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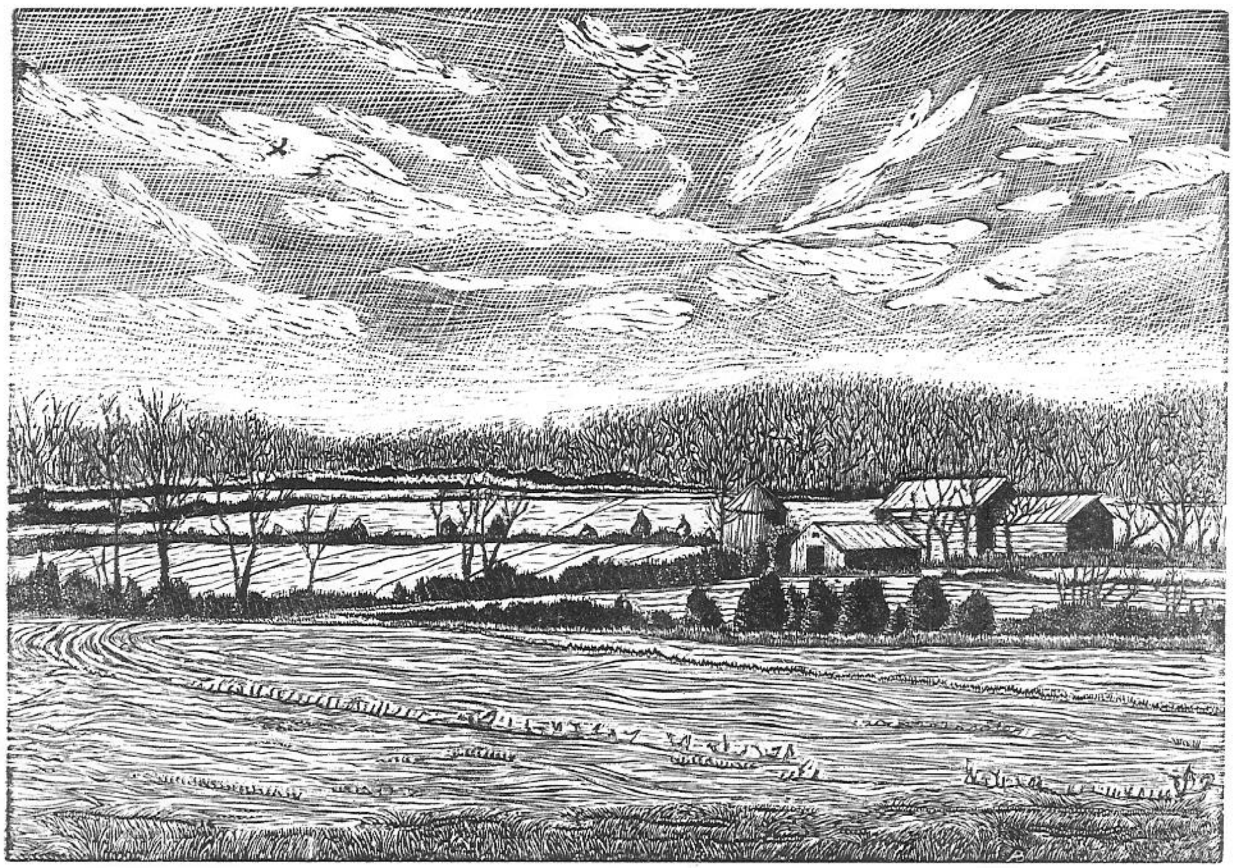

