15 The President Who Swallowed Rat Poison: Preventing the Next Heart Attack

Science progresses as much by serendipity as by deductive reasoning. Discoveries arise from a confluence of chance observations and carefully controlled measurements made by single-minded visionaries who are driven to spend their days and nights in the laboratory. Nowhere is this interplay of the planned and the providential better seen than in the story of hemorrhaging cows, a potent rat poison, a failed suicide attempt, and a president's heart attack—all part of the history of a prescription drug taken every day by more than two million Americans. New treatment strategies with this popular but potentially dangerous medicine are in the vanguard of a burgeoning field called pharmacogenomics, which promises treatments tailored to each person's unique personal DNA code.

Across the prairies of North Dakota and Alberta in the winter of 1921 and 1922, cattle were dying in large numbers from a strange disease. Autopsies revealed severe bruising and unusual swellings under the skin that were filled with blood. Minor procedures such as ear notching led to wounds that did not heal and caused the cattle to leak blood until they died. Entire herds were struck by the mysterious bleeding disease that relentlessly followed its course of thirty to fifty days and ended in death. Farmers who struggled to make a living under the best of circumstances were devastated by this disastrous turn of events.

Frank Schofield, a veterinary pathologist who had emigrated to Canada from England, was the first to decipher the basis of the mysterious outbreak. Initially he looked to bacterial infection for the cause, but he quickly ruled this out because of the lack of a fever in the affected animals, no signs of a bacterial pathogen, and his inability to transfer the disease from sick animals to healthy ones.

By 1922, Schofield had concluded that the sickness was due to sweet clover hay that had turned moldy and was being consumed by the cattle. Indeed, the harvest season of 1921–1922 had been notable for its dampness, which promoted the growth of mold. Lee Roderick, another veterinary pathologist who independently analyzed the outbreak, reported in 1929 and 1931 that the dying cattle were severely deficient in prothrombin, a blood-clotting factor. But the only treatment to arise from the veterinarians' work was transfusion of the sick cows with blood from healthy ones, and the only advice to heartbroken farmers was to find another source of hay. The disease continued to ravage the herds.

In February of 1933, Ed Carlson, a farmer from Deer Park, Wisconsin, drove the 190 miles to Madison in a raging blizzard. Sweet clover disease had killed two of his young cows in December, one of his favorite old ones in January, and two more in February, and his prized bull was "oozing blood from the nose." Carlson headed to the University of Wisconsin's Agricultural Experiment Station. Finding it closed, he entered an unlocked door he came upon and found himself in the laboratory of Karl Link. There, he dumped in front of Link a dead heifer, a milk can of blood that would not clot, and one hundred pounds of spoiled sweet clover.

Link was an agriculturist, a consultant who advised farmers on such concerns as soil quality, crop choice, and animal breeding and disease. A few months earlier, Link had been offered a faculty position at the University of Minnesota by Ross Gortner, chairman of the Department of Biochemistry. For a research topic, Gortner suggested that Link try to identify the agent responsible for sweet clover disease, and pointed him to the publications of Lee Roderick. Instead, Link had accepted a position at the University of Wisconsin in Madison, where he had decided to tackle a different but related problem. Although sweet clover *smells* sweet because of the presence of coumarin, the chemical that produces the characteristic odor of new-mown hay, in fact, this chemical makes the clover *taste* bitter. Link, assuming that the cow is something of an epicurean and prefers to eat the less bitter plants first, set out to develop a strain of sweet clover low in coumarin, to make it more appetizing to the cows.

When confronted with the catastrophe besetting Ed Carlson, Link could do no more than to tell Carlson to stop feeding his cows the spoiled hay and transfuse the sick ones, options that were not available to the poor

farmer. But Link immediately changed his research goals, turning to the problem that the chairman in Minnesota had urged him to tackle: isolation from sweet clover of the "hemorrhagic agent" that was causing the cows to bleed to death. It turned into a six-year effort.

In June of 1939, after working all night in the laboratory, Link's associate Harold Campbell finally had a pure preparation of the hemorrhagic agent. Its analysis showed it to be dicumarol, a compound that results when a coumarin molecule is linked to another coumarin molecule by an enzyme present in the fungus that causes hay mold. The requirement of the fungal enzyme for this process solved the mystery of why only hay that had gone moldy caused the disease.

Dicumarol proved to be an anticoagulant, a compound that prevents blood from clotting by inhibiting a step in that process that requires vitamin K. A high level of dicumarol in the blood leads to uncontrolled bleeding caused by the thinning of the blood, which leaks out of the blood vessels. The cows were bleeding to death from the inside. Link found that dicumarol is also effective in people, and that a high level of vitamin K is an effective antidote in case of an overdose. After successful clinical trials in the early 1940s, dicumarol began to be prescribed for patients who had heart attacks, but its use never became widespread.

