BIOGRAPHICAL MEMOIRS

David Swenson Hogness

November 17, 1925–December 24, 2019
Elected to the NAS, 1976

A Biographical Memoir by Michael W. Young, Kenneth C. Burtis, and Mariana F. Wolfner

Figure 1 David Hogness.

David Hogness's enormous impact on the fields of genetics and molecular biology can be traced to a program of research that he initiated more than fifty years ago. With the birth of recombinant DNA methodology in the early 1970s, it became possible to study purified segments of DNA. As this new technology was emerging, Hogness proposed and developed a series of methods for the collection, ordering, and functional characterization of cloned DNA segments to produce maps of complex eukaryotic chromosomes. In doing so, he was the first to envision the field of genomics, explicitly laying out the fundamental steps by which entire eukaryotic genomes would be described. The research in his lab also made major contributions to developmental biology, both in the discovery of crucial conserved genes and mechanisms and through discoveries of their arrangement in molecular genetic hierarchies.

David Swenson Hogness was born on November 17, 1925, in Oakland, California. In 1930, his family moved to Chicago, where his father became a professor of physical chemistry at the University of Chicago. David majored in chemistry as an undergraduate at the California Institute of Technology (Caltech), staying on to earn a Ph.D. in biochemical genetics under Herschel Mitchell. He then became a postdoctoral fellow with Jacques Monod at the Pasteur Institute in Paris, where he was involved in the lab's early studies of the mechanism of β-galactosidase induction by lactose in *Escherichia coli*. In 1955, Hogness was recruited to the Department of Microbiology at Washington University in St. Louis by Arthur Kornberg. In 1959, he and several colleagues moved to the Stanford University School of Medicine, forming a new Department of Biochemistry.

In a detailed and widely distributed grant application to the National Institutes of Health in 1972, Hogness set forth the rationale through which complex genomes would be physically mapped, specifically focusing on *Drosophila melanogaster* as his model: libraries of total genome DNA would be cloned in prokaryotic vectors. These would first be ordered by in situ hybridizations to regions of the chromosome (taking advantage of the exceptional resolution afforded by the polytene chromosomes of Drosophila) and subsequently arranged within a physical map by iterative hybridizations

among neighboring clones. Transcribed sequences could be delineated by hybridizing a specific RNA (or its cDNA copy)—even contained within a heterogeneous RNA sample—to a cloned DNA. This would establish the boundaries of functional elements. Moreover, comparison of the strengths of hybridization signals from cDNAs derived from the RNAs from different tissues or developmental stages could identify genes with differential expression that could underlie developmental changes.

Hogness realized that this approach would permit a correspondence among physical, transcriptional, and genetic maps. He specifically pointed out how chromosome aberrations could be used to jump between segments of the same or different chromosomes, a procedure that in later years would become more widely known as positional cloning. As demonstrated in the conclusion of his proposal, he clearly anticipated a mapping project that would assemble all these methods—starting with Drosophila's smallest chromosome, chromosome 4—and eventually encompass the entire fly genome.

Hogness's commitment to this collection of ideas came very early and involved considerable risk. His initial career at Washington University and Stanford Medical School was devoted to studies of bacteriophage λ where he (with Dale Kaiser) had been the first to demonstrate the colinearity of DNA (physical) with a genetic map. Hogness could have continued comfortably within this system, but in 1968, he all but dropped λ and the molecular biology of prokaryotes to focus on Drosophila. If anything, the later stages of his λ work likely reinforced his plan to dissect more complex chromosomes. Interest in Drosophila as a model for genetic inquiry had risen dramatically in response to striking observations. First, although the fly's euchromatic genome contained ~25 times the DNA of a bacterium such as *E. coli*, classical genetic analyses could find only ~5,000 genes in the fly—not that different from a bacterium. Perhaps genes were organized in fundamentally different ways in animal cells and in bacteria. Second, the fly's developmental and behavioral biology had been deeply explored, and genes critically involved in the control of such processes had been identified. Molecular biology might now reveal the previously hidden pathway from gene to phenotype. With these possibilities in mind, Hogness spent 1968 on sabbatical, learning Drosophila genetics and cytology from Ed Lewis at Caltech, molecular methods for working with fly DNA from James Peacock at Canberra's CSIRO, and the use of polytene chromosomes from Wolfgang Beerman at the Max Planck Institute in Tübingen. This was an extremely brave move for Hogness; recombinant DNA, while on the horizon, was a concrete four or five years away. Yet, he decided to act on a plan in anticipation of the many technologies that would bring it to life, many of which he and his lab would develop.

In 1974, Hogness published his first results, with the appropriately forward-looking title "A system for mapping DNA sequences in the chromosomes of *Drosophila melanogaster*."[1] This publication can be regarded as a founding paper in the field that would become genomics. In it, and in three more published between 1975 and 1977, Hogness and his colleagues described the production of chromosomal DNA libraries and demonstrated many of the steps to be taken in the physical mapping scheme. They isolated several clones, including both unique and repeated sequence DNAs. These were located on the polytene chromosome map by in situ hybridization as originally proposed, and boundaries of transcribed sequences were precisely located by new techniques. This early work answered fundamental questions about the relative arrangement and likely functions of unique versus repetitive DNAs. For example, some of the repeated DNA occupied dispersed chromosomal positions. Hogness and his colleagues subsequently found these to be transposable elements, the first to be recognized in eukaryotes by molecular methods.[2] His choice to study Drosophila also began to allow for molecular comparisons with mammals, including humans, and eventually led to discoveries of the stunning evolutionary conservation of genetic programs governing animal development and behavior.

