TIMELINE

George Beadle: from genes to proteins

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Abstract | George W. Beadle's life spanned much of the period during which genetics changed from an abstract to a molecular science. Beadle himself catalysed the transition from classical to molecular genetics when, together with Edward Tatum, he discovered that each gene is linked to the production of a protein. This article traces his life from a modest farm to the centre of biology and a principal role in the development of the scientific enterprise.

In the early months of 1941, Edward Tatum asked his Stanford undergraduate biology class a rhetorical question: "What do genes do?" It was not a new question, as it had occupied biologists since the turn of the century. Although it was well known that mutations alter an organism's phenotype, the precise modifications resulting from genetic changes were a matter for speculation. Tatum suggested in his lecture that the various nutritional requirements exhibited by different classes and species of microorganisms reflected the loss of metabolic functions resulting from mutations that had accumulated over evolutionary time. Beadle, who was sitting in on the lecture, was inspired by Tatum's comments to initiate a series of new experiments that would demonstrate that the production of enzymes is determined by genes[1]. Beadle and Tatum collaborated on these experiments and they recognized, for the first time, that genetics and biochemistry were inextricably linked. For their discovery, Beadle and Tatum shared the 1958 Nobel Prize in Physiology or Medicine (FIG. 1). This work laid the foundation for what subsequently became molecular biology[2].

Beadle, who was 38 years old in 1941, was, in fact, a farmer at heart; although an uncommon farmer to be sure. He grew up on a 40-acre farm outside the small town of Wahoo, Nebraska, but gave up on the prospect of farming in favour of genetics after learning about the discoveries in that field at college. Working successively with the top geneticists in the world and absorbing their lore and innovative styles, Beadle carried out seminal research on several organisms[3] (BOX 1).

Turning to *Drosophila melanogaster*

Beadle was inspired to take up the genetics of *D. melanogaster* by his association with Thomas Hunt Morgan's 'Fly Group', which at the time consisted of Alfred H. Sturtevant, Calvin R. Bridges, Theodosius Dobzhansky and Jack Schultz. Their establishment of the chromosomal basis of heredity[4] provided the foundation for much of the fundamental knowledge of genetics. For them, genes were defined by mutations and studied through genetic crosses. They knew that genes are associated with chromosomes in a linear and specific order that could be determined with precision. They understood that pairs of homologous chromosomes carrying paired alleles can exchange segments (through crossing-over; that is, recombination) and that the paired chromosomes separate at meiosis. But the physical nature of genes was still being contested[5] and the question of what genes did was a complete mystery.

Conceptual challenges. Morgan was convinced that genes have a role in development[6], but neither he nor any of the biologists at the California Institute of Technology (Caltech) could imagine how that might occur or how to explore the presumed connection experimentally. It is difficult, if not impossible, to force our minds into the context of the 1930s

Figure 1 | **George Beadle (left) and Edward Tatum (right) receiving their Nobel Prizes.** Image courtesy of the Karolinska Institute, Stockholm, Sweden.

because we now think about genes as defined stretches of a DNA double helix and we know that a gene's function is distinct from the function it encodes. We cannot imagine thinking about genes without seeing in our mind's eye DNA, RNA and proteins. But in the 1930s, the chemistry of these molecules was rudimentary and the idea that genes are discrete, specific molecules was still considered speculative, at best[7]. Beadle's generation therefore faced many conceptual challenges when trying to understand how genes work.

Technical challenges. The challenges were more than just conceptual. The experimental tools and model organisms available for linking genes with development were inadequate. For example, the sea urchin, the development of which had been extensively described, lacked a genetic system and *D. melanogaster*, the 'reigning queen' of genetics, was poorly suited for developmental analysis because of its complex transformation from larva to adult. Nevertheless, with Morgan's blessing, Beadle and Boris Ephrussi (BOX 2), an accomplished Russian-French embryologist who had come to Caltech to learn genetics, agreed to gamble a year to try to develop an experimental approach in flies that might shed some light on the role of genes in embryo development. Their plan was to investigate the effect of *D. melanogaster* eye colour mutations on eye development by manipulating the larval imaginal discs (the patches of embryonic cells that later give rise to the adult eyes).