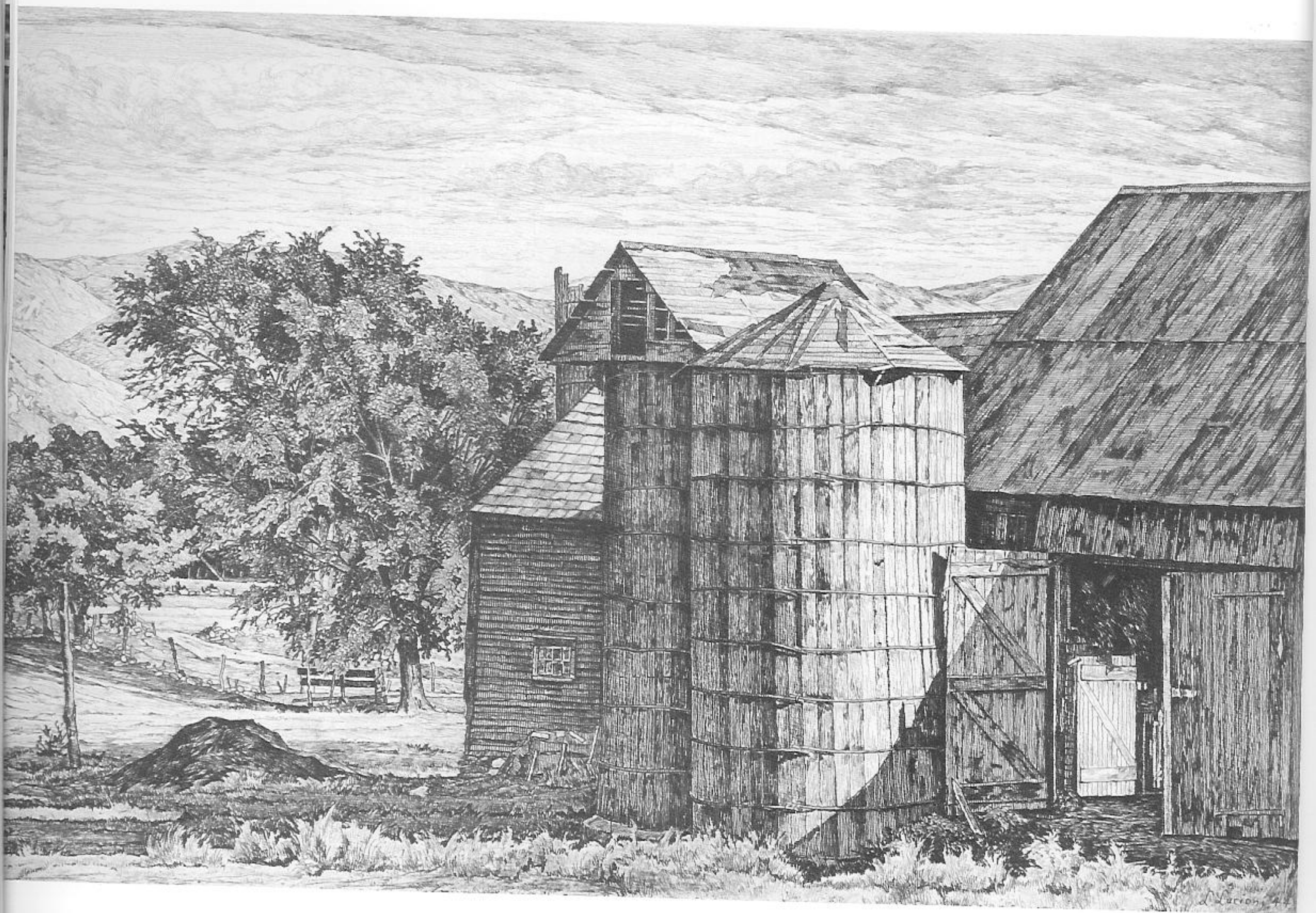

"Late Shadows," by Luigi Lucioni, 1944. Etching, 8¾ by 13¼ inches. Courtesy of Bone Creek Museum of Agrarian Art, gift of Dr. Stuart and Lynn Embury, 2008.18.1.

BIOTECH WITHOUT FOREIGN GENES

PAUL VOOSEN

For the past two decades, promises of crop improvement have been the domain of genetically modified plants: mostly, crops supplemented with bacterial genes to resist pests or weed-killers like Roundup. More than 85 percent of U.S. corn, soy or cotton grown contains such genes.

But there is more than one way to transform a plant.

Using advanced biotechnology, long hidden in the background and only now starting to pay dividends, scientists are changing crops without tapping foreign genes – and often without the regulatory oversight that is given to GM crops.

Many of these crops use latent effects of genes squirreled away in discarded seed varieties to create breeds that at first glance seem artificial. There is corn so infused with vitamin A precursors that it practically glows orange, rice that can survive more than two weeks of flooded conditions, and wheat that resists the advance of devastating aphids.

