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2004 LASKER AWARDS
for
MEDICAL RESEARCH

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DISCOVERERS OF SUPERFAMILY OF NUCLEAR HORMONE RECEPTORS AND INNOVATOR IN CATARACT SURGERY RECEIVE LASKER AWARDS FOR MEDICAL RESEARCH

SPECIAL ACHIEVEMENT AWARD TO A MOLECULAR BIOLOGIST FOR KEY DISCOVERIES IN GENE RESEARCH AND LEADERSHIP ON INTERNATIONAL EFFORTS TO ABOLISH BIOLOGICAL AND CHEMICAL WEAPONS

NEW YORK, Sunday, September 26, 2004 – The **2004 Albert Lasker Medical Research Awards** were announced today. The Lasker Awards are the nation's most distinguished honor for outstanding contributions to basic and clinical medical research. The **Lasker Award for Basic Medical Research** will be presented to three scientists whose discoveries **revolutionized the fields of endocrinology and metabolism** by opening up basic research in nuclear hormone receptors and revealing a superfamily of proteins, unimagined 20 years ago. The nuclear receptor superfamily influences and governs virtually every developmental and metabolic event in humans and animals. The implications of this research for understanding human disease and accelerating drug discovery have been profound and hold much promise for the future.

The **Lasker Award for Clinical Medical Research** goes to the inventor of modern **cataract surgery, a pioneer in noninvasive surgery techniques**, transforming that operation from a risky and lengthy ordeal (two week hospital stay) into a safe and quick outpatient procedure that has spared millions of people throughout the world from blindness. For a lifetime of special achievement, a quintessential experimentalist will be honored both for his **seminal discoveries in molecular biology that laid the foundation for DNA research**, and for dedicated efforts in the international arena aimed toward **eradicating biological and chemical warfare**.

Often called "America's Nobels," the Lasker Award has been awarded to 68 scientists who subsequently went on to receive the **Nobel Prize**, including 15 in the last 10 years.

The Awards will be presented at a luncheon ceremony on **Friday, October 1st** at the Pierre Hotel in New York City. Dr. Mark McClellan, Administrator of the Centers for Medicare & Medicaid Services, will be the keynote speaker.

The **2004 Lasker Award for Basic Medical Research** will be shared by **Pierre Chambon**, of the Institute of Genetics and Molecular and Cellular Biology (Strasbourg, France), **Ronald M. Evans** of the Salk Institute for Biological Studies (La Jolla, California) and the Howard Hughes Medical Institute, and **Elwood V. Jensen** of the University of Chicago for the discovery of the superfamily of nuclear hormone receptors and the elucidation of a unifying mechanism that regulates embryonic development and diverse metabolic pathways.

The **2004 Lasker Award for Clinical Medical Research** will be presented to the late **Charles Kelman**, affiliated with the New York Medical College, for revolutionizing the surgical removal of cataracts through noninvasive surgery, turning a lengthy hospital stay with high morbidity into a simple outpatient procedure with minimal complications.

The 2004 **Lasker Award for Special Achievement in Medical Science** honors **Matthew Meselson** of Harvard University for a lifetime career that combines penetrating discovery in molecular biology with creative leadership in public policy aimed at eliminating chemical and biological weapons.

Dr. Joseph L. Goldstein, recipient of the Lasker Award for Basic Medical Research and the Nobel Prize in Medicine in 1985, is Chairman of the international jury of researchers that selects recipients of the Lasker Awards. He explained the significance of this year's Basic Research, Clinical Research, and Special Achievement Awards with the following comments:

"With open minds and creative thinking, scientists can break into unknown territory and revolutionize the direction of scientific inquiry. This year's Lasker Awards honor three such achievements.

"The **Basic Research Award** honors three individuals whose work created the field of nuclear hormone receptor research, which now occupies a large area of biological and medical investigation. Most importantly, the winners revealed the unexpected and unifying mechanism by which many signaling molecules regulate a plethora of key physiological pathways that operate from embryonic development through adulthood. They discovered a family of proteins that allows chemicals as diverse as steroid hormones, Vitamin A, and thyroid hormone to perform in the body.