Three-eyed flies. Beadle joined Ephrussi at the Institute de Biologie Physico-Chemique in Paris. After failing to induce *D. melanogaster* larval imaginal discs to develop in cell culture, they hit on the idea of transplanting imaginal disc tissue from one larva into another larva or pupa. Much to their delight, they found that after transplantation of eye imaginal discs, an extra eye developed in the abdomen of adult flies (FIG. 2). The genetics community was mesmerized by the sight of an eye staring up from the belly of an adult fly.

Next, using the existing large collection of *D. melanogaster* eye-colour mutants, they learned that transplanted eye discs from larvae of most of the mutants yielded 'mutant' eye colour irrespective of the genotype of the recipient larvae. There were, however, two exceptions. Transplantation of eye discs from either the *vermilion* or the *cinnabar* mutant produced supernumerary eyes of normal colour when transplanted into wild-type or most mutant larvae. Curiously, transplantation of *vermilion* eye discs into *cinnabar* larvae yielded normal colour eyes in the abdomen, but transplanting *cinnabar* eye discs into *vermilion* larvae still yielded *cinnabar* coloured eyes. Beadle and Ephrussi concluded that the formation of eye colour occurred through a pathway that has at least two steps: one led to the synthesis of the vermilion substance and the other to that of the cinnabar substance. From the asymmetrical outcomes of the reciprocal transplants of *vermilion* and *cinnabar* eye discs, they surmised that the *vermilion* gene acted before the *cinnabar* gene. The lasting achievement of the Beadle–Ephrussi collaboration was the realization that genes controlled individual steps in a metabolic pathway[8].

Then, working independently, Beadle and Ephrussi tried to identify the chemical nature of the vermilion and cinnabar substances, hoping that they could get closer to the nature of the genes and how they functioned. Five frustrating years later, Adolph Butenandt had identified the vermilion substance as kynurenine, and subsequently the cinnabar substance was shown to be its metabolite 3-hydroxykynurenine. Although it seemed reasonable to assume that the two metabolites were the products of enzyme action and that vermillion and cinnabar mutations affected the activities of the enzymes, Beadle conceded that it was a "purely gratuitous assumption"[9].

Genes and enzymes

A new approach. Those 5 years convinced Beadle that a better system for examining the gene–enzyme relationship was needed. His insight while listening to Tatum's lecture is best appreciated through his own words[1]: "Observing him [Tatum] writing sequences of reactions on the blackboard, I suddenly realized how stupid we had been all these years. Here were all those enzymatic reactions already worked out by competent biochemists. If our gene–enzyme concepts were correct, then we ought to be able to identify the genes

Box 1 | Mentors matter

Beadle's intelligence and promise was spotted by a Wahoo high-school science teacher who encouraged him, against the wishes of his father, to continue his education at the College of Agriculture, University of Nebraska, in nearby Lincoln. Beadle thrived at the College, which had an outstanding reputation in plant sciences, and garnered many of the academic honours bestowed on undergraduates. More importantly, however, one of his professors, F. D. Keim, recognized Beadle's gifts and engaged him in research. As graduation neared, Keim persuaded him to do graduate work at the College of Agriculture at Cornell University.

At Cornell, Beadle's thesis advisor was Rollins A. Emerson, the world's leading maize geneticist. Emerson himself was a Nebraskan farm boy who was trained in Lincoln. At Cornell, he established a vibrant programme that attracted excellent students. In Beadle's time, the group included Barbara McClintock, G. Fred Sprague (another Nebraskan), Charles Burnham, Harriet Creighton and Marcus Rhoades. Using both classical genetics and the innovative cytogenetic techniques he learned from McClintock, Beadle investigated several sterile mutants of maize and demonstrated that the mutations affected different steps in meiosis.

Beadle's achievements as a graduate student won him a coveted National Research Council Fellowship for postdoctoral work at the California Institute of Technology (Caltech). There he found new mentors among the already famous members of Thomas H. Morgan's 'Fly Group': Alfred Sturtevant, Calvin Bridges, Theodosius Dobzhansky, Jack Schultz and Morgan himself. Although Morgan was no longer active in research when Beadle arrived at Caltech, the members of the fly group welcomed him to their midst. Under their tutelage, he mastered the essentials of *Drosophila melanogaster* genetics, during the course of which he made seminal observations on the mechanism of crossing-over in meiosis.