Such specialized crops are possible because researchers are mastering the science of breeding. Using techniques collectively known as molecular breeding, geneticists have started to return results in a variety of plants, said Ed Buckler, a plant geneticist at Cornell University who recently helped sequence the corn genome.

"We know that old-fashioned good breeding works," Buckler said. "And a lot of that is an intelligent numbers game" based on genetic theories elaborated by Gregor Mendel more than a century ago. Molecular breeding, he added, "is now a way to do that much faster."

Increasingly affordable with improved technology, molecular breeding is becoming the mode of business in the crop world, said Bonnie McClafferty, development head at HarvestPlus, a nonprofit funded by the Bill & Melinda Gates Foundation that supports molecular breeding research into improving plant nutrition in Africa and Asia.

"People don't understand that we're not working with Gregor Mendel anymore," McClafferty said. "The science is advancing, and there's a whole variety of tools to use."

In fact, molecular breeding is only the start of a bewildering diversity of biotech approaches to crop development that defy the conventional notion of splicing foreign genes into plants. This next generation could shake up what has become a stalled debate – call it the Roundup Ready stalemate – by introducing GM crops that, for example, use only their species' native genes or have the expression of their own genes silenced.

While the techniques draw from the same pool of knowledge, and travel together in scientific circles, many environmental groups do not oppose molecular breeding, while stridently critiquing current GM crops, according to Marco Contiero, the European biotech policy director for the environmental group Greenpeace. "Genetic engineering is just a part of modern biotechnology," Contiero said. "We are against this specific application. We are not against marker-assisted selection."

Most scientists believe that molecular breeding and advanced genetic modification will eventually form a powerful tandem, said David Baulcombe, a professor of botany at the University of Cambridge and the chairman of a recent report issued by the United Kingdom's Royal Society on the future of agriculture.

"Within genetic modification, you've got to remember there's a whole bunch of technologies," Baulcombe said. "There's GM where you move plants' genes around. GM where you use artificial genes to silence gene expression. And then there's the technology that is out in the field now in which bacterial genes have been moved into the crop."

For thousands of years, crop breeding remained much the same: Farmers crossbred plants with desirable traits like high yield, as often as not reproducing those traits in offspring. Mendel clarified the situation, but conventional breeding practices today, though stirred by developments like the green revolution's hybrids, would remain roughly familiar to farmers of a century ago.

Molecular breeding has, to some extent, overturned this framework, even prompting some scientists to call for new, post-Mendel theories of breeding. The techniques rely in principle on the increasing inventory of genes that have been identified as influencing, if to a limited degree, traits in plants. For some genetically simple crops, like rice, these clusters of genes have strong effects, while the genes of more complex grains like corn and wheat have been more difficult to pin down.

Most simply, once these genes, or bits of DNA tied to the genes (known as markers), have been identified, molecular breeders can quickly target offspring inheriting the genes for further development, cutting breeding time and improving the crop's "genetic gain," the generational improvements made to a crop, like increased height, by human selection.

To little public notice, the world's largest seed companies, such as Monsanto Co., Pioneer Hi-Bred International Inc. and Dow AgroSciences LLC, have used molecular breeding to improve their seed varieties in parallel with genetic engineering. At Monsanto, the practice has become so common that, in a recent paper, the firm said "molecular marker assisted breeding is becoming our conventional breeding process," noting that many of its commercial crops are derived with the process.

A company like Pioneer is well aware of the expense and European resistance to genetically modified, or transgenic, crops. They will exhaust molecular breeding options before turning to GM, said John Soper, Pioneer's soybean research director.

"Both transgenics and the use of markers have risen in priority. ... It's been a very exciting time for us," Soper said. "I still think it's kind of the tip of the iceberg on both of these issues."

Markers are also being used to breed traits from otherwise discarded varieties back into cultivated crops. A well-known breeding technique called backcrossing has become far more potent recently, as markers have allowed scientists to locate rare offspring that retain only the desired – and now detectable – genes from orphan crops. Previously in backcrossing, many other genes would also migrate from the orphan plant, reducing yield or taste, to farmers' dismay.

