The card players of Caravaggio, Cézanne and Mark Twain: tips for getting lucky in high-stakes research

Joseph L Goldstein

To the scientist, the thrill of discovery is like the thrill of a royal flush to the poker player. Scientists who receive Lasker Awards and Nobel Prizes share many things in common with poker superstars, both of whom take risks and gamble for high stakes. Scientists pit their wits against Nature's puzzles, betting that their efforts will ferret out those rare nuggets of truth embedded in a vast mountain of artifacts. Poker players pit their wits against mathematical probabilities, wrestling with the fact that a deck of 52 cards can be shuffled into 52! sequences, which is $52 \times 51 \times 50 \times 49$ and so on down to 1. This comes to 8.1×10^{67} possible card permutations—a number 53 orders of magnitude greater than the 10^{14} synaptic connections in the human brain and 45 orders of magnitude greater than the 10^{23} stars in the universe.

Given the mathematical odds of being dealt a good card hand and the tightness with which Nature guards her secrets, a key question is whether success, in poker or in science, depends predominantly on luck or on skill. Luck is difficult to define. Perhaps the best definition comes from the great film producer Samuel Goldwyn: "The harder I work, the luckier I get." The skill element in poker depends on acquiring expertise in statistics and probability and on mastering the complexities of betting and bluffing—knowing when to bet, fold or raise at any decision point and knowing how many chips to put on the table. The skill element in science also depends on being bold and knowing when to take risks—not to mention learning the art of asking the right questions and pursuing experimentation passionately and fearlessly.

Philosophers of science have paid little attention to the relative roles of luck versus skill. But in card-playing circles, the luck-versus-skill question has been debated for hundreds of years. Some of the best insights come not from card-playing experts, but from artists such as Caravaggio and Cézanne and from writers such as Mark Twain.

Caravaggio's *Cardsharps*

In the late 1300s, when card playing first became a popular form of entertainment in Italy and France, card cheats and crooked gamblers dominated the game, minimizing the skill factor of the player. This state of affairs is wonderfully captured in *The Cardsharps*, a 1594 painting by the Italian artist Michelangelo Merisi da Caravaggio (**Fig. 1a**). Art historians consider *The Cardsharps* the most influential gambling-themed painting in the history of art. The composition is simple and elegant. An innocent-looking young man has been lured into a card game by a sinister, middle-aged man. Stealing a peek at his victim's cards, the older man signals with his fingers to an accomplice, who holds the 5 of hearts tucked in his belt behind his back. The object of the conspiracy—a stack of coins—sits at the edge of the table.

Caravaggio's genius is the creation of a dramatic scene of concealment in which all three characters are hiding something. The tension and drama are heightened by details such as the split glove that allows the older man to easily feel the marked cards, the black hat of the innocent boy that hides the peering right eye of the older man, and the older man's left hand that seems to come out of nowhere to rest close to the younger cardsharp's dagger. The whole scene keeps the viewer on tenterhooks: any slight movement might reveal the trickery. The young boy may be skillful at his game, but we'll never know—he's the victim of bad luck.

The Cardsharps inspired many artists to take up the gambling theme. One famous imitation is *The Cheat with the Ace of Clubs*, an early-1630s painting by the French artist Georges de La Tour (**Fig. 1b**). In dazzling colors, La Tour depicts the dangers of wine, women and gambling. Here we see a trio of conniving cheats, highlighted by carefully orchestrated gazes and gestures. Is the gaze of the woman with the plunging neckline intended for the maidservant to give her more wine, or is she signaling the cheat to play the ace of clubs?

Cézanne's *Card Players*

Caravaggio's celebrated compositional portrayal of trickery, greed and lust proved so seductive and powerful that artists continued to copy it for 300 years. Then, in the 1890s, Paul Cézanne reinvented the card-playing theme in a revolutionary way. Over a 5-year period, Cézanne executed five paintings of male peasants playing cards. Known collectively as *The Card Players*, the paintings in the series (three of which are shown in **Fig. 2**) vary in size and scale, but all are formally based on a similar composition: two to five stone-faced, drably dressed, stocky men—all wearing unadorned hats—are depicted playing cards and smoking clay pipes while gathered around a plain table. The men look down at their cards rather than at each other; they are totally and intensely absorbed in the ritual of their game—a kind of "collective solitaire," in the words of art critic Meyer Schapiro (Schapiro, M., *Paul Cezanne*; Harry N. Abrams, Inc., New York, 1952). The tense atmosphere of concentration and solemnity is accentuated by shades of brown and blurs of blue.

