E. B. WILSON MEDALISTS, 1983

It is often said that a scientist is lucky to make one great discovery in a career; those rare individuals who make more than one are very special indeed. **Joseph Gall** has made not one but several major discoveries which have both theoretical and practical consequences. His early research on lampbrush chromosomes of amphibians established many facts about chromosome structure. For example, he directly showed that DNA in a chromosome is a double-stranded molecule, something we take for granted now but that had never before been demonstrated. He was a co-discoverer in 1968 of specific gene amplification first shown for the ribosomal RNA genes in *Xenopus*. Not only is gene amplification an important mechanism for the control of gene expression, but it has come to the attention of cancer researchers recently with the discovery that resistance to some drugs used to treat cancer is due to gene amplification. Joe Gall went on to demonstrate gene amplification in the oocytes of certain insects. These accounted for many cytogenetic observations on nuclear structures that had been noted over the years.

In about 1970 Joe Gall and a graduate student, Mary Lou Pardue, developed in situ hybridization technology. This method remains one of the most essential in molecular biology for localizing genes on chromosomes or within cells. He and his colleagues made several important biological findings using this method. For example, the term heterochromatin had been used for many years to describe an especially condensed and genetically inactive form of chromatin. Joe Gall was the first to show that highly repetitive "satellite" DNA is a major constituent of heterochromatin, often located in telomeres and centromeres of chromosomes. With this discovery there was a molecular explanation for the genetic inactivity of heterochromatin—it consists mainly of simple sequence DNA that cannot encode protein. Following up on this, his lab was the first to sequence a simple repeat in satellite DNA. Further, he showed that polytene chromosomes of *Drosophila* replicated only the euchromatin and not heterochromatin. Differential replication of ribosomal RNA genes, embedded in heterochromatin, was discovered in his lab. Recently he has mapped genes on lampbrush chromosomes by hybridizing DNA probes to nascent RNA. The importance of in situ hybridization methods for molecular biology and biomedical research therefore cannot be overestimated. The location of single genes on mammalian chromosomes is now done regularly and chromosomal abnormalities related to oncogenes associated with chromosome breakage in malignant cells are being probed. One does not have to look far for the medical relevance of this basic researcher's discoveries. Indeed, there is no one working today in the area of molecular cytogenics who does not owe much of their knowledge and ability to make advances in their research to Joe Gall.

We have always had the suspicion that Joe Gall was going chapter by chapter through E. B. Wilson's famous book *The Cell in Development and Inheritance* explaining in molecular terms each puzzling cytological finding described therein. It is, therefore, highly appropriate that we honor Joe Gall with the awarding of the E. B. Wilson Medal.

Dr. Gall is currently at the Department of Embryology, Carnegie Institution of Washington.

Dr. Hugh Huxley's career is a superb example of how a focused study of one major cell type, using a variety of techniques, has provided fundamental concepts of widespread importance to the field of cell biology. Dr. Huxley began his career as a physicist interested in biological problems. He developed a new technique for the study of muscle, which he saw was possible because of the structural regularities present in striated muscle, thus pioneering the use of x-ray diffraction in cell biologic research. This led to a wealth of data on muscle organization and influenced later studies on many varieties of striated and smooth muscle. Some of the implications of his findings were followed in his subsequent studies with Jean Hanson in which they showed that in muscle two different proteins were present in two different types of filaments, thus beginning to account for the x-ray diffraction results. They developed improved techniques for electron microscopy and also used interference microscopy to study protein disposition. Dr. Huxley was then able to show that the two types of filaments observed appeared to slide past each other when a muscle contracted. This demonstration, together with the deepening significance of the cross bridges that he discovered, led to a radically new conception of the mechanism of muscle contraction. Dr. Huxley's work then led in the direction of the role of tropomyosin in the regulation of muscle contraction and further studies of the cross bridges. X-ray diffraction of living muscle followed, together with time-resolved studies, which he is now pursuing.