At least one trait added with molecular breeding has already been introduced in

Asia and Africa: New varieties of rice that resist flooding damage are now being adopted in India, Bangladesh and Southeast Asia. And corn rich in vitamin A precursors is being targeted for release in Zambia by HarvestPlus.

Crops made with molecular breeding are not classified as genetically modified, since the first step in their development is pollination – an important distinction. Yet they would be nearly impossible to create without genetic engineering used to evaluate gene function, said Nora Lapitan, a wheat geneticist at Colorado State University.

Recent innovations have made it easier than ever to "knock out" or silence the expression of selected genes. This gene loss can then, in some rare cases, cause large enough changes to demonstrate a genetic function that can be targeted. These are bedrock trial-and-error experiments, Lapitan said. "It's really classic," she said.

On its own, gene silencing is also being used to create GM crops. Pioneer used the method for soybeans that produce oil with no trans fats, the type of consumer-focused GM improvement seed companies have long promised but failed to release. Many other applications are arising – for example, Lapitan's lab discovered that inhibiting one gene can broaden wheat's resistance to the devastating Russian wheat aphid.

Sometime in the near future, it is reasonable to expect that crop genes could be more easily shifted between species – say, adapting the efficient photosynthesis of corn to rice. But even discounting this future, scientists can now move genes within crop varieties, essentially accelerating a natural process, Cambridge's Baulcombe said. It is an open question whether such modification should be considered equal to introducing bacterial genes.

Increased public-sector involvement in crop development – much of which has been ceded to companies over the past decades as seeds evolved into patentable commodities – will be needed to apply increasingly cheap biotech improvements to subsistence crops like cassava, for example, Baulcombe said.

"For many of those [crops], there may not be an incentive for companies to get involved," he said.

Such innovation is required. Food security will be one of the pressing issues of the next half-century as the world's population rises by several billion. That many hungry mouths will necessitate higher yielding and better crops, and advanced GM crops will need to be a part of this mix, the Royal Society said.

However, since many developing nations lack the apparatus to regulate GM crops, molecular breeding may be the quickest way to carve out immediate gains for at-risk populations, like frequently flooded rice farmers in Asia, scientists say.

Asian rice farmers get little warning before floods.

More than 3 billion people in the world depend on rice as their primary food, and nearly one-fourth of the world's crop is grown in rain-fed lowland plots prone to seasonal and sustained flash floods. Even the most common, hardy varieties of rice will die after four days spent underwater. Each year, lowland floods in South Asia destroy 4 million tons of rice, causing chronic food insecurity for subsistence farmers across the region. More than 15 million hectares – an area the size of Bangladesh – is commonly stricken, and the lost rice is enough to feed 30 million people, said Pamela Ronald, a plant geneticist at the University of California, Davis. Now imagine if this rice could maintain its traditional qualities, like its robust yield, but could survive flooded conditions for weeks. "[That] rice has the potential to fill this incredibly huge gap," Ronald said.

Using molecular breeding, Ronald and Dave Mackill, a crop scientist at the International Rice Research Institute in the Philippines, have done just that, developing multiple strains of rice that can survive for more than two weeks in flooded conditions. Varieties of the submergent-resistant rice – nicknamed "scuba rice" – have already been introduced in India and the Philippines, with expansion into Bangladesh expected within a month, Mackill said.

The mass deployment of scuba rice is the culmination of more than a decade of research for Mackill, who long ago identified a gene in rice's DNA, known as Sub1A, that seemed to strongly influence how a weedy but flood-resistant rice variety in India – rejected because it had a low yield and poor taste – could survive so much longer than normal varieties. With molecular backcrossing, Mackill, Ronald and their many colleagues were then able to breed this overexpressed gene into rice already popular in India, such as the legendary Swarna variety. Previous attempts to backcross this trait with conventional breeding had always failed, reducing Swarna's taste or yield. "Conventional breeders can only bring in one trait at a time that are very simple traits," Ronald said. The exciting aspect of submergence was that they could bring in what is known as a "quantitative trait locus" – a more genetically complex region that influences measurable changes to the crop. "This is one of the very first instances where we could tackle" such a locus, she said.

Rice has proved to be the best grain to be manipulated with marker-assisted breeding, Mackill said. It has a limited number of genes – it was the first crop to have its genome sequenced, earlier this decade – and the individual genes tend to exert strong influences. Such individually powerful genes can be rare in other plants. "That's one of the most difficult things to find in any crop," Mackill said.

