental Protection Agency (EPA) and U.S. Department of

Agriculture (USDA) permission to field test the three *Rhizobium* strains in alfalfa fields. Stevens said the company hopes permission is obtained in time to test the strains during this year's fall planting. If the field tests are as successful as greenhouse tests, the company will conduct similar field tests with soybeans and *Rhizobium japonicum* in 1988, Stevens said.

USDA, corporate and academic researchers also are using genetic mutations to develop soybean lines which produce high or low levels of palmitic acid and high levels of stearic acid. According to Niels Nielsen, a USDA scientist at Purdue University, researchers at Purdue also have produced high oleic acid and low linolenic acid soybean lines. USDA-Purdue researcher James Wilcox has been able to lower linolenic acid content from about 8 to less than 4% with no detrimental effect on yield, he said.

Work on changing soybean protein traits also has a good start. "Right now, people are looking at obvious things like sulfur amino acid content, but eventually we'd like to be able to change traits as specific as leavening characteristics in soy flour. But those kinds of changes are a long way down the road," Nielsen said.

Although researchers may want to modify seed proteins, those modified proteins still must be able to act in a normal fashion in seeds, Nielsen said. "We need to develop bioassays to determine whether changes in seed storage proteins are detrimental to assembly. A method has to be developed to monitor the processing and assembly of glycinin in a test tube."

To solve the problem, Nielsen's research group has developed such an assay. "This gives us a tool to evaluate changes engineered into these plant proteins," Nielsen said. Using the technique, a number of genetic constructs have been produced; among these is one that increases the methionine content of one of the proglycinin subunits threefold.

Traits companies might want to manipulate are those which would minimize processing, Nielsen said. One example of this might be the elimination of off-flavors associated with lipoxygenase enzymes in soybeans. "Consumer acceptance of soy products could increase if these flavor problems were eliminated," Nielsen said, noting that recent data from his lab indicate that the removal of the lipoxygenase-2 isozyme improves flavor and makes the beans more stable during aging.

While there are reports that sunflowerseed transformation and regeneration work has been successful, no new products developed under the system have entered the marketplace. However, tissue culture work at Sungene has resulted in sunflowerseed lines with an oleic acid content better than 95% and others with a linoleic acid level higher than 80%. Field testing is in progress; when it is completed, the company plans to develop the oil commercially. The two seed lines are protected by three patents granted in June, covering regeneration methods.

Meanwhile, Unilever researchers involved in the company's palm oil cloning program say that program has been set back temporarily. In 1986, cloned trees planted in 1983 began to produce abnormal flowers and fruits, according to Lloyd Jones, a scientist with Unilever's Colworth Laboratory in England.

The cause of the abnormalities has not been determined, but Jones said researchers believe there was a problem in the scale-up from lab to factory production. "Field tests on clones produced in the lab went well, but when we went from lab to scale-up, problems occurred." Noting that the company has altered its scale-up procedure, Jones added, "It will be three to four years before we can check this generation to determine if the flowers are normal."

The company has built a plant capable of producing 300,000 tree clones per year, but production has been reduced, Unilever's Robert Shields said. Currently, the only sales of cloned trees are within Unilever.

Other research groups also are experiencing problems with abnormal fruiting in cloned oil palm.

While many biotechnology companies focus on altering plants to obtain desired oil and seed qualities prior to processing, some firms have shown interest in using enzymes to change oil characteristics during processing.

Results from a U.S. Department of Agriculture (USDA) Lipid Bioconversion Workshop, held in June 1986, indicate that the fats and oils industry is interested in using enzymes in applications ranging from selective hydrolysis to interesterification. Industry participants expressed particular interest in using enzymes to split specific fatty acids, hydroxylate acyl chains, shorten chains to produce C-12 lengths, produce 12-OH stearic acid, split fish oils, and di-hydroxylate epoxy groups.

Even though industry may be interested in using enzymes, no company is using lipases for hydrolysis and interesterification. Commercial-scale viability has yet to be demonstrated, according to George Abraham, a biochemical engineer at USDA's Southern Regional Research Center.

One application in which there is considerable interest is the derivation of cocoa butter from less expensive raw materials. "People have been trying unsuccessfully for 30 years to economically produce a cocoa butter equivalent from less expensive oils using metal catalysts, but now it's being done using lipases," Abraham said. Unilever, in Great Britain, currently has in operation a semicommercial-scale plant which uses palm oil, and researchers at the Southern Regional Research Center are developing enzyme processes for making cocoa butter equivalent from domestic vegetable oils.