The laboratory styles encountered in Emerson's and Morgan's laboratories were markedly different from the formal styles common in more traditional laboratories in Europe and the United States. They did not pamper students, either intellectually or emotionally; students and postdoctoral fellows were expected to carry out independent projects of their own. Initiative and originality were highly prized but not more than the willingness to share ideas and discoveries. Reflecting once on his collaboration with Sturtevant at Caltech, Beadle recalled that he sensed the excitement that had made the Morgan 'Fly Room' at Columbia University legendary 25 years earlier. Emerson, too, promoted a culture where anybody's business was everybody's business; a novel sighting in the microscope invariably set everyone to view and discuss the new results. His most effective teaching occurred while working alongside the students and postdoctoral fellows from morning until night in the experimental plots where they grew their corn.

The lessons Beadle learned from the environments his mentors fostered remained with him. They became the foundation of his own approach to research and teaching and his relationships with his students, postdoctorate researchers and colleagues.

Box 2 | **Beadle's collaborators: Ephrussi and Tatum**

As with many scientists before and after, Beadle found that collaboration with talented colleagues enhanced his own research. Two colleagues in particular had essential roles in his quest to understand gene action: Boris Ephrussi and Edward L.Tatum.

Ephrussi, a Russian émigré to France with a promising reputation as an embryologist, came to the California Institute of Technology (Caltech) in 1934 to learn genetics. There, he and Beadle hatched a plan to develop an experimental model for studying the effects of genes on development, an intractable problem at the time. Between them, they could apply the distinctive tools and ideas of embryology and genetics. Their collaboration revealed the role of genes in the formation of eye pigments in *Drosophila melanogaster*. Beadle acknowledged that this work laid the groundwork for the idea that genes control the sequential order of chemical reactions within the cell and inspired the effort to relate genes and enzymes using *Neurospora crassa*. After the interruption of his research by the Second World War, Ephrussi made his mark in genetics by discovering that the mitochondria and chloroplasts of animal and plant cells possess specialized DNA mini-genomes that constitute unique cytoplasmic genetic systems. Later, he pioneered a new approach to human genetics by fusing human and hamster cells and selecting survivors containing single human chromosomes.

Beadle needed the participation of a biochemist who was experienced in chemical isolation and analysis if he was to characterize the intermediates in *D. melanogaster* eye-pigment formation. Tatum's extensive experience with the purification and characterization of rare microbial products made him an ideal choice. Tatum obtained the crystalline 'v' substance ('v' is the substance that accumulated in the *vermilion* eye colour mutant) and was on the verge of identifying its chemical nature, when they learned that a German laboratory had beaten them. In spite of this setback, Beadle and Tatum's productive collaboration eventually struck gold in their development of an experimental way to probe the relationship between genes and proteins. Here too, the mix of expertise proved decisive: Beadle's skill in devising genetic means for obtaining and characterizing *N. crassa* mutants with single nutritional requirements was complemented by Tatum's ability to map out the pathways identified in sets of mutants sharing a common nutritional requirement. After leaving Beadle's laboratory, Tatum applied the *N. crassa* concepts to bacteria and created various nutritional mutants in *Escherichia coli*. Such mutants were decisive for J. Lederberg's demonstration (in Tatum's laboratory) of conjugation and genetic recombination between *E. coli* cells.

immediately responsible for specifically known enzyme-catalysed reactions. So why not reverse the approach? Instead of looking for reactions by enzymes controlled by known genes, why not look for genes that control already known chemical reactions? We might then expect to find mutations … characterized by an inability to synthesize essential diffusible substances such as vitamins, amino acids and other building blocks of the cell's protoplasm."

It was a bold concept but it needed testing. Beadle was already well aware of the ascomycete fungus *Neurospora crassa* from earlier associations with Bernard O. Dodge and Carl C. Lindegren. They had established that *N. crassa*, in its vegetative phase, is haploid yet sexually competent, and methods for its genetic analysis had already been worked out. Tatum then found that *N. crassa* can synthesize all of its cellular constituents from simple nutrients, requiring only biotin for growth. It took Beadle and Tatum only 5 months to find the first 3 nutritional mutants in their irradiated cultures; one required pyridoxin, another needed *p*-aminobenzoic acid and the third required thiamin[10] (FIG. 3). The first public announcement of their accomplishment was at a Caltech seminar where Beadle went to recruit people for his research group. Not surprisingly, his news was a bombshell. Norman H. Horowitz, one of the people he recruited, recalls it clearly[11]: "The talk lasted only half an hour, and when it was suddenly over, the room was silent. The silence was a form of tribute. The audience was thinking nobody with such a discovery could stop speaking after just 30 minutes — there must be more. Superimposed on this thought was the realization that something historic had happened. Each one of us, I suspect, was surveying, as best he could, the consequences of the revolution that had just taken place."