The contrast between the card players of Caravaggio and those of Cézanne is striking. Unlike Caravaggio's masterpiece, Cézanne's seminal series depicts no cheating, no money on the table, no melodrama, no skullduggery, no extravagant clothes. Cézanne is telling us that card play is no laughing matter. The key to skillful play and winning is focus, focus, focus. Luck

is not necessary when there are no distractions or trickery of the sort portrayed in Caravaggio.

As to which is more important, luck or skill, Caravaggio leans toward luck and Cézanne favors skill.

Mark Twain's Science vs. Luck

To settle the argument, there is no one better than America's greatest humorist and arguably most creative fiction writer—Mark Twain. Twain was an unabashed lover of poker and was saddened by how few people in the US knew anything about the game, lamenting (in Johnson, M., *A Bibliography of the Works of Mark Twain*; Harper & Brothers, New York, 1935), "I have known clergyman, good men, kind-hearted, liberal, sincere, and all that, who did not know the meaning of a 'flush'. It is enough to make one ashamed of one's species." In an 1870 essay entitled "Science vs. Luck," Twain wrote about a fascinating court case in Kentucky in which a dozen schoolboys were arrested for playing poker for money. Back then, many states had strict laws prohibiting "games of chance," and even at enlightened institutions of higher learning such as Harvard University, errant students incurred the heaviest fines not for drinking or fighting, but for playing cards.

The lawyer hired to defend the 12 poker-playing boys in Twain's essay came up with an ingenious defense: poker was not a game of chance but of skill, thus his clients could not be punished until it was proven otherwise. To make a short story even shorter, the prosecution's witnesses (who were all deacons of the Church) testified that poker was all luck, whereas the defense's witnesses testified in favor of skill. The judge was unable to render a decision, and in his paralyzed state, he called upon the boys' lawyer to suggest a solution. The lawyer quickly replied: "Impanel a Jury of six of each, Luck vs. Science. Give them candles and a couple of decks of cards. Send them into the jury room, and just abide by the results." Six deacons were sworn in as the 'Chance' jurymen, and six experienced poker players were sworn in as the 'Science' jurymen.

After 1 day of deliberation, the foreman of the jury—one of the deacons—read the verdict: "We, the Jury in the case of the Commonwealth of Kentucky vs. John Wheeler *et al.* have carefully considered the points of the case and do hereby unanimously decide that the game is eminently a game of Science and not of Chance. In support of our verdict, we call attention to the fact that the Chance men are all busted; and the Science men have got the money." The judge declared the Chance theory a pernicious doctrine, and then he ruled that poker playing was no longer a punishable offense in the state of Kentucky.

I am sure that most of you are not convinced that Mark Twain's literary experiment settled the question of luck versus skill. Fortunately, the first convincing scientific experiment on the subject was recently carried out by the University of Chicago economist Steven Levitt. Levitt is the author of the best-selling book *Freakonomics*, which describes how the tools of economic research can be used to understand the workings of everyday events and problems. Several representative examples Levitt tackles in his book are: "Which is more dangerous, a gun or a swimming pool?"; "Why do drug dealers still live with their moms?"; and "What do school teachers and sumo wrestlers have in common?".

Levitt's study, called 'Pokernomics,' analyzed the performance of 32,000 players who took part in the 2010 World Series of Poker in Las Vegas. Levitt divided the players into two groups—a highly skilled group and an ordinary group. The highly skilled group consisted of the 720 players—2.3% of the total—who had won the most money in 2009 tournaments. The ordinary group comprised the rest of the 32,000—97.7% of the total. In the 2010 World Series, the skilled poker players made an average return on investment of 30%, whereas the ordinary players had an average loss of 15%. This large gap in return is strong evidence that poker, as it is played today, is a game of skill and not luck.

The luck factor in high stakes research

Do scientists who win Laskers and Nobels produce award-winning research because they are luckier than other scientists? Is luck more important than skill in high-stakes research? Quantifying the luck-versus-skill factor in research is not as straightforward as in the case of Levitt's Pokernomics study. But I think one can come up with a reasonable assessment, depending on one's definition of luck—that is, whether one is referring to blind luck or insightful luck. Blind luck is when a person *en route* to the Lasker Luncheon gets on the elevator at the Pierre Hotel, finds a lottery ticket on the floor of the elevator and wins $10 million. Insightful luck is when the same person, *en route* to the Pierre, stops at the corner kiosk, buys a lottery ticket and wins $10 million.

