Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

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A Centennial: George W. Beadle, 1903–1989

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GEORGE BEADLE was a quadruple-threat man—scientist, teacher, administrator, and public citizen. He excelled in each. Furthermore, he did what very few geneticists did in his time: he studied three different organisms and made outstanding discoveries in every case. He followed his interests and undertook his diverse responsibilities with zeal, confidence, cheerfulness, and equanimity.

In October 2003 a centennial symposium was held at the California Institute of Technology at which several of Beadle's colleagues spoke. Here we present a biography followed by brief vignettes from several of his associates. Most are taken from talks given at the symposium.

A BRIEF BIOGRAPHY (J. CROW)

This account is based mainly on two sources, to which the reader is referred for further information: a biographical memoir for the National Academy of Sciences (Horowitz 1990) and a recent book (Berg and Singer 2003). Horowitz (1990) presents a list of Beadle's many honors and an extensive reference list, which includes his most important articles. Berg and Singer provide a full and beautifully written account of Beadle's scientific, administrative, public, and personal life, along with background information on other workers and the state of genetics at the time.

Beets (as he was known to his friends) was born on October 22, 1903, on a farm near a Nebraska town with the unlikely name of Wahoo. At the urging of a high school teacher who realized Beadle's promise, he entered the University of Nebraska in 1922. He graduated in 1926 and, encouraged by his major professor, F. D. Keim, stayed on for several additional months. At that time he was interested in ecology, and his first publication dealt with pasture grasses (Beadle 1927). He loved the rural life and originally expected to be a farmer. He never abandoned these roots and maintained a lifetime interest in agriculture. No matter how busy his life, he almost always had a garden.

Maize: In 1926 Beadle entered the graduate school at Cornell University, where he was exposed to the excitement of genetics. He soon joined the maize genetics laboratory of R. A. Emerson and enjoyed the stimulating company of fellow graduate students Marcus Rhoades, Charles Burnham, and Barbara McClintock. He was immediately productive and wrote 14 articles based on work done at Cornell. Several of these articles dealt with mutants affecting synapsis, meiosis, or disjunction (Beadle 1930). He was interested in crossing over and later coauthored a classic article on linkage studies and chromosome mapping (Emerson *et al.* 1935). At that time, the density of the linkage map of maize was second only to that of Drosophila. Noteworthy, because of Beadle's later return to this subject, were several articles on teosinte, a wild relative of maize, believed by many to be the ancestor of maize. He showed teosinte's great chromosomal similarity to maize and the intercrossability of the two species. Beadle and Emerson were convinced on genetic grounds that teosinte was the ancestor of domesticated maize.

Drosophila: After receiving his Ph.D. in 1930, Beadle stayed on at Cornell another year. He then received a National Research Council fellowship to work at CalTech. There he worked in E. G. Anderson's corn field and lived close by. He used this period to complete several studies started at Cornell. Soon, however, he caught the excitement of T. H. Morgan's fly group and, moving closer to the CalTech campus, started working on Drosophila. His early work was concerned with recombination and, along with A. H. Sturtevant, the ef-

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fects of chromosomal inversions on crossing over (Sturtevant and Beadle 1936). One of his experiments employed heterozygous attached X chromosomes to demonstrate the four-strand nature of crossing over and the absence of chromatid interference. This was an experimental tour de force, since attached X chromosomes tend to become homozygous. Beadle had to use triploids to introduce markers into the attached X chromosomes and to create heterozygotes (Beadle and Emerson 1935). Later he joined Sturtevant in preparing a genetics textbook that set a new standard of clarity and rigor (Sturtevant and Beadle 1939).

Having made major contributions to the cytogenetics of both maize and Drosophila, Beadle took off in an entirely new direction. All along he had had an interest in gene action, and he saw an opportunity by exploiting the tissue culture techniques used by Boris Ephrussi, who was visiting CalTech. Ephrussi persuaded Beadle to join him in Paris, where they tried to get imaginal discs of Drosophila to differentiate into adult structures in tissue cultures. Failing this, they tried transplanting the disks from one larva to another. After some initial difficulties, the experiments finally worked and were a great success. Aware that the *vermilion* mutation was not autonomous (Sturtevant 1920), they were not surprised that *vermilion* discs transplanted into wild-type larvae developed into wild-type eyes. Naturally, Sturtevant was pleased, as were Beadle and Ephrussi, that their experiments confirmed his initial conclusion.

Beadle and Ephrussi found that the normal alleles of the *vermilion* and *cinnabar* mutants, v^+ and cn^+, act sequentially. The fact that the v^+ and cn^+ genes acted as hormones provided an opportunity for their identification. Meanwhile, Beadle returned to the United States in 1936 to join the faculty at Harvard. He was not happy there, and after a year accepted a position at Stanford. There, he was joined by Edward L. Tatum, who brought chemical skills to identify the substances. Beadle and Tatum soon found that the sought-after substances were derivatives of tryptophan. Eventually, Tatum obtained crystals and by standard chemical methods identified the v^+ and cn^+ substances as kynurenine and OH-kynurenine (Tatum and Haagen-Smit 1940; Ephrussi 1942). But much to his and Beadle's disappointment, a German group headed by Adolf Butenandt had identified them first. Butenandt had simply tested various known derivatives of tryptophan for their ability to modify the eye color (Butenandt *et al.* 1940). Why Tatum did not try this simpler approach is not clear.

