How to win a Lasker? Take a close look at *Bathers* and *Bulls*

Joseph L Goldstein

Some of our most influential scientists have spent their spare time moonlighting as amateur philosophers. Famous figures like the physiologist Claude Bernard, the biochemist Hans Krebs, the immunologist Peter Medawar, the physicist Richard Feynman and the molecular biologist James Watson have offered all sorts of guidance on how to become more creative and make groundbreaking discoveries. There is no shortage of advice to the young scientist. The challenge is to distinguish the good advice from the not-so-good advice.

Aristotle said the one thing that distinguishes humans from all other animals is that "man is a list-making creature." Not one to disappoint Aristotle, I present here my list of the best advice in science, culled from the wisdom of the experts.

- Ask the right question (Claude Bernard, 1813–1878).
- Select the right mentor, one who can teach you how to be ruthless in criticizing your own work (Hans Krebs, 1900–1981).
- Be passionate and obsessive about solving a problem (Peter Medawar, 1915–1987).
- Be audacious and take risks, or as Richard Feynman (1918–1988) would say, "have your tea with lemon *and* cream."
- Avoid boring people (James Watson, 1928–).

Not a bad list, but also not a foolproof formula for a scientific breakthrough that will win you a Lasker Award or a Nobel Prize. In my view, the single most useful piece of advice on how to achieve scientific greatness comes from the British scientist Godfrey H. Hardy (1877–1947), who dominated the field of mathematics in the early 1900s. To the pure mathematician, Hardy's major achievement was in analytic number theory. To the biomedical scientist, Hardy is best known for formulating the Hardy-Weinberg Law, a basic principle of population genetics that is used to calculate gene frequencies.

"Cerebral chills" and "intellectual kicks"

In the last few years of his life, Hardy wrote a short essay on how to become a great mathematician. Published in 1940 with the provocative title "A Mathematician's Apology," it received a rave review in *The Spectator* by the British novelist Graham Greene, who began by saying that Hardy had nothing to apologize for. "I know of no writing—except perhaps Henry James's introductory essays—which conveys so clearly and with such an absence of fuss the excitement of the creative artist," Greene wrote.

In the essay, Hardy likened mathematics to art, arguing that the best mathematicians were those who approached their work like artists rather than practitioners: "the mathematician's patterns, like the painter's … must be beautiful." Hardy's idea of mathematical beauty was a piece of science that gave him a "cerebral chill" and an "intellectual kick"—one that combined the qualities of significance, generality and unexpectedness. These are the same qualities that produce chills and kicks in members of the Lasker jury.

If we follow the logic of Hardy, this purest of all pure mathematicians, then the best way to learn how to become a great scientist is to study how great artists—artists like Matisse and Picasso—create their magic. And this brings me to two magical works, Matisse's *Bathers by a River* and Picasso's *The Bull*. *Bathers* and *Bull* owe their power to two essential ingredients: radical thinking and fearless experimentation.

Matisse's *Bathers*

In the first 20 years of his career, Henri Matisse was best known for his vibrant paintings of exotically dressed young women, lush interiors and pastoral landscapes. By the beginning of the twentieth century, he had become the undisputed master of rich bright colors, as seen in famous works such as *The Red Room*, *The Dance* and *The Woman with a Hat*. Then, in an astonishing five-year period between 1909 and 1913, he abruptly abandoned his signature decorative style and invented a new type of modern art—one that at the time was radical in both its imagery and its technique.

With his new method of construction, Matisse would begin a painting with a realistic scene that he eventually reduced to a nearly abstract image by reworking the surface of the canvas like a sculptor rather than a painter. After applying multiple layers of paint to the canvas, he would scrape, scratch and incise the surface and then reapply more thick paint, repeating the process over and over again until the perfect forms and sculptural depth emerged. The stimulus for this profound change in Matisse's thinking was the realization that he was losing his top-dog position in the Parisian avant-garde scene to Picasso, who was then inventing Cubism. As Samuel Johnson famously said, "there is nothing like the prospect of a hanging to concentrate the mind."