In the meantime, Dr. Huxley had discovered the polarity of actin in vitro in thin filaments, and the self-assembly of myosin, both of which illuminated the sliding filament model. To do this, he perfected the method of negative staining which he also used to study ribosome structure. These discoveries and methods have deeply influenced the study of cytoplasmic fibrous structures in a variety of cell types. Actin and myosin are widely distributed and it is hard to find an area of the cytoplasm or a cell type to which his ideas and methods have not penetrated. The importance of cross-bridging and subsequent sliding between two different proteins is now as accepted in the area of microtubule–dynein interaction as in actin–myosin interaction. It appears to be relevant even to the rotary cytoplasmic streaming in plant cells.

Dr. Huxley's work has been distinguished by its high quality, its penetration, elegance, and thoroughness. The clarity of his ideas is matched by his mastery of different techniques as needed for a given aspect of a given problem. He has contributed deeply to our understanding of how cells move. But he has not been a lonely scientist, for he has encouraged many young investigators, not only in the field of muscle contraction. Because of his innumerable fundamental contributions to the field of cell biology, we honor Dr. Hugh Huxley this evening with the awarding of the E. B. Wilson Medal.

Dr. Huxley is currently at the Molecular Biology Department, Medical Research Council.

E. B. WILSON MEDALISTS, 1984

Dr. Harry Eagle is certainly a promethean scientist: he has made daring and original discoveries in so many fields that one has difficulty in encompassing all of them. For cell biologists his most immediate contributions have been in tissue culture and cell nutrition. In the early 1950s, having had to use cultured cells in his classic studies on the mechanisms of action of penicillin, and dissatisfied no doubt with the ill-defined media then in use, Dr. Eagle turned his attention to defining the nutritional requirements of cells in culture. He defined the basic growth requirements for animal cells, the threshold levels of amino acids required for growth, and the parameters of protein turnover. He determined that some of the nutritional requirements for cells were population dependent, and were no longer essential at high densities, and that mammalian cells were unable to derepress genes under nutritional stress. Eagle's medium provided the means for obtaining pure cell populations in culture. These were monumental contributions for genetic, immunologic, biochemical, and cell biologic investigations, and are the foundation for much of what has happened in all of biology and experimental medicine since his fundamental work.

Dr. Eagle has also made signal discoveries in other, diverse fields. He has likened himself to a butterfly flitting from problem to problem: I would draw the analogy rather to a bee, making the purest honey from diverse sources. Indeed, it is clear that his odyssey through many fields was not random but was occasioned by new problems striking his original and insightful mind, and drawing his creative attention.

Harry Eagle graduated with an M.D. degree from Johns Hopkins at the rather young age of 21. At first he flirted with a career in clinical medicine, but his curiosity in the mechanisms underlying infectious diseases was piqued to the extent that he embarked on a full-time career in research. One of his first interests was in syphilis, and he rapidly acquired a worldwide reputation, particularly in the serology of this disease. Dr. Eagle established the physical basis for the flocculation test (Eagle's test), and improved its sensitivity and accuracy. He developed techniques for growing the causative organism and defined its nutritional requirements; in the pre-antibiotic era, his studies on the use of arsenicals in treatment of syphilis, trypanosomiasis, and leishmaniasis, founded on quantitative laboratory observations, established a rational basis for chemotherapy. In addition, he introduced BAL as a treatment for arsenic poisoning, still the favored mode of therapy. He was one of the first to show the efficacy of penicillin in the treatment of syphilis, and the large-scale trials that he planned and participated in made the colossal contribution to the public weal in that penicillin was (and still is) the effective drug of choice. His studies on optimal methods for administering antibiotics, and his work establishing the role of bacterial population densities in resistance to penicillin are classics, and the bases for rational therapy.

Numerous blood samples were involved in the syphilis studies, and Dr. Eagle, in characteristic fashion, thus became intrigued by blood clotting. In pioneering and prophetic studies he showed that the clotting cascade was a series of sequential, proteolytic actions.

Not merely satisfied with using penicillin in efficacious treatment, Dr. Eagle investigated its mode of action, demonstrating specific binding to susceptible bacteria, but no binding to insusceptible cells, including mammalian cells. Having obtained mammalian cells from Dr. Earle for these studies, Dr. Eagle then decided to grow cells himself, and turned his attention to the problems of cell culture, which led to the epoch-making studies on cell culture and nutrition we have already cited.