Besides Horowitz, Beadle persuaded David M. Bonner to join the new effort and a short time later Herschel K. Mitchell was on board. Before long, the laboratory had generated many mutants with only a single altered gene and a single nutritional requirement for an amino acid, a vitamin or a nucleic-acid component. Nutrient-dependent phenotypes could be interpreted as developing from the loss of metabolic enzymes resulting from mutations in corresponding genes. Initially, this idea took the form of a one gene–one metabolic reaction but soon after was christened 'one gene–one enzyme'.

Convincing the sceptics

Many in the scientific community were sceptical and resisted Beadle's idea because it seemed too simplistic and restrictive as a role for the activity of genes. But there were also substantive concerns voiced by Max Delbrück about whether the experimental design was adequate to detect mutations that had pleiotropic effects. In a few years, however, Horowitz parried the Delbrück objection

Figure 2 | **Boris Ephrussi (left) and George Beadle (right) transferring imaginal discs.** Image courtesy of the California Institute of Technology archives.

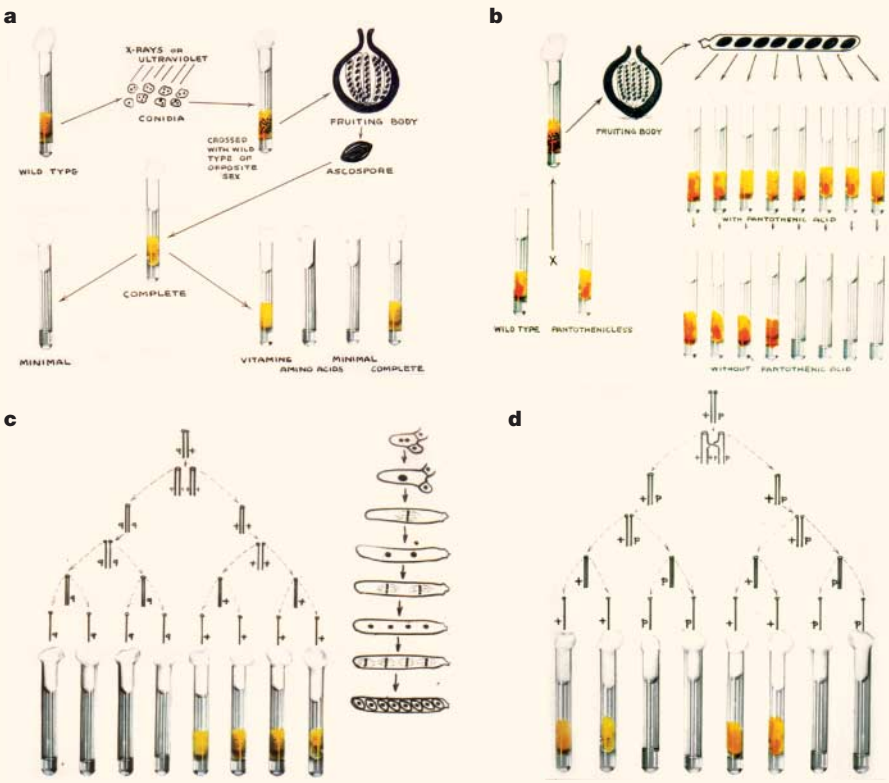

Figure 3 | **Beadle as an artist.** Four drawings made by George Beadle to illustrate the principle for creating (**a**); identifying (**b**); and genetically characterizing mutations (**c** and **d**). **a** | Outline of the experimental scheme for obtaining *Neurospora crassa* mutants with nutritional deficiencies. Irradiated wild-type spores are germinated and crossed with non-irradiated wild types; the resulting spores are tested for growth on minimal and complete media, and those that grow on complete but not on minimal media are tested for growth with various supplements. In this example, the mutant grows with a supplement of vitamins. **b** | Spores obtained by crossing the vitamin-requiring strain (in this example, a pantothenate-requiring isolate) with the wild type, are of two types: 4 grow without a pantothenate supplement and 4 require pantothenate for growth. This 4:4 pattern shows that the pantothenate requirement is the result of a single mutation. **c**,**d** | Variable distribution of 8 spore types depending on whether crossing over occurs in crosses between the pantothenate-requiring mutant with the wild-type mutant. **c** | The 4:4 distribution of spore types is the result of meioses without crossing over. **d** | The 2:2:2:2 distribution reflects the outcome of meioses when crossing over between the mutant and allelic wild-type chromosomes occurs. +, wild-type chromosome; p, chromosome carrying a pantothenate-requiring mutation. Diagrams courtesy of the California Institute of Technology archives.