The supreme example of Matisse's new approach to painting is the monumental *Bathers by the River*[1]. When Matisse started *Bathers* in 1909, it was intended as one of three large decorative panels commissioned for the drawing room of a wealthy Moscow collector. The design for the original version of *Bathers* was an idyllic landscape scene rendered in pastel colors depicting five nude women, two of whom were luxuriating in a waterfall (**Fig. 1a**). The Moscow patron bought two of the panels but turned down *Bathers*—too much nudity for his grand staircase. The timing of this rejection coincided with the beginning of Matisse's new sculptural approach to painting. In a frenzy of experimentation over the next eight years, from 1909 to 1917, Matisse repeatedly reworked *Bathers*, revising the composition more than 20 times, as documented with the latest technologies of X-radiography, infrared reflectography and stereoscopic microscopy. Conservatory experts at the Art Institute of

Chicago have distinguished 17 different states of color in the finished painting that were left over from earlier versions. Most amazing of all, the finished version contains traces of green and blue from the very earliest 1909 version.

The finished *Bathers by a River* (**Fig. 1b**), which hangs today at the Art Institute, looks very different from the 1909 original (**Fig. 1a**). One of the five bathers has been removed, and the remaining four have been transformed from fleshy and languid women to abstract and totem-like figures, which are segmented in the four vertical bands of dark green, black, gray and light blue that define the spatial contours of the painting. The blue-and-white waterfall of the original has been transformed into the vertical black band, onto which a white snake crawls.

Before *Bathers* was acquired by the Art Institute in 1953, it hung during the 1930s and 1940s in the lobby of an art gallery on East 57th Street in New York. The eminent art critic Clement Greenberg claimed that he was so mesmerized by *Bathers* and saw it so often that he could copy it by heart. *Bathers* also influenced many budding young artists, such as Jackson Pollock, Willem de Kooning, Mark Rothko and Barnett Newman. Perhaps more than any other single painting, *Bathers* was the bridge that connected the representational art of Cézanne with the full-blown abstract expressionism of Jackson Pollock and his contemporaries.