In late 1945, Link suffered a recurrence of an earlier tuberculosis infection and was confined to bed for eight months to recuperate. Rather than just "vegetate like a topped carrot," Link later wrote, he decided to read, of all things, "the history of rodent control from ancient to modern times." Mulling over this history, he had the stunning realization that an anticoagulant like dicumarol might make the ideal rat poison: it has no taste or odor, it is effective in small doses, and it is water-soluble and stable in cereal grains. Most critically, it does not cause immediate symptoms. This last feature of a poison is important because rats are not dumb: if one eats a bait that causes it rapidly to get sick, it makes an immediate connection and thinks: "I'm not eating any more of *that*!" Even more troublesome for a rodenticide developer, when rats see their buddies lying dead next to poisoned food, they think: "Maybe that stuff is not so good to eat." But an anticoagulant-treated rat would die several days later at a location distant from the bait, and not even the smartest rodent has the wits to think: "It must have been that dinner he ate last Wednesday."

Link appreciated that dicumarol might not be the most effective anticoagulant of its type, so he had more than a hundred different chemicals similar to dicumarol synthesized. When he returned to the laboratory the next year, he had the various derivatives tested for their anticoagulant activity on rabbits, rats, mice, and dogs. As a result of these tests, he selected compound number 42, which was much more potent than dicumarol, as the best choice for a rodenticide. Link assigned the patent rights to the Wisconsin Alumni Research Foundation, which had supported his research, and appropriated the initials of the foundation, "warf-," plus the suffix "-arin" (from coumarin), for the name of the compound: warfarin (not, as many think, from "warfare" against rats). In the decade after 1950, more than 140 million pounds of bait containing warfarin were sold under trade names such as d-Con and Rax.

We don't know why Link chose to use his convalescence to read up on rat control rather than on the origins of cancer, the building of the pyramids, the history of the Civil War, or any number of other topics. But we suspect that he already had an inkling that his long-sought and now purified hemorrhagic agent that sickens cows might somehow prove of value in the task of killing rats. Many of the best ideas in science—maybe in most disciplines—lie at the interface of apparently unconnected fields, and become apparent only when someone has the imagination to make the (seldom obvious) connection.

Today's scientists must swim through an ocean of scientific literature of a size that Link would surely have found unfathomable, and we fear that this vastness is causing many scientists to miss some crucial connections. As part of their training, all scientists are urged to read widely in the scientific literature so as to gain the knowledge necessary to recognize that the oddball fact discovered in one study is relevant to a seemingly completely different problem. But that is now almost impossible. Even in scientific journals that publish reports in just a narrow area of study, only the occasional article relates directly to a scientist's particular research focus; the rest are like the descriptions of rat poison to a group trying to cure cattle of a mysterious bleeding disease. To make sense of this prodigious scientific literature, biologists now sign up for services that email them a notice that a paper relevant to their research has been published and is ready for download. It's an efficient means to keep up, but we

suspect that opportunities are being lost to make that next crucial connection that results in an important new research direction.

Ever eager to see novel applications of his research, Link surmised that warfarin, his wildly popular rat poison, might work in humans as a better anticoagulant than dicumarol. But, Link wrote, whereas "in 1941 the clinicians had literally snatched the 'cow poison' from us, . . . the transition to a substance originally promoted to exterminate rats and mice was a bit more than they could accept with real enthusiasm."

In April 1951, a twenty-two-year-old Army inductee was admitted to the hospital after a failed suicide attempt. He had become depressed by his entry into the service and tried to kill himself by ingesting rat poison: over a six-day period he had consumed d-Con containing 567 milligrams of warfarin. On admission to the hospital he complained only of back pain and nosebleeds, the latter symptom not surprising in view of a test showing that his blood was taking more than sixteen times longer to clot than did that of a person who did not partake of rat poison. The patient was treated with blood transfusions and vitamin K, and his blood tests showed that the clotting time became faster with each day of treatment. He was eventually released in good health. His doctors concluded that "accidental poisoning of an adult [by warfarin] is almost inconceivable" (although, as we'll soon see, they were more sanguine about the risks than turns out to be prudent).

This incident convinced doctors that the anticoagulant warfarin could be used to treat heart attack patients to prevent clotting, and it replaced the less potent and slower-acting dicumarol. In September 1955, when President Dwight Eisenhower suffered a heart attack, he was successfully treated with warfarin, and the publicity added substantially to the drug's luster. Warfarin came to be the long-term treatment of choice to prevent clotting after a heart attack, stroke, or surgery, as well as for people with blocked arteries, with artificial heart valves, or with the irregular heartbeat known as atrial fibrillation. And it still is.

