Paradigm shifts in science: insights from the arts

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This year marks the fiftieth anniversary of the publication of a highly influential book, *The Structure of Scientific Revolutions* by the physicist and historian Thomas Kuhn[1]. This is the book that introduced the world to the principles of "paradigms" and "paradigm shifts." Ironically, it is also the book in which the author underwent his own paradigm shift by debunking the prevailing theory of how scientific progress comes about.

Prior to Kuhn's 1962 book, historians and philosophers of science considered the scientific enterprise to be a rational endeavor in which progress and knowledge are achieved through the steady, day-to-day, painstaking accumulation of experimental data, accredited facts and new discoveries. Kuhn referred to this traditional approach as "normal science," and he used the then-obscure word paradigm to refer to the shared ideas and concepts that guide the members of a given scientific field.

Kuhn's great insight was to realize that real progress did not result from the puzzle-solving of normal science. Instead, he argued that true breakthroughs arise in a totally different way—when the discovery of anomalies leads scientists to question the paradigm, and this in turn leads to a scientific revolution that he termed paradigm shift. Kuhn based his model on the classic paradigm shifts in physics, including the Copernican, Newtonian and Einsteinian revolutions, the development of quantum mechanics, which replaced classical mechanics at the subatomic level, and the accidental discovery of X-rays by Roentgen, one of the great unanticipated anomalies in the history of science.

In one sense, Kuhn viewed normal science as a mopping-up operation. Yet he did recognize the essential importance of normal science, appreciating that most discoveries occur during periods of normal science. To illustrate with a contemporary example, consider the Higgs particle, which high-energy physicists believe to be fundamental for the existence of all matter. On the one hand, in the Kuhnian sense, finding the Higgs particle is normal science operating in the context of the existing paradigm of the standard model of particle physics. On the other hand, not finding the authentic Higgs particle would be a paradigm-shifting anomaly, pointing to a new physics beyond the standard model.

Speaking of anomalies, there are several that surround Thomas Kuhn. How did a scientist who was passed over for tenure at Harvard write one of the great books of the last 50 years—a book that has become a cultural icon like *1984* and *The Double Helix*? Since its publication in 1962, *The Structure of Scientific Revolutions* has sold 1.5 million copies in 16 languages, is still required reading in courses in the history and philosophy of science and is cited more often than the classic works of Sigmund Freud, Noam Chomsky and James Watson. Its success is even more surprising when one takes a look at its first review published in *Scientific American* in 1962. The last sentence reads: "The book succeeds in presenting sound but familiar reflections on the nature of science; it is also much ado about very little." So much for bad reviews!

The most obvious reason for *Structure*'s astonishing success is the thought-provoking way in which Kuhn framed his thesis, adorning it with the two unfamiliar but sexy catchwords. In the last ten years, paradigm and paradigm shift have pervaded virtually every aspect of our culture. Today, you can purchase audio and video equipment from Paradigm Electronics in Ontario, Canada; you can buy bonds and stocks from Paradigm Financial Partners in the UK; you can obtain solutions to your human resource problems from Paradigm Shift Consulting Service, Ltd. in India; or—best of all—you can read a provocative Paul Krugman op-ed piece in *The New York Times* entitled "The Ponzi Paradigm."

One of the most surprising anomalies in relation to Kuhn is the lack of any mention in *Structure* of the two greatest paradigm shifts in the biological sciences—Darwinism and Mendelism. The most likely explanation is that Kuhn was totally focused on physics, which in the 1950s and 1960s was top scientific dog.

It is ironic that the year in which *Structure* appeared was the same year in which the first molecular structures of DNA and protein were awarded Nobel Prizes—one in Physiology or Medicine to James Watson and Francis Crick and the other in Chemistry to Max Perutz and John Kendrew. If ever a science was on the verge of a paradigm shift, it was molecular biology in 1962. The genetic code had just been cracked, and recombinant DNA and gene cloning were just around the corner. To paraphrase Virginia Woolf, on or about December 10, 1962, the world of science changed.