Somehow, with all these scientific activities, Dr. Eagle has found the time and energy to be a major force in creative scientific and medical administration such as Scientific Director of the National Cancer Institute during the fledgling days of NIH, a prime mover in the development of The Albert Einstein College of Medicine, and Director of The Cancer Institute at Einstein. Nevertheless, he has always worked at the bench. Many accolades, awards, and citations have been conferred on Dr. Eagle. From his laboratory, affectionately known as "Eagle's nest," many eaglets have emerged who have also flown high to achieve fame and prominence.

In recognition of his outstanding contributions to Biology and Medicine we have the honor to present to him the E. B. Wilson Medal.

Dr. Eagle is currently at the Cancer Research Center, Albert Einstein College of Medicine.

It is given to few scientists to create and establish a new scientific discipline. **Dr. Theodore Puck** is one of these rare individuals. He obtained his Ph.D. in Physical Chemistry from The University of Chicago. As a fellow at The California Institute of Technology, he was greatly influenced by Max Delbruck. Dr. Puck's early studies in the kinetics of phage attachment and infection are classics. Emerging from this background in biophysics, phage, and microbial genetics, Dr. Puck had the brilliant vision to apply the same quantitative principles and methodologies as pertained to microbial genetics to the study of the growth and genetics of mammalian cells grown in culture. In essence Dr. Puck developed clonal analysis whereby single somatic cells could be isolated and grown up into colonies and genetically and quantitatively analyzed, free of the complications and complexities that characterize the human condition, such as long generation times of human mating and impossibility of carrying out specific matings. A discipline of somatic cell genetics, simple and powerful as that of microbial genetics, was thus developed.

In the 1950s Dr. Puck developed suitable biopsy methods for taking somatic cells from individuals, reproducibly growing such cells into large, genetically stable populations, and obtaining in a rapid, quantitative fashion, macroscopic colonies from single cells: such colonies arising from single cells are truly clonal, and thus mutant cells could be recognized and used as markers. At first, reliable growth from single cells was not routinely obtainable. The technique of using x-irradiated feeder layers, now widely used in sustaining growth of differentiated cells, was thus devised. Later, the feeder layer could be dispensed with, when the nutrient media were

further improved. The stage was set for the flourishing of the new discipline of somatic cell genetics.

Dr. Puck developed techniques of single cell survival curve analysis, which allowed for precise and quantitative study of the effects of agents on cell reproduction. This approach showed that the mean lethal dose of x-irradiation for mammalian cells was much less than hitherto thought, and led to new insights into the radiotherapy of tumors and the mammalian radiation syndrome.

As simple routine methods for long-term cultures with stable karyotypes had been established by Dr. Puck, and as new cytogenetic and karyotyping methods had become at that time available, the human chromosomes were systematically characterized. The Denver system of classification of human chromosomes was then devised and is still in force. Mapping of the human genes proceeded energetically in Dr. Puck's laboratory and those of others.

Another important advance from Dr. Puck's group was the creation of selection methods for auxotrophic mutants, i.e., mutants that require nutrients not necessary for the parental cells. This was achieved by wide application of the BUdR near-visible light technique. Direct isolation of mutant survivors, resistant to a lethal drug, and replica plating techniques, also greatly extended the range of mutations available for genetic analysis.

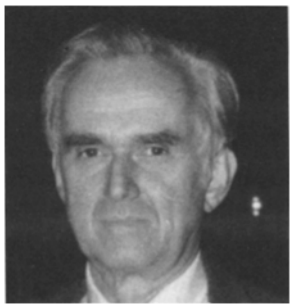
With these approaches, and by testing for dominance and recessiveness among single allelic genes, Dr. Puck was able to show that the Mendelian concepts of dominance and recessiveness could be applied equally well to mammalian cells in vitro. This allowed for complementation analysis in vitro, and the families of genes whose products are required for particular biosynthetic pathways could be identified. Furthermore, mutations affecting specific steps in single biosynthetic pathways, or mutants that have abnormal biosynthetic regulation, have also been isolated and characterized in Dr. Puck's laboratory. In all, Dr. Puck has shown that the whole sweep of modern genetical analysis can be effectively and powerfully undertaken at the level of individual cells.