Blind luck is basically irrelevant to scientific discovery, but insightful luck is not. The person who purchases a lottery ticket has positioned himself or herself to win a prize. Whether or not he or she wins is a matter of mathematical probability. The same can be said for insightful scientists who purchase their skills by doing experiments, making observations, reading the literature and keeping the right company—by which I mean going to the right meetings and associating with people smarter than they are. Such a scientist has deliberately positioned and prepared him- or herself to be a strong candidate for good fortune. He or she is discovery-prone in the sense of Louis Pasteur's famous dictum: "Chance favors the prepared mind."

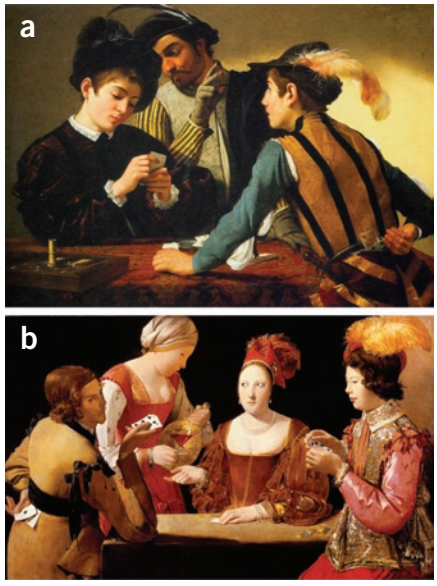

Figure 1 Two gambling-themed paintings. (**a**) Caravaggio. *The Cardsharps*, *c.* 1594. Oil on canvas, 94.2 × 120.9 cm. Kimbell Art Museum, Fort Worth, Texas, USA. (**b**) Georges de La Tour. *The Cheat with the Ace of Clubs*, *c.* 1630–1634. Oil on canvas, 97.8 × 156.2 cm. Kimbell Art Museum, Fort Worth, Texas, USA.

The driving force that moves a scientific field in a new direction is the unexpected result—the surprise finding. The highest achievements in science come from skilled and prepared-of-mind individuals who can recognize the surprise result, act on it and follow it wherever it leads.

There is no better example of the benefits of a prepared mind than the story of the invention of the microwave oven. In 1946, Percy Spencer, an electrical engineer and physicist at the Raytheon Company in Waltham, Massachusetts, visited a lab where magnetrons, the power tubes of radar sets, were being tested. Suddenly, he felt a chocolate peanut candy bar begin to melt inside his shirt pocket. According to Raytheon history, Spencer immediately sent a messenger boy to fetch a package of popcorn kernels. When Spencer held the kernels near the magnetron, popcorn exploded all over the room. Nine years later, in 1957, the first home microwave ovens were sold by Raytheon, and in 1999, Spencer was inducted into the National Inventors Hall of Fame. Spencer was not the first person to notice that microwaves generate heat, but he was the first to think of using their heat to cook food.

Spencer was a man with restless curiosity and an intense passion to explore every wonder in the world. He clearly had skill and the itch to discover. But did he have luck? Spencer created his own luck by eating candy bars. What if he had

Figure 2 Paul Cézanne. *The Card Players.* Three of the five paintings in this series are shown: (**a**) *c.* 1890–1892. Oil on canvas, 65.4 × 81.9 cm. The Metropolitan Museum of Art, New York. (**b**) *c.* 1892–1896. Oil on canvas, 47 × 56 cm. Musée d'Orsay, Paris. (**c**) *c.* 1892–1896. Oil on canvas, 60 × 73 cm. The Courtauld Gallery, London.

been overweight and on a strict Atkins-like diet? Then he would have had bad luck—as would Raytheon's stockholders, not to mention couch potatoes all over the world!

All of the lucky scientists I know have a common phenotype: they are excessively inquisitive, passionate and persistent, and they have the uncanny instinct for being in the right place at the right time. And like Percy Spencer, they have the skills they need to create their own luck. To repeat Samuel Goldwyn's dictum: "The harder I work, the luckier I get." But the last word, as always, belongs to James Watson of DNA fame: "I was very, very lucky. But, you know, they give prizes for people who are lucky."