What about paradigm shifts in the arts? Kuhn believed that great works of art retain their value throughout time even in the face of new revolutionary movements. To quote Kuhn, "Picasso's success has not relegated Rembrandt's paintings to the storage vaults of art museums."[2] So what should we call Pablo Picasso's and Georges Braque's transition from impressionism to cubism or Jackson Pollock's and Willem de Kooning's transition from realism to abstract expressionism? If they are not paradigm shifts, given the cutthroat competitive nature of the art world, what about paradigm rifts? Or paradigm tiffs?

James Rosenquist and instantly forming ideas

Although Kuhn's paradigm model may not be strictly relevant to the arts, artists have nonetheless shed light on a key question that

was never answered by Kuhn: Where do the daring ideas in science that bring on paradigm shifts come from? Some ideas, according to the American artist James Rosenquist, arise explosively in a light-bulb moment in the middle of the night. Rosenquist is one of America's most creative contemporary artists. Together with Andy Warhol and Roy Lichtenstein, he was one of the three founding members of the Pop Art movement in the 1960s. One of his signature paintings of 1960, entitled *President-Elect*, shows a charismatic President John F. Kennedy juxtaposed with a woman's hand holding a piece of devil's food cake and with a 1960 Pontiac. The devil's food cake is a stand-in for a tempting female, and the car is astonishingly prophetic, foreshadowing by three years Kennedy's ill-fated motorcade death.

Now that Rosenquist is approaching 80 years of age, his artistic interests have shifted from visualizing popular culture to visualizing the philosophy of ideas. According to Rosenquist, "A good idea that spurs you on to do something should have pictorial power. After all, what does a great idea look like?"

So, in 2007, Rosenquist created a series of sculptures and paintings that deal with the origin of ideas[3]. **Figure 1a** shows a sculpture entitled *Idea—Middle of the Night*. The pencils that pierce the light bulb articulate the hands of a clock. The pencils also have to do with writing down an idea that pops into your head in the wee hours of the night. **Figure 1b** shows a painting entitled *Idea, 2:50 a.m.* The bulb is the light that goes off suddenly in your mind in the middle of the night like an intellectual alarm clock. The bulb is also the light that you need to write down your fleeting inspiration before it is forgotten.

In the painting in **Figure 1c**, entitled *Idea, 3:50 a.m.*, the light bulb represents the beginning of an idea that explodes in so many different directions that it becomes an abstract version of itself, ultimately developing into something completely new—like a paradigm shift.

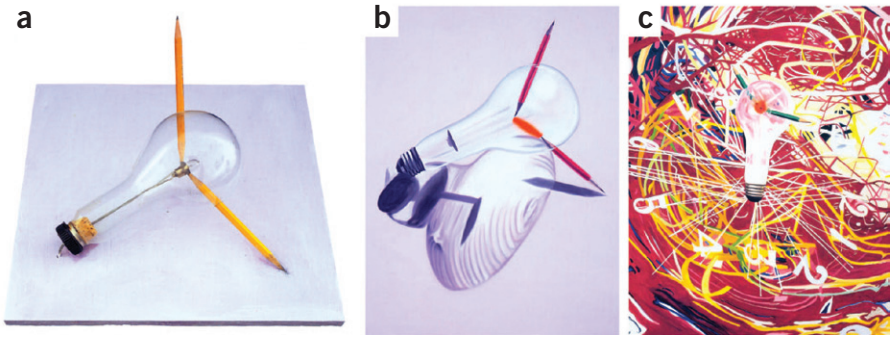

Figure 1 Instantly forming ideas. (**a**) James Rosenquist, *Idea—Middle of the Night*, 2007. Light bulb, pencil and electric wiring on painted wood. 7.5 × 12 × 12 inches. (**b**) James Rosenquist, *Idea, 2:50 a.m.*, 2007. Oil on canvas. 57 × 44 inches. (**c**) James Rosenquist, *Idea, 3:50 a.m.*, 2007. Oil on canvas. 63 × 49 inches. Exhibited at Acquavella Gallery, New York, New York.