"In the early 1960s, **Elwood Jensen** transformed scientists' thinking about how hormones work when he discovered that the steroid hormone estrogen binds a receptor protein inside the nucleus of cells in female tissues. Binding of estrogen to its receptor alters the receptor's shape in such a way that it can now turn on the genes that execute the hormone's physiological effects. Following Jensen's lead, endocrinologists soon found that the receptors for the other five major steroid hormones, such as testosterone, progesterone, and cortisone, worked essentially the same way.

"But no one anticipated the next big breakthrough in the field, made by **Pierre Chambon** and **Ronald Evans** in 1986. They discovered that the six classic steroid hormone receptors were merely the tip of the iceberg of what would turn out to be a large family of structurally related nuclear receptors, now known to consist of 48 members. Evans and Chambon unearthed a number of these receptors, which revealed new regulatory systems that control the body's response to essential nutrients (such as Vitamin A), fat-soluble signaling molecules (such as fatty acids and bile acids), and drugs (such as the glitazones used to treat Type 2 diabetes and retinoic acid for certain forms of acute leukemia).

"The **Clinical Research Award** honors an ophthalmologist who transformed the fate of people with cataracts, which is the leading cause of blindness in the world, whose victims at one time faced risky surgery, a complicated and lengthy recuperation, and the need to wear superthick spectacles. With ingenuity and single-minded persistence, **Charles Kelman** pursued the bold fantasy of making cataract surgery into a safe and speedy outpatient procedure, pioneering noninvasive surgical techniques that are now commonly applied in many other kinds of operations. Today, Kelman's technique is the most accepted approach to cataract surgery in the United States and throughout the world, restoring vision to millions of people.

"The **Special Achievement Award** honors a researcher who has made extraordinary contributions to both science and public policy. In the early days of molecular biology, **Matthew Meselson** laid the biochemical groundwork for several key areas: DNA replication, DNA repair, DNA recombination, and DNA restriction. He is revered by his scientific colleagues for carrying out the Meselson-Stahl experiment, which pointed to the correctness of the prediction of the Watson and Crick model for the replication of DNA. This experiment has remained a classic in molecular biology for more than four decades, and has been referred to as "the most beautiful experiment in biology." Not content to be an armchair academic, Meselson also has been tireless and passionate in leading successful efforts to persuade the United States government to abandon its biological and chemical weapons programs. He also has been highly influential in helping solve puzzling issues of strategic military importance, such as "yellow rain" and a suspicious outbreak of lethal anthrax in the Soviet Union."

The Lasker Awards, first presented in 1946, are administered by the Albert & Mary Lasker Foundation. The late Mary Lasker is widely recognized for her singular contribution to the growth of the National Institutes of Health and her unflagging commitment to government funding of medical research in the hope of curing devastating diseases. Her support for medical research spanned five decades, during which she was the nation's foremost citizen-activist on behalf of medical science.

Lasker Award recipients receive an honorarium, a citation highlighting their achievements, and an inscribed statuette of the Winged Victory of Samothrace, the Albert and Mary Lasker Foundation's traditional symbol representing humanity's victory over disability, disease, and death.

The list of the 2004 Lasker Award recipients with their current professional and institutional affiliations is included with the full press kit. **All press materials are available** from **www.laskerfoundation.org.** Additional materials include:

- Photographs of the Awardees;
- Interviews with the Awardees;
- Information about past Awardees; and,
- Links to Web sites for additional information about the Awardees.

Full descriptions of the work of the recipients of the **2004 Lasker Awards** follow*:

* *Page numbering may be subject to format adjustments when this document is transmitted electronically.*

The Albert Lasker Award for Basic Medical Research

Presented to: Pierre Chambon, Ronald M. Evans, and Elwood V. Jensen

For the discovery of the superfamily of nuclear hormone receptors and elucidation of a unifying mechanism that regulates embryonic development and diverse metabolic pathways

The **2004 Albert Lasker Award for Basic Medical Research** honors three scientists who opened up the field of nuclear hormone receptor research. Their work elucidated the unexpected common mechanism by which a diverse group of signaling molecules—steroid hormones, thyroid hormone, and fat-soluble molecules such as Vitamins A and D—regulate a plethora of physiological pathways that operate from embryonic growth through adulthood.