Neurospora: Beadle and Tatum now recognized the limitations of Drosophila for further biochemical work. Pondering this, Beadle had a wonderful insight. While still a graduate student at Cornell, he had learned of B. O. Dodge's work on the bread mold Neurospora. Later, at CalTech, Carl Lindegren had worked out its meiotic details (Lindegren 1936). Neurospora seemed made to order for genetic research. It had the convenient properties of being haploid and producing meiotic spores in linear order in an ascus. Furthermore, it was able to grow on a minimal medium with only a carbon source and biotin. Beadle reasoned that he could produce mutants lacking in the ability to synthesize a nutrient and could identify them by their ability to grow on complete but not on minimal medium. The 299th spore had the requisite property. It was then a straightforward process to find the specific requirement, which turned out to be pyridoxine. Soon after, mutants requiring thiamine and *p*-aminobenzoic acid were discovered, and the floodgates were open (Beadle and Tatum 1941). Gene control over enzymes had long been realized by Garrod, Haldane, Wright, and Cuénot (Hickman and Cairns 2003), but Beadle's technique delivered enzymatic deficiencies in wholesale numbers. It marked the beginning of biochemical genetics as a systematic study. Tatum later found that the same methods could be used in *Escherichia coli*, and this led to his discovery with Lederberg of a sexual process. It was a major step in what Muller (1947; see also Lederberg 1991) called "the coming chemical attack on the gene" and what Warren Weaver termed "molecular biology." There were immediate practical applications, such as bioassay and selection of more efficient penicillin producers. Beadle's lab was indeed an exciting place.

Beadle also proposed the one-gene, one-enzyme theory (Beadle 1945a,b). Although exceptions increasingly appeared, it was highly influential in the thinking of the time. Furthermore, this idea and the beautiful techniques attracted biochemists to the field.

CalTech: In 1946 Beadle returned to CalTech to succeed Morgan as chairman of the Biology Division. Building on the already strong genetics program, he recruited a stellar group of faculty colleagues. From Stanford he brought Norman Horowitz, Herschel Mitchell, and Mary Houlahan (later Mary Mitchell). He soon added Max Delbrück, Ray Owen, Renato Dulbecco, Roger Sperry, and Robert Sinsheimer. Beadle immediately realized that the job of running a department was a big one and allowed no time for research. He felt that his first obligation and responsibility were to get the place back to its original glory, so he became a full-time administrator. His combination of informality, openness, and strength of leadership made him an outstanding chairman. Among other things, he played an important role in getting CalTech to accept women as graduate students.

By 1958, Beadle had built up the program in Pasadena so that it had become a world center for molecular biology. Much, probably most, of his time was involved with obligations outside of CalTech. The Biology Division was going beautifully, so he decided to take a sabbatical and accepted an offer to spend a year at Oxford, where, as Eastman Professor, he taught courses and absorbed the Oxford culture. It was during this period that Beadle and Tatum shared the Nobel Prize with

Joshua Lederberg. Further honors had already begun pouring in. Eventually, he received a total of 37 honorary degrees, 11 major awards, and 15 honorary society memberships. For a complete list as well as a bibliography, see Horowitz (1990).

Public service: Beadle had become increasingly active in other ways. He regarded public education in genetics as a personal responsibility and gave frequent speeches before diverse groups. These included school children, whom he particularly enjoyed and whom he thought especially important for the future of science. He was also highly successful as a fundraiser for CalTech biology. At the same time he became increasingly active in national committees. An increasing fraction of his time was spent on airplanes, where he took care of much of his handwritten correspondence.

Beadle was on the original committee that recommended genetic studies on the children of Hiroshima and Nagasaki survivors. He was able to attend a bomb test in Nevada. Although he was scrupulously careful with the nation's military secrets, he was active in protecting scientists who were regarded as security risks, including his CalTech colleague, Linus Pauling. Beadle became an advisor to the Biology Division of the Atomic Energy Commission. In 1954 he was president-elect of the American Association for the Advancement of Science (AAAS) and took a strong stand against excessive secrecy. He was a member of the National Academy committee on the Biological Effects of Atomic Radiation (BEAR), which issued an influential report (BEAR 1956). After that, he became chairman of the committee, which issued a second report in 1960 (BEAR 1960). Beadle also served as chairman of the Scientific Council of the American Cancer Society. He was instrumental in getting the Society to adopt a broader view of what could be studied under the name of cancer research.

Chicago: In 1961 Beadle surprised everyone by accepting the presidency of the University of Chicago. This came as a particularly great shock to his CalTech associates. Although Beadle's name had been mentioned more than once in connection with university presidencies, his decision to go to Chicago was made without his CalTech colleagues knowing what was happening.