Industry experts say factors limiting the widespread industrial utilization of lipases are cost and lack of availability of lipases to meet specific needs.

At least two factors contribute to the cost of using lipases, Abraham said. Their production, separation and purification are very complex. They also are a delicate catalyst; they denature easily and can be lost in the reaction products. In order to cut down on catalyst loss, lipases need to be held immobile on some type of support which would allow fats and oils to pass through them over and over again, Abraham said.

Michael Haas, a researcher at USDA's Eastern Regional Research

Center, said that although industry may want a certain enzyme, it simply may not be on the market. Of those available, not all are fully characterized as to functionality; some, he said, are produced without a complete understanding of what they do. "There's no real biochemical database for lipases—only a handfull have been fully characterized."

Before widespread industrial use of enzymes occurs, there are other research problems to work out, Abraham said. Probably one of the most difficult scale-up problems, especially when moving a reaction from a beaker-sized vessel to a 75,000-gallon vessel, is mass transfer, according to Abraham. "Mass transfer involves putting the oil, water and lipase in proper orientation to each other at the right time to get a reaction. Once the three are together and react, the lipase must be made available for the next molecules to react." He explained that while mixing helps solve mass transfer problems, it also generates heat and shear forces which denature enzymes.

Some researchers believe better integration between the fields of biology and chemistry is the only way to solve some of the problems related to using lipases in oleochemical processing and modification.

"It will take protein engineering to get the kinds of enzymes we want, because enzymes were designed for biological systems rather than chemical ones," A.J. Poulose said. Both Poulose and Michael Arbige, researchers at South San Francisco-based Genencor Inc., believe that all enzymes used on an industrial scale in the future will be "built" for a particular need.

"The breakthroughs will come when enzymes are designed to suit chemical environments. The potential for these kinds of enzymes is unlimited. Traditionally (in industrial applications), we have changed the chemical environment to suit the enzyme," Arbige said.

Genencor's plan is to create enzymes capable of working in particular environments. The company's most recent accomplishment is the isolation and cloning of a Pseudomonas lipase whose characteristics have been altered to favor transesterification reactions over hydrolysis.

The work is based on the company's earlier work on the protease subtilisin. With the subtilisin model, Genencor researchers showed that by substituting certain amino acids in the hydrolytic enzyme, transesterification reactions were favored over hydrolysis.

The company also has isolated a membrane-bound lipase from *Aspergillus oryzae* which speeds cheddar cheese aging through the hydrolysis of triglycerides of intermediate length.

Arbige estimated that approximately $400 million worth of enzymes were sold last year, with lipases making up about 3% of enzyme sales. Food applications such as emulsification and flavor development are by far the dominant usage for lipases. If lipases were used on a larger scale in the fats and oils and detergent industries or in the development of health care products, sales could increase by orders of magnitude, Arbidge said.

Measuring "success" in the business

The relative "success" of biotechnology companies is not measured by the size of their balance sheets. Instead, industry representatives say the worth of a company is measured by the potential of the techniques it uses, the caliber of its scientists and its marketing capabilities.

To date, few companies have registered a profitable year. Estimates in *Biotech 86: At the Crossroad*, an Arthur Young survey of the biotechnology industry, indicate that, on average, agritech firms showed a pre-tax loss in excess of $2.5 million. In fiscal year 1986, the publicly held Calgene Inc. showed a net loss of $905,000, an improvement over the $4.3 million lost in 1985. The Davis, California company had its first profitable period during the second quarter of 1987. Privately held companies also are reportedly narrowing their losses.

Although many biotechnology companies have no products to sell, they can improve their financial picture by making contract or collaborative research agreements with companies seeking the talent and technologies they have, according to Steven Burrill, chairman of the Arthur Young High Technology Group, which advises such biotechnology firms as Genentech, Cetus and Calgene.

"Synergy is the guts of the issue," Burrill said. "The scientific tools at the disposal of biotechnology companies and a business partner's ability to manufacture and market can create a powerful combination."

Calgene has nearly a dozen collaborative agreements with companies such as Nippon Steel Corp., Japan; Proctor & Gamble, U.S.; Kemira Oy, a Finnish chemical company, and Rhône-Poulenc, Agrochimie, a European chemical company. For Procter & Gamble and Nippon Steel, Calgene will develop specialty rapeseed oils. Agreements with the other two companies involve development of herbicide-tolerant crops. Sungene Technologies Corp., in Palo Alto, California, has agreements with Lubrizol Enterprises to produce specialized sunflowerseed oils.