A New Model for Hormone Action

Hormones control a vast array of biological processes, including embryonic development, growth rate, and body weight. Scientists had known since the early 1900s that tiny hormone doses dramatically alter physiology, but they had no idea that these signaling molecules did so by prodding genes. The 1950s, when Jensen began his work, was the great era of enzymology. Conventional wisdom held that estradiol—the female sex hormone that instigates growth of immature reproductive tissue such as the uterus—entered the cell and underwent a series of chemical reactions that produced a particular compound as a byproduct. This compound—NADPH—is essential for many enzymes' operations but its small quantities normally limit their productivity. A spike in NADPH concentrations would stimulate growth or other activities by unleashing the enzymes, the reasoning went.

In 1956, Jensen (at the University of Chicago) decided to scrutinize what happened to estradiol within its target tissues, but he had a problem: The hormone is physiologically active in minute quantities so he needed an extremely sensitive way to track it. He devised an apparatus that tagged it with tritium—a radioactive form of hydrogen—at an efficiency level that had not previously been achieved. This innovation allowed him to detect a trillionth of a gram of estradiol.

When he injected this radioactive substance into immature rats, he noticed that most tissues—skeletal muscle, kidneys and liver, for example, started expelling it within 15 minutes. In contrast, tissues known to respond to the hormone—those of the reproductive tract—held onto it tightly. Furthermore, the hormone showed up in the nuclei of cells, where genes reside. Something there was apparently grabbing the estradiol.

Jensen subsequently showed that his radioactive hormone remained chemically unchanged once inside the cell. Estrogen did not act by being metabolized and producing NADPH, but presumably by performing some job in the nucleus. Subsequent work by Jensen and Jack Gorski established that estradiol converts a protein in the cytoplasm, its receptor, into a form that can migrate to the nucleus, embrace DNA, and turn on specific genes.

From 1962 to 1980, molecular endocrinologists built on Jensen's work to discover the receptors for the other major steroid hormones—testosterone, progesterone, glucocorticoids, aldosterone, and the steroid-like Vitamin D. In addition to Jensen and Gorski, many scientists—notably Bert O'Malley, Jan-Ake Gustafsson, Keith Yamamoto, and the late Gordon Tompkins—made crucial observations during the early days of steroid receptor research.

Clinical Applications of Estrogen-Receptor Detection

Clinicians knew that removing the ovaries or adrenal glands of women with breast cancer would stop tumor growth in one out of three patients, but the molecular basis for this phenomenon was mysterious. Jensen showed that breast cancers with low estrogen receptor content do not respond to surgical treatment. Receptor status could therefore indicate who would benefit from the procedure and who should skip an unnecessary operation. In the mid-1970s, Jensen and his colleague Craig Jordan found that women with cancers that contain large amounts of estrogen receptor are also likely to benefit from tamoxifen, an anti-estrogen compound that mimics the effect of removing the ovaries or adrenal glands. The other patients—those with small numbers of receptors—could immediately move on to chemotherapy that might combat their disease rather than waiting months to find out that the tumors were growing despite tamoxifen treatment. By 1980, Jensen's test had become a standard part of care for breast cancer patients.

In the meantime, Jensen set about generating antibodies that bound the receptor—a tool that provided a more reliable way to measure receptor quantities in excised breast tumor specimens. His work has transformed the treatment of breast cancer patients and saves or prolongs more than a hundred thousand lives annually.