when he established that their experimental design did not discriminate against mutations that caused irreparable or pleiotropic phenotypes. The demonstration that sickle-cell disease, a classic Mendelian gene defect, results from a structural alteration of haemoglobin lent further support for the gene–protein structure relationship[12]. Soon after, it was confirmed that different mutations affecting a single gene led to the production of proteins with distinctively altered catalytic and physical properties[13]. Once, during the 10 years, when the one gene–one enzyme hypothesis was under fire, Beadle remarked that "the number of people whose faith remained steadfast could be counted on the fingers of one hand — with a couple of fingers left over"[14].

Beadle recognized that the gene–enzyme paradigm had rich antecedents: notably, Archibald E. Garrod had observed at the turn of the twentieth century that alcaptonuria was an inherited characteristic[15]. Soon after, William Bateson recognized that the inherited alcaptonuria behaved as a single recessive Mendelian factor[16] and, some years later, the affected individual's trait was confirmed to be associated with a deficiency of the enzyme p-hydroxy-phenylpyruvate hydroxylase[17]. There was also ample evidence that the colour variation of certain ornamental flowering plants was genetically determined[18]. When accepting the Nobel Prize in 1958, Beadle acknowledged Garrod's remarkable surmises, conceding that all that he and Tatum had provided was a simple way to explore the gene–enzyme relationship. Nevertheless, the Nobel Foundation's citation acknowledged that their "daring and astute" experimental approach to studying the gene–protein relationship had laid "one of the foundations of modern genetics"[19].

One gene–one enzyme: the legacy

Evolution of the one gene–one enzyme concept. As with most good scientific ideas, the one gene–one enzyme concept has changed over the years since its first exposition. It became 'one gene–one protein' and then 'one gene–one polypeptide' to reflect the findings that many proteins are constituted of several polypeptides. Later, some genes were found to specify ribosomal and tRNA molecules as well as a family of novel small RNA molecules that are not translated into proteins. Increasing appreciation of biological complexity has revealed that some genes encode more than one polypeptide through alternative splicing or post-translational modifications, and even that some polypeptides are specified by more than one gene. Contemporary concepts of a gene include non-coding regions such as introns, promoters and enhancers. There seem to be as many current definitions of a gene as the number of biologists polled. But for most of us, our thinking about a gene begins in the one gene–one polypeptide framework that was set out half a century ago.

Ramifications of the one gene–one enzyme concept. In ascribing an instructional role to genes, Beadle and Tatum acknowledged implicitly that genes are physical realities, the structures of which embody hereditary information. But regarding the nature of that information, scientific opinion was split between the DNA and protein constituents of chromosomes. Beadle, along with many others, thought that DNA — then widely believed to consist of repeated tetranucleotide units — was too simple to be the source of that information, but that proteins could provide that information because their variable composition was considerably more complex. But the demonstrations that bacterial[20] and bacteriophage genes[21] are made of DNA, the discovery of DNA's double-helical structure[22] and its mode of replication[23] sealed the case in favour of DNA. Both Francis H. C. Crick in his seminal paper on the 'sequence hypothesis'[24], and Robert Olby in his history of the path to the genetic code[25], acknowledged that the one gene–one polypeptide axiom was a guidepost in conceiving the collinear correspondence between the two sequences and therefore the existence of a 'genetic code'.

