cosmetics and food supplements. Marc Rivière, Æterna's vice president of clinical affairs, says that laboratory studies showed the substance (which the firm calls Neovostat) blocked blood-vessel development, suggesting it would block tumor growth, and that in small-scale human studies, those receiving a higher dose of Neovostat experienced less tumor progression and weight loss than did those taking lower doses. The trial will combine cartilage treatment or a placebo with a standard regimen of chemotherapy and/or radiation.

Although Neovostat is considered a drug and thus must be approved by the FDA, more than a dozen other versions of shark cartilage labeled as dietary supplements are exempt from FDA scrutiny and available in supermarkets and health food stores.

Other expansive trials include a study co-sponsored by the National Institute of Mental Health and NCCAM to determine the effectiveness of St. John's Wort in curbing depression, as well as another NCI/NCCAM trial examining the effects of a complex nutritional regimen on pancreatic cancer. "We're concerned about the wide use of these remedies," says Varmus. "The NIH has a public health responsibility" to determine which substances might work and which ones are potentially toxic.

Although the center's scientific mission is clear, the need for a higher profile is open to debate. "We could have done this through the existing office," says Varmus. But in a floor speech advocating creation of the center, Harkin complained that the office had no control over its grants process and that alternative medicine specialists were conspicuously absent from the peer-review panels passing judgment on alternative medicine studies.

Now that the center is a fait accompli, Varmus hopes to put it on a solid scientific footing. His first move will be to appoint a new director. OAM's chief, Wayne Jonas, who has been criticized for a dearth of results during his tenure, stepped down this month after 3 years to return to family practice at the nearby Uniformed Services University of the Health Sciences. Varmus says he's looking for a "serious scientist" to lead the center—one with strong credentials in clinical trials and experience with alternative medicine. Jonas and other NIH officials say that any center-funded study must use randomized trials with placebos whenever possible. Center officials pledge that will happen, but outside critics say that OAM's record should have been thoroughly reviewed before Congress spent more money on alternative medicine and elevated its status. They contend that the office, in an effort to distribute funds broadly, conducted small trials that lacked placebo groups. "Clearly the political push for expanding [the office] into a center didn't want to wait for any critical review," says Nobel prize–winning biologist Paul Berg of the Stanford University School of Medicine.

Nevertheless, Berg and Goodenough both say they would support rigorous clinical trials of treatments such as acupuncture, homeopathy, and herbal therapies. As Varmus puts it: "I think there's a lot to learn; there's probably a lot to debunk."

—JENNIFER COUZIN

BIOTECHNOLOGY

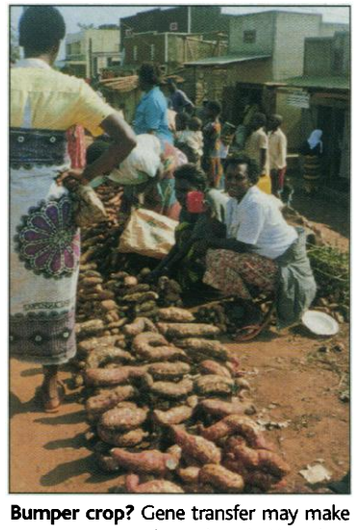
Toting Up the Early Harvest Of Transgenic Plants

Many plants sporting foreign genes are winning big and others show promise, but some efforts to develop new plants are lagging

In the early 1980s, after centuries of improving their crop plants and domestic animals the old-fashioned way—by breeding in desirable traits—agricultural scientists took a big step. They decided to circumvent the uncertain, and often lengthy, standard breeding process by using the tools of modern molecular biology to introduce genes into plants and animals for the traits they wanted. Some 15 years after the first such gene transfers, 700 researchers and policy-makers from 30 countries attended the Second Agricultural Biotechnology International Conference, held last summer in Saskatoon, Canada, to assess the fruits of their past labors and look ahead.

Although researchers have had some success in genetically modifying animals, especially in producing sheep or cows that make medically valuable human proteins (see sidebar), most progress so far has been with plants. For example, several major crop plants, including corn, oilseed canola, soybean, and cotton, have been engineered with genes that make them resistant to insect pests or to the herbicide glyphosate, so that the weedkiller doesn't threaten the crop.

Such transgenic plants have met opposition in many European countries because of fears that they may be unsafe for the consumer, damage the environment, or lead to further, costly surpluses (*Science*, 7 August, p. 768). But they are winning acceptance in other countries, including the United States, Argentina, China, and Canada. During this past growing season, at least 30 million hectares worldwide were planted with the modified crops. As a result, more than one-half of the world soybean harvest and about one-third of the corn harvest now comes from plants engineered with genes for herbicide or disease resistance. These commodities find their way into hundreds of foods, such as breakfast cereals, cooking oils, corn syrup, soft drinks, and candies.