Long Lost Relatives

By the early 1980s, interest in molecular endocrinology had shifted toward the rapidly developing area of gene control. Chambon and Evans had long wondered how genes turn on and off, and recognized nuclear hormone signaling as the best system for studying regulated gene transcription. They wanted to know exactly how nuclear receptors provoke RNA production in response to steroid hormones. To manipulate and analyze the receptors, they would need to isolate the genes for them.

By late 1985 and early 1986, Evans (at the Salk Institute in La Jolla) and Chambon (at the Institute of Genetics and Molecular and Cellular Biology in Strasbourg, France) had pieced together the glucocorticoid and estrogen receptor genes, respectively. They noticed that the sequences resembled that of v-erbA, a miscreant viral protein that fosters uncontrolled cell growth. This observation raised the possibility that v-erbA and its well-behaved cellular counterpart, c-erbA, would also bind DNA and control gene activity in response to some chemical activator, or ligand. In 1986, Evans and Björn Vennström simultaneously reported that c-erbA was a thyroid hormone receptor that was related to the steroid hormone receptors, thus uniting the fields of thyroid and steroid biology.

Chambon and Evans set to work deconstructing the glucocorticoid and estrogen receptors. By creating mutations at different spots and probing which activities the resulting proteins lost, they dissected the receptor into three domains: One bound hormone, one bound DNA, and one activated target genes. The structure of each domain strongly resembled the analogous one in the other receptor.

Chambon and Evans wanted to match other members of the growing receptor gene family with their chemical triggers. Because the DNA- and ligand-binding regions functioned independently, it was possible to hook the DNA-binding domain of, say, the glucocorticoid receptor to the ligand-binding domain of another receptor whose ligand was unknown. The ligand for that receptor would then activate a glucocorticoid-responsive test gene.

Evans would use this method to identify ligands for several novel members of the nuclear receptor family, and both he and Chambon exploited it to discover a physiologically crucial receptor. In the late 1970s, scientists had suggested that the physiologically active derivative of vitamin A, retinoic acid, could exert its effects by binding to a nuclear receptor. This nutrient is essential from fertilization through adulthood, and researchers were eager to understand its activities on a molecular level. During embryonic development, deficiency of retinoic acid impairs formation of most organs, and the compound can hinder cancer cell proliferation. So Chambon set out to find a receptor that responded to retinoic acid. He isolated a member of the nuclear receptor gene family whose production increased in breast cancer cells that slowed their growth upon exposure to the chemical. Simultaneously, Evans identified the same protein. He tested whether more than a dozen compounds activated an unknown receptor and one passed: retinoic acid.

Remarkably, in 1986, the two scientists had independently—and unbeknownst to each other—identified the same retinoic acid receptor, a molecule of tremendous significance. The discovery of this molecule provided an entry point for detailing Vitamin A biology.

Rx for Lonely Receptors: **RXR**

The list of presumptive nuclear receptors was growing quickly as scientists realized that the common DNA sequences provided a handle with which to grab these molecules from the genome. Because their chemical activators weren't known, they were called "orphan" receptors, and researchers were keen on "adopting" them to ligands. Some of these ligands, they reasoned, would represent previously unknown classes of gene activators. The test system that Chambon and Evans used to match up retinoic acid with its receptor, in which they stitched an unknown ligand-binding domain to a DNA-binding domain for a receptor with known target sequences, could be harnessed to accomplish this task.

Evans had identified some potential nuclear receptors from fruit flies. He decided to pursue a human orphan receptor that closely resembled one of these receptor genes, reasoning that a protein that functioned in both flies and mammals was likely to perform an important job.

This receptor responded to retinoic acid in intact cells but did not bind it in the test tube, so Evans called it the Retinoid X Receptor (RXR), thinking that its ligand was some retinoic acid derivative. In cells, enzymes convert retinoic acid to metabolites and it seemed possible that one of these compounds was RXR's ligand. In 1992, Evans's group and one at Hoffmann-La Roche discovered that 9-cis-retinoic acid, a stereoisomer of retinoic acid, could activate RXR, identifying the first new receptor ligand in 25 years. This finding launched the orphan receptor field because it provided strong evidence that the strategy could unearth previously unknown ligands.