Basic Award: an awesome piece of work

This year's Lasker Basic Medical Research Award is given for discoveries concerning the cell's protein-folding machinery, exemplified by cage-like structures that convert newly synthesized proteins into their biologically active forms. The story begins 50 years ago, when in the early 1960s, the protein chemist Christian B. Anfinsen established the principle that the primary amino acid sequence of an unstructured polypeptide chain contains all the information required for it to fold into its native state. Anfinsen's insights, for which he received the 1972 Nobel Prize in Chemistry, emerged from *in vitro* denaturation-renaturation experiments of a small 124-amino-acid, single-domain protein (bovine pancreatic RNase) that was studied at very dilute concentrations that were orders of magnitude lower than those in the cytoplasm of intact cells. Not surprisingly, most complex proteins have proven notoriously difficult to refold spontaneously when studied at the high protein concentrations that prevail in the cell. During the several minutes it takes for the ribosome to translate a typical protein of 400–600 amino acids, the emerging polypeptide chain exposes non-native features, such as hydrophobic and charged patches, that are prone to disordered aggregation and denaturation. How, then, is proper folding achieved in the intact cell?

A key insight came with the discovery of protein-folding pathways and machines by this year's Lasker awardees—Franz-Ulrich Hartl (Max Planck Institute of Biochemistry) and Arthur L. Horwich (Yale University School of Medicine). Their now-classic work began in 1989 with the publication of two papers—one genetic and the other biochemical. In the first paper, Horwich, Hartl and their colleagues carried out a genetic screen in yeast, searching for mutations that altered the folding and/or assembly of nuclear-encoded proteins after they had been imported into the mitochondria. One such mutation, which impaired the function of a mitochondrial heat-shock protein called Hsp60, was identified. But at what step was Hsp60 acting: did it promote protein folding or subunit assembly? In the second, biochemical paper, Hartl and Horwich distinguished between these two possibilities by studying, in isolated mitochondria, Hsp60-mediated import of a monomeric enzymatic protein that did not require subunit assembly. Folding of the enzyme and acquisition of its functional activity occurred on the surface of Hsp60 in an ATP-mediated reaction and was followed by release of the mature protein. These two landmark papers established unequivocally the principle of protein-assisted protein folding—a radical departure from the earlier view that protein folding in the cell is a spontaneous process.

Over the next 15 years, Hartl and Horwich carried out a series of incisive studies spanning the gamut from biochemical reconstitution to electron microscopy to X-ray crystallography to NMR spectroscopy. With these experiments, they elucidated a pathway for protein-assisted protein folding and dissected its mechanism. Although the two scientists carried out their mechanistic studies independently, their results were remarkably complementary. For experimental simplicity, both scientists turned to the bacterial ortholog of Hsp60, referred to as GroEL, and its co-chaperone GroES.

The basic function of the GroEL-GroES complex is as a protein machine that encapsulates a single molecule of newly synthesized, non-native protein in a cage-like structure, sequestering it from the rest of the cell, thus allowing folding to occur unimpaired by aggregation. The GroEL component of the GroEL-GroES folding chamber is a cylindrical complex (of ~800 kDa) consisting of two rings, each with seven identical 57-kDa subunits. The two ring-like GroEL components (referred to as the *cis* and *trans* rings) are positioned one on top of the other like two stacked donuts. The single GroES component of the structure is a dome-shaped ring (70 kDa) consisting of seven identical 10-kDa subunits. At any one time, the GroES ring is bound to only one of the two GroEL rings, capping one end of the cylinder in a lid-like fashion and producing an asymmetrical structure. The GroES lid cycles on and off GroEL in a manner regulated by the ATPase activity of the GroEL cylinder. The GroEL-GroES structure is referred to as the GroEL-GroES chaperonin machine.