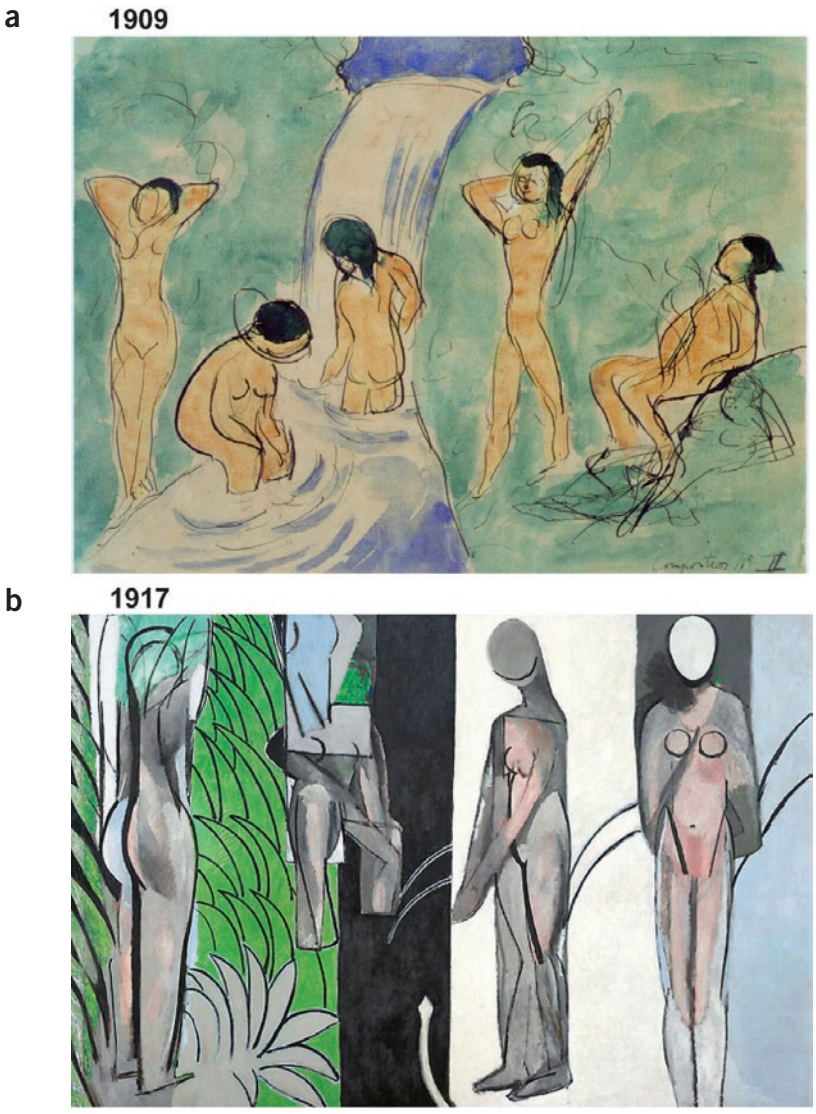

Figure 1 Matisse's *Bathers*: from start to finish, eight years. (**a**) Henri Matisse, *Composition No. II*, 1909. Watercolor on paper, 21.9 × 29.5 cm. State Pushkin Museum of Fine Arts, Moscow. This watercolor was the starting design for what eventually became *Bathers by a River*. (**b**) Henri Matisse, *Bathers by a River*, 1917. Oil on canvas, 260 × 392 cm. Art Institute of Chicago.

Picasso's *Bull*

Like Matisse, Pablo Picasso was a radical thinker and a fearless experimenter. But there was one profound difference between Matisse and Picasso: Picasso produced his work with prodigious speed. He could take the bull by the horns like no other artist. Not surprisingly, bulls—the iconic emblem of macho Spain—became one of Picasso's favorite subjects, second only to his wives and mistresses.

To celebrate the end of World War II and the liberation of Paris, Picasso engaged in a nonstop orgy of lithographic printmaking, in which he used the bull to illustrate how the artist turns reality into abstraction[2]. Over a 45-day period and with a single plate of stone, Picasso produced a suite of 11 prints, each depicting the bull in a different body form. In the print from the third lithographic plate, the bull emerged as a beefy, plump, well-nourished beast (**Fig. 2a**). Picasso then reworked the plate to create eight new versions of his original bull, with the bull getting leaner (**Fig. 2b**) and leaner (**Fig. 2c**) in each successive version. He was deconstructing the bull by carving away slices of its beef from the stone lithographic plate. After slicing the stone, Picasso would look at his assistants and exclaim, "look, we ought to give this bit to the butcher. The housewife could say, 'I want that piece or this one.'" In the last version, plate number 11, the bull was reduced to its essential elements: the body was an outline of only a few strokes, the head the size of an ant and the genitalia the size of a pea (**Fig. 2d**). Picasso's 45 days of goring the bull captured the essence of the beast in as minimal an image as possible—a vivid example of radical thinking and fearless experimentation.

Like Matisse and Picasso, this year's Lasker awardees are imaginative thinkers and fearless experimentalists, and their scientific accomplishments fulfill G.H. Hardy's three axioms for scientific greatness: significance, generality and unexpectedness.

Basic Award: conjoined mice, conjoined discoveries

This year's Basic Medical Research Award is given to Douglas L. Coleman (The Jackson Laboratory) and Jeffrey M. Friedman (The Rockefeller University) for their discovery of leptin, a hormone that regulates appetite and body weight—a breakthrough that opened the field of obesity research to molecular exploration.

The story begins 60 years ago, when an obese mouse arose at random at The Jackson Laboratory. The mouse ate continuously and weighed three times as much as wild-type mice. Breeding studies showed that the obesity resulted from homozygosity for a mutation in a single gene, named *ob*. Ten years

later, in the early 1960s, Coleman identified another massively obese mouse that spontaneously appeared in the Jackson colony. The obesity in this new mouse also resulted from homozygosity in a single gene, named *db*. *db/db* mice resembled *ob/ob* mice phenotypically in body weight, but diabetes was more severe in the former than in the latter.

Soon after the discovery of *ob/ob* and *db/db* mice, Coleman began a series of ingenious and technically demanding experiments in which he conjoined the circulatory systems of two mice, one of each type, in a technique called parabiosis. When the *ob/ob* and *db/db* mice were sewn together, the *ob/ob* partner stopped eating, lost weight and died of starvation, whereas the *db/db* partner remained obese. Coleman concluded that *ob/ob* mice fail to produce a functional hormone that inhibits appetite and eating, whereas *db/db* mice overproduce the hormone but lack the receptor to respond to it. His conclusion that the *db/db* mouse overproduces a satiety hormone to which it cannot respond was verified in further parabiotic unions of *db/db* mice with normal mice, which resulted in starvation and death of the normal partner.

