The 2000 GSA Honors and Awards

The Genetics Society of America annually honors members who have made outstanding contributions to genetics. The Thomas Hunt Morgan Medal recognizes a lifetime contribution to the science of genetics. The Genetics Society of America Medal recognizes particularly outstanding contributions to the science of genetics within the past fifteen years. The George W. Beadle Medal recognizes distinguished service to the field of genetics and the community of geneticists. We are pleased to announce the 2000 awards.

Evelyn M. Witkin

The 2000 Thomas Hunt Morgan Medal

Evelyn M. Witkin

WHEN one meets Evelyn Witkin, one is struck both by her intellectual boldness and her personal modesty. From the beginning, Evelyn was propelled by a desire to answer big questions; her achievements are a testimony to the power of that approach. Evelyn decided on graduate work in genetics because she felt it important to test Trofim Lysenko's now largely discredited ideas on how heredity could be altered by the environment. After a few months of study, she realized that his theory had no merit. However, her scientific course was set. She devoted her career to an understanding of DNA mutagenesis and the nature of DNA repair mechanisms. For over 40 years, Evelyn not only made seminal discoveries but also played an absolutely crucial role in defining and establishing the field of "biological responses to DNA damage," which was the topic of the millenium Cold Spring Harbor Symposium on Quantitative Biology. Her infectious enthusiasm and personal encouragement stimulated many younger scientists to work in the field. Her generosity of spirit and willingness to share ideas and unpublished results helped to unify the field and give it cohesion. Despite her extreme importance to this field, if Evelyn herself were writing this perspective, it would be a bare-bones account indeed, the very antithesis of a self-promotional document.

Evelyn's Ph.D. studies on induced mutagenesis immediately established her intellectual independence. Although working with Theodosius Dobzhansky, she chose to use *E. coli* rather than Drosophila as her experimental organism, having been influenced by the 1943 publication of Luria and Delbruck that demonstrated the feasibility of studying genes in bacteria. Happily, Dobzhansky arranged for Evelyn to spend a summer at the Carnegie Institute of Washington in Cold Spring Harbor, studying bacteria with his friend Milislav Demerec, and her career was launched. With her very first experiment, Evelyn made history, identifying a strain of *E. coli*, B/r, that was more resistant to radiation than the parental *E. coli* B strain. For the first time, mutations conferring increased resistance to radiation had been isolated. Understanding the genetics of this radiation resistance became the subject of her Ph.D. dissertation.

Evelyn returned to Cold Spring Harbor in 1945 to finish her thesis research and remained there for the next 10 years, first as a postdoctoral fellow with Demerec and Salvador Luria and then as a Staff Scientist. At that time, experiments demonstrating that bacteria could repair DNA damage were just emerging. Evelyn bolstered the notion of a repair process in bacteria by observing that slowing the growth rate of bacteria cultured in the dark prevented the accumulation of a class of UV-induced mutants. These pioneering experiments eventually led her to speculate on the existence of an enzymatic "dark repair" mechanism complementary to photorepair by visible light and then to isolate a mutant defective in this process. Many years later, this mutant was shown by Asiz Sancar to be defective in transcription-repair coupling factor. Evelyn carried out the early portion of this work while raising her two small children, aided by the foresight of Dr. Vannevar Bush, then President of the Carnegie Institution of Washington, who allowed her a flexible work schedule so she could pursue both science and child rearing.

In 1955 Evelyn moved to the Department of Medicine at Downstate Medical Center in the State University of New York where she remained until 1971. Working alone, she began the experiments that eventually culminated in the idea that bacteria carry out a multifaceted response to UV irradiation, which includes not only DNA repair, but also filamentation of cells, UV-induced mutagenesis, and prophage induction. Her initial experiments were published in several articles, which she at first thought were unrelated. In one, she showed that the same conditions that induce prophage also caused filamentation, leading her to propose that DNA damage generates an inducing signal that coordinately inactivates both a cellular repressor controlling a division inhibitor and a prophage repressor. In the others, she showed that both the *lexA* and *recA* genes were required for UV mutagenesis and speculated that this phenomenon was due to error-prone translesion replication by either a new or modified DNA polymerase. Together these articles were amazingly prescient, foreshadowing the correct solution to this regulatory puzzle. A decade later, it was finally shown that DNA damage generates a signal sensed by RecA, which then acts as a coprotease to facilitate destruction of several repressors, including the cellular LexA repressor, which controls the cell division inhibitor SulA and the prophage repressor. Just recently, the predicted error-prone DNA polymerases were identified.