Over the years Dr. Puck's laboratory has been a font of training in somatic cell genetics. His "clones" have grown to "macroscopic" fame and distinction throughout the world. He has received many prestigious awards and honors, and has been highly active in public service to the scientific community and the public. He has served as Director of the Eleanor Roosevelt Institute of Cancer Research in Denver since 1962. His classic book, *The Mammalian Cell as a Microorganism* (1972), has had profound impact, and inspired many to enter the exciting world of somatic cell genetics.

Somatic cell genetics has become a powerful force in studying human genetics, in providing potent tools for analyzing human disease, including cancer, and for furthering our basic understanding of problems in cell biology. For this magnificent achievement, we are pleased to present to Dr. Puck the E. B. Wilson Medal.

Dr. Puck is currently at the Roosevelt Institute of Cancer Research, University of Colorado Medical Center.

E. B. WILSON MEDALIST, 1985



We are here today to present the E. B. Wilson medal to **Hewson Swift**. Born in 1920 in Auburn, New York, Hewson received his Bachelor of Arts degree in Zoology from Swarthmore in 1942 and continued his initial graduate studies toward a Master's Degree in Zoology at the State University of Iowa. There Hewson honed his longstanding interests in arachnids and insects, particularly the *Hymenoptera* that were the subjects of his first publication. Hewson received his M.S. degree in 1945, and, after working briefly for the USDA as an entomologist, was appointed Curator of Spiders at the National Museum in Washington, D. C. He remained there until 1947, when the opportunity of a Lectureship in the Department of Zoology at Columbia University permitted him to return to his studies in zoology and his deepening interests in cytology.

The Department of Zoology at Columbia University, which E. B. Wilson himself had helped to found, was outstanding. Credit is usually given him for making the department one whose faculty and students had included Thomas H. Morgan, Bridges, Sturtevant, Franz Schrader, Dobzhansky, and many others who did so much to lay the foundations for the recognition of the chromosomal basis of heredity and for the broad advances in cell and molecular biology that were to follow.

Although many of the quantitative analytical techniques that make biology such a promising endeavor today were lacking 35 years ago, it was an exciting time to enter cell biology. The discovery by O. T. Avery and his colleagues in 1944 that genetic information is contained in and transmitted by DNA was known to many, but it raised puzzling questions, such as those about the quantity of DNA in eukaryotic chromosomes. Several observations, including some made in Schrader's and Pollister's laboratories, to which Swift had been attracted, suggested that the quantity of DNA in the nucleus was not constant, even within the nuclei of one cell type. As a result of these and many other unanswered questions, Avery's conclusions did not themselves immediately settle the question of whether the chemical nature of the gene was protein or nucleic acid. As Hewson Swift put it in one of the major publications that came from his Ph.D. thesis, "It is not too naive to assume that the material of which genes are made possesses remarkable properties of chemical stability and is precisely determined in the nuclei of organisms." Thus, the task Swift set for himself was to find whether or not DNA could fill the exacting quantitative requirements of a gene component.

Realizing the importance of the questions raised, and appreciating the need for careful quantification, Hewson initiated a series of studies that substantially bolstered the validity of microspectrophotometry. While insisting on a thorough understanding of basic theory, Hewson was neither intimidated nor fooled by obstacles that discouraged others. An excerpt from his 1952 review in the *International Review of Cytology* captures this spirit: ". . . there is a healthy combination between a practical and a theoretical approach to cytophotometry. Obstacles such as inhomogeneity, which has been estimated on theoretical grounds to give very large errors in measurements on nuclei . . ., often can be shown empirically to be of much less consequence. A certain amount of optimism seems desirable." Notice what Hewson is saying here, because it reflects his approach in science. Hewson is an optimist, not because he thinks that obstacles can be swept under the rug but precisely be-

cause he thinks that only when the obstacles are out from under the rug can one expect to cope with the issues realistically, dispassionately, and accurately.