Why did he do it? For one thing, Beadle had always liked a change, and he had been at CalTech for 15 years. For another, this was a challenge, and Beadle liked a challenge. The University of Chicago felt that it was losing academic standing. It was also losing faculty and needed more money. Furthermore, there were serious problems of student unrest and urban renewal in the University area.

It was a wise decision on the part of the University. Beadle increased the faculty size by 25% during his 7-year tenure and he improved the standing markedly. By his retirement, he had doubled the budget and had achieved his aim of raising $160 million. His ability to glide calmly through the most contentious academic and community problems is part of the Beadle legend. Surprisingly, he did not achieve as much as he had hoped in biology and medicine, although in later years Chicago became a leader in these areas. And, as was his lifetime custom, he had a garden.

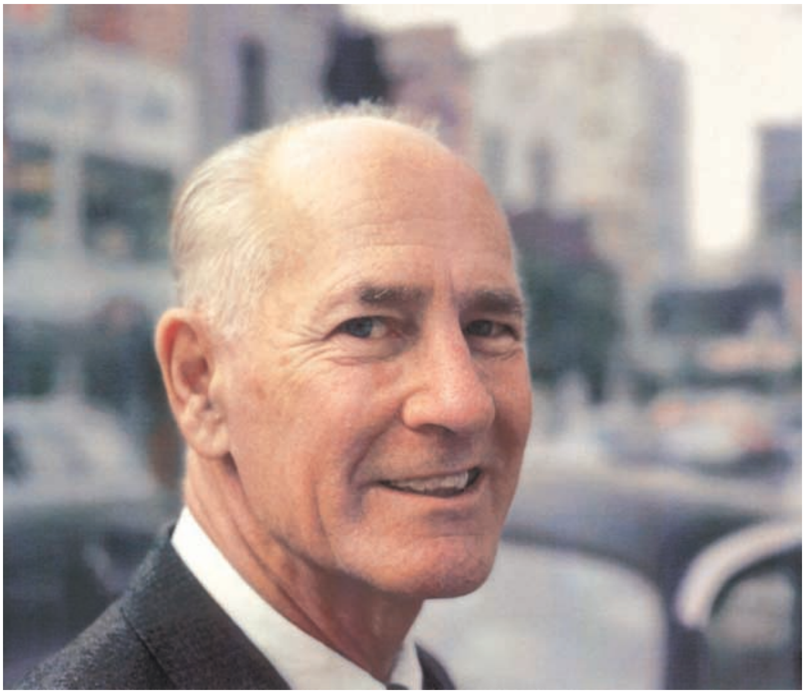
Retirement: In 1968 at age 65, Beadle reached the mandatory retirement age and was succeeded by Edward Levi, who as Dean of the Law School had been most effective in persuading Beadle to accept the Chicago challenge. Beadle stayed in Chicago, but he did not stop working. He held a couple of short appointments, but mainly he returned to his first love, the origin of maize.

As a graduate student, he had known that maize is closely related to teosinte, both genetically and cytologically. He and Emerson thought that teosinte was the most likely ancestor of maize. During his busy years of research and administration, he had no time to pursue this interest, but he became increasingly annoyed by a theory proposed by Mangelsdorf and Reeves (1938). Mangelsdorf believed that maize was derived from an extinct or unknown ancestor that, by crossbreeding with tripsacum, produced maize. Teosinte, he thought, came later from hybridization of tripsacum and maize.

Beadle was convinced that this was dead wrong. For one reason, maize has 10 pairs of chromosomes and tripsacum 18, and the hybrids are sterile. Busy as he was with an active research program, Beadle took time off to argue his case for teosinte (Beadle 1939). After retirement, he did extensive genetic experiments and became convinced that a rather small number of mutations could convert teosinte into a reasonable facsimile of maize. He also showed that the hard kernels of teosinte could "pop," just like popcorn; he suggested that this made it easily edible and provided an incentive for early farmers to cultivate it. He not only did small-scale experiments in his several garden plots, but also in 1971 and 1972 organized two teosinte mutation hunts in southern Mexico. Beadle worked long hours, attested by the fact that he personally examined several million seeds. His last article (Beadle 1981) added some new evidence: ancient pollen grains that he interpreted as diploids from a tetraploid teosinte.

There were several acrimonious group meetings during the "corn wars" in which he and Mangelsdorf debated. In the end, Beadle provided the most convincing genetic evidence and, as later shown by Doebley (see below), he was right in most particulars.

Beadle's personal life: While at Cornell, Beadle met and in 1928 married Marion Hill, a graduate student in botany. They worked together on some experiments. A son, David, was born in 1931. Later, they were divorced, and in 1953 Beadle married a gifted writer, Muriel Barnett. She wrote several books. Most pertinent to this article are *These Ruins Are Inhabited* (Beadle 1961), based on the Oxford experience, and *Where Has*



G. W. Beadle on November 27, 1971, at the time of the teosinte mutation hunt in Mexico. Photograph by Hugh Iltis.

All the Ivy Gone (M. Beadle 1972), an account of their days in Chicago.