In the meantime, Chambon had found that the purified retinoic acid receptor, in contrast to the estrogen receptor, did not bind efficiently to its target DNA. Other nuclear receptors too needed help grasping genes. In the test tube, the retinoic acid, thyroid hormone, and Vitamin D3 receptors could attach well to their target DNA only when supplemented with cellular material, which presumably contained some crucial substance. Chambon and Michael Rosenfeld independently purified a single protein that performed this feat, and it turned out to be none other than RXR. This ability of RXR to pair with other receptors—forming so-called heterodimers—would turn out to be key for switching on many orphan receptors. These heterodimeric couplings yield large numbers of distinct gene-controlling entities.

Chambon revealed the power of mixing and matching in these molecular duos through his thorough and extensive genetic manipulations in mice. He has shown that Vitamin A exerts its wide-ranging effects on organ development in the embryo through the action of 8 different forms of the retinoic acid receptor and 6 different forms of RXR, interacting with each other in a multitude of combinations.

Clinical Applications of the Superfamily Work

The concept of RXR as a promiscuous heterodimeric partner for certain nuclear receptors led to the unexpected identification of a number of clinically relevant receptors. These proteins include the peroxisome proliferator-activated receptor γ (PPARγ), which stimulates fat-cell maturation and sits at the center of Type 2 diabetes and a number of lipid-related disorders; the liver X receptors (LXRs) and bile acid receptor (FXR), which help manage cholesterol homeostasis; and the steroid and xenobiotic receptor (PXR), which turns on enzymes that dispose of chemicals that need to be detoxified, such as drugs.

Because the nuclear receptors wield such physiological power, they have provided excellent targets for disease treatment. The anti-diabetes compounds glitazones, for example, work by stimulating PPARγ, and the clinically used lipid-lowering medications called fibrates work by binding a closely related receptor, PPARα. Retinoic acid therapy has dramatically altered the prognosis of people with acute promyelocytic leukemia by triggering specialization of the immature white blood cells that accumulate in these individuals. The three-dimensional structure of nuclear receptors with and without their ligands, which Chambon and his colleagues first solved, promises to accelerate drug discovery in the whole field.

Nuclear hormone receptors have touched on human health in other ways as well. Genetic perturbations in the genes for these proteins cause a variety of illnesses. For example, certain forms of rickets arise from mutations in the Vitamin D receptor and several disorders of male sexual differentiation stem from defects in the androgen receptor.

The discoveries of Jensen, Chambon, and Evans revealed an unimagined superfamily of proteins. At the start of this work almost 50 years ago, no one would have anticipated that steroids, thyroid hormone, retinoids, Vitamin D, fatty acids, bile acids, and many lipid-based drugs transmit their signal through similar pathways. Four dozen human nuclear receptors are now known, and scientists are working out the roles of these proteins in normal and aberrant physiology. These discoveries have revolutionized the fields of endocrinology and metabolism, and pointed toward new tactics for drug discovery.

The Albert Lasker Award for Clinical Medical Research

Presented to: Charles D. Kelman, M.D.

For revolutionizing the surgical removal of cataracts, turning a 10-day hospital stay with high morbidity into an outpatient procedure with minimal complications.

The **2004 Albert Lasker Award for Clinical Medical Research** honors an ophthalmologist who transformed cataract surgery. By devising a relatively noninvasive procedure for removing a flawed lens, **Charles D. Kelman** replaced a high-risk operation that required a lengthy hospital stay with a 10-minute outpatient procedure. This procedure is now the most frequently performed surgery in many countries of the western world. It aids about three million people annually in the United States and approximately the same number in Western Europe – figures that are increasing as the population ages. Kelman's innovation of removing a relatively large piece of tissue through a tiny incision paved the way toward similar “keyhole” surgeries on many other parts of the body.