These stories make warfarin seem like a wonder drug, but in reality its use is fraught with complications, so much so that in October 2006, Bristol-Myers Squibb, which sells the drug under the name Coumadin, added a black box warning on the packaging that cautioned of possible "major or

fatal bleeding." This bleeding risk often occurs at the earliest stage of treatment, when a patient is first placed on warfarin therapy. In fact, adverse issues related to treatment with warfarin are the cause of a surprisingly large number of hospital admissions.

There are three principal problems with warfarin treatment. First, the dosage range that produces the desired beneficial effect without being toxic—the therapeutic index—is quite narrow, so that there is little margin of safety: underdose with warfarin and the patient is subject to forming blood clots; overdose with warfarin and the risk of bleeding is high. The dosages that lead to these polar outcomes are not drastically different, so warfarin is said to have a narrow therapeutic index.

Second, individuals can vary by more than a factor of twenty in the amount of warfarin they need to be usefully treated: where one person requires 0.5 mg of warfarin per day to achieve a desired anticoagulant effect, another might need twenty times more, or 10 mg, to get the same level of anticoagulation.

Third, warfarin interacts with a large number of other drugs, many of which are common and most of which increase its anticoagulation potency. Since about 30 percent of Americans over the age of sixty-five, and even more of those over seventy-five, take five or more prescription drugs per day, you can appreciate the magnitude of this problem.

The primary means for a physician to decide what dose to give a patient embarking on warfarin therapy has been trial and error; the doctor begins with a standard dose, tracks the time it takes for the blood to clot, and adjusts the dose as necessary to get it in the right range. The problem is more serious than the fact that most people don't enjoy serving as a pincushion while the correct dose is established. Individuals highly sensitive to the drug have a high risk of experiencing incidents of bleeding that can be serious, even fatal, during the first month of treatment, while the correct dose is being established.

There may be a better way, one that is coming from a new field, called pharmacogenomics, that promises individualized drug treatments matched to each person's personal DNA code. What happens when you take a drug? What does the body do to the drug? How is it distributed among the various tissues and how is it eventually disposed of? The drug first has to gain entrance into the body, most commonly by swallowing a pill or

liquid, although injection, inhalation, and numerous other creative strategies have also been used. Once inside the body, the drug must cross a biological barrier, typically within the small intestine, to gain access to the bloodstream. The drug must then be transported throughout the body via the bloodstream and generally must leave the blood to reach its site of action (of course warfarin's site of action is in the bloodstream). Some locations, such as the brain, are protected and do not allow access to most drugs. Along the way, the drug gets chemically modified in the body, primarily by enzymes in the liver. This chemical modification of the drug usually makes it more likely to be excreted. Finally, the drug and its modified forms are filtered out of the blood by the kidneys and eliminated in the urine.

Some obvious factors influence relative dosage sizes. It may be easy to look at a 300-pound football player and think he'll need a higher warfarin dose than a 110-pound fashion model, or that someone with a liver disease that affects the production of drug-metabolizing enzymes might not tolerate the average dose. Older people usually require lower doses of most drugs than do younger people of the same weight, and males and females often differ in their therapeutic doses.

But acting along with these visible factors are differences in patients' genes, which play less perceptible yet perhaps more relevant roles in determining the effect of the drug. In the case of warfarin, one gene that influences a person's sensitivity to the drug encodes a member of a family of liver proteins, called cytochrome P450s, that metabolize drugs and begin the process of their elimination. Some people carry a variant of this particular P450 gene that makes a much less active enzyme. As a consequence, their bodies are not as efficient at eliminating warfarin, and their risk of bleeding with higher doses is increased. Unfortunately, this variant gene explains at most no more than 10 percent of the differences in warfarin sensitivity between individuals.

In 2005, researchers at the University of Washington in Seattle and Washington University in St. Louis found another gene, this one accounting for much more—about 25 percent—of the variation in warfarin dose sensitivity between individuals. This gene encodes a protein with another mystifying name, vitamin K epoxide reductase (abbreviated to VKORC1 by geneticists), which is actually the target of warfarin. This protein is involved in recycling the vitamin K that is used in the clotting process so that it

can be used again. Warfarin reduces the amount of vitamin K in the bloodstream by inhibiting this enzyme, thereby slowing down the action of several clotting factors that depend on vitamin K.

The Seattle and St. Louis team found that there are several different versions of the *VKORC1* gene in the population. The DNA sequence differences between these variants do not affect the amino acids that make up the VKORC1 protein but instead affect how much of the protein is made. Because each of us has two copies of the *VKORC1* gene, we can carry high/high, low/low, or high/low versions of the gene in our personal DNA code. The research team analyzed individuals who had all been stabilized at their own maintenance dose of warfarin to see how the two forms of the *VKORC1* gene correlate with the dosages. The team found that those with the high/high gene combination were being treated with an average of 6.2 mg/day of warfarin, those with the low/low combination were on 2.7 mg/day, and those with one of each type of gene were on an intermediate level of the drug: 4.9 mg/day. Contrast these results with a popular regimen for beginning patients on warfarin therapy that starts everyone out on 10 mg, and you can see the value of pharmacogenomics: the knowledge of an individual's *VKORC1* genes along with environmental factors such as age and body weight now allow physicians to account for more than half of the variability in appropriate warfarin dose between individuals. As a result, patients can begin their therapy with a dose of warfarin likely to be closer to their personal therapeutic range, thereby reducing their risk of overdosing.