Some years after his retirement, Beadle began to experience memory loss. He stayed in Chicago and continued his experiments as long as he could, but finally returned to California. In 1983, at age 80 he was diagnosed as having Alzheimer's disease and died on June 9, 1989. Muriel survived him by 5 years.

SOME VIGNETTES

Following are several short items, reflecting views of those who knew Beadle in one way or another. Most (those by N. Horowitz, P. Berg, M. Singer, and J. Doebley) are extracts from talks given at CalTech in October 2003, celebrating the centennial of Beadle's birth.

Memories of a colleague (N. Horowitz)

It is a pleasure for me to take part in this symposium of distinguished scientists assembled to celebrate the centennial of my old friend, George Beadle. It was in this room, 62 years ago, that Beadle presented the results of the experiments that he and Tatum were then carrying out at Stanford University with the red bread mold Neurospora. These experiments founded the science of what Beadle and Tatum called "biochemical genetics." In actuality, they proved to be the opening gun in what became molecular genetics and all the developments that have followed from that.

I would like to try to convey something of the mood of that seminar. The year was 1941. It was the Golden Age of classical genetics. T. H. Morgan was still active as the first chairman of the Biology Division. The room was full. Beadle was well known at CalTech. He had been a postdoc here and had coauthored a highly regarded textbook of genetics with Sturtevant (Sturtevant and Beadle 1939). Beadle was introduced, and he presented the astonishing results of the revolutionary article that was then in press in the Proceedings of the National Academy of Sciences of the United States of America (Beadle and Tatum 1941). He described the first three nutritional mutants of Neurospora, mutants with requirements for pyridoxine, thiamin, and *p*-aminobenzoic acid, respectively. He spoke for just 30 minutes and then sat down. There was no applause, because the audience could not believe that someone with such findings could talk about them for just 30 minutes. We had never heard such experimental results before. It was the fulfillment of a dream, the demonstration that genes had an ascertainable role in biochemistry. We were all waiting—or perhaps hoping—for him to continue. When it became clear that he actually was finished, the applause was deafening. Professor Frits Went, whose father had done the first nutritional experiments with Neurospora in Java early in the century, stood up and turned to a group of graduate students sitting in the audience and said "You see—biology is not a finished subject—there are still great discoveries to be made!"

A few years later, Beadle summarized the Neurospora findings with the statement "one gene, one enzyme" or, more broadly, "one gene determines the structure of one protein." This was the keystone of molecular genetics.

The full breadth of Beadle and Tatum's discovery soon became clear. They had shown that a class of lethal

An impression of Beadle by Pam (Mrs. E. B.) Lewis.

mutants new to genetics—mutants requiring essential substances, such as vitamins, amino acids, purines, pyrimidines, or their precursors—could be recovered by working with a microorganism that could be grown on a synthetic medium. In the case of Neurospora, the medium was a simple inorganic one containing sugar and biotin. In short, they had demonstrated that genes have an essential role in biosyntheses. At the time, some nongeneticists still believed that genes governed only trivial biological traits, such as eye color and bristle pattern, while basic biochemistry was determined in the cytoplasm by an unknown mechanism. Many respected geneticists believed that gene action was far too complex to be resolved by any simple experiment. In other words, Beadle and Tatum had brought about a real revolution.

The one-gene, one-enzyme theory in retrospect (P. Berg)

Formulated in the mid-1940s, the one-gene, one-enzyme maxim gave physical meaning and function to genes. While imprecise in detail, the notion that each gene specifies a unique enzyme (protein) was, in its time, a "bombshell." As with most concepts in biology, time and the advancing knowledge modified the original one-gene, one-enzyme proposal. First came the change to one gene, one protein, to be replaced by one gene, one polypeptide as it became clear that many proteins contain more than one polypeptide chain, each specified by a different gene. Then we learned, particularly in eukaryotes, that one gene often gives rise to more than one polypeptide as a consequence of the organization of genes into polypeptide-encoding exons and noncoding introns and the phenomenon of alternative splicing. And some genes do not encode a polypeptide at all, but rather encode functional RNA molecules.

In ascribing an instructional role to genes, Beadle and Tatum implicitly accorded genes an informational property. This insight provided a foundation for a genetic code. Admittedly, not until Avery's and Hershey's proof that DNA was the genetic material, Sanger's demonstration that proteins have a defined linear array of amino acids, and Watson-Crick's solution of the DNA structure was there a basis for thinking about a genetic code. In his seminal article on the "sequence hypothesis," Crick conceded that the one-gene, one-protein axiom made it likely that the linear array of base pairs in DNA specified the linear array of amino acids in the protein.