Cataracts are the single most common preventable cause of blindness in adults. Before Kelman's breakthrough, cataract surgery was a grim prospect. To rectify the cloudy vision that characterizes cataracts, surgeons cut the eye almost half open to remove the blemished lens**.** Bleeding, retinal detachment, and infection commonly threatened to destroy vision. Recovery required more than a week of hospitalization, with the patient's head immobilized by sand bags. Other complications arising from a lengthy hospital stay and the inability to move—blood clots, bedsores, and muscle atrophy—made the procedure a major ordeal. At home, weeks of recuperation followed. Eventually, the patient would receive ultrathick glasses to compensate for the absence of the lens. In addition to their lack of cosmetic appeal, these spectacles distorted and magnified objects.

In the early 1960s, Kelman (a newly appointed staff ophthalmologist at the Manhattan Eye, Ear, and Throat Hospital in New York City) began to fantasize about a procedure that would cause less trauma, restore vision quickly, and get people back on their feet sooner. He conjured up the idea of removing a cataract through a tiny slit. To extract the lens, he would need to liquefy or fragment it inside the eye and then suck out the debris through the incision—a procedure that would become known as phacoemulsification—"phaco" for "lens" and "emulsi" for "milk out."

For three years, he attacked this problem with a $299,000 grant from the John A. Hartford Foundation and cats as patients. In his first scheme, he snared the lens in a small rubber pouch, crushed it, and slid out the bag. But the bags broke and couldn't be sufficiently miniaturized. Next he tried breaking up the lens using small drills and blenders. But they sometimes snagged the iris and, even if they didn't, Kelman had to chase the lens around inside the eye, marring other structures in the process. He realized he needed a way to hold the lens in place while he drilled—but even with that innovation, the cats went blind: Splintering the lens hurled material against other parts of the eye.

On the brink of failure—six months before his grant would run out—he visited his dentist. At the time, ultrasonic probes for removing tartar were relatively new. When Kelman felt the vibrations and heard the high-pitched noise of that apparatus, the solution popped into his head. He needed a tool that accelerated so quickly, the lens could not back away, vibrate, or rotate with the tip. An ultrasound machine would pulverize the lens without damaging the surrounding tissue, he realized.

Working with engineers, Kelman adapted the gadget for his purpose. He outfitted the unit with a small hole through which to suction off the broken up cataract. To avoid boiling the eye with heat generated by the vibrations, he devised a cooling system. He finally succeeded in removing a cat's cataract without blinding the animal.

Eventually, Kelman developed a phacoemulsification unit from which today's are derived. He practiced for several years, improving the apparatus so it would perform reliably enough to be used on a person.

In 1967, he carried out the procedure on his first human. This patient's eye was blind and painful from glaucoma, and it needed to be removed. It also had a cataract. Kelman didn't intend to fix the eye, but to find out whether the procedure was feasible. More than four-and-a-half difficult hours later, he had completed the task, but he had mangled other parts of the eye—the cornea and the iris--in the process. For the next couple of years, he refined his strategy. He realized, for example, that he needed a gentle, controlled vacuum that would suck out the broken cataract without also collapsing the cornea. Eventually he made the device work safely. He continued to improve the tool so other ophthalmologists could reliably conduct the surgery—and he began to teach the technique, thus ensuring its large-reaching impact. By 1985, about 15% of all cataract removals in the U.S. were done by phacoemulsification; by 1990, that number had risen to 50%, and by 1996 it had reached 97%.

Artificial lenses were invented in 1949 by the ophthalmologist Harold Ridley, but their implantation in patients undergoing cataract operations was relatively limited until the 1980s. By then, a number of ophthalmologists, including Kelman, had enhanced their design. The improvements led to flexible folded lenses that fit through the small incision and unfurled once within the eye. These lenses restore good peripheral vision and depth perception with minimal distortion and magnification. Advances in this realm have helped obviate the need for the unwieldy and optically inadequate glasses.

Today cataract surgery involves a 1.5-3 millimeter incision. Instead of submitting to eight or ten sutures, patients usually need none. They go in for cataract surgery in the morning and can be back at work in time for lunch. Visual acuity returns almost immediately and people return to their normal activities within hours or days.

