FOREWORD

Towering science: an ounce of creativity is worth a ton of impact

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Here is a mind-boggling statistic. For every minute you spend reading this article, one new article will enter the world's biomedical literature. Last year, 500,000 new articles were published in more than 4,000 journals archived by the National Library of Medicine's MEDLINE Database. Even if only 1/1,000 of last year's 500,000 articles contain novel information that ultimately proves useful, we are still left with 500 potentially important articles published each year, any one of which could contain the first hint of a great scientific discovery. We are clearly immersed in a flood of information.

Given this relentless rise in scientific knowledge, how does a group of ordinary mortals, such as the 24 members of the Lasker Jury, evaluate and rank the hundreds of different discoveries made over the last several decades? I've wrestled with this question for the past 10 years and could never come up with a satisfying answer until several months ago when I went to the Roof Garden at the Metropolitan Museum of Art in New York City.

Each summer, the Metropolitan Museum invites a different artist to exhibit his or her work at the Roof Garden that overlooks Central Park. This year's installation is by the British sculptor Andy Goldsworthy. Goldsworthy is noteworthy and newsworthy for his monumental environmental sculptures made of stone and wood.

Inspired by the architectural backdrop of Central Park, Goldsworthy has created a 14-foot tower of 17 balanced stones—one stone stacked on top of another in a tapered pyramidal fashion (**Fig. 1**). As you look from bottom to top, each successive stone becomes smaller and smaller. The bottom stone is gigantic; it weighs 1.5 tons and is 5 feet wide and 3 feet tall. The 17th stone at the top is teeny; it weighs only 2 ounces and is the size of a silver dollar. The bottom stone is 20,000 times heavier than the top stone. To most viewers, this tapering tower of stones symbolizes a Manhattan skyscraper. To me, the tower of Goldsworthy reveals how we decide which scientific discoveries are true milestones and prizeworthy of being etched in Lasker stone.

There are two ways to view Goldsworthy's stone tower—from bottom to top or from top to bottom. Scientific discoveries can be viewed similarly. A typical bottom-to-top discovery is the type that you read about every week in *The New York Times* and *USA Today*: researcher X identifies a gene that will soon lead to a cure for cancer or schizophrenia. This bottom-up type of discovery starts out like the bottom stone in Goldsworthy's tower—with huge impact and tons of media coverage. However, other scientists soon find that researcher X's bottom stone is not a stepping-stone to new concepts, and with the passage of time its impact diminishes like the stones of Goldsworthy's tower, viewed bottom to top.

The second type of discovery, the top-down type, is extraordinarily difficult to spot early on. That's because it starts out like the teeny stone at the top of the Goldsworthy tower—with little or no impact and not an ounce of media coverage. Other scientists soon find that the stone at the top is the stepping-stone that unturns a new field of science. With the passage of time, as ever more scientists extend the initial discovery, its impact becomes ever larger, like the stones of Goldsworthy's tower, viewed top to bottom. Because top-down discoveries arise out of the blue, they are discoveries in the true sense of the word, and often many years—sometimes decades—pass before their full biological and medical importance is appreciated.

Two of the most intensely studied mechanisms of cell signaling, protein phosphorylation and protein ubiquitination, are classic examples of top-down discoveries that began in a modest way with virtually no impact and no media attention for many years. Thirty-four years passed from the time of phosphorylation's discovery (1957) until the award of a Lasker Prize (1991), and 37 years until the award of the Nobel Prize (1994). After ubiquitination was discovered in 1968, 22 years passed before the Lasker Prize was awarded (2000), and it is still waiting for Nobel recognition. Like the awards for phosphorylation and ubiquitination, the 2004 Lasker Awards in Basic and Clinical Medical Research celebrate towering achievements that epitomize top-down scientific discoveries.

Basic Medical Research Award

This year's award in Basic Medical Research is given to three scientists for discoveries concerning the superfamily of nuclear hormone receptors. Their research led to the elucidation of a unifying mechanism of cell signaling that regulates diverse metabolic pathways that operate from embryonic development to adulthood. The three honored scientists are Pierre Chambon (at the Institute of Molecular and Cellular Genetics and Biology in Strasbourg), Ronald Evans (at the Salk Institute in La Jolla, California) and Elwood Jensen (formerly at the University of Chicago; now at the University of Cincinnati College of Medicine).