As soon as a newly synthesized polypeptide chain emerges from the ribosome, it undergoes successive interactions with several different chaperones (DnaK (or Hsp70), DnAJ, GrpE) that relay the polypeptide to the GroEL-GroES chaperonin machine for final folding. The incompletely folded protein now binds to a patch of hydrophobic amino acids that line the interior rim of the non-lidded, or *trans*, ring of the GroEL cylinder. Capture of the unfolded polypeptide triggers the binding and hydrolysis of ATP in the open *trans* ring, which leads to dissociation of the GroES lid from the *cis* ring. The released GroES, together with ATP, rapidly rebinds to either GroEL ring, apparently with equal chance. However, only the binding of GroES to the polypeptide-containing GroEL ring will lead to productive folding. At this point, closing the lid induces a major confor-

mational change in the polypeptide-containing ring, producing a shift in the surface properties of GroEL from hydrophobic to hydrophilic. The result is that the unfolded polypeptide (still with its hydrophobic patches exposed) is released from the now-hydrophilic walls of GroEL into the chaperonin cavity, where it is allowed to fold. The enclosure time is ~10 s, reflecting the time required for hydrolysis of seven ATP molecules in the polypeptide-containing ring. This second ATP binding and hydrolysis event triggers the rapid dissociation of the GroES lid, allowing the polypeptide chain, whether native or not, to exit the GroEL chamber.

Any incompletely folded intermediates that still possess hydrophobic surfaces will be rapidly recaptured by the hydrophobic GroEL ring for another folding attempt. As many as ten folding cycles of capture, ATP binding and hydrolysis, and release may be required for a protein to attain its native conformation.

Titia de Lange, Lasker jury member and professor at The Rockefeller University, has come up with a gambling metaphor that vividly illustrates the GroEL-GroES reaction cycle. In roulette, the little ball (the unfolded polypeptide chain) falls into the wheel (the GroEL chamber), and the croupier says, "No further bets" (the closure of GroES lid). The ball bounces around, but then the ATP runs out and the wheel stops (the opening of GroES lid). The ball may or may not be in the winning slot. Like the polypeptide chain, the ball is lifted out and thrown back in for another chance (a new folding cycle) when the wheel (GroEL) binds ATP and starts spinning again.

The elegant GroEL-GroES chamber-like structure for folding and assembling proteins brings to mind the artistic creations of John Chamberlain, a contemporary American sculptor famous for his mastery of the art of assemblage.

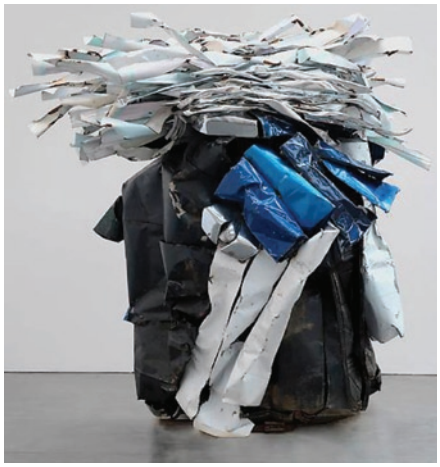

Figure 3 John Chamberlain. *AWESOMEMEATLOAF.* 2011. Painted and chrome-plated sheet. 106 × 118 3/4 × 82 in. Gagosian Gallery, New York.

Starting with abandoned automobile parts and other industrial material, Chamberlain constructs sculptures by folding, bending and twisting the metals to form works of art, often on a monumental scale. **Figure 3** shows one of Chamberlain's recent assemblages, titled *AWESOMEMEATLOAF*. Chamberlain's chamber-like structure, not withstanding its title, is itself an awesome piece of work, striking in its structural resemblance to the awesome GroEL-GroES chamber created by Nature and revealed to us by the awesome studies of Horwich and Hartl.

The discoveries of Hartl and Horwich are as universal and basic to biology as understanding the nature of genes and how they are expressed and translated into proteins. If proteins do not fold properly, cells will not function properly. Horwich's and Hartl's pioneering work has stimulated many scientists to characterize folding pathways and folding machines in multiple organisms from all three kingdoms of life. Bacterial cells and endosymbiotic organelles, such as mitochondria and chloroplasts, use detachable lid–based GroEL-GroES chaperonins of the Hartl-Horwich type. Archaea and eukaryotic cells use a folding machine that resembles the GroEL chamber in its dual ring structure and its ATP requirement but that differs in the amino acid sequence of its subunits and in its use of a built-in protrusion structure, rather than a GroES-lid structure, for encapsulation.

The medical implications of the Horwich-Hartl work are just starting to be realized. Human misfolding diseases occur when mutant proteins adopt non-native conformations that promote aggregation and formation of pathological intracellular and extracellular deposits. The most common neurodegenerative diseases arise from altered protein misfolding and accumulation of abnormal deposits in the brain—amyloid in Alzheimer's disease, Lewy bodies in Parkinson's disease, and polyglutamine-rich proteins in Huntington's and other CAG-triplet repeat diseases. Another pattern of protein-misfolding disease, as in cystic fibrosis and retinitis pigmentosa, is one in which the mutant proteins, although functionally active, fail to reach their final destination in the cell, owing to impaired transport out of the endoplasmic reticulum. The concept that disordered proteins can be chaperoned into their native state provides a therapeutic approach to these diseases that is now being vigorously pursued by many scientists.