"Our safety net, from a business point of view, is a broad-based portfolio which includes the operation of profitable businesses," Robert Goodman, executive vice president of research and product development at Calgene, said, noting that Calgene has acquired an oil marketing company and a seed company. "We're most enthusiastic over arrangements where we can sell products, get royalties and keep the ownership of the technology," he added.

According to Wallace Beversdorf at Allelix Inc. in Canada, "Biotechnology companies gain credibility

According to Terry Gallagher, sales manager for Amano International Enzyme Co., the soaps and detergents industry has specific lipase needs. The company has 15 lipases available; three are for detergents, but those are not well suited for certain types of detergent mixtures. The biggest obstacle so far is producing a surfactant-resistant lipase, Gallagher said.

One of the Japanese-based company's research interests is developing an alkaline lipase that does not need calcium to become activated and which would function between pH9 and pH11 for granular formulations, and between pH7 and pH8 for liquids. Gallagher said the company would like to have that enzyme within a year. "The lipolytic enzymes for detergent purposes possess the greatest market potential for Amano and also offer us our greatest current challenge.

Other enzyme industry representatives said the soaps and detergents industry needs lipases that will remain thermally stable at 60-70 C and that can work at varying water hardnesses. "If anyone had a truly suitable lipase for the soap and detergent industry, the industry would be beating down doors to get it," according to Michael Crossin, marketing manager for Gist-Brocades.

Although there are enzymes available for particular applications, some enzyme producers said it has been difficult to convince different industries that they could take advantage of the available technology. "Part of the problem (in convincing industry) is we don't know enough about the real cost comparison between chemical fats and oils modification relative to enzymatic modification," Carl Miller, a Novo Laboratories researcher, said.

While enzyme sales have maintained a steady growth, Miller said, "The use of enzymes hasn't increased in industry at nearly the same rate as the number of new players in the game." When the immobilized enzyme used in converting corn syrup to fructose began to show profitability, other companies showed more interest in enzyme development; the promise of the technology was enough to increase competition, Miller said.

Although profits are low and competition is growing in the burgeoning industry, Burrill believes that the long-term potential for biotechnology will be immeasurable. "However, the industry is still young. A lot of scientific research is being done to develop new products, and work is being done to determine what the markets are. There are still many unknowns; it's not like established industries," Burrill said, adding, "If you were a shoemaker, for example, you would know there was a market for shoes, and you would know how to make the shoes. In the biotechnology business, no one is exactly sure what the markets are or how the products will perform."

and market access when they make agreements with larger, more mature companies." He believes the agreements also are a good way for small biotechnology companies to learn about market demands, marketing and product development.

Not beneficial are contract research agreements which take the company away from its particular goals, according to William Scowcroft, vice president of research and development at Biotechnica Canada. "We don't have time for straight contract research. At the end of the day, the contractor walks away with all the work you've done. No additional revenue comes in."

Current estimates from Arthur Young indicate that the young agritechnology industry obtains about 30% of its revenue from contract and collaborative research, while research and development uses nearly 42% of the operating budget. One industry spokesman said research and development make up nearly 70% of his company's operating budget.

While research costs remain high and profits are low, the losses (in the biotechnology business) are not necessarily troublesome, Burrill said. "By spending for research, a company is building its greatest asset. Historical accounting doesn't really measure this creative value."

Although biotechnology companies have been very successful at raising money to fund research, their success is going to depend on products that suit the market, according to Ray Dull of Experience Inc., based in Minneapolis. "Many biotechnology companies have designed their goals around technology that they then sell to the investment companies. What they've been hyping is what investors find exciting rather than what the market will bear," he said.

Dull believes companies need more market-justified planning. Problematic in the oilseed market are the factors which drive the oil and meal complexes. "What would happen, for example, if you changed the oil content of soybeans? Right now, soybeans are a meal-driven commodity, but if biotechnology could push the value of oil up, we'd have to deal with meal surpluses," he pointed out. When oilseeds are manipulated, more consideration has to be given to the factors which would affect both commodities, he explained.

Measuring a biotechnology company's health is difficult, "but by the end of the year, we'll see some kind of a shakeout," Dull said. "There's increasing pressure, particularly on smaller companies, to show a revenue flow. R&D partners are starting to ask, 'When are we going to get around to making money?'"

Biotechnology companies, however, have indicated they are willing to wait for profits. Most predicted that the industry would not be truly profitable until the late 1990s or the turn of the century. "Give us until 1993 to show what we've got," Calgene's Goodman said. "We envision ourselves doing $100 million worth of business by then."