Partly because other grains are not so easily influenced by a few genes, molecular breeding is not as popular in public breeding circles as was hoped a decade ago, when it first arose. Besides scuba rice, most other published applications have been used for disease or pest resistance, which are genetically simpler to breed.

There are other reasons for this lull. Many genetic markers have only been discovered this decade, prompting Mackill to predict a large increase in molecular breeding next decade. And, he adds, while seed firms like Monsanto and Pioneer have invested heavily in molecular breeding, none of their research has been published, due to competition.

Over the past two years, Pioneer has stressed its use of molecular breeding to improve its soy varieties, most of which are also genetically modified. The base for Pioneer's soybeans is relatively simple, and a lot of natural variation lies outside the varieties typically used, said Soper, Pioneer's soybean research director. "In the future," Soper said, "we'll be using some of these new molecular tools to fish some needles in the haystack that we can pull out."

For a century, individual breeders, scientists and firms have bred crops for their capacity to improve yield – the amount of crop grown. Yield is a far more complex trait than Mackill's flood tolerance. It is not a matter of one or two genes – it takes "dozens if not hundreds of genes to get what farmers perceive as yield," Soper said.

"We've done extensive modeling to find genes that have been selected over time," he said. "Since we know that plant breeders have bred for yield, we have a theory that a lot of the genes have increased in selection over time."

These genes have had tangible yield impacts, some increasing soy's production by up to a bushel. Over the last five years, Pioneer has learned much about these individual genes, and is now probing how they interact, Soper said. "It's not about simply adding genes and stacking them," he said. Combine two genes that separately increase yield, and suddenly the improvements disappear. Add two others together, and the effect doubles. "It's complex," Soper said.

Corn, also known as maize, is genetically complex – its genome, only recently sequenced, was much more difficult to piece together than the human genome. Its genes have been active over the past 5 million years, behaving selfishly and scrambling the genome, giving the crop an incredible diversity, Cornell's Buckler said.

"There is as much diversity between any two maize varieties as between chimp and man," Buckler said. "This is why breeding efforts have been so successful in maize."

Partially because of this complexity, however, the type of molecular breeding used for scuba rice has had limited success for corn. Buckler made this clear in a paper looking at what genes influenced the time corn took to flower, where the many genes surveyed had little impact on the trait.

"There really are no big effect [genes], at least for flowering time," Buckler said. "That has an implication of how we're going to make progress in the future. ... [It] means we can make very powerful predictions, but also means it will be harder to figure out individual genes."

Given the limited power of individual genes in corn, Buckler has established a research method called nested association mapping. His lab grows row upon row of corn in upstate New York, crossbreeding one reference strain – the widely grown B73 – with 25 different varieties. (It took seven years to breed the populations.) These diverse populations, combined with high-powered computation, should allow breeding predictions for a variety of incremental improvements in traits like drought tolerance, nitrogen use, and aluminum tolerance.

Buckler's lab and many others have begun to use what is considered the next step in molecular breeding, called genomic selection. First pioneered by cattle scientists earlier this decade – there is an actual field called "bovine functional genomics" – genomic selection capitalizes on computing power and the large number of markers now available to rapidly make breeding decisions based on every gene influencing a trait, not just a few.

"[It] allows very accurate predictions even with small effects," Buckler said.

Buckler's fields have already helped identify genes that provide a threefold increase in the vitamin A provided by corn, turning ears a brilliant orange. The crop will be used by HarvestPlus in Zambia, part of its effort to develop staples that contain nutritional, and not just yield, improvements.

Buckler, Ronald and others are bullish on the potential of molecular breeding and advanced GM crops. But they remain wary of making predictions of genetic mastery that characterized the field previously. Much needs to be learned about the influence of environment on gene expression, they stress.

Yet it is clear that the promise of genetic engineering and molecular breeding has at least started to catch the hype.

With so many crop genomes sequenced, there is "so much more information that is available now than 10 years ago ... an overwhelming amount," Ronald said. "There's enough to occupy us geneticists for the ends of our lives," she said.

New Jersey Farm - Fall, by Ansell Bray.