Evelyn moved to Rutgers in 1971 where her research efforts continued to lead her down the tortuous path that led finally to an understanding of the cellular response to UV. In that year, Miroslav Radman, then a postdoctoral fellow at Harvard, sent her a memorandum suggesting that both the "Weigle phenomenon" (whereby UV irradiation of phage is only mutagenic when the host has been UV irradiated) and UV mutagenesis of bacteria are caused by a mutagenic form of replication, which he called "SOS replication." Evelyn was excited by this idea because it fit so well with her own ideas of attributing diverse UV-induced phenomena to a common mechanistic basis. Initially unconvinced by Radman's experiments, Evelyn did additional experiments that converted her to a believer. In 1973 and 1974 Witkin and Radman expanded the list of putative UV-inducible functions whose regulated expression depended upon *recA* and *lexA*. These functions were collectively called the "SOS response," to convey the idea of coordinate control of disparate events that together respond to a lifestyle crisis. Evelyn continued to study various aspects of the SOS response until she retired in 1991.

Evelyn has received many awards recognizing her extensive accomplishments. Among these was election to the National Academy of Sciences in 1977. Evelyn was one of the first women to be so honored and at the time, the Diploma announcing this honor used only masculine pronouns, crediting her election to "his accomplishments." Evelyn politely inquired of David R. Goddard, then The Home Secretary of the National Academy of Sciences, whether this wording could be changed. After some back and forth, Evelyn prevailed and that missive is now devoid of references to gender.

Since retiring, Evelyn's intellectual life has continued to expand. She is on the Advisory Board of the Molecular Biology Department at Princeton University and has active connections with many of the young people at the University, providing them with encouragement and wisdom. She is involved in science education in the public schools. She often joins with a group of humanities scholars for discussions about science and has become entranced with cosmology.

A last vignette testifies to the range and richness of Evelyn's intellectual forays: she has initiated a program of study on the poet Robert Browning, who was a contemporary of her beloved Darwin. Amazingly, Evelyn has managed to find a very likely intellectual connection between these two. Browning is known to have used "The Wonders of the Little World," written by Nathaniel Wanley, as a continual source of ideas for his poetry. Evelyn has now provided strong evidence that, as a child, Charles Darwin was also strongly influenced by this same book. This collection of brief excerpts of writings on the history and scope of human beings provides many examples of heritable diversity among people, coupled with tidbits on faraway places. Evelyn suggests that early imprinting by this book not only stimulated Darwin's desire to travel, leading to his voyage on the Beagle, but also predisposed him to look for heritable variation within other species, thus influencing the cornerstone of his theory of evolution by natural selection. As a testament to her growing stature in the Browning field, Evelyn has been elected Vice President of the New York Browning Society. Evelyn Witkin is an inspiration to us all.

CAROL A. GROSS

The 2000 T. H. Morgan Medal Essay

H. J. Muller and the Nature of the Gene

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GENETICS was at a turning point in the early 1940s. The classical period had matured and was ripe for the transition to the molecular era. Geneticists had established that a gene has a precise location on a particular chromosome. They had explained the transmission of genes in heredity, and their recombinations, by the dance of the chromosomes in meiosis. They had characterized and mapped hundreds of mutants in Drosophila, mice, maize, and other organisms. A good many of the complexities and subtleties of heredity had yielded to their analysis, including sex linkage, crossing over, nondisjunction, pleiotropy, position effects, epistasis, and quantitative inheritance. The neo-Darwinian "new synthesis" had united genetics and Darwinian evolution, which had long been considered incompatible. The gene itself, however, remained almost as abstract and operational a concept as the "factor" had been to Mendel. Most of the geneticists of the Morgan school, and indeed, most classical geneticists, had felt no need to concern themselves with the chemical basis of genes or mutations.