Until Beadle and Tatum's experiments with Neurospora, mutations were used primarily as genetic markers for studying the mechanisms of inheritance. Geneticists relied on spontaneous, random events that altered an observable or measurable property of an organism. There was no need to know the function of the mutated gene to determine its linkage to other genes or to follow its inheritance from one generation to the next. But with more efficient means for making mutations, Beadle and Tatum's experimental paradigm provided a way to analyze metabolic pathways. Soon afterward it became the preferred way to dissect complex biological systems such as embryonic development, cell division, the nature of sensory systems, and aging. Today, mutational analysis is the preferred way into a complex biological problem, especially as it provides access to the genes and protein players.

Beadle was an early articulate spokesman for the integration of biochemistry and genetics. Although not a biochemist, he assailed the barriers between biochemists and geneticists. He was prophetic in believing that the biochemist could not understand what goes on chemically in the organism without considering genes any more than the geneticist could fully appreciate the gene without taking account of what it is and what it does. He coined and consistently used the term biochemical genetics, seemingly preferring it to molecular biology although the latter won out in the end.

The flowering of molecular biology and the emergence of genomics has occupied center stage during the past 50 years and in that time produced its own set of "heroes." Beadle was never a direct participant in the explosive advances that followed the solution of the DNA structure. His modest demeanor and "nice guy, straight arrow" manner would likely have put him at odds with the flamboyant and quirky behavior of several of the major players of the new biology. They likely viewed him as "a noncombatant" figure from the past.

Beadle as a public citizen (M. Singer)

After World War II, the emergence of the Cold War and the resulting national paranoia with security and loyalty coincided with the growth of federal grant support. Scientists and others were subject to public charges of disloyalty. Beadle accepted the necessity of keeping the nation's nuclear secrets, but he was troubled by the government's procedures for routing out security risks. The cases against individuals under suspicion were often built on rumor, innuendo, and guilt by association. The situation offended Beadle's sense of justice, and he publicly defended several wronged individuals. Security issues came especially close to Beadle when they threatened David Bonner, one of his outstanding students then on the faculty at Yale. A security investigation was begun when Bonner accepted an offer to move to the Atomic Energy Commission's (AEC) Biology Division at Oak Ridge. Beadle wrote to the AEC saying that Bonner was a "reliable person of complete loyalty to the ideals of our country," and he traveled to Oak Ridge to testify at Bonner's hearing. To his dismay, Bonner was denied clearance and lost the Oak Ridge position as well as his grants for unclassified research. Beadle then helped with Bonner's successful appeal. A few years later, in an article in CalTech's magazine, Engineering and Science, he decried the security clearance system because "it violates the basic principles of justice in a free society" (Beadle 1954).

One reason that Beadle was so involved with these issues was the maelstrom surrounding his CalTech colleague, Linus Pauling. Pauling had convinced Beadle to return to Pasadena, and the two of them worked together to make CalTech a leading center for molecular biology. Pauling was vocal with his strong and idealistic views about how to promote peace in the atomic age. Periodically, the CalTech trustees, convinced that he was a communist, called for Pauling's dismissal although even the FBI found no evidence supporting that contention. Senator Joseph McCarthy made Pauling's alleged communist connections front page news. The U.S. Public Health Service rescinded his National Institutes of Health (NIH) grants at one time and later withdrew grants from another CalTech scientist with no formal proceeding or opportunity for the accused to counter the allegations. With Beadle's support, the CalTech faculty courageously voted that "no new Public Health Service research grants be accepted until such time as the present policy is appropriately modified." CalTech's trustees guaranteed $1 million for at least 1 year if all the current grant money were returned to the NIH. The faculty agreed. Beadle informed the surgeon general of this action, and the surgeon general reinstated the grants. Beadle wrote defending Pauling: "I admire the courage with which he stands by his convictions even at times when his views may not meet with popular favor. I am proud to belong to the faculty of an institution with the foresight to see his greatness and the wisdom to give its development full freedom."

As president-elect, Beadle helped draft the AAAS statement on "Strengthening the Basis of National Security" (AAAS 1954). The critical sentence is still important today: "Continued scientific progress provides a better guarantee of military strength and security than does excessive safeguarding of the information we already possess." Beadle's pragmatic, nonideological views and leadership earned him a reputation as a wise and prudent defender of science and scientists.

Beadle and Tatum (J. Lederberg)

The one-gene, one-enzyme theory, namely that a gene acts by controlling the formation of a specific enzyme in some fairly simple manner, was already implicit in the research on pigment biosynthesis. Its evolution can be related to the broad reach of mechanistically oriented research in biology. Haldane's speculative discussion is closely parallel, but the theory was never so concretely asserted nor used to plan such effective lines of enquiry before 1941. The Neurospora work suggested that any biochemical trait could be readily studied in like fashion; Beadle and Tatum plausibly extrapolated from several diverse examples that all such traits would have an equally direct relationship to corresponding genes. This generalization is now rephrased in the terms that the DNA sequence provides the information for protein structure. The numerics might sometimes be more complex: many genes might be involved in the quantitative regulation and environmental responsiveness of enzyme synthesis and, sometimes, of families of enzymes. Enzymes are sometimes complex multichain ensembles or may contain nonprotein cofactors, requiring the participation of many genes. The role of RNA as a message intermediate between DNA and protein, the complexities of intervening sequences in RNA, RNA processing, and post-translational processing were future developments requiring more sophisticated biochemical analysis, but all were inspired by and made great use of the concepts concretized by, and of the tools generated from, the Neurospora studies. Beadle and Tatum's essential contribution therefore is composed of several parts:

