Unlocking the Green Pharmacy

We live in an age when research on the human genome promises to revolutionize the way we cope with disease. At such a time, the most traditional of healing systems, plant medicine, would seem to have little to offer. But plants may hold therapeutic benefits far more remarkable than we have yet been able to understand—and modern science may at last have the tools to reveal them.

by Joel L. Swerdlow

The modern Western world, with the United States in the vanguard, is the first culture in recorded human history to abandon plants as the core of its medicine. And why not? When science has begun to read the secrets of the human genome and to hold out the promise of astonishing future medical breakthroughs, of what possible relevance can plant medicine be? But, in fact, we have an extraordinary amount still to learn about the therapeutic value of plants, and our progress in genome research argues, perhaps surprisingly, not that we should abandon plant medicine but that we should join it to modern medical science.

The term *genome*, as now commonly used, means the sum of all chromosomes in an entity. Chromosomes contain genes, and genes, among other things they do, give instructions for the production of various chemicals. As we improve our understanding of plant genomes along with our understanding of the genomes of human beings and disease-causing agents, we will be able to prevent and combat disease in ways hitherto impossible. And, in the process, we will erase the unnecessary and, indeed, harmful distinction between prescription drugs and so-called herbal supplements, many of which are plant medicines sold over the counter.

That advances in genome research should lead us back to plant-based medicine, which is so often dismissed by scientists as primitive and of unprovable worth, may seem absurd. But the seemingly absurd has an honored place in scientific innovation. Jacques Monod, who won the 1965 Nobel Prize in medicine for describing the genetic regulation of enzyme and virus synthesis, has said that scientists often react in two stages to a new idea. Initially they call the idea absurd. Then they call it obvious.

If there is to be a resurgence of interest in plant medicine, we must first acknowledge the extent to which modern medical science has abandoned plants, and we must understand why that has happened.

Americans commonly, and mistakenly, believe that many of our drugs come from plants and that many of those plants originate in the rain forest. The reality is that, of the more than 5,000 prescription drugs the U.S. Food and Drug Administration (FDA) has approved since the early 1960s, fewer than a dozen are based on plants or the chemical formulas derived from substances found in plants. No modern pharmaceutical drug has come from the Amazon River

A Diego Rivera mural depicts Mexican medicinal preparations from pre-Columbian to modern times.

Basin other than the drugs derived from plants that the conquistadors and their successors encountered more than 300 years ago (such as ipecac, coca, and pariera, a component of curare). Rain forests elsewhere in the world likewise have yielded very few new drugs.

We need to recognize what is at stake in our turning away from plants as sources of medicine. The Madagascar rosy periwinkle, for example, has chemicals (isolated by scientists in the late 1950s) that cure most cases of lymphatic leukemia and are also effective against Hodgkin's disease and testicular cancer. Madagascar is home to more than 10,000 known plant species, perhaps 70 or 80 percent of which are indigenous. And yet, no plant indigenous only to Madagascar other than the rosy periwinkle has contributed to any drug approved by the FDA. Why have we not derived two anticancer drugs from Madagascar's flora? Or three? After all, the periwinkle is a flowering plant much like other flowering plants, and if it can be a source of effective medicine, there is every reason to believe that many other species of plants can be as well.

There are some 300,000 known plant species in the world, and that may be only a small percentage of the *actual* number of species. Yet several hundred plants, at most, currently yield drugs produced by the pharmaceutical industry, and fewer than a dozen have yielded anticancer drugs. Because the pharmaceutical industry in the United States spends what experts estimate to be only about one percent of its annual $23 billion research budget on plant-based research, the chances of discovering a significant number of additional plant-based pharmaceutical drugs are small. Pharmaceutical

Vinca rosea (rosy periwinkle)

researchers these days have relatively little interest in reading what Shakespeare called nature's "infinite book of secrecy."