In 1992, President George H. W. Bush awarded Kelman the National Medal of Technology, and this year he was inducted into the National Inventors Hall of Fame. His peers named him Ophthalmologist of the Century in 1994.

Kelman's success marked a radical moment not only in cataract surgery, but in multiple medical specialties, turning myriad inpatient procedures into outpatient ones and bestowing on millions of people gifts of health and quality of life. Practitioners in other areas picked up on his idea of removing unwanted tissue through a tiny hole to improve, for example, gall bladder and joint surgery. Neurosurgeons have also adopted the emulsification machine to dissect tumors from the brain and spinal cord. Surgeries that used to require multiple-week hospitalizations can now be performed in minutes, thus reducing the risk of life-threatening clots and difficult-to-treat hospital-acquired infections as well as other complications.

Kelman died on June 1, 2004. At the request of his widow, Ann Kelman, the Lasker honorarium will be awarded to the International Retinal Research Foundation in his memory.

The Albert Lasker Award for Special Achievement in Medical Science

Presented to: Matthew Meselson

For a lifetime career that combines penetrating discovery in molecular biology with creative leadership in public policy aimed at eliminating chemical and biological weapons.

The **2004 Albert Lasker Award for Special Achievement in Medical Science** honors a researcher who has made world-class contributions to two different aspects of the scientific enterprise: molecular biology and public policy. **Matthew Meselson** has deciphered fundamental biological problems and has helped to prevent the manufacture and spread of biological and chemical weapons.

In 1958, Meselson (then a graduate student of Linus Pauling at the California Institute of Technology in Pasadena) and Franklin Stahl showed that DNA duplication produces two identical daughter molecules, each containing one parental and one newly formed strand. This work provided compelling support for Watson and Crick's proposed mechanism of DNA replication and for their double-stranded helical model of DNA. To perform this experiment, Meselson and Stahl first grew bacteria in broth that contained heavy nitrogen and then switched the microbes to broth that contained light nitrogen. Because the cells incorporate nitrogen into DNA, this scheme allowed the scientists to distinguish between old (heavy) and new (light) strands. To analyze the DNA generated during the experiment, Meselson invented a technique called equilibrium density gradient centrifugation, which allowed him to distinguish between DNA molecules that differed slightly in density. In this way, he and Stahl showed that a parental helix made of two heavy strands duplicates to give two molecules, each composed of one heavy and one light strand.

This powerful method has also resolved other key issues in molecular biology. For example, in 1961 Sydney Brenner and Francois Jacob, working with Meselson at the California Institute of Technology, used this procedure to establish the existence of messenger RNA, the genetic intermediary between genes and proteins. That same year, Meselson used the density gradient method to learn how two DNA molecules produce new ones that contain a mixture of the parents—a process known as genetic recombination. In this experiment, he infected cells with distinct viruses, one labeled with heavy nitrogen and heavy carbon and the other unlabeled. By showing that recombinant molecules contained discrete segments from both parents, Meselson established in this and additional experiments that the recombinant molecules result from the breaking and joining of the two parent DNA molecules. Density gradient centrifugation has since been used by scores of scientists to answer a variety of biological questions.

Later, Meselson (by then on the faculty at Harvard University) turned his attention to another scientific issue. Researchers knew that bacteria destroy DNA from foreign strains by chopping it up. He found the first known protein to perform this feat—called a "restriction enzyme" because of its ability to restrict, or reject, DNA. A related group of enzymes turned out to be invaluable for manipulating DNA because they cut at defined sequences. The discoverer of that class of restriction enzymes, Hamilton Smith, credited Meselson's influence on his work in his 1978 Nobel prize lecture. In other pioneering studies, Meselson correctly predicted the existence of methyl-directed mismatch repair, a process by which cells correct mistakes in their DNA.