In the early 1970s, when Coleman first advanced the concept that the *ob* gene encodes a circulating satiety hormone and the *db* gene encodes its receptor, the idea was far too radical to be taken seriously by mainstream endocrinologists. Its validation at a molecular level did not come until 20 years later, when Friedman began his independent scientific career with the bold goal of identifying the *ob* gene by positional cloning. This was an especially arduous task because the *ob* trait is recessive, so heterozygous mice do not show a phenotype. In a tour de force of molecular biology, Friedman used virtually every technique of modern genetics, including recombinational analysis of distant mouse strains together with microdissections of sorted chromosomes (done in collaboration with Rudolph Leibel), construction of yeast artificial chromosomes bearing the *ob* gene, and exon trapping in yeast to obtain probes that allowed cloning of the definitive DNA. After a seven-year search, the *ob* gene was identified in 1994 and found to encode a hormone-like polypeptide that Friedman named leptin (from the Greek *leptos*, meaning "thin").

Leptin is produced exclusively in white adipose tissue, which was an unexpected finding because fat cells were believed to function as a storage tissue for triglycerides and were not known to synthesize and secrete hormones. The availability of the *ob* gene sequence allowed Friedman and his colleagues to manufacture a recombinant version of the protein in *Escherichia coli*, which, when administered to *ob/ob* mice, triggered dramatic weight loss owing to a drop in food intake. Administration of leptin directly into the third ventricle of the brain was 50-fold more effective in reducing food intake than an equivalent dose administered intraperitoneally, pointing to the brain as the site of action of the receptors for leptin. Shortly after the discovery of leptin, the putative gene for the leptin receptor was identified by Louis Tartaglia (Millenium Pharmaceuticals), and one of its six encoded isoforms (resulting from alternative splicing) was shown by Friedman and Tartaglia to be defective in the *db/db* mouse, putting the final nail in the coffin for skepticism over Coleman's parabiosis experiments.

The discovery of leptin and its receptor has led to an explosion in knowledge of how fat cells signal the brain to control energy balance. Friedman showed that leptin acts directly in the hypothalamus to trigger a cascade of signals that regulate food intake. This key finding has prompted scientists to use leptin as the entry point for mapping neuronal circuits that mediate the complex feedback system regulating eating and energy expenditure. These circuits, which can be either inhibited or stimulated by the leptin–leptin receptor system, are responsible for the production of a variety of appetite-modulating neuropeptides and neurotransmitters such as neuropeptide Y, agouti-related peptide and melanocyte-concentrating hormone.

The importance of leptin for humans has been shown by the clinical genetic studies of Stephen O'Rahilly and Sadaf Farooqi (Cambridge Institute of Medical Research), who identified massively obese children with loss-of-function mutations in the leptin gene. These human *ob/ob* equivalents have insatiable appetites from birth: in one affected child, a weight of 42 kg was recorded at three years of age. Leptin therapy reduced this child's food consumption and led to rapid weight loss. O'Rahilly and Farooqi have also identified mutations in the leptin receptor gene that produce massive obesity in children—the human equivalents of the *db/db* mouse.

Mutations in leptin and the leptin receptor are very rare in humans, and the vast majority of people with obesity have leptin levels that are actually higher than those of lean individuals. This sounds counterintuitive if the function of leptin is to suppress appetite. But it turns out that as people become obese, their expanding mass of adipose tissue produces and secretes more and more leptin, which in turn leads to leptin resistance at the level of the receptors in the hypothalamus. A major area of current research is devoted to delineating the molecular basis for leptin resistance.