Giuseppe Penone and slowly forming ideas

The Italian sculptor Giuseppe Penone, in contrast, tells us that a great idea does not arise in an explosive moment but rather forms in a very slow process of aggregation and crystallization, such as that which occurs in the formation of a rock.

Penone is widely regarded as one of Italy's leading contemporary artists. He is best known for his outside environmental installations in which trees sculpted out of wood or bronze are integrated with nature in a thematic way. Penone's most recent installation was commissioned as the centerpiece for this year's Documenta exhibition of contemporary art, which takes place every five years in Kassel, Germany[4].

Penone's piece, entitled *Idee di pietra* (*Ideas of Stone*), consists of a bronze structure of a large nut tree (30 feet tall) with a stone lodged high in its branches (**Fig. 2**). The stone is a type of granite rock that contains billions of crystals of silicate minerals that were formed over many years by the natural processes of weathering and erosion. Penone purposely selected a stone that has the shape of a human brain, thus producing a brain of billions of silicate crystals, each crystal possessing a precise geometry that symbolizes order and logic like great thoughts produced by neurons in the brain. So in this sense, Penone's structure is telling us that the big idea forms like the stone at the top of the tree—through a slow and gradual process of crystallization and organization of billions of tiny thoughts (tiny crystals) into one big idea (one big stone).

Of the two different ideas for the origin of ideas, Rosenquist's dream theory of the eureka moment is more apocryphal than real. Perhaps the most famous example in science is August Kekulé's somnolent vision of a snake biting its tail, which supposedly revealed to the German chemist the true structure of the benzene ring. But the dream vision most relevant to biomedical science occurred to the German physician, Otto Loewi, who won a Nobel Prize in 1936 for his discovery of acetylcholine as a neurotransmitter. Before Loewi's light-bulb moment, it was unclear whether signaling across a synapse was electrical or chemical. Loewi's dream-inspired experiment, done within hours after he awoke, provoked him to remove the beating hearts from two frogs, one with the vagus nerve attached and the other with the vagus nerve removed. Both hearts were placed in separate salt solutions. When Loewi stimulated the vagus nerve of the first heart, it beat slower. Then, when he took the fluid from this stimulated heart and added it to the second heart that had no vagus nerve, the second heart beat slower, proving that a soluble chemical, which turned out to be acetylcholine, was released from the vagus nerve and controlled the heart rate.

Did the shy and reserved Otto Loewi tell his tale as it really happened? One expects tall tales from certain Texas Nobel laureates, but not from a taciturn German one. As you will read in the essays of this year's Lasker winners, the daring ideas that led to their awards were formed in a complex way that combines the slow-hunches of Penone with the instant light-bulb moments of Rosenquist.

Basic Award: a set of daring experiments

This year's Lasker Basic Medical Research Award is given to three scientists for their discoveries concerning the biochemical mechanisms and cellular actions of cytoskeletal motor proteins. The three recipients are Michael Sheetz (Columbia University), James Spudich (Stanford University) and Ronald Vale (University of California–San Francisco).

Motor proteins are mechanoenzymes that use the energy of ATP to contract muscles and power the movement of intracellular vesicles and organelles, chromosomes and mRNA-protein complexes through the cytoplasm. Eukaryotic cells contain three types of motor proteins—myosin, kinesin and dynein—that move along two different systems of tracks made up of specific protein polymers. Myosin moves along actin filaments in a unidirectional way; kinesin and dynein move along microtubules in opposite directions.

Sheetz, Spudich and Vale developed sophisticated *in vitro* assays that allowed

the biochemical reconstitution of cellular movement from its constituent components; enabled the discovery of kinesin; revealed the nature and force of each molecular step by which the three motor proteins convert the chemical energy of ATP into mechanical work; and led the way to single-molecule analysis of biological systems.