Prior to and contemporaneous with the work of Horwich and Hartl, many scientists working on a variety of different biological systems provided biochemical insights that were highly influential to Hartl and Horwich in their early studies. In particular, Costa Georgopoulos (then at Stanford University), John Ellis (University of Warwick), George Lorimer (Du Pont de Nemours & Co.) and Hugh Pelham (Medical Research Council) each identified and characterized components of the core protein machinery (such as phage assembly factors, Rubisco subunit-binding protein, proteins upregulated by stress and so on) that ultimately proved crucial for protein folding in the cell. In addition, Gottfried Schatz (University of Basel) and Walter Neupert (University of Munich) pioneered the methodology for studying import of nuclear-encoded proteins into mitochondria used by Horwich and Hartl in their 1989 genetic and biochemical studies. But what distinguishes the contributions of Hartl and Horwich from all others in the field is their elucidation of a specific and universal pathway for protein folding that involves a container-like structure within which protein folding occurs—a revolutionary concept in cell biology. In this regard, special mention should be made of the contributions of the late Paul B. Sigler, an exceptionally talented biophysicist and crystallographer who collaborated with Horwich for 10 years. Together, they obtained the crystal structure of the GroEL-GroES chaperonin, which provided invaluable insights into how folding machines work.

Clinical Award: an awesome addition to the *Medicine Cabinet*

This year's Lasker~DeBakey Clinical Medical Research Award is given to Youyou Tu (China Academy of Chinese Medical Sciences) for the discovery of artemisinin, a drug therapy for malaria that has saved millions of lives across the globe, especially in the developing world. For more than 500,000 years, mosquitoes have been biting humans, producing malaria and eluding every remedy ever devised. Today, more than 250 million people are infected every year, and about 1 million die from it, most of them children.

The name *mal aria*, meaning "bad air," originated in ancient Rome, where it was believed that the fever of malaria was caused by unwholesome vapors emanating from the ground. To avoid the dreaded vapors, the ancient Romans built their grand villas high in the hills and prayed for relief to Febris, the goddess of fever. In the second century AD, the Roman emperor Caracalla concluded that praying to Febris was a no-win situation, and he challenged his physician, a clever man named Serenus Sammonicus, to develop a cure for malaria. Sammonicus's ingenious solution turned out to be the world's first antimalarial quick fix—wear an amulet around your neck inscribed with a powerful incantation: "Abracadabra." Sammonicus's Abracadabra invention has stood the test of time, becoming the universal secret weapon that explains how

all magicians create their magic—by relying on both luck and skill.

In the last 100 years, we have had four more Abracadabra cures for malaria. The first, appearing in the early 1900s, involved spraying mosquito-infected puddles of water with a thin layer of oil to smother the larvae. The second cure came in the 1930s with the drug quinine, soon followed in the 1940s by a third cure, chloroquine. Then, in the 1950s, the fourth Abracadabra cure, DDT, was hailed as the perfect insecticide. Together, antimalarial drugs and DDT sent the global malaria toll plummeting from 350 million cases a year to 100 million. But this success didn't last long: mosquitoes rapidly developed resistance to drugs and chemicals. By the time of the Vietnam War in the mid-1960s, quinine- and chloroquine-resistant strains of malaria had become widespread.

They were so widespread that Ho Chi Min, the leader of North Vietnam, entered into a secret military project with China to discover new drugs for chloroquine-resistant malaria. Project 523, so named for the date of its announcement, began on 23 May 1967, just after the beginning of the Chinese Cultural Revolution. Chairman Mao Zedong empowered multiple teams of scientists at the China Academy of Traditional Medicine to explore every Chinese herb known to exist. The scientist selected to lead one of the teams was a phytochemist named Youyou Tu. After 5 years of screening 380 herbal extracts in a mouse model of malaria, Tu's team discovered antimalarial activity in the leaves of a sage bush called *Artemisia annua L.* (or sweet wormwood), a medicinal herb that in China had been used for over 2,000 years to treat all types of fevers. The standard medicinal extraction procedure—boiling herbs at high temperatures—yielded no anti-malarial activity. The key to Tu's discovery was the use of a radically different method: extraction with ether at low temperatures.