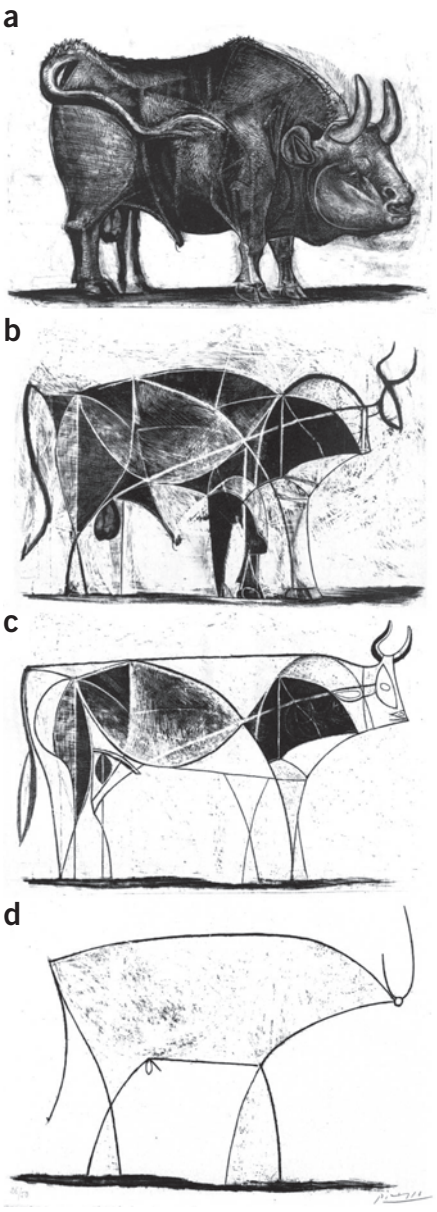

Figure 2 Picasso's *Bull*: from start to finish, 45 days. This montage shows four of the 11 progressive states of composition of Picasso's *The Bull*, created between 5 December 1945 and 17 January 1946. Lithographs on stone, 33.2 × 43.2 cm. Printer: Mourlot, Paris. (**a**) State III. (**b**) State VI. (**c**) State VIII. (**d**) State XI. Museum of Modern Art, New York.

Obesity is now recognized as one of the world's major public health problems—possibly topping the list. Globally, there are more overweight people than undernourished people. Obesity not only predisposes to type 2 diabetes, the metabolic syndrome and atherosclerosis; it is becoming apparent that it is also a substantial risk factor for many types of cancers, including cancers of the colon, uterus and breast. Before

the Coleman-Freidman discoveries, virtually nothing was known about the endocrinological and molecular aspects of the system that controls body weight. Their groundbreaking work has changed the public perception of obesity from a psychological condition marked by personal failings and lack of willpower to a complex behavioral condition that can be influenced by one's genetic makeup.

The story of leptin is one of conjoined mice (*ob*/*ob* and *db*/*db*) and conjoined discoveries (physiological and molecular). The beauty and power of the conjoined state is marvelously illustrated in a sculpture entitled *Conjoined* by the contemporary American artist Roxy Paine (**Fig. 3**). *Conjoined* is a large (40 feet tall by 45 feet wide) hand-wrought stainless steel sculpture of two trees whose branches are united in mid-air. Each branch of one tree joins imperceptibly with a branch from the other tree in such a way that it is unclear where one tree begins and the other ends.

Figure 3 Roxy Paine, *Conjoined*, 2007. Hand-wrought stainless steel, 40 × 45 ft. This sculpture of two conjoined trees was exhibited at Madison Square Park in New York in 2007. It was fabricated from 7,000 metal pipes and rod elements of 30 different diameters, assembled by cutting, bending, welding, grinding and polishing. The artist is represented by the James Cohan Gallery in New York.

Clinical Award: a Napoleonic victory against blindness

This year's Lasker~DeBakey Clinical Medical Research Award is given to Napoleone Ferrara (Genentech USA) for his discovery that vascular endothelial growth factor (VEGF) is a major mediator of angiogenesis and for his leadership role in the development of an effective anti-VEGF therapy for the severe wet form of macular degeneration, a leading cause of blindness in the elderly.

Age-related macular degeneration (AMD) is a chronic eye disease occurring in people over 50 years of age that involves damage to the macula, the part of the retina responsible for high-acuity central vision. Because the macula contains the densest concentration of photoreceptors in the retina, any damage to this region profoundly affects a person's ability to see fine detail, read, watch television and recognize faces. AMD occurs in several different forms. In the dry form, abnormal deposits of lipid and protein accumulate in the macula without substantial abnormal growth of blood vessels. About 10–20% of cases of the dry form progress to the wet form, in which neovascularization of the choroid layer of the retina develops and is accompanied by increased vascular permeability and fragility. The wet form leads eventually to subretinal hemorrhages, detachment of retinal layers, fibrotic scars and blindness. The precise molecular pathways leading to angiogenesis of the macula in wet AMD have yet to be delineated, but a common pathogenetic feature is an enhanced expression of angiogenic cytokines such as VEGF.

Although wet AMD constitutes only 10–20% of all forms of AMD, it is the form responsible for more than 80% of cases of severe visual loss and legal blindness, defined as a visual acuity of 20/200 or worse. As many as 1.5 million people in the US are afflicted with the advanced, vision-threatening form of wet AMD, and millions more have early ophthalmologic signs of the disorder. Among individuals over age 50, AMD causes 55% of all visual impairment and 25% of blindness. About 10% of people between 65 and 74 years of age have evidence of AMD, and the prevalence increases to 30% at age 75 to 85. As the elderly make up a higher and higher proportion of the population, AMD will become an increasingly important public health problem. The National Eye Institute of the US National Institutes of Health estimates that by 2020 the number of people with wet AMD in the US will rise to 3 million.