A powerful experimental paradigm. Besides assigning genes a physiological role in coding for proteins, the Beadle–Tatum experiments introduced a powerful experimental paradigm for the analysis of complex biological systems. Traditionally, plant and animal genetics relied on spontaneous mutations to generate novel phenotypes, the segregation in subsequent generations of which formed the basis for identifying the chromosomal locations of the mutated genes. Inducing mutations at substantially greater frequencies using radiation enabled geneticists to amass large numbers of mutants that affect various stages of a particular biological process. In time, following publication of Beadle and Tatum's reports of their work in *N. crassa*, mutational analysis became the predominant means for identifying the individual steps of metabolic pathways, thereby enabling the identification of the enzymes and intermediates as well. A particular example was the identification of all the genes, enzymes and the regulatory proteins and DNA sites that control the biosynthesis of tryptophan in *Escherichia coli*[26] and histidine in *Salmonella typhimurium*[27].

The mutagenesis paradigm has been increasingly used for the analysis of considerably more complex physiological processes that are essential to eukaryotes. Today, it is being applied to such challenging and diverse biological processes as the cell cycle, the temporal processes of embryonic development, memory, learning, vision, olfaction and even ageing. The assumption that a 'genetic programme' directs the orderly progression of these physiological processes is the underlying rationale for using mutations to block or alter one or another of the steps in these fundamental mechanisms. For example, the complexity and nature of the regulatory proteins governing progression of the yeast cell cycle[28,29] were first explained using a discrete set of mutants, each of which arrested the cycle at a unique stage. There is general agreement that the breakthrough in studies of *D. melanogaster* development stems from Edward B. Lewis's collection[30] of mutants with aberrations of the body plan and from the vast collection of mutations affecting the earliest steps in the fly's development, created by Christiane Nusslein-Volhard and her colleagues[31]. Similarly, genes that prolong the lifespan in various model organisms[32] or that affect learning in *D. melanogaster*[33] have been identified using the mutagenesis paradigm. Tagging or insertional mutagenesis provide ways not only to alter a function, but also to allow cloning of the affected gene, determination of its structure, identification and production of the cognate protein and determination of the protein's function or activity.

Leadership beyond research

All but one of the scientific advances associated with Beadle's name were made in the 16 years between 1930, when he left Cornell with his Ph.D., and 1946 when he returned to Caltech to chair the biology division. When he was back in Pasadena, Beadle abruptly ceased active research. According to his own testimony, "unlike a number of his more versatile colleagues" he could not effectively both do research and carry out his administrative responsibilities. The biology division needed dedicated attention as it had lost its lustre during Morgan's last years as chair and the ensueing years when a faculty committee tried to lead. Between 1946 and 1960, two issues, in addition to promoting the one gene–one enzyme concept, were primary for Beadle: rebuilding the division and helping to address the main national post-war challenges to science[3].

The Caltech biology division. Rebuilding the division meant creating a strong curriculum and graduate programme, recruiting an outstanding faculty and raising the funds necessary for them to succeed. Sturtevant remained a principal contributor to genetics, but both Morgan and Bridges had died. The remaining faculty was solid, if not outstanding. Beadle's exceptional scientific position and the great respect he attracted as a straightforward and fair person, together with Caltech's reputation, assured his success in recruiting such scientists as Norman Horowitz, Ray D. Owen, Robert L. Sinsheimer and future Nobel Prize winners Edward B. Lewis, Max Delbruck, Renato Dulbecco and Roger W. Sperry. Beadle, together with the chair of Caltech's chemistry division, Linus Pauling — who was instrumental in recruiting Beadle to Pasadena — built research and educational programmes that set high standards and expectations for the development of what would soon be called molecular biology. This was, for Beadle, a selfless enterprise, in which the interests of science and of Caltech were primary.

Upholding the integrity of science. The central role of science in the Allied victories in the Second World War, convinced the US government that science could have an equally important role in the post-war world. Consequently, the support of scientific research and education began to expand through the National Institutes of Health and the National Science Foundation (established in 1950). Scientists were sought out for advice on national policies for science, health and technology. Beadle was an active participant, both as an individual and through important institutions such as the American Association for the Advancement of Science (AAAS). This rise in the perceived importance of science coincided with the beginning of the Cold War and the national paranoia over citizens and foreigners who might sympathize with the USSR. Scientists were not immune to unfounded public accusations and guilt by association; including the demagoguery by Senator Joseph McCarthy. Although Beadle's colleagues knew little or nothing about his political preferences, they learned that they could count on his leadership to be fair, open-minded and unflinching in countering injustice. He publicly defended those he believed to be falsely accused, including Pauling and David Bonner. And he led, with the Caltech trustees' support, the faculty's successful challenge to the US Public Health Service when it began rescinding grants from suspected communists without a hearing or other elements of due process. Beadle believed that it was important to protect the nation's nuclear secrets, but he objected to government procedures for routing out security risks, and the restrictions placed on researchers doing unclassified work. In 1955, as President of the AAAS, he used his access to the editorial page of *Science Magazine* to inform the scientific community of the need to protect the integrity of science against government interference and unscientific propaganda.