Bumper crop? Gene transfer may make sweet potatoes, shown here in Uganda, a better protein source.

CREDIT: C. S. PRAKASH

"The speed of commercialization of agribiotech applications has taken many by surprise," says Anatole Krattiger, executive director of the International Service for the Acquisition of Agribiotech Applications in Ithaca, New York. He adds that for industrialized nations, agbiotech can increase the efficiency of producing existing crops by reducing the need for pesticide applications and other costly treatments; in developing, food-short nations, it can increase yields, essentially without the cost of additional inputs, such as pesticides. And a few genetically modified plants that promise entirely new products—including some that make ingestible vaccines for human diseases and at least one, sweet potato, with an improved protein content—are moving through the pipeline.

But not all efforts to genetically engineer plants are going smoothly. Researchers are running into trouble in their efforts to transform conventional crops into factories for high-value novel products, such as a "natural" cotton/polyester blend grown by cotton plants, or for substances traditionally supplied by synthetic chem-

Down on the Animal Pharm

Although cloned sheep and cattle have just recently caught the public and scientific imagination, agricultural researchers have in fact been tinkering with the genes of livestock for at least a decade. Unlike much of the genetic engineering done on plants, which is aimed at making them more productive or more nourishing (see main text), the goal is to turn sheep, cattle, goats, or other livestock into pharmaceutical factories on the hoof for valuable human proteins.

Getting the necessary genes into the animals is a painstaking and inefficient process, however, which explains part of the appeal of cloning: It should make it easier to duplicate the rare animals in which the gene transfer has succeeded. But even without cloning, researchers have developed herds of sheep and other animals making human proteins, some of which are in advanced clinical trials. "Recombinant protein therapeutics from animals will reach the marketplace soon," says molecular biologist Jeffrey Turner of Nexia Biotechnologies in Quebec, Canada. And, he adds, "they will offer significant cost savings."

One protein already being harvested is alpha-1-antitrypsin, which inhibits elastase, an enzyme that helps break down connective tissue and is found in excess amounts in the surface fluid of the lungs of cystic fibrosis patients. Alpha-1-antitrypsin is being tested as a potential treatment for this disease, but it is very expensive to obtain from its current source, human serum. To develop a cheaper supply, researchers including Ian Wilmut at the Roslin Institute, Edinburgh (the same group that cloned the sheep "Dolly") introduced the human alpha-1-antitrypsin gene into a sheep about 10 years ago. The goal was to develop a herd of animals that would secrete the protein into their milk so that it could be easily obtained.

Early on, skeptics wondered whether the transferred gene would be transmitted to successive generations and, if so, whether the animals would produce the protein in biologically active form and secrete it in sufficient quantities to make recovery practical. But all these hurdles have been cleared. Indeed, "Tracy," the first sheep transformed with the alpha-1-antitrypsin gene, now has 800 granddaughters, and some are producing enough of the protein—from 13 to 17 grams per liter of milk—for it to be undergoing clinical trials in cystic fibrosis patients in the United Kingdom.

Other human proteins made in animals are also undergoing clinical testing. After proving that the anticlotting agent human antithrombin III produced in goat's milk is safe when administered to humans, Genzyme Transgenics Corporation of Boston, which produces the protein, has begun clinical trials in the United States and Europe to test its efficacy as an anticlotting therapeutic in coronary bypass patients. Also in the pipeline, although at an earlier stage of development, are various vaccine proteins and monoclonal antibodies that might be used for treating diseases such as cancer.

What's more, getting genes into livestock may be much easier in the future, thanks to a new technique reported just last month by Robert Bremel, formerly of the University of Wisconsin, Madison, and now managing director of the biotech firm Gala Design in Sauk City, Wisconsin, and his colleagues (*Science*, 27 November, p. 1619). By introducing the foreign genes into cow oocytes still undergoing meiosis and fertilizing them later, the researchers were able to increase the gene transfer efficiency from the current 10% or less to nearly 100%. A new field of agriculture, livestock "pharming" may turn into a lucrative business for 21st-century farmers. **–A.S.M.**

istry, such as plastics. And sometimes even successful genetic transformations can be stymied by practical concerns.

Take the Flavr-Savr tomato, genetically engineered by the biotech firm Calgene Inc. of Davis, California, with a so-called "antisense" gene that slows down the activity of polygalacturonase, an enzyme that degrades cell walls. By inhibiting rotting, this change allows the fruit to ripen on the vine instead of being picked green and hard. But the Flavr-Savr tomato had to be pulled from the market, mainly because conventional tomato-picking and packing equipment damages the soft, naturally ripened vine fruit.