The beginning of molecular genetics is usually marked by the "one-gene one-enzyme" hypothesis of George Beadle and Edward Tatum, by Max Delbruck's choice of bacteriophage as a way to understand the gene, or by Salvador Luria's demonstration, with Delbruck, that bacteria have real genes and are suitable material for genetics. There was also Erwin Schrodinger's 1944 book, *What Is Life*, which attracted so many physicists to genetics. Taken together, all of these served powerfully to focus attention on the need to solve the mysteries of gene structure, gene replication, and gene action at the molecular level (JUDSON 1979). The discovery of sex in bacteria (LEDERBERG and TATUM 1946) turned *Escherichia coli* into a model system for genetics. The revolution was off and running.

Like most revolutions, this one was foreshadowed by earlier precursors. Most notably, Archibald Garrod concluded that each of the individual Mendelian gene mutations responsible for certain human hereditary diseases had inactivated a particular metabolic enzyme

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(GARROD 1909). By 1920, the gene's remarkable autocatalytic capability had become the subject of attention and speculation. But throughout the '20s and '30s one geneticist, Hermann J. Muller, thought more deeply, wrote more extensively, and spoke more passionately about the nature of the gene than anyone else. Indeed, Muller laid the conceptual foundation of molecular biology to an extent that is not generally recognized. E. O. Wilson has said that progress in a field of science is measured by how soon its founders are forgotten. Perhaps, but H. J. Muller's pioneering contributions to gene theory deserve to be remembered.

By the age of nineteen, in 1909, Muller had already become committed to genetics and to the chromosome theory of heredity. He was then an undergraduate at Columbia University studying with cytologist Edmund B. Wilson. His avid reading of physiologist Jacques Loeb's books convinced him of the physicochemical basis of biological phenomena. This conviction strongly influenced his thinking as he began, not much later, to develop a theory of the gene (CARLSON 1981).

Muller, a brilliant young maverick full of enthusiasm and bursting with ideas, went on to do graduate work on Drosophila under Thomas Hunt Morgan in Columbia's famous "fly room." He made major contributions to the work of that historic group and became one of the coauthors of Morgan's classic *The Mechanism of Mendelian Heredity*. In 1915, armed with his new Ph.D., he accepted a position in Texas and initiated an independent and radically new line of research. He decided to study the individual gene and its mutations as a way to gain information about gene structure. His idea that one ought to be able to measure mutation rates seemed bizarre to Morgan's group, who were used to depending on pure luck to find an occasional mutant. Muller was later awarded the Nobel Prize in Medicine for his discovery in 1927 that X rays induce mutations in Drosophila, a discovery that depended on his first developing an ingenious method to detect and quantify lethal mutations. It was his conviction that genes must be extraordinarily stable chemical structures, and his intense desire to understand that structure, that led him to consider high-energy radiation as a likely mutagen.

The depth and prescience of Muller's thinking about

the nature of the gene are already evident in a remarkable speech that he delivered to the American Association for the Advancement of Science in 1921 and published a year later (MULLER 1922). He had been developing his concept of the gene for over a decade, and here he distilled its most salient features. Some of them are briefly summarized below.

The size and complexity of the gene: Muller concluded that the gene is ultramicroscopic in size. He estimated its maximum size by dividing the known length of one of the large Drosophila chromosomes by the minimum number of genes known to be contained on it. He believed that the gene must be complex in structure, based in part upon its extraordinary capacity for autocatalysis and also upon the existence of multiple alleles, which indicated that a gene can exist in several different stable states.

The gene as the basis of life: That the gene is the basis of life was a theme of Muller's from his earliest writings. He believed that genes "play a fundamental role in determining the nature of all cell substances, cell structures and cell activities" thereby affecting the character of the entire organism. This was far from appreciated in the '20s, even by most geneticists, and certainly not by most other biologists. Genetics was widely seen as a peripheral subdiscipline of biology, concerned primarily with the heredity and variation of superficial traits. Whereas today we might more accurately say that life depends upon the coexistence of nucleic acids and proteins, Muller's early recognition of the pivotal and pervasive role of genes was a profound insight.