The story begins in 1956, when Elwood Jensen, an organic chemist at the time,

Figure 1 British sculptor Andy Goldsworthy standing next to one of his stone towers during its installation at the Iris and B. Gerald Cantor Roof Garden on top of The Metropolitan Museum of Art in New York City. The exhibit, "Andy Goldsworthy on the Roof," runs through October 31, 2004 (*Stone Houses*, 2004, wood and stone, courtesy of the artist and Galerie Lelong; © Andy Goldsworthy; courtesy Galerie Lelong). Photograph by Karen L. Willis, The Metropolitan Museum of Art.

synthesized [^{3}H]estradiol, injected immature rats with it intravenously and noticed that it accumulated only in tissues known to grow in response to the hormone—the female reproductive tract. This now-historic experiment provided the first stepping-stone to the discovery of the estrogen receptor and subsequently to the receptors for all the other major steroid hormones, including testosterone and dihydrotestosterone, progesterone, glucocorticoids, aldosterone and the steroidlike vitamin D. As is typical of top-down discoveries, Jensen's first presentation in 1958 at a biochemistry congress in Vienna did not create much of a stir. It was attended by five people, three of whom were other speakers. Jensen's session coincided with a major symposium on steroid hormone action in which 1,000 people came to hear how estrogens act on target tissues by stimulating the enzymatic production of NADPH, the prevailing concept at the time.

By 1980, after two decades of intensive research, steroid hormone receptors came to be viewed as ligand-dependent transcription factors that activate mRNA synthesis by binding to specific DNA sequences in their target genes. The attractiveness of this receptor system for studying regulated gene transcription in eukaryotic cells caught the attention of Ronald Evans and Pierre Chambon. They realized that, to explore steroid hormone action molecularly, they would need cDNA clones for the steroid hormone receptors. By early 1986, Evans had cloned and sequenced the cDNA for the glucocorticoid receptor, and Chambon had done the same for the estrogen receptor.

With their new molecular tools, Chambon and Evans, working independently and uninterruptedly, made a series of remarkable and unexpected observations over the next 6 years. First, they discovered that the genes encoding the classic steroid hormone receptors belong to a superfamily consisting of 48 members that include the receptors for thyroid hormone, retinoids (vitamin A and its derivatives), lipids (fatty acids, prostaglandins, oxysterols, bile acids) and xenobiotics (drugs and foreign chemicals). Second, they developed a novel chimeric receptor strategy for identifying ligands for the so-called orphan nuclear receptors. The first to be identified was all-*trans*-retinoic acid, the ligand for the retinoic acid receptor (RAR). The discovery of RAR was particularly noteworthy in that it provided the molecular entrée to analyzing vitamin A's essential role in embryonic development and to solving the first three-dimensional structure of a bound and unbound member of the nuclear receptor family.

Of the numerous Evans and Chambon experiments, perhaps the most biologically pregnant was the discovery of the retinoid X receptor (RXR). RXR is a promiscuous nuclear receptor family member that forms heterodimeric partnerships with 17 of its 47 receptor siblings, including RAR, vitamin D receptor and thyroid hormone receptor. These RXR liaisons are essential for each receptor's specific DNA-binding and gene-activating functions. The promiscuous partnering property of RXR proved to be the Rosetta stone for discovering several hitherto-unknown nuclear receptors, many of which have profound implications for normal physiology, disease pathogenesis and drug discovery. Such receptors include the peroxisome proliferator-activated receptor γ, which stimulates adipogenesis and is the target for the glitazone class of drugs that are used in the treatment of type 2 diabetes; the liver X receptors and bile acid receptor, which regulate cholesterol homeostasis by activating genes for removing cholesterol from the body; and the pregnane X receptor, which activates the genes for P450 enzymes that detoxify drugs and foreign chemicals that enter the body.

In the past 45 years, many scientists have contributed to the impressive body of research that revealed the unimagined superfamily of 48 nuclear receptors and their plethora of physiological actions. Yet the discoveries of Jensen, Chambon and Evans stand out. Jensen, the patriarch of the field, established the paradigm with his pioneering work on the estrogen receptor, the matriarch of the superfamily. Evans and Chambon, with their superb molecular skills and creative biological insights, developed the grand sweep of the nuclear receptor superfamily, revealing how it influences virtually every developmental and metabolic pathway in animals and humans.

Clinical Medical Research Award

This award is given each year in celebration of a scientific contribution that has profoundly improved the clinical care of patients. This year's award is given to the person who single-handedly revolutionized the surgical removal of cataracts. The recipient is the late Charles D. Kelman, who before his recent death in June 2004 was a practicing ophthalmologist affiliated with the New York Eye and Ear Infirmary in New York City.

Cataracts are the most common cause of reversible blindness in the world, affecting about 20 million people. More than one-half of the population over 65 years of age deve-lops visual impairment caused by cataracts. Before Kelman's pioneering work, cataract surgery was a major ordeal for patients that required a hospital stay of 10 days often accompanied by serious complications, as well as a convalescence of several months.

