Launching the Age of Biochemical Genetics, with Neurospora: the Work of George Wells Beadle

An Inositolless Mutant Strain of Neurospora and Its Use in Bioassays (Beadle, G. W. (1944) J. Biol. Chem. 156, 683–690)

George Wells Beadle (1903–1989) grew up on a 40-acre farm near the small town of Wahoo, Nebraska. Beadle might have become a farmer himself had it not been for the influence of his high school science teacher, Bess MacDonald, who persuaded him to enroll at the University of Nebraska College of Agriculture. After earning a B. S. in 1926, Beadle remained at Nebraska to obtain an M. A. with Franklin D. Keim. Through his work with Keim, Beadle became interested in fundamental genetics and was persuaded to apply to graduate school at Cornell University rather than return to the farm.

Beadle entered Cornell in 1927 and joined Rollins Adams Emerson’s laboratory to work on the cytogenetics of maize. Over the next 5 years he published 14 papers dealing with his investigations on maize, all initiated while he was a graduate student at Cornell. With the completion of his graduate work in 1931, Beadle headed off to the California Institute of Technology to work with future Nobel laureate Thomas Hunt Morgan. There he became interested in Drosophila and began doing research on genetic recombination. In 1934, Boris Ephrussi, a Rockefeller Foundation Fellow from Paris, came to Morgan’s laboratory at Caltech to study Drosophila genetics. Beadle and Ephrussi teamed up and began examining eye pigment development in Drosophila after devising a method for larval embryonic bud transplantation. These studies were performed in Ephrussi’s laboratory in Paris. From these experiments, they proposed that eye color changes in mutant strains of Drosophila could be caused by inactivation of specific proteins, acting in a single biosynthetic pathway. This suggested that development could be broken down into a series of gene-controlled biochemical reactions and laid the foundation for the one gene-one enzyme theory that Beadle would eventually propose and make famous.

The idea that specific proteins were produced by specific genes was first alluded to in 1909 by Sir Archibald Garrod, an English physician. Garrod proposed that alkaptonuria, an inherited condition in humans in which the urine is black due to the presence of homogentisic acid, was associated with a recessive gene, Garrod called them Factors, in some way responsible for the further metabolism of homogentisic acid. In 1958 others showed that the liver of a patient with alkaptonuria was without measurable homogentisic acid oxidase activity (1). However, the first explicit articulation of the one gene-one enzyme phrase, and probably the concept, would have to wait until the 1940s when Beadle and biochemist Edward L. Tatum performed several experiments, with a simpler organism, that confirmed the direct relationship between one gene and one enzyme.

In 1937 Beadle accepted an appointment as Professor of Biological Sciences at Stanford University and invited Tatum to join him as a research associate. While auditing a course that Tatum was teaching on comparative biochemistry, Beadle learned that although microbial species share the same basic biochemistry, they differ in their nutritional requirements. He reasoned that if these differences were genetic in origin, it should be possible to induce gene mutations that would produce new nutritional requirements. This would allow identification of the genes governing biochemical reactions that form known products.

For his experimental organism, Beadle chose the red bread mold Neurospora crassa, whose life cycle had been characterized, making it an ideal organism for genetic study. He and Tatum
knew from the studies of others that *Neurospora* could grow on a minimal medium composed of a sugar, salts, and the one vitamin, biotin. Then they used x-rays to attempt to produce *Neurospora* mutants that had lost the ability to grow on their minimal medium. Beadle once recalled upon reflecting on these experiments, “We believed so thoroughly that the gene-enzyme reaction relation was a general one that there was no doubt in our minds that we would find the mutants we wanted. The only worry we had was that their frequency might be so low that we would get discouraged and give up before finding one” (2).

The 299th mutagenized culture they tested proved to be the lucky one. It did not grow in their minimal medium, but it did survive and grow when vitamin B$_6$ was added. To prove that a single gene had been mutated, Beadle and Tatum performed a genetic cross between the mutant strain and a wild type strain and tested cultures derived from the eight single spores that were the progeny of a single meiosis. Their tests showed that cultures from four progeny spores required vitamin B$_6$ whereas the other four did not, confirming that a single gene had been mutated (3).

Before long, mutants requiring amino acids, purines, and pyrimidines were also found, and the science of biochemical genetics was born.

In the *Journal of Biological Chemistry* (*JBC*) Classic reprinted here, Beadle discusses some of the practical applications in the isolation and characterization of one of his *Neurospora* mutants. He and Tatum had produced five *Neurospora* strains that required inositol for normal growth and had established that each of these mutants was altered in the same gene. Because mutant growth rate was a function of inositol concentration, Beadle reasoned that any one of these mutants could be used to assay for inositol. In the Classic, Beadle focuses on one strain and shows that his bioassay is reproducible and fairly precise at quantitatively estimating inositol concentrations in a variety of natural materials.

Beadle and Tatum’s *Neurospora* investigations further showed that the biosynthesis of any one substance is dependent upon the function of a set of nonallelic genes. A mutation in any of these genes results in loss of synthesis due to the presumed inactivation of a single enzyme catalyzing a reaction in a multistep biosynthetic pathway. Beadle summarized this concept in an historic article in 1945 in which he claimed that “a given enzyme will usually have its final specificity set by one and only one gene” (4). This statement eventually became known as the “one gene-one enzyme” theory of gene action.
However, when Beadle first presented this theory few scientists accepted the concept that one gene specifies the sequence of one enzyme. This was due in part to the widespread belief in the pleiotropic action (multiple effects) of genes, which was somewhat correct since single gene mutations often had multiple consequences. Several scientists still suspected that genes governed only trivial biological traits whereas important characteristics were determined by cytoplasmic interactions involving as yet unknown mechanisms. The one gene-one enzyme theory was eventually verified and accepted, when subsequent investigations by others established that genetic material was DNA and that DNA had a double helical structure, and determined how genetic material is replicated and how it functions in protein synthesis.

Tatum later applied their methods to produce bacterial mutants. Using these mutants, Tatum’s graduate student, Joshua Lederberg, demonstrated genetic recombination in *Escherichia coli*, thereby founding the field of bacterial genetics. In 1958, Beadle, Tatum, and Lederberg shared the Nobel Prize in Physiology or Medicine for their pioneering studies with *Neurospora* and *E. coli*.

In 1946 Beadle returned to Caltech, succeeding Morgan as chairman of the Division of Biology. He continued to work in the laboratory until administrative demands absorbed all of his time. He published his last experimental paper on *Neurospora* in 1946, after which his scientific writings consisted of reviews, lectures, historical essays, and a prize-winning book for young people he wrote with his wife Murial called *The Language of Life: an Introduction to the Science of Genetics* (5). In 1961 Beadle left Caltech to become president of The University of Chicago. After retiring in 1968, he resumed research, returning to a problem he studied during his Cornell days—the origin of maize.1,2

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REFERENCES


1 All biographical information on George Wells Beadle was taken from Refs. 6 and 7. Additional information on George Wells Beadle can be found in the biography written by Paul Berg and Maxine Singer (8).
2 We thank Charles Yanofsky, Emeritus Professor of Biological Sciences at Stanford University, and Paul Berg, Emeritus Professor of Biochemistry at Stanford University Medical School, for their assistance in writing this JBC Classic Introduction.