The relation between gene and character: Because a pair of genes, in some cases, determines the presence or absence of an enzyme or of a certain agglutinin in the blood, Muller pointed out, it would be absurd to conclude that the gene itself is an enzyme or an agglutinin. He believed that the relation between gene and character is highly complex and depends upon "an intricate and delicately balanced system of reactions, caused by the interaction of countless genes." Every aspect of an organism's structure or activities may therefore become altered in some way when this reaction system is perturbed by a mutation in any of the component genes. Muller was led toward this position when he found that numerous modifier genes, mapping far from a particular mutation, could alter the expression of the mutant phenotype. It would be many years before it became the prevailing view in genetics.

Mutable autocatalysis: The most distinctive property of the gene, said Muller, is its capacity for self-propagation, or autocatalysis, whereby it converts some of the surrounding cytoplasmic material into an end product identical with itself. This reaction "is in each instance a rather highly localized one, since the new material is laid down by the side of the original gene." (At the time, of course, it was not known that the gene's apparent self-propagation requires the participation of numerous extragenic elements such as enzymes and other proteins.)

The self-duplicating capacity of the gene had been noted many times by others, but Muller recognized and emphasized an aspect of this property that had not been appreciated. He pointed out that the most remarkable aspect of the gene's autocatalytic capacity is that it duplicates its changes. A change in the gene—a mutation—results not in the destruction of its autocatalytic power but in a modification of the autocatalytic process that now duplicates the altered gene. Since this phenomenon, which he called "mutable autocatalysis," persists through change after change in the gene, it must depend upon "some general feature of gene construction, common to all genes, which gives each one a general autocatalytic power—a 'carte blanche'—to build material of whatever specific sort it itself happens to be composed of." How easily this 1921 inference of Muller's translates into the biochemical language of DNA!

The central issue in genetics: The most fundamental question of genetics, Muller asserted, is how to explain "the general principle of gene construction that permits this phenomenon of mutable autocatalysis." This formulation of the field's prime challenge had no great impact at the time, nor did it take center stage until some 20 years later, when Delbruck and his phage group, and then Schrodinger, defined the central issue in genetics in much the same way. Delbruck, who met Muller at a conference in Denmark in 1933, may have been familiar with some of his ideas. Schrodinger, a physicist who had probably not read Muller's papers, may have assumed that this was the conventional wisdom in genetics, as indeed by 1944, thanks largely to Muller, it had come to be. Elof Carlson, in an article on Muller's contributions to gene theory (CARLSON 1971), has called *What Is Life* "an unacknowledged physical paraphrase of Muller."

Genetics and evolution: Perhaps the most far-reaching conclusion that Muller described in his 1921 speech was that the gene's unique capacity for mutable autocatalysis "lies at the heart of organic evolution, and hence of all the vital phenomena which have resulted from evolution." He asserted that any materials having this capacity would automatically evolve, becoming at first different from other inorganic matter, and then increasing in the "complexity, diversity and so-called 'adaptation' of the selected mutable material." Thus, Muller was an early neo-Darwinian, evoking mutable autocatalysis as the key to the origin and evolution of life, at a time when many leading geneticists, including Morgan and Bateson, were not convinced that Mendelian genetics had any relevence to evolution as Darwin envisaged it. They could not reconcile the kinds of mutations they were observing with Darwin's idea that evolutionary change occurs gradually through the cumulative natural selection of small variations. Muller, however, noted

that, in Drosphila, "the smaller character changes occur oftener than the larger ones . . . and this raises the question of how many mutations are absolutely unnoticed, affecting no character, or no detectable character, to any appreciable extent at all."