Twenty-five years before the research of this year's Basic Award winners, the physicist Richard Feynman gave the oft-quoted lecture "There is Plenty of Room at the Bottom" at the California Institute of Technology. In it, he speculated on the potential use of individual atoms and molecules to manipulate matter, foreshadowing the field of nanotechnology. At the end of his lecture, Feynman offered a prize of $1,000 to the first person who could build a tiny working motor that would fit inside a cube 1/64 of an inch on each side (1/64 inch is one-half the thickness of a credit card). Little did Feynman realize that each of the cells in all plants and animals contains thousands of tiny molecular motors that are tens of thousands of times smaller and infinitely more efficient than what he imagined. Thanks to the elegant work of Sheetz, Spudich and Vale, we now know at the single-molecule level how nature's motor proteins—myosin, kinesin and dynein—convert chemical energy into mechanical work.

Clinical Award: a mastery of surgery and immunosuppression

This year's Lasker~DeBakey Clinical Medical Research Award is given to two surgeons who pioneered the development of liver transplantation, which has restored normal life to thousands of patients with end-stage liver disease. The two recipients are Roy Y. Calne (University of Cambridge) and Thomas E. Starzl (University of Pittsburgh).

Fifty years ago, transplantation of the human liver was widely believed to be impossible, owing to insurmountable technical, physiological and immunological difficulties. The technical challenges involved the need for multiple and complex vascular and biliary anastomoses. The physiological challenges involved the need to maintain the liver's essential functions (coagulation factors to prevent bleeding, nutrient supply to prevent hypoglycemia and detoxification to prevent accumulation of toxic products of metabolism)—all in the absence of interim support measures analogous to hemodialysis in kidney transplantation or cardiopulmonary bypass in heart transplantation. And most formidable of all were the immunological challenges, owing to the lack of effective drugs to prevent rejection of the transplanted foreign liver.

Many of the technical and physiological aspects of orthotopic liver transplantation were largely resolved in dog and pig experiments done in the 1950s and early 1960s, and new immunosuppressive agents—azathioprine and antilymphocyte serum—had become available by the early 1960s. Yet the first human liver transplants performed in 1963 failed miserably, the first five patients dying of clotting abnormalities or liver infarctions.

The first short-term success, defined as a one-year survival, was achieved in 1967 by Starzl and in 1968 by Calne. This initial success depended on technical refinements in the surgical procedure and on the addition of several new immunosuppressive agents—prednisone introduced by Starzl and cyclosporine by Calne. Over the next 30 years, with great tenacity and zealous dedication, Starzl and Calne continued to optimize and refine their surgical techniques and their immunosuppressive protocols, with Starzl introducing FK-506 (Tacrolimus) in 1989 and Calne adding rapamycin (Sirolimus) soon thereafter.

Today, in the US, more than 6,000 people receive a liver transplant each year. Since 1988, a total of 120,000 patients in 100 medical centers have received transplants. Liver transplants are successfully done for virtually every form of inherited and noninherited liver disease, ranging from biliary atresia (absence of the bile ducts) in children to cirrhosis caused by chronic hepatitis C or alcoholism in adults.

Current survival statistics are impressive. The one-year survival rate is 89%, the five-year survival rate is 80% and the ten-year survival rate is 60%. More than 50,000 people in the US are currently living with a transplanted liver, allowing them to return to gainful employment and normal activities. The world's longest living survivor, now in her forty-third post-transplant year and in excellent health, was operated on by Starzl in 1970 when she was three-and-a-half years old. At the time of her transplant, she was severely jaundiced, suffering from severe liver failure caused by biliary atresia. She received the liver and gallbladder from a seven-year-old boy killed in an automobile accident.

Figure 2 Slowly forming ideas. Giuseppe Penone, *Idee di pietra (Ideas of Stone)*, 2012. Bronze and granite stone. 30 × 10.8 feet. Exhibited at Karlsaue Park, Documenta 13, Kassel, Germany.