1. A methodology for the investigation of gene-enzyme relationships exploiting experimentally acquired genetic mutations affecting specific biosynthetic steps.
2. A conceptual framework, the one-gene, one-enzyme theory, that provided a context for the search for and characterization of these mutants and reflected back to a primary model that the chromosomal genes contained (substantially) all of the blueprints of development and that enzymes (and other proteins) were the mediators of gene action.
3. The (temporary, as it turned out) dethronement of Drosophila as the prime experimental material for physiological genetic research, in favor of the fungus Neurospora, which helped open the way to bacteria, viruses, and tissue cells cultured as if they were microbes. (This is an extract from Lederberg 1990.)

Memories of a student (M. Susman)

I met George Beadle in 1957, when I arrived at CalTech as a new graduate student in the Division of Biology. I had been offered a teaching assistantship to support my first year of study, but the offer did not specify the course I would be teaching. As it turned out, I was assigned to the team of teaching assistants (TAs) in Bio 1, the introductory biology course in which George Beadle and James Bonner were the lecturers. I had, of course, heard of both Beadle and Bonner before I arrived at CalTech, and I was pleased to be given an assignment that would give me an opportunity to get to know them.

Beadle was a wonderful lecturer, clear and well organized, and students could easily see that he was fascinated by the enormous breadth and complexity of biology. The job of the TAs was simply to oversee the labs in the course and to try to convey in the lab the same sort of enthusiasm that Beadle conveyed in the lectures. Beadle's frequent and cheerful interactions with the TAs were helpful. In our weekly discussions of the upcoming labs, he was always able to point out the elements in the lab that the students would find most interesting and provocative. And I particularly remember grading sessions in which we all sat in one room and struggled to evaluate short essay answers that were often quirky or syntactically bewildering. These sessions were both hilarious and instructive, thanks to Beadle's happy acceptance of the oddities of undergraduates and his long experience in making sense of their rambling prose.

I want to mention Beadle's introduction to his lecture on evolution, because it differed so dramatically from the introduction that I had heard when I was a freshman biology student. My professor at Washington University had started the lecture by saying that the Missouri Synod of the Lutheran Church, to which many of the students in the class belonged, rejected the idea of evolution. "When the church and science are in conflict on some issue," said the professor, "the church had better back down." This statement made a good many students extremely unhappy. Beadle, on the other hand, introduced the subject by saying that some religious people were uncomfortable with the theory of evolution, but he did not see why. If you wanted to think of God as the creator of all living things, what would be wrong with thinking that God used evolution as the mechanism? It was clear that Beadle was no more religious than my professor at Washington University, but he was certainly more diplomatic.

The TAs were so comfortable with Beadle that we called him "Beets." I do not think he ever invited us to use his nickname, but he was so egalitarian in his dealings with us that it seemed natural to address him as his faculty colleagues did. Beadle was chair of the Division of Biology at the time, and, of course, the Division of Biology at CalTech was a collection of all stars, among whom Beadle sparkled as brightly as any. There was, however, no hint of pomposity in Beadle.

Beadle invited the TAs in Bio 1 to his house for dinner. That evening remains vivid in my memory. Beadle and his wife, Muriel, lived in the Morgan house, which had been the residence of Thomas Hunt Morgan, and Beadle clearly considered it to be hallowed ground. He told us a bit about Morgan's contributions to genetics just to make sure that we appreciated the significance of being in Morgan's house. We met Beadle's cats, and he told us about their breeding. Beadle liked Siamese cats, but disapproved of their raucous voices. His cats were the result of his own breeding experiments to discover the genetic basis of the annoying voice and to produce Siamese cats with mellifluous meows. Beadle grilled the steaks for dinner and instructed us in how to prepare them. You started with the best top round steak from Jorgensen's Market and marinated it in a mixture, the ingredients of which he listed for us. He had us gather around the grill so that we could learn how to prepare the charcoal and turn out a perfect round steak.

Beadle showed us a beautifully illustrated book on the mountains of Alaska, in which he was identified as a member of the first team to climb Mount Doonerak. He was as proud of climbing that mountain, he said, as he was of anything he had ever done. Beadle told us that he had taken up rock climbing around the age of 50 and that, while he was still a novice, he had made a challenging climb with a group of students, all of whom were much younger. When they reached the top, one of his fellow climbers, a medical student, suggested that, since they had all just entrusted their lives to one another, it might be nice to learn each other's names. On hearing Beadle's name, the student asked, "You are not by chance the Beadle of Beadle-and-Tatum?" Beadle admitted that he was. The student said, "Man, I thought you were dead!" Beadle was clearly delighted by this story.