Keep it simple. The modifications that have worked best are the simplest: those that can be accomplished by introducing just one or a few foreign genes into a plant, with minimal effects on its physiology. For example, researchers made plants resistant to the herbicide glyphosate by transforming them with a natural bacterial enzyme that is highly resistant to the herbicide, while insect-resistant plants are created by adding the gene for one of the toxins produced by *Bacillus thuringiensis*, a type of bacterium that infects and kills insects. This can pay off economically. In 1997, in U.S. corn belt states, corn transformed to express a BT protein had a 7% increase in yield per acre, bringing the farmer, on average, an increased net return per acre of $16.88.

Buoyed by these successes, researchers are now expanding their efforts. One goal is to use genetic engineering to enhance food quality. Early indications are that some of these attempts will work, particularly those involving the manipulation of only one gene. At the meeting, for example, C. S. Prakash of Tuskegee University in Alabama described progress in improving the quality of the proteins made by sweet potato, an important, easy-to-grow food crop in areas such as the poorer countries of the tropics, where high-quality protein foods may be hard to come by. Prakash inserted into sweet potato plants a synthetic gene coding for a storage protein that has a high content of the so-called essential amino acids, ones that the human body can't make for itself.

Early on, Prakash worried that the energy drain imposed by synthesis of the foreign protein would reduce the harvests of the transgenic sweet potato plants, but his fears proved unwarranted. Although the protein content of two strains of the genetically engineered plants increased by 2.5- to 5-fold, the first field trials in Alabama during the summer of 1997 showed, if anything, a slight increase in yields. The transgenic plants produced between 64 and 68 bushels per hectare, compared to the control plants' 61 bushels per hectare. "We had a bountiful harvest," Prakash says.

These transgenic potatoes are not yet in commercial production, as researchers are just beginning to assess their nutritional quality. A first feeding trial on hamsters looks promising, though. Animals fed the transgenic, high-protein potatoes weighed 56% more than controls after 28 days and showed no evidence of any toxic effects.

Other efforts are aimed at getting plants to make commercially useful products. For example, at the Hebrew University in Jerusalem, Joseph Hirschberg has induced tobacco plants to make a carotenoid pigment called astaxanthin, which can be used to tint flowers, farm-raised shrimp, and salmon and, when fed to chickens, can color egg yolks a vibrant orange. Currently, astaxanthin is extracted from seashells or synthesized chemically and carries a price tag of about $2600 per kilogram. But Hirschberg's efforts may help bring that price down.

He has taken a gene from a green alga (*Haematococcus pluvialis*) that codes for a ketolase enzyme and introduced it into tobacco plants. There the enzyme converts betacarotene to a compound called canthaxanthin, which the plants' own enzymes can use to make astaxanthin. "We've shown that

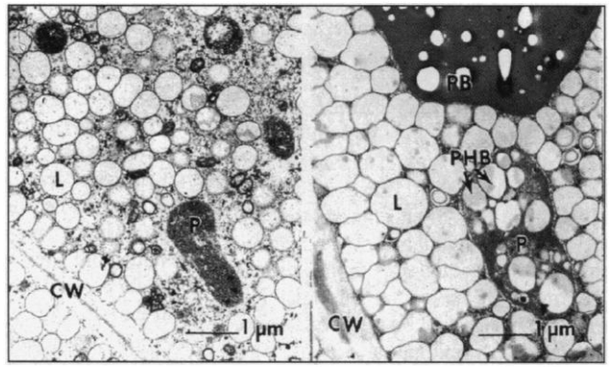
all you need is one enzyme to redirect biosynthesis" to astaxanthin, says Hirschberg. High levels of the chemical accumulate in the flower's nectary, from which it can be extracted. Hirschberg says the transgenic system has been licensed to European food and feed firms.

Still in development are plants that would produce edible vaccines. These could be a big help in the Third World, where the cost of transportation, the lack of refrigeration, and the hazard of using needles can make conventional vaccine administration impractical. Edible vaccines might be used, for example, to protect against diarrhea, a major cause of infant mortality in developing countries.

At the conference, Hugh Mason and his Boyce-Thompson Institute (BTI) colleagues reported on their efforts to protect against two diarrhea-causing pathogens: the bacterium *Escherichia coli* and Norwalk virus. In one set of experiments, the researchers introduced the gene for an *E. coli* protein into potatoes, which made the protein. When eaten raw by volunteers at the University of Maryland School of Medicine in Baltimore, the modified potatoes induced production of antibodies to the protein. The researchers now hope to do clinical trials in which the immunized volunteers will be given the disease-causing form of *E. coli* to test whether the antibodies can in fact protect against diarrhea. The work with Norwalk virus isn't as far along, but the BTI group has introduced the gene for a viral coat protein into potatoes.