Calne and Starzl 'double-handedly' transformed liver transplantation from an experimental endeavor in animals to a vibrant clinical practice in humans. Their role in this miraculous achievement is universally acknowledged. Starzl and Calne possess four personal characteristics that account for their success: (i) an exceptional command of hepatic physiology and disease; (ii) masterly skills as surgeons and clinicians; (iii) unwavering persistence, perseverance and focus in devising better and better approaches to immunosuppression; and (iv) the boldness and tenacity to ignore substantial skepticism and criticism from the biomedical community. This last characteristic reflects the philosophy of Thomas Kuhn, who wrote, "progress consists of a series of great and small revolutions against authority" and "a great advance necessitates the overthrow of an established dogma."

Special Achievement Award: a special pair with a deep love for science

The Lasker~Koshland Special Achievement Award is given to a scientist whose lifetime contribution to medical science is universally admired for its creativity, importance and impact, and whose professional statesmanship has engendered within the biomedical community the deepest feelings of awe and respect. This year's award is particularly special in that it is given to not one but two scientists, Donald D. Brown (Carnegie Institution for Science in Baltimore) and Tom Maniatis (Columbia University College of Physicians and Surgeons), for their fundamental discoveries concerning the molecular nature of genes and for their selfless commitment and generosity in promoting the careers of young scientists.

Donald Brown. Beginning in the early 1960s when virtually nothing was known about the structure or regulation of eukaryotic genes, Brown was among a handful of scientists to approach molecular biology the way it is done today—by purifying individual genes and analyzing their structure, function and regulation. His experimental system was the amplified ribosomal RNA genes in *Xenopus laevis*, and his biochemical tool was density gradient centrifugation. With a purified ribosomal 5S gene in hand, Brown established a cell-free transcription system that allowed him to define the control elements upstream, downstream and (most surprisingly) internal to the gene. The finding that transcriptional control elements may not be limited to the upstream region of a gene (the classic promoter in the François Jacob–Jacques Monod paradigm) overturned existing dogma, foreshadowing a phenomenon that is now commonly observed for many genes.

Another of Brown's key achievements was the identification of a transcription factor, now called TFIIIA, that recognizes the internal control element of the 5S gene. TFIIIA, the first gene-specific eukaryotic transcription factor to be characterized, was subsequently purified by Robert Roeder and shown by Aaron Klug to be the founding member of the zinc finger category of DNA-binding proteins. A wonderful example of Brown's scientific generosity was his gift, with no strings attached, of purified 18S and 28S ribosomal RNA genes to Herb Boyer and Stanley Cohen for use in their classic 1974 cloning work that opened the study of eukaryotic genes to recombinant DNA.

With the enormous amount of information currently available on eukaryotic gene structure and function, it may be difficult for contemporary biomedical scientists to appreciate the boldness, originality and historical significance of Brown's research. To those who entered the fields of molecular biology in the days just before the arrival of recombinant DNA, Brown's discoveries served as a guiding light and inspiration to their work.

As director of the Department of Embryology at the Carnegie Institution from 1976 to 1994, Brown created a culture of intellectual rigor, unrestricted creativity and respect for colleagues. His department launched the careers of an incomparable group of scientists, including Peter Agre, Igor Dawid, Nina Fedoroff, Andrew Fire, Douglass Koshland, Steve McKnight, Richard Pagano, Robert Roeder, Gerry Rubin and Allan Spradling. Two in the group, Peter Agre and Andrew Fire, began their Nobel Prize–winning work in Brown's department.

In addition to his scientific legacy, Brown has been a selfless leader at a national level. In 1982, he created from scratch the Life Science Research Foundation (LSRF), an organization that has provided postdoctoral stipends to 450 outstanding young scientists over the last 30 years. Inasmuch as LSRF has no endowment, each year for 30 years Brown has single-handedly cajoled and persuaded corporations, nonprofit organizations and disease foundations to provide funds to support 10–20 new postdoctoral fellows every year. Over these 30 years, Brown has not taken a single LSRF postdoctoral fellow in his own lab, and he has not received any remuneration for his service. His LSRF work is a labor of love for young scientists.