Modern medicine began to abandon plants in the late 19th century, when it developed the capability to manipulate individual chemicals and to manufacture synthetic drugs. The number of plant-based entries in the official United States Pharmacopoeia peaked at about 600, or 59 percent of the total, in 1890. By 1940, plant entries had fallen to 28 percent, and they are now at less than two percent. Advances in synthetic chemistry led to a new reliance on drugs that consist of a single active molecule, rather than on plants, each of which can have hundreds, and perhaps thousands, of compounds that act on one another at the same time as they affect the human body

The single-active-molecule approach drove plant-based drugs from pharmacy shelves and has now dominated Western scientific thinking for more than a century. It makes drugs easier to discover, standardize, and patent. Pharmaceutical research did not turn away from plants because tests showed them to be harmful or ineffective. Plants lost out because what they offer is too complex. Given the overwhelming emphasis on synthetic chemistry in pharmaceutical research, it is hardly surprising that the Nobel Prize in medicine, which has been awarded since 1901, has never been given for work on the medicinal use of plants.

The single-active-molecule approach is at the center of the current debate about the safety and effectiveness of herbal supplements. Annual sales of plant-based supplements amount to $5 billion in the United States alone, which certainly suggests that the public, at least, is in no mood to give up on plants. In fact, the public and the scientific community share the most common concerns about herbal supplements: They want them to be proven safe and effective, and they want them to carry accurate and understandable labels. But the supplements have so many ingredients that it is usually impossible to know exactly what to test and measure. Consider echinacea, on which Americans now spend about $300 million a year to combat symptoms of colds and flu. The herb contains compounds such as caffeoyl-tartaric acid, chlorogenic acid, cichoric acid, and echinacoside that serve as markers for bioactivity (activity that affects living cells), but no one knows how many chemical compounds in echinacea actually have an effect on the human body or precisely what their effect may be.

The genomes of plants, which can be far more massive and complex than the human genome, are responsible for the production of chemicals found nowhere else. Most plants use those chemicals to transform sunlight into sugar and carbon dioxide into oxygen; the extraordinary chemical capabilities of plants also allow them to generate new organs throughout their lives. Humans cannot grow new hearts or lungs, but plants can grow new flowers. We take that for granted, yet it's an amazing occurrence.

Until the early 1990s, scientists thought that most of the chemicals produced by flowering and other plants were useless waste products of the plants' basic metabolism. They called the chemicals "secondary metabolites," to distinguish them from "pri-

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mary metabolites" (amino acids, for example), which are essential to functions such as absorbing water. But we now know that secondary metabolites perform numerous functions that help plants survive. And their survival record is extraordinary. Flowering plants have been on Earth for more than 100 million years. They prevailed against whatever killed the dinosaurs, and they have devised intricate chemical defenses against bacteria, fungi, viruses, insects, and herbivorous animals.

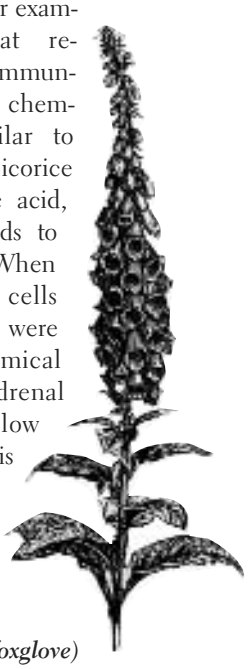
Flowering plants lack sensory organs, yet the chemicals they use in their sensory processes, which govern their contact with the world, are more sophisticated than those found in animals. Instead of eyes, for example, plants developed proteins in light-sensitive compounds that collect clumps of light energy. And plant roots contain chemicals that can detect nitrates and ammonium salts in the soil; the roots then move toward those elements, which are vital to their growth.

Plants are at the mercy of microbes, insects, and hungry animals. They can't run from their enemies, so they have developed an arsenal of bioactive substances with which to wage chemical warfare. The arsenal often includes chemical communications. Sensing the arrival of a disease-causing virus, some plants (such as tobacco) release chemicals that both protect their leaves and travel through the air to alert nearby plants of the approaching virus; when the neighboring plants receive the message, they begin to generate their own defensive chemicals. Other plants are capable of sensing from the presence of a caterpillar's saliva that their leaves are being eaten. So the plants emit substances that attract a wasp; the wasp lays eggs in the caterpillar; and as the eggs develop, they kill the caterpillar.