Bacteriophage as an approach to the gene: Near the end of his talk, Muller called attention to the recent discovery of a "striking phenomenon, which must not be neglected by geneticists. This is the d'Herelle phenomenon." In 1917, d'Herelle had discovered a self-propagating filterable substance capable of dissolving dysentary bacilli, later identified as bacteriophage. Muller pointed out that the d'Herelle substance met the definition of an autocatalytic substance, and since it existed in different varieties, must share with the gene the capacity for mutable autocatalysis. He said ". . . if these d'Herelle bodies were really genes, fundamentally like our chromosomal genes, they would give us an utterly new angle from which to attack the gene problem. It would be very rash to call these bodies genes, yet there is no distinction between genes and them. Hence we cannot categorically deny that perhaps we may be able to grind genes in a mortar and cook them in a beaker after all. Must we geneticists become bacteriologists, physiological chemists and physicists, simultaneously with being zoologists and botanists? Let us hope so."

Muller went on to write a great many papers, expanding and refining his ideas about the nature of the gene and fleshing them out with vast amounts of data (MULLER 1962). In 1927, he published his landmark paper demonstrating the power of X rays to induce lethal, semilethal, and visible mutations in Drosophila (MULLER 1927). It had taken him years to develop the stocks and crosses necessary to detect and quantify induced lethal mutations. This article created worldwide excitement, brought Muller worldwide recognition and broadly extended the influence of his thinking. Important as this and others of his later articles were, the article based on his 1921 speech remains noteworthy for its avant garde perceptions and insights. It can be read as an early prologue to the drama of molecular biology.

In later years, Muller could still cut to the heart of a new phenomenon in genetics. When Avery, McCleod, and McCarty, in 1944, showed that the Pneumococcus

transforming factor was DNA, Muller, like most geneticists, was not immediately convinced that this result established DNA as the material of the gene. But OLBY (1974) reports that in 1946, at a conference in New York, when Delbruck described a similar result he had obtained with bacteriophage, Muller put forward the following idea: "To my mind, this suggests strongly that in both Delbruck's and Avery's cases what really happens is a kind of crossing over between chromosomes or protochromosomes of the killed inducer strain and those of the viable strain." That, of course, is precisely what happens in transformation.

Muller's research output was prodigious. He was preeminent in the fields of mutagenesis and radiation biology. He was also a committed humanist, who worked actively for world peace, for limiting nuclear proliferation, for the improvement of humanity through genetics, and against all forms of authoritarianism. He lived until 1967 and so had the deep satisfaction of seeing Watson and Crick and Wilkins and Franklin take up his challenge and show how mutable autocatalysis follows from the structure of DNA.

Author's note: I read Muller's 1922 paper in the library of Columbia's Department of Zoology during the first year of my graduate work there. It transformed the way I thought about the gene and was largely responsible for my decision to work on mutagenesis.

LITERATURE CITED

CARLSON, E. A., 1971 An unacknowledged founding of molecular biology: H. J. Muller's contributions to gene theory, 1910–1936. J. Hist. Biol. **4:** 149–170.
CARLSON, E. A., 1981 *Genes, Radiation and Society: The Life and Work of H. J. Muller.* Cornell University Press, Ithaca, NY/London.
GARROD, A., 1909 *Inborn Errors of Metabolism.* Oxford University Press, London.
JUDSON, H. F., 1979 *The Eighth Day of Creation: The Makers of the Revolution in Biology.* Simon & Schuster, New York.
LEDERBERG, J., and E. L. TATUM, 1946 Novel genotypes in mixed cultures of biochemical mutants of bacteria. Cold Spring Harbor Symp. Quant. Biol. **11:** 113–114.
MULLER, H. J., 1922 Variation due to change in the individual gene. Am. Nat. **56:** 32–50.
MULLER, H. J., 1927 Artificial transmutation of the gene. Science **66:** 84–87.
MULLER, H. J., 1962 *Studies in Genetics.* University of Indiana Press, Bloomington.
OLBY, R., 1974 *The Path to the Double Helix.* University of Washington Press, Seattle.