Until recently, there was no therapy for patients with severe wet AMD to improve their visual acuity. This dismal situation has been transformed over the last five years because of the imaginative thinking and fearless experimentation of Napoleone Ferrara, who identified VEGF as the long-sought master regulator of angiogenesis and then went on to lead efforts at Genentech to develop an effective VEGF-specific monoclonal antibody therapy for wet AMD.

The story of angiogenesis research has a fascinating history beginning in the late 1930s, when Gordon Ide showed that the rapid growth of tumor explants is dependent on a rich blood supply to provide nutrients and oxygen. In 1945 Glen Algire advanced the hypothesis that tumors produce factors that stimulate blood-vessel proliferation, and several years later Issac Michaelson proposed that a diffusible factor produced by the retina is responsible for the neovascularization in diabetic retinopathy. Then, in 1968, two groups directly showed that cancer cells release a diffusible factor that promotes blood-vessel proliferation. These seminal studies by Melvin Greenblatt and Philippe Shubick in melanoma cells and by Robert Ehrmann and Mogens Knoth in choriocarcinoma cells provided the experimental and conceptual framework for an influential paper published in 1971 by Judah Folkman, in which he proposed the innovative idea of developing angiogenesis inhibitors to treat human cancer. Folkman's paper inspired scientists throughout the world to search for tumor angiogenesis factors. Over the next 20 years, many candidate molecules were proposed to have activity in various *in vitro* angiogenesis assays, but none of them—including Folkman's original tumor angiogenesis factor, transforming growth factor, epidermal growth factor, tumor necrosis factor, fibroblast growth factor (FGF) and angiogenin—passed the acid test of stimulating tumor angiogenesis *in vivo*.

Ferrara's entry into the angiogenesis field was not a traditional one. After graduating from medical school at the University of Catania in Italy, he did residency training in obstetrics and gynecology. In 1983, he moved to the University of California–San Francisco for a research fellowship in reproductive endocrinology, where he worked in the laboratory of

Denis Gospodarowicz, a leading figure in the FGF field. In his research with Gospodarowicz on basic FGF and its role in angiogenesis, Ferrara became aware that none of the putative angiogenic factors known at the time had panned out in physiological studies, suggesting that the relevant molecules remained to be discovered and that a radical new way of thinking was needed. During his postdoctoral work, Ferrara began experimenting with pituitary follicular cells as a source of new angiogenic factors. These cells were later to play a key part in the discovery of VEGF.

As a card-carrying obstetrician and gynecologist with research experience in reproductive endocrinology, Ferrara was hired in 1988 by Genentech to work on a project that aimed to develop the polypeptide hormone relaxin as a treatment to promote cervical relaxation during labor. Unfortunately for Ferrara, relaxin turned out to be more potent in rodents than in primates, and the project was eventually discontinued. But fortunately for Ferrara, Genentech gave him the freedom to pursue his own ideas while struggling with relaxin, and he followed up on his postdoctoral observation that pituitary follicular cells secrete factors with an angiogenic activity.

In 1989 Ferrara reported the identification, purification and cDNA cloning of a potent endothelial cell mitogen that he named VEGF. The protein was active at a concentration of 1 ng ml^{-1} and showed high specificity for endothelial cells. Concurrent with Ferrara's publication, scientists from Monsanto reported the purification and cDNA cloning of a secreted factor from tumor cells that induced the permeability of blood vessels. This vascular permeability factor (VPF), which had originally been discovered in 1979 by Harold F. Dvorak (Beth Israel Deaconess Medical Center), turned out, surprisingly, to have the same amino acid sequence as VEGF, indicating that VEGF and VPF were one and the same molecule.

In subsequent work, Ferrara identified and cloned the first VEGF receptor (with L.T. Williams), extensively characterized the physiological role of VEGF in animal tumor models and observed that heterozygous VEFG mutant mice die at midgestation from vascular insufficiency. These pioneering studies, more than any other single body of work, contributed to the currently accepted view that VEGF is the sought-after master angiogenesis factor that regulates vascular growth in response to tissue hypoxia.