I have one other personal recollection of Beadle that demonstrates something of his leadership style. My wife gave birth to our first son in the spring of my first year as a graduate student. Our health insurance adequately covered the costs of the hospital, but not the bill from the obstetrician. The bill was so much larger than we had anticipated that I decided I would have to drop out of graduate school and get a job. I made an appointment with Beadle to ask whether CalTech would be willing to hold a place for me so that I could return to graduate studies after I had paid off our debt. Beadle was outraged at the size of the obstetrician's bill. He asked the doctor's name and phoned him immediately. "What do you think you're doing, man?" he asked the obstetrician. "This kid's a CalTech graduate student. He can't afford to pay medical bills like that." The doctor promptly reduced his bill, and I was able to continue my graduate studies.

The origin of maize (J. Doebley)

In the early twentieth century, considerable controversy surrounded the origin of maize. Most crop plants differ from their wild progenitor in a simple quantitative way: wild tomato is merely a small-fruited version of the large-fruited domesticated tomato, wild sunflowers are miniature forms of the large-headed cultivated sunflower, and so on. But maize has no morphologically equivalent wild form and therefore no clear progenitor. Mangelsdorf and Reeves (1938) claimed to solve the problem of the origin of maize by proposing that maize evolved from a "wild maize" that looked like the diminutive counterpart of modern maize. No one had ever seen this hypothetical wild maize, they explained, because it went extinct shortly after having been domesticated.

Although maize has no obvious progenitor in the morphological sense, it does have a close wild relative in the genetic sense, teosinte (Beadle 1932a,b). As shown by Emerson and Beadle (1932), maize and teosinte form fully fertile hybrids with normal chromosome pairing. Curiously, this close genetic relationship is not reflected on the morphological level, maize bearing its kernels naked and in pairs around the entire circumference of its rigid ear and teosinte bearing its kernels encased in hardened fruitcases, borne singly, and positioned on just two sides of an ear that disarticulates at maturity.

Less than a year after Mangelsdorf and Reeves proposed their "wild maize" hypothesis, Beadle (1939) challenged it with his "teosinte hypothesis." Beadle claimed that teosinte was the progenitor of maize and that just a few mutations might have been sufficient to convert teosinte into a primitive form of maize. One mutation would liberate the kernel from the fruitcase, a second would block the disarticulation of the ear, a third would convert single into paired kernels, and a fourth would change the ear from having two to having multiple rows of kernels around its circumference.

Beadle set aside his work on maize evolution for the next 30 years, while Mangelsdorf promoted his wild maize hypothesis so effectively that it was viewed as an established fact by many. Upon his retirement, Beadle felt that this situation could not be left to stand. In 1972, G. W. Beadle (1972) published the first in a series of articles critiquing Mangelsdorf's theory and supporting his own view that teosinte was the progenitor of maize. His principal experimental evidence was that 1/500 maize-teosinte F_2 plants resembled either the maize or the teosinte parent, suggesting that as few as four or five genes governed the key morphological differences between these plants.

During the 1970s, Beadle was joined by colleagues Hugh Iltis, Walton Galinat, Jan de Wet, and Jack Harlan, who agreed with his teosinte hypothesis and provided supporting evidence from genetics, cytogenetics, taxonomy, and morphology. During this time, Beadle also further developed his own views about how teosinte was converted into maize. He incorporated into his thinking the view that the *Tunicate* locus was responsible for freeing the teosinte kernel from its fruitcase (Beadle 1977). He accepted a previously published but poorly documented account that a single gene (*paired-spikelets*) controlled the difference in paired *vs.* single kernels.

My laboratory followed up on Beadle's work, using quantitative trait locus (QTL) mapping in maize-teosinte F_2 populations (Doebley and Stec 1993). Contrary to expectations, we found no case in which traits were simply inherited. Rather, traits like paired *vs.* single spikelets varied in a quantitative fashion with ears on many plants possessing mixtures of both single and paired spikelets. We found that all traits were controlled by multiple QTL. None of the QTL controlling naked *vs.* encased kernels mapped to the *Tunicate* locus as proposed by Beadle (1977). Notably, we uncovered nine QTL for rigid *vs.* disarticulating ear, a trait for which Beadle and others had postulated a single gene.

Our results did affirm Beadle's primary experimental result. We found that all of the QTL of large effect mapped to five chromosomal regions. There were smaller-effect QTL on all 10 chromosomes, but most of the observed effects on the traits mapped to just five regions. A question that we continue to work on is whether these five regions possess single genes of large effect or multiple linked genes.

Our studies of one of the five regions have shown that it possesses a locus of large effect that exhibits Mendelian segregation when analyzed in the uniform background of a maize inbred (Dorweiler *et al.* 1993). We named this locus *teosinte glume architecture* (*tga1*) and demonstrated that it has pleiotropic effects on multiple traits related to the formation of the fruitcase that surrounds the kernel in teosinte. *tga1* represents exactly the type of locus predicted by Beadle to free the kernel from the fruitcase, although he incorrectly suggested that *Tunicate* was the gene involved.