In the past several years, Meselson has been tackling another central question: How does sexual reproduction contribute to evolution? Mixing two parents' characteristics produces offspring with new combinations of traits, and prevailing theory asserts that asexual animals and plants are doomed to extinction. Meselson and his colleagues have provided strong evidence that rotifers of the Class Bdelloidea, a group of tiny aquatic invertebrates, have evolved for tens of millions of years without sex—a conclusion that challenges current evolutionary thinking.

Alongside his work in molecular biology, Meselson has devoted much effort toward preventing the production and use of biological and chemical weapons. In 1963, he was invited to work at the Arms Control and Disarmament Agency in Washington, where he began exploring the U.S. biological weapons program. He reasoned that the United States had no need for such weapons and that pioneering them would only stimulate other countries and groups to acquire them. This rationale propelled him to persuade the government to abandon biological and chemical weapons, in part by writing papers for Henry Kissinger when Kissinger was Richard Nixon's national security advisor. Nixon unilaterally ended the biological weapons program in 1969 and subsequently extended the ban to weapons based on toxins, poisonous chemicals produced by living creatures.

Meselson helped to resolve other issues of military and strategic importance. During the Vietnam War, he led an expedition to Vietnam at the request of the American Association for the Advancement of Science. His group showed that the United States was mistaking civilian rice fields for enemy soldiers' crops. Meselson's findings prompted President Nixon to end U.S. herbicide operations in Vietnam.

Meselson's scientific fieldwork also helped solve two contentious puzzles of the Cold War. He investigated the "yellow rain" in Southeast Asia during the 1980s, purportedly a poison that the Laotians and Vietnamese, with Soviet assistance, were spraying on anti-government tribespeople. Meselson traveled to Southeast Asia, where he and his colleagues identified this substance as bee droppings—pollen eaten by the insects, which they then excreted in massive showers.

Another international controversy brought Meselson to Russia. In 1979, an anthrax epidemic killed more than 60 people in Sverdlovsk, U.S.S.R. The Soviets blamed tainted meat, whereas U.S. intelligence agencies suspected an airborne leak from a biological weapons facility. Meselson stated in Congressional testimony that the Soviet explanation was plausible, but that an on-site inquiry was needed. He repeatedly attempted to bring independent investigators to Sverdlovsk. Finally, in 1992, the Russian government allowed him and his wife, medical anthropologist Jeanne Guillemin, to bring a team to Sverdlovsk and probe the cause of the epidemic. The group examined preserved tissue samples, talked to city officials to learn how they responded to the outbreak, and initiated interviews with family members of those who died. The next year, Guillemin and Meselson returned to Sverdlovsk to conduct additional interviews. The victims lived in scattered locations, but the discussions revealed that their workplaces fell within a long narrow zone, with one end at the suspicious facility. Because bad meat doesn't travel in straight lines but wind often does, the researchers concluded that an airborne leak had caused the outbreak. Using local meteorological records, Meselson was able to pinpoint the day the germs had escaped.

With Julian Perry Robinson of the University of Sussex, Meselson directs The Harvard Sussex Program, which aims to increase the contribution of scholarship to the formation of public policy on issues involving biological and chemical weapons. Aided by experts in international law, Meselson and Robinson drafted a treaty in the late 1990s that would prohibit biological and chemical weapons under international criminal law. This pact would give courts of participating countries jurisdiction over any individual who orders the use of these weapons—much like the existing international agreements that govern airline hijacking, torture, and hostage-taking. The organization is trying to persuade governments to adopt the treaty, which would make purveyors of biological and chemical weapons international criminals.

While engaged in these policy-related activities, Meselson has maintained an active laboratory. His graduate and postdoctoral students include numerous scientific stars: Mark Ptashne (Lasker Basic Research Award, 1997), Susan Lindquist (Director of the Whitehead Institute), Steven Henikoff (Investigator of the Howard Hughes Medical Institute), and Sidney Altman (Nobel Prize in Chemistry, 1989). The contributions of these investigators highlight Meselson's mentorship talents.

Meselson is widely respected for his penetrating intellect and innovative insights. Among his scientific peers, he stands out as one whose talents and contributions have spanned molecular and international events alike.