The 2000 Genetics Society of America Medal

Jack W. Szostak

JACK W. SZOSTAK was awarded the 2000 Genetics Society of America Medal in recognition of his fundamental contributions to the understanding and uses of genetic recombination, to the field of artificial chromosomes, and to the creation of *in vitro* genetics. Jack Szostak is one of the world's most original, path-breaking geneticists. He was the codiscoverer of double-strand breakage as an initiating event in recombination, was the codiscoverer with Elizabeth Blackburn of the portable nature and functional activity of telomeres, created the first artificial linear chromosomes, and more recently has become a leader in the field of directed evolution of biopolymers.

Jack was born in 1952, in London, England. He received his B.S. degree at McGill University of Montreal in 1972, and a Ph.D. degree at Cornell University (Ithaca, NY), in the laboratory of Professor Ray Wu. In 1979, he became an assistant professor at the Dana Farber Cancer Institute and the Department of Biological Chemistry of Harvard Medical School in Boston. Over the next two decades Jack stayed at Harvard, becoming professor of genetics in 1988, Investigator of the Howard Hughes Medical Institute, and more recently the Alex Rich Distinguished Investigator at the Department of Molecular Biology, Massachusetts General Hospital.

In 1981, Szostak and Rodney Rothstein made the discovery that a free end of a double-stranded DNA molecule is highly recombinogenic in yeast transformation experiments. Subsequent characterization, in Szostak's lab, of recombination events stimulated by a double-strand break revealed that they shared almost all properties of meiotic recombination events. Szostak and colleagues made an insightful proposal, controversial at the time, that double-strand breaks could be the initiating event in normal meiotic recombination. Szostak went on to provide strong support for this conjecture, showing that double-strand breaks do occur at the time and place of initiation of meiotic recombination and that genetic defects that block the appearance of double-strand breaks also block the initiation of recombination. Detailed genetic analysis by Szostak and co-workers of meiotic recombination events at the *ARG4* locus extended the classical work of Fogel and showed that meiotic recombination followed the bidirectional gradient expected from double-strand break initiation, with the peak of the gradient corresponding to the location of the observed double-strand breaks; deletion of the pre-sumed initiation site also showed the predicted disparity of recombination. Although the double-strand break repair model remained controversial for a number of years, subsequent work by the Szostak, Kleckner, Nicolas, and other laboratories has abundantly confirmed the role of double-strand breaks as the initiating lesions in the normal meiotic pathway of *Saccharomyces cerevisiae*. Yet another, and major, consequence of this advance was the method for single-step gene replacement using linearized DNA molecules. This method, stemming from Szostak's and Rothstein's original insight, ushered in a revolution in targeted mutagenesis that has allowed gene knockouts to be done on a genomic scale in yeast. Through the work of Capecchi and Smithies, this approach has also become the central technique of mouse genetics.

In 1982, Szostak collaborated with Elizabeth Blackburn to show that Tetrahymena telomeres could be attached to the ends of linearized yeast plasmids to yield linear plasmids, which in turn served as vectors for the cloning of yeast and other eukaryotic telomeres. Analysis of telomere modification reactions in yeast led to the prediction by Szostak and Blackburn of the telomerase enzyme activity. This early work on telomeres also led Szostak to the first creation of artificial linear chromosomes. He and his student Andrew Murray achieved this by combining all of the then-known chromosomal elements (telomeres, centromeres, and replication origins). Further work by Szostak identified total length as another critical determinant of chromosome stability, allowing him to produce the first yeast artificial chromosomes (YACs). This advance has transformed the approaches to dissection of the human and other large genomes and continues to play a major role in the technology that enables the current Genome Projects.

In the mid-1980s, Szostak became interested in the new field of catalytic RNA. His early studies of the Tetrahymena self-splicing intron focused on combining phylogenetic and genetic tools for the analysis of ribozyme structure and function. These studies led to the first evidence bearing on the physical location of the guanosine substrate binding site on the ribozyme and for the existence of several other tertiary nucleotide interactions. Despite the success of these studies, it became clear to Szostak that classical genetic analysis was not powerful enough in this setting. He began to search for new genetic tools that could provide a less biased and

wider sampling of sequence space. This led to the *in vitro* selection technique, which was immediately applied in the Szostak lab as a genetic tool for the analysis of RNA structure, both for ribozymes and for the HIV Rev binding site structure. The power of this approach was most conclusively demonstrated by selecting for novel functional RNAs from large samples of completely random RNA sequences. An essentially identical method, referred to as SELEX, was developed independently by Tuerk and Gold, and the laboratory of Gerald Joyce also developed similar technology, referred to as directed evolution.