Convinced of its safety after toxicity studies in mice and in normal human volunteers, Tu's team administered the extract to patients infected with *Plasmodium vivax* and *Plasmodium falciparum* and compared the results with those for a control group treated with chloroquine. Because these clinical studies were done secretly during the Cultural Revolution, there are no contemporaneous publications documenting the observations. But according to retrospective interviews with Tu and other team members, the very first clinical results were impressive: the *Artemisia* extract reduced fever and decreased the number of malaria parasites in blood much faster than chloroquine.

By 1977, Tu and her team had purified the active component of the extract, named it artemisinin, and determined its chemical structure—a sesquiterpene lactone peroxide with a molecular weight of 282. Shortly thereafter, in collaborative clinical trials, Guo-Qiao Li (Guangzhou College of Traditional Chinese Medicine) and Keith Arnold (Roche Far East Research Foundation, Hong Kong) showed the effectiveness of combined therapy using artemisinin and the quinine-like drug mefloquine. The publications of these trials in *The Lancet* in 1982 and 1984 were highly influential in bringing artemisinin to the attention of the Western world.

In the late 1980s, scientists at the Academy of Military Medical Sciences in Beijing recognized the superior effectiveness of artemisinin when it is combined with a quinine-like aryl alcohol called lumefantrine. These two drugs differ in molecular target, and in mode and duration of action. Once human hemoglobin is taken up and degraded in the parasite's digestive vacuole, the released iron-containing heme cleaves artemisinin's endoperoxide ring, generating reactive oxygen radicals that kill the parasite. Lumefantrine is believed to prevent the detoxification of heme, thus prolonging the action of artemisinin. The combination drug containing an artemisinin derivative (short acting) and lumefantrine (long acting) is called Coartem. When tested in several Asian countries in the late 1980s, Coartem had virtually no toxicity and was highly effective, with cure rates of over 96%, even in areas of multi-drug-resistant disease.

In 1990, Chinese officials met with representatives of Novartis Pharmaceutical Corp., and the two parties agreed to develop, manufacture and patent Coartem through a joint venture—the first such collaboration of its kind and involving the first internationally patented drug in Chinese history. In 2001, Novartis and the World Health Organization (WHO) signed an agreement to distribute Coartem at cost to the public sector of malaria-endemic countries. This unprecedented agreement is now backed by many other organizations, including UNICEF, Doctors without Borders and the US President's Malaria Initiative, as well as the Holy Trinity of Gates, Bono and Clinton.

Over the last 10 years, Novartis has supplied, without profit, more than 340 million treatments of Coartem, including a dispersible form designed for infants. The price per treatment pack for the developing world is 76 cents for adults and 36 cents for children. More than 1 million lives have been saved. Coartem has been approved for use in 80 countries and received US approval in 2009.

Will Coartem end up as another Abracadabra cure for malaria? Only time will tell, but for the moment, the discovery of artemisinin by Youyou Tu and her team has revolutionized the treatment of malaria, saving millions of lives worldwide. WHO now lists artemisinin in its catalog of 'Essential Medicines'. Artemisinin also deserves its place as an awesome addition to the *Medicine Cabinet* series by Damien Hirst, the contemporary British artist famous for his iconic body of work that includes formaldehyde-pickled sharks, butterfly assemblages and diamond-encrusted skulls. Hirst's *Medicine Cabinets*, one of which is shown in **Figure 4**, is a series of 14 cabinets displaying rows of packaged drugs—each carefully placed and meticulously selected—behind a glass cover. The sculptures convey the impression that society places drugs on a pedestal with the hope that they will cure our ills, even in the face of hopelessness. Today, we are hopeful that artemisinin will not disappoint.

Figure 4 Damien Hirst. *Medicine Cabinet: Problems.* 1989–2010. Glass, faced particle board, ramin, wooden dowels, plastic, aluminum and pharmaceutical packaging. 54 × 40 × 9 in. White Cube Gallery, London.

Joseph L. Goldstein is Chair of the Lasker Awards jury.
email: joe.goldstein@utsouthwestern.edu

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To read the formal remarks of speakers at the Lasker ceremony, as well as detailed information on this year's awardees, please refer to the Lasker website at http://www.laskerfoundation.org/.

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