Pharmacogenomics is in its infancy, and as this field matures, more drug treatments will be tailored to our genetic makeup. Moreover, pharmacogenomics will have a tremendous effect on the drug development process itself by enabling "personalized medicine." This is a prospect that brings up all kinds of new social and ethical issues, especially with regard to cost and privacy, that raise the stakes of the research findings.

Cases of genetic variation among individuals that affect their response to other drugs are increasingly being uncovered. The breast cancer drug Herceptin is effective in only about one quarter of patients, women whose tumors produce a protein called HER2, which promotes uncontrolled growth of the tumor. Herceptin binds to HER2 and prevents it from carrying out its function, slowing tumor growth. But other types of breast cancer are due to tumors that grow uncontrollably for other reasons; the

cells in those tumors don't express the HER2 protein, so the drug is of no use and should not be prescribed for that kind of cancer.

Another area in which pharmacogenomics will have impact is drug safety and effectiveness. Some drugs build up to toxic levels in some people but not in others, prompting searches for the genes responsible for these differences. In addition to drug-metabolizing enzymes and the direct targets of drugs, other proteins whose genes are being examined include some that bring drugs into cells or pump them out, and others that bind to drugs and carry them to their site of action.

It may also be possible to identify those people in which specific combinations of drugs are likely to be toxic. Adverse drug reactions are estimated to contribute to more than one hundred thousand deaths each year in the United States, as many as are due to breast and colon cancer combined, making it the fifth leading cause of death. So the potential value of pharmacogenomics is obvious.

Some diseases that are difficult to treat, such as depression, currently may oblige patients to go through a plethora of drugs until one is found that alleviates the symptoms without toxic side effects. The sometimes torturous road to relief is likely to become easier to navigate with a map of the patient's personal DNA code.

Pharmacogenomics also promises to advance drug development. Pharmaceutical companies are beginning to test prospective medicines on individuals with a variety of known genetic backgrounds. Some potential drugs are eliminated early in the process because they have too many unwanted side effects for too many people. But by identifying a small number of people who respond favorably to a drug, these companies may be able to salvage it to the benefit of these patients, and their own profits. This grouping of patients should lead to faster adoption of drugs, because those most likely to suffer adverse effects will not end up being medicated, and compliance will be better among those who are medicated.

Pharmacogenomics also should enable preventative medicine. If you learn you are at high risk of a common but life-threatening illness because of your personal DNA code, it might be wise to begin drug treatment years before clinical symptoms become manifest.

This all sounds wonderful, but can we afford pharmacogenomics and personalized medicine? It is expensive to develop and use on a routine basis the genetic tests needed to identify gene variants. It is incredibly

expensive to develop new drugs, and if they are of use to only a small segment of the population the drug companies may not be able to recover their investment. The United States is already spending more than seven thousand dollars per person every year on medical care, about 10 percent of which is for drugs. If new drugs are developed for smaller and smaller slivers of the population, their cost will need to rise to provide profit for their makers.

There is little problem with the cost of drugs when the overall benefit is large, especially when younger and healthier groups of people are the intended users. But what about the drug that works only for a small subset of those with an advanced-stage cancer and that provides only a few additional months of life? Is this a luxury our society can afford? We need to establish our medical priorities and figure out how to cover the costs of those priorities.

There are also issues of privacy. Pharmacogenomics relies on revealing increasing amounts of our personal DNA code to physicians, hospitals, insurers, and the DNA testers. Many people are concerned about potential misuse of this information, although knowledge of a person's ability to metabolize a drug may provoke less fear of discrimination than does a positive test for the mutation leading to, say, Huntington's disease. As genetic tests become more common, we applaud recently passed federal regulations that prevent the results from endangering our ability to obtain insurance or treatment.

Pharmacogenomics deals with how our genetic inheritance affects our responses to specific drugs, but the same principles at work can be applied to many other environmental exposures, and may well lead to discovery of how our genes affect our response to pollutants, to toxins, to allergens in our food, and to all sorts of other chemicals to which we are exposed. Pharmacogenomics may be only the forerunner of a much bigger field: ecogenomics, which will explain how our genetic differences affect our interactions with the environment.

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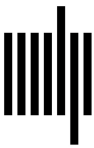

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