Tom Maniatis. Beginning in the mid 1970s, soon after Boyer and Cohen invented gene cloning, Maniatis pioneered the development of methods for isolating a single-copy protein-coding gene or its corresponding mRNA (that is, cDNA) from the rest of the genome or from total mRNAs in the cell. Together with his collaborators, Agriris Efstratiadis and Fotis Kafatos, he was the first to successfully clone a full-length cDNA molecule, the cDNA for the rabbit β-globin gene. In 1978 Maniatis constructed the first human genomic DNA library containing all the genes in the human organism. From this library, he and his colleagues isolated the entire cluster of α- and β-globin genes and then developed expression systems in cultured mammalian cells to test their function. Maniatis made his human genomic library freely available to scientists throughout the world, thus permitting the isolation of numerous normal and disease-causing genes.

Maniatis's list of original scientific achievements does not stop with his cloning accomplishments. He and his colleagues delineated the fundamental two-step biochemical mechanism for pre-mRNA splicing (independently done by Philip Sharp), including the discovery of the key RNA intermediate, the lariat. He identified and biochemically characterized the virus-inducible interferon-β transcriptional enhancer, introducing the concept of the enhanceosome and the combinatorial control of gene expression. He discovered new aspects of the signaling pathways involved in innate immunity—in particular the role of the ubiquitin system in the nuclear factor-κB pathway and the identification and purification of the multicomponent IκB kinase (IKK), the key enzyme that activates nuclear factor-κB in response to tumor necrosis factor, interleukin-1 and other effectors. And this list does not include his two most recent pursuits: study of the cadherin-like proteins and how they mediate cell-cell interactions in the brain and study of the mechanistic basis of the motor neuron damage in amyotrophic lateral sclerosis.

Much of Maniatis's success in mastering such a wide range of biomedical research can be attributed to his dedicated mentorship over the last 35 years of 52 graduate students and 65 postdoctoral fellows, many of whom have become leading scientists. Three have become members of either the US National Academy of Sciences (Gary Struhl) or the Royal Society of London (Nick Proudfoot and Richard Treisman), and one received the 2012 National Academy of Sciences Award in Molecular Biology (Zhijian "James" Chen).

In addition to his scientific accomplishments, Maniatis has shown a generosity that is a model for all scientists. During the early days of recombinant DNA, he shared his ideas and his reagents without strings attached, and for many years he gave tirelessly of his time and energy to teach courses on the new science of

molecular cloning at the Cold Spring Harbor Laboratories. David Botstein has pointed out that Maniatis served the modern molecular biology and medicine community in the early 1980s in the same way that Luria and Delbrück served the pioneers of molecular biology in the middle of the twentieth century.

In 1982, Maniatis assembled his laboratory protocols and, together with Joseph Sambrook and Edward Fritsch, published a laboratory manual entitled *Molecular Cloning: A Laboratory Manual*, which taught the world how to use the techniques of recombinant DNA. In the 1980s and 1990s, the name Maniatis became a household word in the lingua franca of biomedical scientists. The 'Maniatis Manual', now in its fourth edition under the current lead editorship of Joe Sambrook, has sold more than 250,000 copies and has become the 'Bible' that graduate students and postdoctoral fellows read religiously. I daresay that in the last three decades, many more scientists have studied the gospel of Saint Maniatis than the gospel of Saint Matthew.

Don and Tom. Although Don Brown and Tom Maniatis never worked together, they share a number of personal characteristics that account for the awe and respect accorded to them by their peers. These include: (i) a preternatural combination of generosity, integrity and humility; (ii) the highest standards of rigor; (iii) a knack for picking 'impossible' problems; (iv) an indomitable courage to tackle these impossible problems; (v) a technical virtuosity that is unique in the sense that their expertise in technology is not limited to technology *per se* but is directed toward solving key biological problems; and (vi) most important of all—a deep love for science that they share with everyone.

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Lasker Award recipients receive an honorarium, a citation highlighting their achievement and an inscribed statuette of the Winged Victory of Samothrace, which is the Lasker Foundation's symbol of humankind's victory over disability, disease and death.

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/.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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