In vitro selection has been the basis for much of the Szostak laboratory's work on the directed evolution of RNA in the 1990s. As before, he brought to this field his originality and systematic rigor, a rare combination of gifts that is characteristic of Szostak and underlies all of his major successes. Szostak and co-workers have selected RNA aptamers that bind specifically and tightly to many biologically important small molecules, including ATP and several cofactors. Over the last several years, this work has been extended by a number of other laboratories. These critical experiments by Szostak and co-workers provided direct genetic evidence that RNA can form structures that contain binding sites for essentially any small molecule, a remarkable and, for many, unexpected conclusion. Szostak then explored the possibility of evolving new types of catalytic RNA molecules. In a landmark paper, Bartel and Szostak isolated large numbers of new ribozymes directly from random sequences, showing that catalytic RNA sequences were far more common than previously thought. Subsequent selection experiments by the Szostak lab have shown that many different catalytic activities can be isolated

this way, including kinases, alkylating ribozymes, and acyl transferases. These experiments extended the range of known ribozyme activities far beyond those found in nature and have provided considerable support for the RNA World hypothesis, by showing that RNA-based organisms could indeed have maintained a chemically diverse metabolism, including the core reactions of protein synthesis.

Recently, Szostak has pioneered a new approach to the directed evolution of peptides and proteins. This method, developed by Richard Roberts and Szostak, subverts the normal cellular translation apparatus, with the remarkable result that a newly translated protein becomes covalently attached to its own mRNA. Selection for a particular function can thus be applied to the protein, while the linked RNA allows for the amplification of the protein-coding genetic information. This approach has great promise as a tool for the study of protein evolution, folding, and function.

Over the last two decades, Szostak made several exceptionally important contributions to genetics, including molecular genetics. His discoveries and inventions in the fields of recombination, telomeres, and chromosome structure have opened up new areas of research. One of his major contributions is the development of *in vitro* selection. Since this selection operates directly on molecules instead of organisms, it is a true hybrid of genetics and biochemistry. *In vitro* selection is particularly well suited for the exploration of sequence space, because it allows the sampling of huge numbers of sequences ($>10^{15}$). Jack Szostak is one of the most original thinkers in genetics today. His name will grace the roster of GSA Medal awardees.

ALEXANDER VARSHAVSKY

Bob Waterston (left) and John Sulston.
Photo by Eric Green.

The 2000 George W. Beadle Medal

John Sulston and Robert Waterston

I N the year 2000, the Genetics Society of America awarded the George W. Beadle Medal to John Edward Sulston and Robert Hugh Waterston for their outstanding contributions to the scientific community. Their collaborative work on whole-genome sequencing reflects remarkable vision, integrity, and hard work. And more importantly, their achievements have benefited innumerable scientists around the world. It is a great pleasure to recognize them with this most fitting award.

John Sulston has spent most of his career working on nucleic acids. His thesis focused on the synthesis of oligonucleotides and earned him a Ph.D. in organic chemistry from the University of Cambridge, England. His postdoctoral studies, with Leslie Orgel at the Salk Institute, tackled oligonucleotide synthesis from the perspective of prebiotic chemistry. When John returned to England in 1969 as a staff scientist at the MRC Laboratory of Molecular Biology in Cambridge, he began to mix biology with chemistry. His early article, "The DNA of *Caenorhabditis elegans*" (Genetics **77:** 95–104), foreshadowed the extraordinary project he began a decade later.

John Sulston has always reveled in *big* projects. His first was a description of the complete cell lineage of the nematode *Caenorhabditis elegans*. This enormous feat, which was completed in the early 1980s, provided a cellular database that has been essential for analyzing cell lineage controls over the past two decades. John then turned his attention back to nucleic acids and embarked on an even larger and more ambitious project—mapping and sequencing of the complete *C. elegans* genome.