Upon completing his Ph.D. in 1950, Hewson received an appointment at the University of Chicago. The studies Swift had initiated during his Ph.D. work were among the first to use direct photometric measurements of Feulgen-stained nuclei on an extensive series of different tissues from several different animals and led to seminal discoveries on the constancy of DNA. Turning his attention to plant material, where polyploidy and other difficulties had misled others, Swift demonstrated that in plants too the DNA per nucleus showed a constant value equivalent to an appropriate multiple of the haploid content. These and other studies that quantified the RNA and protein within cells demonstrated that DNA was the one constituent of chromosomes showing the quantitative behavior that might be expected from a carrier of genetic specificity. Equally important were the studies of DNA content during mitosis, meiosis, and development in a broad range of plant and animal organisms. These studies made it clear that DNA doubling occurred during interphase, after the end of telophase and before the visible onset of prophase, not, as some studies may have led people to believe, during karyokinesis.

A characteristic feature of Hewson's contributions is the variety of organisms that he uses in his studies. These are not random selections. Rather, one senses a disciplined recognition that for every biological question there must be an ideal organism.

The relation between genomic organization and the quantifiable and structural features of the nucleus has been a major and continuing theme in the Swift laboratory. Swift recognized early on that the regulation of gene expression in eukaryotes may depend on processing activities that could occur in the nucleus; another continuing theme from his laboratory has been the study of RNA–protein complexes in the nucleus and, more recently, the role of specific enzymatic modifications that might alter protein synthesis. Aside from his and his students' original investigations in these areas, Swift's insights, masterful reviews, and summaries have pointed the way for many workers and have been enormously influential, both within and outside of his laboratory. Swift's grasp of the cytological and cell biological literature is phenomenal; there are few investigators today who have his command of both the classic and the modern literature.

Soon after his move to Chicago, Swift became interested in the biogenesis of chloroplasts and mitochondria and in the presence of their independent pools of nucleic acids. Using a rigorous combination of cell fractionation and light and electron microscopy together with enzyme extraction routines and quantitative cytochemistry, Swift and his colleagues provided the first clear demonstration of ribosomes in chloroplasts and mitochondria that were different from those in the cytoplasm, and also reinforced other evidence for the presence and special nature of the organellar DNA, especially mitochondrial DNA. The relations between nuclear and mitochondrial and chloroplast nucleic acids has been a continuing theme in the Swift laboratory and has led to important papers characterizing and comparing the cytoplasmic and nuclear genomes in higher plants, algae, and yeasts.

One of Swift's major contributions is his commitment as a teacher. Hewson has had a constant and sincere interest in undergraduate and graduate education in cell biology. He has always had an amazing ability to present and analyze cell biology very critically and carefully. Swift's courses were designed to make students aware of the problems and train them to ask critical questions rather than to catalogue facts. Contemporary comment has it that his course sometimes came to an end before Swift got far out of the nucleus, but that didn't matter! His approach did, and served as a model to many students and present-day researchers who worked with him. His Whitman Laboratory at the University of Chicago was an active place, and day or night one could find several discussions going on about various aspects of cytoplasmic or nuclear cell biology.

Swift was more than just available to talk and offer advice. The breadth of his knowledge and his willingness and ability to collaborate on many different problems attracted individuals from a rich variety of fields. Those who were Ph.D. or post-doctoral students in his laboratory look on that part of their education as a time of great importance, for he created an atmosphere in which they could do and discuss their research and be creative. While always there to provide help and guidance, he encouraged those around him to pursue their own interests. As a result, when one brings together Swift's ex-students, postdocs, and colleagues—as was done this last weekend on the happy occasion of his 65th birthday—it is hard to discern the common link in their interests and expertise: one finds protozoologists, botanists, ecologists, molecular biologists, and of course cell biologists. Rather than confine them to a narrow specialization in some aspect of cell biology, Swift let them excel in their own areas of interest. As a result, there are very few founders of the American Society for Cell Biology who have had as profound an influence in so many current areas of biological science and few who are as richly deserving of the E. B. Wilson medal.

Dr. Swift is currently at the Department of Biology, University of Chicago.