

## Harold Weintraub (1945-1995)

Hal Weintraub died on March 28, 1995, at the age of 49. A creative intellect, he contributed profoundly to our understanding of the molecular biology of development. From his early work on the structure of the eucaryotic chromosome to the recent identification of genes capable of eliciting an entire program of cellular differentiation, Hal repeatedly identified important problems in biology and solved them in an elegant fashion. For those fortunate enough to have shared Hal's enthusiasm for science or to have been touched by his humanity, his premature death is an immeasurable loss.

Hal Weintraub grew up playing baseball and basketball on the streets of Newark. He began his training in science as an undergraduate at Harvard College and received M.D. and Ph.D. degrees from the University of Pennsylvania, working in the laboratory of Howard Holtzer. As a Ph.D. student in the early 1970s, Hal became intrigued by the problem of how the regulation of gene expression during development leads to the differentiation of specific cell types. Insight into the molecular mechanisms of gene control had only recently emerged for a few phage and bacterial genes. Despite the complexity of mammalian development, Hal initiated a bold effort to understand the relationship between the structure of eukaryotic genes in the chromosome and the regulation of their expression during development.

Experiments initiated at the Medical Research Council in Cambridge, England, when Hal was a fellow with Sidney Brenner and Francis Crick, showed that nucleosomes reside on active genes in the chromosome, but that the nucleosomal structure is altered when the gene is transcribed. At Princeton University and later at the Fred Hutchinson Cancer Center, Hal used the globin gene clusters as a model system to define the concept of a transcriptionally active chromosomal domain. The globin gene domains contain the cluster of developmentally regulated globin genes and tens of thousands of base pairs of DNA on either side. The entire domain exhibited enhanced sensitivity to nuclease in erythroid cells, and discrete sites of hypersensitivity appeared adjacent to the individual genes as they were sequentially activated during development. This work established an important relationship between gene activity and chromosome structure.

In the early 1980s Hal began to think about the problem of identifying genes central to embryonic development in vertebrates. Recognizing the difficulty in obtaining useful developmental mutants in vertebrates, Hal introduced the idea of using antisense RNA to elicit specific mutant phenotypes. This approach, in which a complementary strand of mRNA is expressed in cells or embryos to inhibit the expression of specific mRNAs, allows the generation of

lack-of-function phenotypes and permits the assessment of the role of specific genes in development in the absence of classical developmental genetics.

More recently, in a remarkable series of experiments, Hal identified a single gene, *myoD*, which can elicit the entire program of muscle differentiation when introduced into nonmuscle cell types. He demonstrated that muscle cell differentiation could be elicited in fibroblasts following the transfer of genomic DNA from muscle cells. This led Hal to the isolation of the *myoD* gene, which encodes a transcriptional activator that promotes myogenesis by directly binding to a control region shared by muscle-specific genes. Moreover, MyoD activates its own transcription, creating an autoregulatory loop that stabilizes the commitment to myogenesis. Structure–function analysis allowed the definition of a complex set of interactions between MyoD and distinct heterodimer partners to generate either positive or negative regulatory proteins.

Hal Weintraub and his colleagues pioneered virtually every stage in the discovery and elucidation of the function of MyoD, from its structure, to the mechanism it uses to activate the myogenic program, to how MyoD itself is transcriptionally and posttranscriptionally regulated during development. These experiments led to the notion of *myoD* and its homologs as regulatory genes that together play central roles in the flow of myogenic information from the early embryo to the mature myofibril, a concept of general importance in cellular differentiation.

This brief summary of Hal's accomplishments, however, does not adequately portray his unique approach to biology. His efforts were driven by a creative intuition coupled with a courage to explore his ideas experimentally. One of his greatest strengths was his ability to conceive of simple experimental approaches that led to major advances in our understanding of complex biological phenomenon. His scientific persona was characterized by an odd mix of naivete and confidence that led him in directions where others feared to venture.

The breadth and intensity of Hal's interest in science was strongly felt, not only by his students and fellows, but by an entire community of biologists. He listened to the efforts of others with excitement and contributed his thoughts and ideas generously. Despite Hal's gentle and soft spoken manner and his aversion to the politics of administration, he brought together an exciting group of young scientists to create an exceptional research organization at the Fred Hutchinson Cancer Center.

Hal was sustained through his brief but courageous battle with brain cancer by a close relationship with his wife Nancy and his sons, Adam and Joshua, and by the devotion of his collaborator and friend, Mark Groudine. During his illness, science remained a source of great comfort. On the morning of his brain surgery, he phoned one of us, wanting to talk while waiting to be taken to the op-

erating room. "We need to talk," he said. Indeed we did, for we didn't know if we would ever see each other again. Then he said, "I read your paper. It's full of holes." Hal was an inexhaustible well of enthusiasm and ideas, and he has left an important legacy to a generation of biologists.

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