The second chromosomal region that we investigated in some detail has a large effect on the differences in plant architecture between maize and teosinte (Doebley *et al.* 1995). Teosinte plants typically have long lateral branches tipped by tassels, while maize has short branches tipped by ears. We identified a candidate gene called *teosinte branched* (*tb1*) in this region and showed, by complementation tests, differences in gene expression, and evidence for past selection, that *tb1* was involved in maize evolution. Although *tb1* appears to be a key gene involved in maize evolution, it is not one that Beadle predicted.

How should we remember Beadle's contribution to maize evolution? Just as in the case of one gene, one enzyme, the answer to this question depends on whether one wants to credit Beadle for his insight or to quibble with him about the exceptions to the principles he defined. There are enzymes encoded by more than one gene, and there are single genes that encode multiple enzymes; however, the one-gene, one-enzyme hypothesis fits most genes. Similarly, one could challenge Beadle on some specifics such as the prominent role he afforded the *Tunicate* locus. However, Beadle's central conviction that changes in a modest number of genes as a result of human selection could convert teosinte into a primitive form of maize over the course of a few hundred years remains the only reasonable interpretation of the available information. His seminal 1939 article and his postretirement efforts were key to the resolution of the origin of maize and to the acceptance of the teosinte hypothesis by the broader scientific and lay audiences.

Some personal memories (J. Crow)

I first met Beadle around 1950 when he gave a seminar talk at the University of Wisconsin. Two things particularly impressed me. The first was the clarity of the talk and his interesting manner of presentation. Second was the grace with which he dealt with questions. His openmindedness and modesty were apparent when he encountered considerable skepticism about the one-gene, one-enzyme theory.

In 1956 I attended an International Symposium on Genetics held in Japan. It was an exciting time, since most of us had never been to Japan. J. B. S. Haldane was at his boorish worst. First, he refused to stay in the accommodations that had been provided for him. Second, he refused to ride on the same bus with a Japanese reporter who had written something he did not like; the reporter obligingly got off. Third, Haldane was scheduled to give the opening plenary address. Despite heroic efforts on the part of the organizers, he was not satisfied with the speaking arrangements and refused to give his talk. Beadle was scheduled to give the closing address. It was a busy time for him. He was constantly sought after and had a full agenda for the visit. Among other duties, as chairman of the BEAR committee, he spent many hours with Daigoro Moriwaki, his Japanese counterpart. Always the gentleman, he agreed to give his lecture on the opening day. By the end of the symposium some days later, Haldane was satisfied with the arrangements and gave his talk. The talk was marred by frequent interruptions from the large audience by his wife, Helen Spurway.

Sometime around 1957, Beadle visited the University of Wisconsin. R. A. Brink had arranged for an informal gathering with light refreshments. He then asked casually of Beadle whether anything of interest had happened at CalTech recently. Beadle replied that the answer was yes, and he agreed to tell us about it. So we all went into a small lecture room where Beets proceeded to give a wonderfully lucid lecture on the Meselson-Stahl experiment. I think it was totally new to everyone. We were all impressed by the beauty of the work, but also by Beadle's crystal clear, off-the-cuff description. I vividly remember how excited I was to hear about what has been called "the most beautiful experiment in biology."

My first chance to get well acquainted with Beets was on the BEAR committee. This committee was chaired by Warren Weaver, who, although a mathematician, turned out to very quickly grasp the subject of genetics. The committee, as so often happens, got bogged down in an argument, not about what we should conclude, but how we should explain it. Wright and Muller were completely at odds, and for a while it looked as if we would not have a report. Wright had written a statement, a thorough analysis as only Wright would do, but Muller thought that it would dilute the impact of the report. Wright was finally persuaded not to have it included (Crow 1995). The report appeared in 1956 and was widely publicized. It set the tone for radiation protection standards from that time on. Beadle, who succeeded Weaver as chairman, negotiated to have Wright's lengthy statement included with the 1960 report. Wright was not entirely happy with the postponement, for he knew that any later report would be largely ignored, which was true.

At about this time Beadle, as was always the case, was involved in all sorts of activities. In particular, he was on a committee to oversee a series of science programs on national television sponsored by Bell Telephone. Beadle naturally arranged to have one of these programs on genetics and asked me to be the scientific consultant. The film was made in the Warner Brothers Studio in California. It was my first (and last) experience with the Hollywood culture. Beets got Norman Horowitz to work with me. The project turned out to be more work than I had expected and involved several trips to California. What made the trips most pleasant, however, was that each time I was a house guest of Beets and Muriel, both gracious hosts.

While Beadle was still at CalTech, the University of Wisconsin was looking for a president. A leading candidate was Lee DuBridge, who promptly turned it down. All along, Beadle had also been considered. A group of Wisconsin regents went to CalTech to interview Beadle, and this drew from a confused DuBridge the comment, "Can't these people understand that I have said 'no'?" It turned out that a local Wisconsin candidate was named. I do not know whether Beadle would have accepted. At least he was willing to move, for not long after, he took the position in Chicago.

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