Research has documented that a plant's chemical-based defense system may rival the complexity of the human immune system. Plant defenses even have chemical memory, which scientists call "systemic acquired resistance." After combating a particular disease-causing virus, a plant can retain a resistance to that virus and related microbes—a rough counterpart to acquired immunity in humans. Another plant defense is the capacity to order cells near an invader to die and, thereby, to exude acidic chemicals that poison the invader. Some plant cells can stiffen to exclude and wall off invaders, while still others produce the equivalent of antibiotics. Sophisticated chemical defense mechanisms can even time the greening of leaves to the absence of herbivores, or protect plants from the damage caused by direct exposure to sunlight.

In recent years, science has offered more and more evidence that a genetic commonality links us to plants. Plant-human connections are remnants of a common evolutionary origin billions of years ago, before multicellular life divided into plants and animals. Many plants, for example, generate an amino acid called glutamate, which they use for internal communications. Humans also create glutamate, which serves as an important chemical messenger in the human brain; faulty glutamate signaling has been associated with Alzheimer's disease and schizophrenia. Further research into the genetic workings of plants and into how they produce substances such as glutamate may well lead to a better understanding of debilitating human diseases.

Other instances of genetic commonality are evident in the apparently countless ways plant-generated chemicals bind to human receptors. Spinach, for example, produces what researchers call an "immunoactive material" with chemical properties similar to those of insulin. And licorice produces glycyrrhizic acid, an alkaloid that binds to human kidney cells. When that happens, the cells respond as if the acid were aldosterone, a chemical released by the adrenal glands to combat low blood pressure. That is why herbalists advise people with *high* blood pressure not to take licorice.



Digitalis purpurea (foxglove)

Salicylic acid is yet another chemical involved in systemic acquired resistance in plants, though its exact contribution to the process remains a mystery. When taken by humans, salicylic acid, popularly known as aspirin, not only relieves headaches but reduces the incidence of cancer, heart disease, and strokes. Exactly how it does so is still not understood.

Although there is no predicting where further research into plant-human genetic ties may take medicine, genetic research has revealed unexpected links between plants and human diseases. For example, sequencing the genome of *Xylella fastidiosa*, bacteria that attack citrus plants, yielded the presence of genes closely resembling the genes that cause meningitis in humans. Does that mean that the chemicals citrus plants produce to fight the bacteria hold clues that might be useful in the human fight against meningitis? No one knows for sure. But for those who doubt a relationship between plants and human ailments, the following account of foxglove, or digitalis, a drug widely prescribed today for heart failure, might be instructive.

In 1775, William Withering, a physician in Birmingham, England, had a female patient with severely swollen legs, a condition then called dropsy. Although it was not known at the time, such swelling is often a sign of congestive heart failure, the heart being simply too weak to pump blood effectively. Withering could do nothing for his patient and assumed she would die. When he heard a few weeks later that she was doing well, he paid her a visit and learned that she was taking an herb tea provided by an old woman who ministered to people beyond the help of doctors. The old woman showed Withering the components of the herb tea recipe. Looking at what he described as the "twenty or more" herbs in the woman's medicine, and knowing that in cases of dropsy a diuretic is needed to get water out of the system, he decided that "the active herb could be no other than the Foxglove." (To this day, we do not know what the other herbs were.)

The powdered leaves of foxglove had been used as a medicine in Europe for hundreds of years. One herbal book contemporary with Withering noted that "six or seven spoonfuls of the decoction produce nausea and vomiting, and purge," and other books reported foxglove's effectiveness against epilepsy, hereditary deafness, skin ulcers, and eye tumors.

In subsequent years, Withering used foxglove to treat his patients for a range of ailments. He tried several varieties and strengths of the plant—roots, leaves, leaves in powder, leaves picked when the plant was flowering, green leaves picked in winter, and leaves mixed with small amounts of opium. Although he believed that the foxglove only eliminated fluids, he recognized as well that it "has a power over the motion of the heart to a degree yet unobserved in any other medicine."

In 1785, after 10 years of experimentation, Withering published a book entitled *An Account of the Foxglove*. More and more people were taking foxglove, he wrote in the preface, and he wanted the benefit of his experience to lessen the risk of their being harmed by its improper use. He also wanted to make sure that "a medicine of so much efficacy should not be condemned and rejected as dangerous and unmanageable."