In 1993, in a historic experiment, Ferrara showed that inhibition of VEGF by specific monoclonal antibodies markedly suppressed growth of a variety of mouse tumors *in vivo*. With his colleagues at Genentech, he developed a humanized VEGF-specific monoclonal antibody (bevacizumab; Avastin), which received approval from the US Food and Drug Administration (FDA) in 2004 as a first-line therapy for metastatic colorectal cancer, in combination with chemotherapy.

Soon after the discovery of VEGF, several groups of ophthalmologists reported elevated levels of VEGF in ocular fluid samples from individuals with various eye diseases caused by neovascularization of the retina. These observations led Genentech and collaborators to carry out clinical trials of anti-VEGF therapy in subjects with wet AMD. For this purpose, Genentech developed a Fab fragment of the humanized anti-VEFG (ranibizumab; Lucentis) that is injected intravitreally on a monthly basis. Lucentis was approved by the FDA in June 2006 for treatment of wet AMD. The approval was based on clinical trials showing that, over a two-year follow-up period, Lucentis slowed the rate of progression in virtually all patients and that 33% of treated patients (as compared to only 3.8% of controls) actually had their vision improved by 15 letters or more on an eye chart. Serious side effects of the monthly injections were minimal—uveitis and endophthalmitis occurring in less than 3% of treated patients.

Avastin and Lucentis are both recombinant versions of humanized antibodies directed against VEGF. The two antibodies differ in their size and affinity for VEGF. Avastin is a full-length antibody with two binding sites for VEGF, whereas Lucentis is a Fab fragment with a single affinity-matured VEFG binding site, so its affinity for VEGF is several-fold higher than that of Avastin. Although Avastin is approved for the treatment of colorectal and other cancers, it has not yet been approved for wet AMD. Nonetheless, it has been used off label to treat wet AMD by many ophthalmologists, who believe that Avastin remains in the eye longer than Lucentis and thus may allow for less frequent injections. The National Eye Institute has recently started a multicenter clinical trial to compare the relative safety and effectiveness of Avastin and Lucentis.

Blindness ranks with cancer as one of the most feared diseases afflicting humans. Napoleone Ferrara's discovery of VEGF as a master regulator of angiogenesis and his leadership in the development of anti-VEGF therapy for the severe wet form of AMD is saving the eyesight of millions of people throughout the world.

Special Achievement Award: honoring international statesmanship

The Lasker~Koshland Special Achievement Award is given every year to honor a scientist whose lifetime contribution to medical science is universally admired and respected for its creativity, importance and impact (or as G.H. Hardy might say, for its significance, generality and unexpectedness). In essence, this award honors someone who exemplifies scientific statesmanship at its best. This year's awardee, David Weatherall (University of Oxford), is not only a statesman of biomedical science but an international statesman to boot. Weatherall is honored for a 50-year career exemplified by his discoveries concerning genetic diseases of the blood (the thalassemias and other hemoglobinopathies) and for his leadership role in bringing improved clinical care to thousands of children in the developing world who are afflicted with severe anemia.

The thalassemias are a group of inherited disorders in which production of one of the globin chains in hemoglobin is reduced; hundreds of different point mutations or deletions in either the α-globin gene or the β-globin gene can give rise to the deficit. If the body fails to produce the correct amount of either globin chain, a deficiency of hemoglobin results, causing anemia. As a group, the α- and β-thalassemias are among the most common monogenic diseases in humans, occurring with the highest frequencies in Mediterranean countries, Africa, the Middle East, India, southern China and Southeast Asia.

In 1956, Weatherall received his MD degree from the University of Liverpool, and after two years of house-officer training he joined the UK's Royal Army Medical Corps to complete the military service that was then compulsory in Britain. Even though he had no training in pediatrics, he was assigned to a children's ward at the British Military Hospital in Singapore. One of his patients was a Gurkha child from Nepal who had a mysterious form of anemia requiring multiple blood transfusions. Although he had no training in either hematology or medical genetics, he diagnosed homozygous β-thalassemia after discovering high HbA_2 concentrations in the blood of the child's heterozygous parents. HbA_2 is a minor variant form of hemoglobin containing α-chains and δ-chains, but no β-chains. To make the diagnosis, Weatherall had to find someone in Singapore who had experience with the then-new technique of starch-gel electrophoresis, which revealed the HbA_2 variant—an early example of his remarkable resourcefulness.