And complementing this work, in the October issue of *Nature Biotechnology*, William Langridge and his colleagues at Loma Linda University in California report that it might even be possible to use transgenics plants to make an edible form of the hormone insulin. They introduced into potatoes a hybrid gene that produces human insulin fused to a cholera toxin subunit, which directs the insulin to lymphoid tissue in the gut. This allows animals to build tolerance to the insulin, suppressing the animals' inappropriate immune response to the protein. Feeding the transgenic potatoes to mice with a genetic form of diabetes delayed the onset of symptoms by 4 to 8 weeks.

Plants may also be used to mass-produce expensive monoclonal antibodies that, after appropriate modification, such as sugar addition, might be used to treat various ills. For example, in the December *Nature Biotechnology*, Kevin Whaley of Johns Hopkins University and his colleagues report that antibodies made in soy plants prevent infection of mice by the genital herpes virus, and Julian Ma of Guy's Hospital, London, has previously used antibodies made in tobacco to deter the bacterial infections that often result in tooth decay. Antibodies produced by plants should be less expensive and perhaps safer than those made in mice and other animals.



Plastic plant. A plastid (P) in transgenic canola seed (right) contains the plastic PHB, while there is none in a control seed's plastid (left).

Green factories? Although these simple gene modifications are succeeding, more complex manipulations are proving harder to pull off. One hope, for example, was that plants could be used to produce plastics, such as polyesters, now synthesized from nonrenewable sources such as petroleum products. Early results looked promising.

The work made use of the fact that many bacteria synthesize and store natural, biodegradable polyesters, such as poly-3-hydroxybutyrate (PHB). However, large-scale bacterial production of this class of natural polyesters seemed impractical and costly, in part because fermentation equipment the size of several breweries would be needed to produce commercially significant amounts. But only three genes are required to make PHB, and Chris Somerville of the Carnegie Institution of Washington at Stanford was able to transfer all three into the plant *Arabidopsis*. The plants transformed with the gene made some PHB, but they were sickly, for reasons not clearly understood.

Somerville and his colleagues solved this problem about 4 years ago by adding a targeting sequence to the genes that directs the expressed biosynthetic enzymes to the chloroplasts of the plant cell. The result was much higher PHB production and relatively healthy plants. Researchers believe that this tinkering helped because the chloroplast is the major biosynthetic factory for the plant cell and, thus, better designed for polymer production. Unfortunately, PHB is too brittle to be commercially useful.

More recently, Monsanto polymer biochemist Ken Gruys and his colleagues induced both *Arabidopsis* and canola to produce a copolymer of PHB and poly-3-hydroxyvalerate (PHBV) by transferring four genes into the plants. This material, which is much more pliable than PHB, has been produced commercially by fermentation. Biochemist William Page of the University of Alberta says, however, that even if these efforts succeed, extracting the plastic is likely to be difficult. As a result, he says, "the savings of producing polyester in the field may be lost in extraction."

In a different effort to make bulk commodities in genetically engineered plants, Maliyakal John and his colleagues at Agracetus (now part of Monsanto) transformed cotton plants to synthesize polyester in the hopes of producing a natural polyester/cotton blend. But they too have hit an impasse. The researchers have been unable to get the polyester genes expressed in the boll, where the cotton is made, and the project has been put on a back burner. To revive the idea, researchers will need a better grasp of how cotton plants direct synthesis of proteins to specific locations, such as the boll.

Indeed, how plants regulate gene expression is one of the big issues researchers need to grapple with, especially if they try to develop improved plant varieties by tinkering with large gene clusters, such as the packets of genes that direct nitrogen fixation or photosynthesis. So far, researchers have done little with these systems, because, says BTI president Charles Arntzen, "they're too complicated." But that doesn't mean researchers have given up—just that they will need to understand the systems better to try to identify modifications that might improve their efficiency. Says Kenneth Gruys, "What seems routine now, such as transforming a plant with a single gene to yield a new commercial product, was deemed extremely difficult not that long ago." Successful manipulations of multiple genes will be realized, too, he predicts. **–ANNE SIMON MOFFAT**

AREA OF TRANSGENIC CROPS PLANTED (MILLIONS OF HECTARES)

Country	1997	1998
U.S.A.	8.1	20.5
Argentina	1.4	4.3
Canada	1.3	2.8
Australia	0.1	0.1
Mexico	<0.1	0.1
Spain	0.0	<0.1
France	0.0	<0.1
South Africa	0.0	<0.1
Total	**11.0**	**27.8**

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