In 1967, Kelman developed a totally new way to remove cataracts that, over the next 25 years, would replace traditional inpatient cataract surgery with an outpatient procedure that is virtually free of complications. Kelman called his procedure phacoemulsification (*phako* being Greek for 'lens'; *emulsi* for 'milk out'). In its currently practiced form, phacoemulsification involves making a small incision in the cornea and then inserting an ultrasonic probe, the sonic vibrations of which break up and liquefy the cataractous lens. The emulsified fragments of lens are then suctioned through the sonic tip, and a foldable intraocular lens is inserted through the small incision. Once inside the eye, the flexible lens unfolds like a parachute, and visual acuity is restored typically to 20/20 or 20/40. The entire procedure, which can be done in 5–10 minutes, has now become the single most commonly performed elective surgical operation in the western world. In the United States alone, nearly three million Kelman-type cataract operations were performed last year.

The idea for phacoemulsification came to Kelman in 1964 in an epiphanous moment while sitting in his dentist's chair and having his teeth cleaned. This story is recounted in my article on pages xix–xx, describing the story behind the development of phacoemulsification. As shown in Figure 2 of that article, from 1967 to 1985 the impact of phacoemulsification, as judged by the percentage of cataracts removed by this procedure compared to the traditional inpatient operation, was tiny, like the top stone on the Goldsworthy tower. With the passage of time, however, as Kelman and others improved the procedure, a steep rise in its acceptance took place; the percentage of all cataract operations in the United States done by phacoemulsification increased from 16% in 1985 to 50% in 1990 and 97% in 1996. This is a towering achievement, illustrating again how an ounce of creativity is worth a ton of impact.

Special Achievement Award in Medical Sciences

This award, inaugurated in 1994, is given periodically to honor a scientist whose lifetime contributions to biomedical research are universally admired and respected for their creativity, importance and impact.

This year's award is given to Matthew S. Meselson of Harvard University. Meselson is cited for a 50-year career in science that combines penetrating discovery in molecular biology with creative leadership in public policy aimed at eliminating chemical and biological weapons.

Meselson's contributions to biochemistry and genetics are legendary, beginning from his days as a graduate student in the mid-1950s, when he invented the technique of equilibrium density-gradient centrifugation for analyzing the density of giant molecules. He used this technique in two classic experiments that were central to the foundation on which molecular biology was built: first, the Meselson-Stahl experiment in 1958, showing that DNA replicates semiconservatively as predicted by the Watson-Crick model, and second, the Brenner, Jacob and Meselson experiment in 1961, demonstrating the existence of mRNA. The history of the Meselson-Stahl experiment, often referred to as "the most beautiful experiment in biology," is recounted in a recent book by Frederic L. Holmes, entitled *Meselson, Stahl, and the Replication of DNA* (Yale University Press, 2001).

In addition to DNA replication, Meselson has contributed in fundamental and original ways to four other areas of DNA biology: (i) DNA recombination (demonstration of breakage and cross-joining of two parental DNA molecules and the concept of heteroduplex junction between recombining molecules) (ii) DNA repair (the existence of methyl-directed mismatch repair for correcting mistakes in DNA) (iii) DNA restriction (the first purification of restriction enzymes and methodology for their characterization), and (iv) DNA evolution (molecular genetic analysis of an aquatic invertebrate, *Bdelloid rotifer*, which defies current evolutionary thinking because it has evolved over tens of millions of years in the absence of sexual reproduction or genetic exchange).

Not content to be an armchair academic who sits back and criticizes public policy, Meselson became a self-taught expert in biological and chemical weapons and a tireless campaigner for their abolition. Over the past 35 years, he has used his incisive thinking and scrupulous behavior to influence several major public policy decisions and events, including President Nixon's 1969 decision to cancel the US government's offensive biological weapons program;, the negotiation of the Biological Weapons Convention at Geneva in 1972 and its ratification by the US Senate in 1975;, the discovery that the puzzling phenomenon of 'yellow rain' in Southeast Asia during the 1980s was not a form of chemical warfare dropped by communists but the harmless feces of honeybees; and, finally, the discovery that the epidemic in Sverdlovsk, USSR that killed 60 people in 1979 was caused by an airborne leak of anthrax from a biological weapons facility and not by tainted meat as originally proposed by the Russians.

'Ingenious,' 'logical' and 'incisive' are three of the terms that Meselson's scientific peers repeatedly use to describe his biochemical and genetic experiments. These same terms are apt descriptors of his approach to dealing with high government officials and politicians in his efforts to control the manufacture and spread of chemical and biological weapons. Meselson is a towering figure in science—a very special scholar who has contributed imaginatively not only to discovery in chemistry and biology but also to prevention of its misuse.

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Chair, Lasker Awards Jury

Lasker Award recipients receive an honorarium, a citation highlighting their achievements 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/.