The cases for which Withering used foxglove were, he wrote, "the most hopeless and deplorable that exist," and he did not resort to the drug until "the failure of every other method compelled me to do it." Thus, he was once called by a fellow doctor to see a female patient "nearly in a state of suffocation; her pulse extremely weak and irregular, her breath very short and laborious, her countenance sunk, her arms of a leaden colour, clammy and cold. She could not lye [sic] down in bed, and had neither strength nor appetite, but was extremely thirsty. Her stomach, legs, and thighs were greatly swollen." Withering hesitated before administering his digitalis preparation, for he believed the woman would die and give the new drug a bad name. After taking the mixture, she began to vomit. Then she urinated eight quarts of water, her breath came easier, and her swelling subsided. Nine years later, Withering reported, the woman was still alive.

Modern science has never been able to

devise a chemical that achieves what the raw plant chemical digitalis achieves, or to improve upon it. Like most bioactive plant chemicals, it has a mode of action and a structure that are beyond the power of scientists in a laboratory to imagine. What scientists have been able to document is that foxglove is among a group of plants whose leaves, flowers, seeds, roots, and bark contain glycosides. Glycosides are chemicals that act on the contractile force of the cardiac muscle. They slow the heart rate and increase the force of contractions. And when the heart pumps blood more efficiently, the kidneys are better able to cleanse the blood of wastes and toxins.

Digitalis is a plant-produced chemical that can be isolated, which means that it fits in well with the single-active-molecule approach to modern pharmaceuticals. But screening for single active chemicals from tens of thousands of other plants, many of them widely used in traditional medicine, has yielded few usable drugs. The consistent failure suggests that looking for a single active molecule as the healing component of a plant is like opening a radio to find the one piece that produces the sound. To benefit from the inherent chemical complexity of plants, we must devise drugs that have numerous active ingredients. Research on the human genome demonstrates why such drugs are so important.

A decade ago, scientists expected that they would one day be able to target the one gene responsible for each major disease. Early successes, such as the isolation of one gene "linked" to Duchenne muscular dystrophy and one linked to hemophilia, seemed to bear out that expectation. But the discoveries led to little in the way of actual treatment. In fact, researchers have coined the word *oligogenic* to signify that most major diseases involve many genes. So a treatment using many drugs, each of which affects a different biochemical process, makes sense. Such multimodal treatments, whose complexity resembles the complexity found in plants and plant medicine, now pervade modern medicine. Perhaps the most prominent example is the "AIDS cocktail," a combination of several types of drugs. Other combinations include chemotherapy cocktails to treat cancer, the use of four or more antibiotics to treat tuberculosis, and the simultaneous use of two or more drugs to treat heart attacks, malaria, rheumatoid arthritis, chronic hepatitis C infections, and diabetes.

Echinacea purpurea

Multimodal treatments usually combine unrelated drugs that act in different ways on different parts of the body. Treatment for difficult cases of diabetes, for example, may combine one standard drug that reduces the liver's production of blood sugar with another that makes muscles more sensitive to insulin. A treatment for persistent depression may include the prescription of three major antidepressant drugs, each of which affects the human brain's production of a different neurotransmitter.

At the same time, evidence of the extraordinary power of another type of multimodality is growing. Hundreds of studies document with surprising consistency that the more fruits and vegetables people eat, the less likely they are to suffer from heart attacks, strokes, or cancer. There is a link between that finding and our growing knowledge of genes. In the next few years, physicians are likely to have at their disposal tests that identify patients with a genetic tendency toward cancer or heart disease. Having few resources at their disposal to treat the problem genes directly, the doctors will urge, among other things, that their patients eat lots of fruits and vegetables.

But getting the most out of fruits and vegetables, despite their proven health benefits, is not always a simple matter. How foods are prepared can affect the levels and bioavailability of *nutraceuticals*—a word coined in the early 1990s to describe chemical components in dietary fruits and vegetables that may have little or no food value but that help to prevent and treat disease. Cooking

can significantly affect those chemicals, for better or for worse. Cooking garlic, for example, seems to eliminate many of its disease-fighting chemicals, while cooking tomatoes markedly increases the availability of lycopenes, chemicals that are effective against some cancers.