Bob Waterston began his scientific career in the medical sciences. He obtained a Ph.D. and an M.D. from the University of Chicago in 1972, with his thesis research focusing on immunology. Bob then went to the MRC Laboratory of Molecular Biology in Cambridge, England, where he did postdoctoral studies with Sydney Brenner on the molecular genetics *C. elegans*. It was at this time that Bob first met John Sulston.

Bob Waterston joined the faculty of Washington University in 1976 and has stayed in St. Louis since. During this time, Bob has made many important contributions to our understanding of animal biology. His early work pioneered the genetics and molecular biology of major muscle genes, in particular myosin and paramyosin. Later, the scope of his research expanded into the cell biology of muscle and early embryogenesis, topics that he continues to address even now.

In the mid-80s, John Sulston and Bob Waterston joined forces to tackle the sequence of the *C. elegans* genome. At the time, no cellular genome, much less that of a metazoan, had been sequenced. Most scientists thought the very idea of whole-genome sequencing was

crazy—overly ambitious and a waste of money. This meant that John and Bob had to meet the challenge of winning governmental support in the face of public disapproval, in addition to figuring out how to approach one of the largest scale scientific ventures ever attempted. It soon became clear that achieving this gargantuan task would require an unusually large team of scientists and considerable organization. Although neither John nor Bob had administrative ambitions, John Sulston assumed the directorship of the Sanger Centre in Hinxton, England, and Bob Waterston became director of the Genome Sequencing Center in St. Louis. Among the teams assembled at the two sites was the *C. elegans* Sequencing Consortium, which completed the *C. elegans* sequence in 1998. This remarkable achievement provided the first glimpse of a metazoan genome. Furthermore, the *C. elegans* genome became inextricably linked with projects to sequence the genomes of other organisms, and John Sulston and Bob Waterston became key players in several other genome sequencing efforts, including the human genome project.

John Sulston and Bob Waterston deserve our most profound respect and admiration—not only because they broke through scientific and political barriers to sequence the first metazoan genome, but also because of their commitment to the scientific community. How scientific results are communicated—when, where and to whom—is a matter of continuous debate. These decisions can retard or accelerate scientific progress. In addition, those decisions make a major impact on how it feels to do science. From the very start, John and Bob insisted that all their data be shared and open for everyone—not only in the *C. elegans* community, but in the larger scientific community as well. Indeed, a major underlying principle of the project was to make data and reagents publicly available, sometimes years before either was published. This all-embracing spirit of community has, at least in part, spread beyond the *C. elegans* field to the genome projects of other organisms, which is a terrific legacy for these two inspiring men.

JUDITH KIMBLE

Previous Recipients of These Awards

	Thomas Hunt Morgan Medal	**Genetics Society of America Medal**	**George W. Beadle Medal**
1981	Barbara McClintock and Marcus M. Rhoades	Beatrice Mintz	
1982	Sewall Wright	Gerald R. Fink	
1983	Edward B. Lewis	Charles Yanofsky	
1984	George W. Beadle and R. Alexander Brink	David S. Hogness	
1985	Herschel L. Roman	Philip Leder	
1986	Seymour Benzer	Gerald M. Rubin	
1987	James F. Crow	Sydney Brenner	
1988	Norman H. Giles	David Boststein and Ira Herskowitz	
1989	Dan L. Lindsley	Allan C. Spradling	
1990	Charles Yanofsky	Nancy Kleckner	
1991	Armin Dale Kaiser	Bruce S. Baker	
1992	Edward H. Coe, Jr.	Maynard V. Olson	
1993	Ray D. Owen	Jonathan R. Beckwith	
1994	David D. Perkins	Leland H. Hartwell	
1995	Matthew Meselson	Eric Wieschaus	
1996	Franklin W. Stahl	Elliot Meyerowitz	
1997	Oliver Evans Nelson, Jr.	Christine Guthrie	
1998	Norman H. Horowitz	Ronald W. Davis	
1999	Salome G. Waelsch	Charles H. Langley	Michael Ashburner