Weatherall excitedly wrote up his clinical discovery and published his first paper in the *British Medical Journal* in 1960. Much to his amazement, he was summarily reprimanded by his military superiors for publishing infor-

mation about bad genes without official permission. Fortunately for biomedical science, Weatherall was not intimidated by the British War Office, and the rest is history: he went on to become the world's foremost expert on the thalassemias, mastering every aspect of the disease—its natural history, population genetics, molecular pathology, diagnosis and treatment.

Stimulated by the Gurkha patient, Weatherall became a fearless experimentalist in developing a method to accurately and rapidly measure the synthesis of different globin chains in the blood of people with thalassemia. In 1965 he and his colleagues John B. Clegg and Michael A. Naughton achieved this goal by incubating intact reticulocytes with radioactive amino acids, separating the individual radiolabeled globin chains by carboxymethyl-cellulose chromatography and quantifying them by scintillation counting. With their new method, Weatherall and his colleagues provided the first clear-cut demonstration that the thalassemias result from an imbalance in the production of either α- or β-globin chains. Yuet Wai Kan, recipient of the 1991 Lasker Clinical Award for his discovery of DNA polymorphisms and their use in diagnosis of human diseases, said he was attracted to the hemoglobin field by the "sheer elegance" of the Weatherall technique for measuring globin chain synthesis[3]. To this day, Weatherall's classic experiments, done 45 years ago, remain some of the earliest and best examples of what is now referred to as translational medicine.

The Weatherall scientific oeuvre includes many other original contributions, such as the discovery and molecular characterization of new hemoglobin variants (for instance, those producing methemoglobinemia and polycythemia), the development of a sheep model for studies of the switch from fetal to adult hemoglobin synthesis, the pioneering use of recombinant DNA techniques for prenatal diagnoses of the hundreds of different mutations causing the thalassemias, and the discovery of a form of mental retardation resulting from deletions of the region of chromosome 16 that harbors the α-globin genes.

In 1989, Weatherall created the Oxford Institute of Molecular Medicine, the first such institution of its kind. This 400-person endeavor was renamed the Weatherall Institute in 2000 to honor its founder. For the last 30 years, the Institute has maintained a research partnership with institutions in countries throughout the developing world. It invites physicians from its partner countries (including Thailand, India, Myanmar (Burma), Sri Lanka, Indonesia, Vietnam and Kenya) to go to Oxford, where they are trained in the clinical and laboratory study of thalassemias. The training provides the molecular tools to identify local mutations, allowing the visiting physicians to establish prenatal diagnostic programs in their home countries. More than 300,000 children are born each year with a severe monogenic hemoglobin disorder that can be detected prenatally. The program's participants are also instructed in the latest therapies for prevention and treatment of iron overload, a potentially fatal condition that occurs in patients with thalassemia who receive multiple blood transfusions.

Not only is Weatherall an institution builder, he is also a tireless educator. He has reached a global audience through prolific writing—authoring or coauthoring more than 600 primary research articles, 85 review articles and 14 books. His book *The Thalassemia Syndromes*, now in its fourth edition, is the bible of the hemoglobin field. Also of note is *The Oxford Textbook of Medicine*, which Weatherall began in 1984 as the first international medical textbook with a special emphasis on tropical diseases. Currently in its fifth edition, the text is 4,500 pages long, and Weatherall, wisely, is no longer the lead editor. Finally, there is Weatherall's marvelous 1994 book on the history of medical research from Galen to the present, entitled *Science and the Quiet Art*, in which he espouses his philosophy on the education of physicians in the molecular era:

"The principal problem for those who educate our doctors of the future is how, on the one hand, to encourage a life-long attitude of critical, scientific thinking to the management of illness and, on the other, to recognise that moment when the scientific approach, because of ignorance, has reached its limit and must be replaced by sympathetic empiricism. Because of the dichotomy between the self-confidence required at the bedside and the self-critical uncertainty essential in the research laboratory, it may always be difficult to achieve this balance. Can one person ever combine the two qualities? Possibly not, but this is the goal to which medicine must aspire."

David Weatherall is one person who, for 50 years, has successfully combined the two essential qualities of the physician-scientist—self-confidence at the bedside and self-critical uncertainty at the bench—another example of the beauty and power of the conjoined state.

Joseph L. Goldstein is chair of the Lasker Awards jury.
e-mail: joe.goldstein@utsouthwestern.edu

Lasker Award recipients are given an honorarium, a citation highlighting their achievement and an inscribed statuette of the Winged Victory of Samothrace, 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 visit the Lasker website at http://www.laskerfoundation.org/.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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