To obtain therapeutic effects equal to those that could be derived from eating particular quantities of food may require the extraction of chemicals from fruits and vegetables and their transformation into what we would call a medicine. Most people are probably unwilling to eat several cloves of fresh garlic every day, even though chemicals in garlic lower cholesterol, combat hypertension, and may help fight stomach cancer. Hence, a leading brand of garlic pills contains "aged garlic extract" that is said to deliver chemicals without causing upset stomach or "garlic breath." Extracts of garlic and other foods provide far more disease-fighting compounds than people could ever obtain from eating the foods. The limonene in oranges, for example, appears to slow the formation of tumors, and even to shrink existing tumors. But to get effective levels of limonene, you would have to eat 400 oranges a day, as you would have to eat massive quantities of nuts, many of which are high in compounds such as ellagic acid, a health-promoting antioxidant, to obtain their therapeutic benefit.

What's worse, the very chemical in a food that fights disease may make the food difficult to eat. Sulforaphane in broccoli, for example, stimulates enzymes that detoxify chemical carcinogens, but it gives the broccoli a bitter taste, perhaps to discourage animals from eating the plant. The broccoli available in stores has been bred to have a milder taste, which makes it less effective against carcinogens. Genetic manipulation might one day produce broccoli that is high in chemicals similar to sulforaphane without the bitter taste. Research might even create a broccoli pill containing concentrated sulforaphane or a synthetic version of sulforaphane. But there is at least one significant obstacle: Sulforaphane is unstable and is released only when broccoli is chewed. The pills might work, but they might also sacrifice benefits found in the natural package known as broccoli, including many benefits not yet identified by modern science. Alas, there may be no way to obtain all the benefits of bitter-tasting broccoli without eating the real thing.

That fruits and vegetables fight disease makes sense. If substances from the Madagascar rosy periwinkle can kill cancer, why should plants that people eat as food not have a comparable therapeutic effect? But because plant foods, like medicinal plants, contain hundreds, and perhaps thousands, of chemicals, we cannot yet explain exactly how they combat disease.

The use of fruits and vegetables as medicine has an important precedent in vitamins, which were called "accessory food factors" when they were first identified in the early 20th century. A lack of sufficient vitamins can result in crippling and often fatal diseases, such as scurvy and beri-beri, just as a lack of sufficient nutraceuticals can lead to disease. Continuing research on nutraceuticals may be especially important because the per capita consumption of fruits and vegetables in America remains much too low, despite years of advice from mainstream medical authorities. Americans may be so addicted to convenience that they'll never experience the medicinal benefits of eating enough fruits and vegetables until those benefits are available in simple pill form.

Still, obtaining the health-enhancing effects of plant-based chemicals is a simple matter compared with creating pharmaceutical drugs. To manufacture "green" drugs that are safe and have predictable effects, modern science must figure out how to penetrate the complexities of medicinal plants. And if it is to do that, it must move beyond the search for drugs that rely on a single active ingredient.

Money is not the answer, because the investment of more money would in all likelihood only produce more of the same, which is virtually nothing. Since the discovery of drugs from the rosy periwinkle 40 years ago, the National Cancer Institute and pharmaceutical companies have spent billions of dollars looking for single active

Plant samples taken from a rain forest in Madagascar will be sent to the National Cancer Institute, which screens more than 20,000 natural compounds annually, including many that could offer new drugs.

chemicals in plants and other natural sources. The results have produced promising leads and chemicals that act strongly against cancer, HIV infection, and other conditions in laboratory tests. But very few of those chemicals have reached human clinical trials, and fewer still have been the basis for the production of new drugs. Never before, in fact, has a society collected so much information about medicinal plants that it is unable to use, because it is so accustomed to defining "use" as isolating and extracting a single active ingredient.

If we are to embrace the complexity of plants while maintaining the precision and the virtues of modern science, we need a new conceptual framework and a new approach. "You can't depend on your eyes," Mark Twain warned, "when your imagination is out of focus." The good news is that the imaginations of scientists who accept the research challenge will have help from two powerful sources: computers, whose data-crunching capacity is growing exponentially, and chaos or complexity theory, which demonstrates that extraordinarily complex phenomena such as tornadoes and enzymal interactions can have relatively simple and manipulable beginnings. The study of various forms of complexity already indicates that straightforward rules may govern bioactive chemicals whose relationships now seem impossibly chaotic. Who knows what advances we may achieve by applying the combined power of computers and complexity theory to the study of human and plant genes?