This phase of work also included the invention of colony hybridization by Hogness and Michael Grunstein in 1975.[3] This procedure allowed rapid collection of overlapping DNA sequences from bacterial/phage libraries, enabling positional cloning of genes previously defined only by classical genetic mapping. Because positional cloning permits a gene's isolation without prior knowledge of its molecular properties, it is one of medical science's most powerful tools for the study of inherited human disease. Hogness coined the term "chromosome walk" for this method and was first to apply it, in a series of publications beginning in 1980. The colony hybridization method also allowed selection of DNA sequences within total genome libraries that were homologous to specific components of a complex cellular RNA preparation. This allowed the Hogness lab to isolate the Drosophila ribosomal RNA genes,[4] histone genes,[5] heat-inducible heat-shock genes,[6] and, through the differential cDNA hybridization methods that they developed for RNA isolated from developmentally staged tissues, the genes that were activated or repressed by the steroid hormone ecdysone. DNA microarrays and more contemporary methods for sorting elaborate patterns of gene expression are direct extensions of the principles embodied in the Hogness lab's work. Fittingly, the first use of modern microarray technology for Drosophila research was one of the final publications from the Hogness lab.[7]

The final layer of Hogness's plan began in the late 1970s and culminated in the identification of genes and "gene

Figure 2 David Hogness with his son Peter. This 1958 photo, taken by Challiss Gore, is courtesy of the Hogness family.

hierarchies" important in two major areas of animal development: the *Hox* genes that pattern the initial body plan and steroid-responsive genes that mediate later development and metamorphosis. In the first area, his lab positionally cloned the bithorax complex, whose genes regulate key aspects of Drosophila and—as later shown—mammalian development. Identification of this gene complex required the mapping of more than half a million base pairs of chromosomal DNA, a task of unprecedented scale at the time. In these studies, most of the elements of Hogness's original vision were demonstrated. One walk began from the site of *rosy* (encoding xanthine dehydrogenase), encompassing more than 300 kilobases of DNA.[8] Inversion breakpoints were sought in this interval that connected it to the bithorax region. Chromosome "jumping" allowed a second walk through *bithorax* (200 kilobases). More than twenty-five mutations were located on the physical map of the bithorax complex alone. These delineated the functional elements of the complex, providing astonishing insights into the sources of most mutations (transposable elements) and the likely arrangement of RNA coding regions.[9] This work showed the feasibility of creating long-range physical maps of the eukaryote chromosome and the utility of integrating information at all levels of the original plan. In the second area, the Hogness lab used a combination of differential cDNA hybridization and chromosomal walking to identify first genes that were repressed by the surge of the steroid hormone ecdysone at the start of metamorphosis,[10] and later primary response genes that were induced by ecdysone to initiate a cascade of gene expression leading to pupal differentiation through action of secondary targets of the primary response genes.[11,12] One of the primary response genes identified in this project was subsequently useful via low stringency hybridization for finding the receptor for ecdysone itself, a crucial component of this genetic hierarchy.[13] The lab also produced many elegant functional analyses of the components comprising both the *bithorax* and ecdysone hierarchies over the years.[14,15]

Hogness was elected to the National Academy of Sciences in 1976, and his many contributions to the creation of genome analysis and molecular analysis of developmental genes were recognized by several distinguished scientific awards, including the Genetics Society of America Medal (1984), the March of Dimes Prize in Developmental Biology (1997), the Thomas Hunt Morgan Medal (2003), the International Prize for Biology from the Japan Society for the Promotion of Science (2007), and the Warren Alpert Foundation Prize (2013). These formal accolades fall far short of reflecting the deep admiration that so many biologists of his generation expressed for his work as it was unfolding, and whose discoveries and vision he always widely and generously shared informally, whether or not it was published.

The Hogness lab was uniquely attractive to students and postdocs because Hogness had developed such a lead in taking the wealth of classical genetics and developmental biology to a new level of molecular understanding. Nowhere else was such a breadth of possibilities available. Moreover, Hogness was extremely supportive of each of his mentees—intellectually, personally, and in their professional development. Members of the lab routinely initiated projects that became the basis for celebrated careers, with many of them becoming members of the National Academy of Sciences and others given analogous honors in their home countries. Hogness's appetite for deep insights and beauty in experimental biology attracted dozens of students whose fondest hope was to fashion something similar themselves.

In 2001, the completion of the human genome draft sequence was hailed as a milestone in science, one that will in time affect all aspects of health and medicine, particularly through studies of molecular variations that illuminate heritable disease. Along with the intellectual framework provided by Hogness beginning in the late 1960s, his further development and verification of methods for the alignment of physical and functional maps of the eukaryote chromosome through the 1970s and into the early 1980s, and discovery of hierarchies of gene actions, fixed a path for modern genetics and provided a compass for the exploration of genomes in all branches of life.

David Hogness died at the age of ninety-four on December 24, 2019. He was preceded in death by his wife of 66 years, Judith (née Gore), in 2014. Judy and Dave led a life full of friendship, humor, warmth, love of nature (and dogs), and commitment to social justice and related political causes. They are survived by two beloved sons, Peter and Chris.

David Hogness's lasting legacy to science includes his ideas and research accomplishments, as well as the vast number of people influenced by his kind and agile mind and his generosity. These people include the nearly 100 members of his lab and the researchers whom they subsequently trained, and the many colleagues around the world from whom Hogness so enjoyed learning and who were privileged to learn from him over the decades. Dave's was a life well lived, as a person and as a scientist. He is greatly missed.

Note

This article is an expanded version of MWY's 2020 obituary for Dr. Hogness (*Current Biology* 30:194-196) and KCB and MFW's January 17, 2020 post for the *Genes to Genomes Blog* (Genetics Society of America).

Acknowledgments

The authors of this memoir would like to thank Peter Hogness for contributing the 1958 photo [Figure 2] and Howard Lipshitz for comments on the memoir.

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