The word 'fallout' was coined in the 1950s to describe the troubling effects of atmospheric testing of nuclear weapons. The official statements of the US Atomic Energy Commission (AEC) were designed to assuage growing public fear by claiming that the resulting radiation was safe. Geneticists were aghast; the AEC was ignoring (or ignorant of) possible genetic effects. The National Research Council, with funds from the Rockefeller Foundation, put together a study panel, the roster of which was a who's who of genetics including Beadle, Sturtevant, Sewell Wright, Miloslav Demerec and Herman J. Muller (who co-discovered the mutagenic effects of ionizing radiation in the 1920s). The panel was busy for 5 years and Beadle became Chairman in 1956. Although the geneticists wanted to provide the public with accurate information, they were frustrated by official secrecy concerning essential data, as well as by deep disagreements between Muller and Wright[34]. Beadle's pragmatic approach and judicious views were instrumental in shaping the final reports. These reports included advice on limiting the total individual's radiation exposure (including medical X-rays) and a research agenda that predicted the biological research of the next

few decades. Unlike the official position of the AEC, the panel concluded "that from a genetic point of view there appears to be no threshold level of exposure below which genetic damage does not occur"[35].

University presidency. After a tumultuous and disruptive period following the end of the Second World War, and a seemingly endless number of financial and community crises lasting through the 1950s, the University of Chicago persuaded Beadle to become its seventh Chancellor/President in 1961 (REF. 3). His prestige and achievements at Caltech made him a prime prospect to restore the university's former academic eminence. During his 7 years at Chicago, Beadle presided over several key developments, but surprisingly few were in the biological sciences, an area that he all but neglected. The 1960s at Chicago, as at other universities, was notable for the students' increasing opposition to the 'establishment' and the consequent disruptions through protests against the university's handling of local civil-rights issues, and its response to the encroachment of the Vietnam war and draft on students' futures. Beadle was generally judicious, firm and fair in his handling of the sit-ins, but in the end he regretted the irrationality of the debates and the intransigence of both the students and the faculty. Many of his colleagues and critics conceded that his main achievement was restoring the eminence of the faculty and re-establishing an atmosphere of civility and confidence between the faculty and the administration. More substantively, before retiring at the age of 65, he guided a campaign that achieved what was then a monumental fund-raising goal of 160 million US$.

Research during retirement. After 20 years away from research, Beadle returned to the corn field after his retirement. The problem that drew him back was one he had begun as a graduate student — the origin of modern corn. For more than a decade after his retirement, he laboured to prove that teosinte, a Mexican wild grass closely related to *Zea mays* by chromosome number, homology and ability to interbreed, was the probable precursor of cultivated corn. Like an old warhorse, Beadle relished the battles with those who discounted his theory that teosinte was the genetic antecedent to modern corn. Beadle's extensive genetic and cytological experiments indicated that the two species differed by no more than 4–5 genes, an approximation that has since been strengthened[36]. Beadle believed that early Native Americans were well aware of teosinte's nutritive value and were encouraged to select varieties that enhanced their ability to provide a readily cultivatable food supply. To reinforce that view, he prepared cookies made from teosinte flour and teosinte 'popcorn', both of which he gleefully shared with friends, colleagues and neighbours.

By the time he reached the age of 80 (in 1983), Beadle had been diagnosed as suffering from Alzheimer disease and he was becoming increasingly divorced from reality. Ironically, it was an aberrant enzyme reaction that was progressively robbing him of his mind. As the disease took its toll, even the pleasure he obtained from working in the garden was lost, and until his death in 1989, he lived in his own world, far removed from science.

Conclusions

Beadle's name is not recognized by many of the biologists who daily depend on the one gene–one protein paradigm, albeit in its modern form. Similarly, many scientists who daily engage the public policy challenges that now surround biology do not realize that Beadle and his generation established the relevance of genetic knowledge to societal issues. For both biology and its implications, Beadle was a pathfinder.

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