Moving beyond the single-active-molecule tradition will meet resistance from scientists trained in the current era, which began with the discovery of antibiotics in the middle of the 20th century and nurtured the belief that medicines must be finely targeted magic bullets. That belief could become even more deeply entrenched as we begin to tinker with our genes. But resistance to new ideas is hardly uncommon in the history of modern medicine. The acceptance of germ theory, for example, did not become widespread among physicians until some 40 years after the theory had been proved definitively. And Florence Nightingale, who led efforts to introduce modern standards of cleanliness into America's hospitals, refused to believe that diseases are linked to bacteria; she died in 1910 holding to the accepted wisdom of her youth that diseases are

caused by miasmas, noxious gases emanating from the earth.

There is a growing body of evidence that may lower resistance to the use of plants as medicines. Double-blind placebo studies, the gold standard of pharmaceutical research, are revealing the limits of the single-active-compound approach. Many of the studies focus on skin diseases, the manifestations of which are relatively easy to see and measure. In one study, all the participating patients had severe cases of atopic dermatitis, a disease of unknown origin characterized by red, thickening, scaling patches of skin on the face, feet, and hands. Modern medicine had been unable to improve their condition. Some of the participants received a combination of Chinese herbs; others drank the same amount of a placebo combination of herbs with "no known benefit to atopic dermatitis" but with "a similar smell and taste to the active treatment."

As reported in *The Lancet* in July 1992, every patient taking the Chinese herbs experienced "a rapid and continued improvement in both erythema [redness of the skin] and surface damage," which led the authors to conclude "that TCHT [traditional Chinese herbal therapy] affords substantial clinical benefit in patients whose atopic dermatitis had been unresponsive to conventional therapy." Although "an understanding of the pharmacological basis for the beneficial effect" of these plants is "limited," the authors wrote, the plants are known to have anti-inflammatory, sedative, and immunosuppressive effects, and they might also have stimulated the patients' genes to increase the production of particular beneficial enzymes or decrease the production of harmful ones.

Studies of this kind argue that modern medicine can tap into the wisdom of other healing cultures. The extensive Chinese pharmacopoeia uses hundreds of plants, in tens of thousands of combinations, and yet it has contributed to only two Western pharmaceutical drugs (one a decongestant and stimulant of the nervous system, the other an antimalarial). Ayurvedic medicine, the healing system in India that dates back thousands of years, has yielded only one Western drug (used against high blood pressure and as a tranquilizer), and the Native American pharmacopoeia one such drug at most (a female oral contraceptive). These traditional systems of healing, which are often, and wrongly, dismissed as primitive, share two fundamental characteristics with contemporary genetic medicine: an emphasis on prevention, and the tailoring of treatment to each individual patient. Those fundamental similarities should encourage us to embrace ancient systems as we move into the age of genetics.

In the rural Bengal region of eastern India, a snake charmer, heeding the teachings of his father, eats leaves from several plants whenever he is bitten by a cobra. Laboratory experiments at the University of Calcutta have demonstrated that the leaves keep cobra venom from harming laboratory rats, but no one has yet identified the chemicals in the plant that cause the immunity or explained why they are effective.

Parasites that invade human red blood cells and cause malaria have grown resistant to chloroquine, the powerful Western antimalarial drug. Somehow the parasites keep the chloroquine from entering red blood cells. So local healers in Madagascar tell malaria patients to eat a particular kind of leaf when they take the chloroquine. And in the presence of chemicals from the leaf, the chloroquine enters the blood cells and kills the parasites.

Such stories are entertaining and provocative, but they will lead to scientific breakthroughs and new medicines only if we become alert to the research opportunities all around us. As Proust said, the true voyage of discovery is not a journey to new places; it is learning to see with new eyes. If we are to rediscover the medicinal power of plants, we must learn to see them differently. The skeptic may ask why we should begin to base more of our medicines on plants at a time when we are making such extraordinary advances in genetics. Wouldn't that be an absurd thing to do? On the contrary, it's the obvious thing to do. ❑