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INSPIRED CHOICES

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Looking back over the past 150 years of biological research (especially genetics), it is clear that success has frequently been contingent on the choice of the experimental system. Mendel's breeding experiments with pea (*Pisum*) plants, which defined the early science of genetics, are rarely acknowledged as setting that precedent. His choice of peas, although not original—Darwin and others before him had bred garden peas—was key to his success. With peas, Mendel could control pollination and develop highly inbred varieties that bred true and had clearly defined, easily observable traits (phenotypes). The importance of the right choice of organism is highlighted by Mendel's inability to obtain comparable results with hawkweed plants (*Hieracium*). This failure was not because the fundamental laws of inheritance he had deduced with pea plants lacked generality. Rather, it was because the results were confounded by a hawkweed peculiarity that was discovered only decades later: Seeds often develop from diploid cells without fertilization.

The rediscovery of Mendel's work at the turn of the century owed much to plant breeders. An American apostle of mendelism, R. A. Emerson at the University of Nebraska, adopted Indian corn (maize) as his experimental organism. Each of the kernels on a corn cob is the result of a separate fertilization, making it possible to observe many offspring, thereby enhancing the statistical significance of the data. Using maize, Emerson and E. M. East established the novel idea that "quantitative traits" result from the independent inheritance of several different genes and their alleles, and the consequent effect each has on the others. Thus Emerson, along with the scientific dynasty he founded at Cornell beginning in 1914—including M. Demerec, G. F. Sprague, B. McClintock, G. W. Beadle, and M. M. Rhoades—contributed to the extension and generalization of mendelian ideas and to the development of the American corn industry.

By 1914, *Drosophila melanogaster*, commonly called the fruit fly, had displaced corn as the more advantageous organism for genetic investigation. Its relatively short reproductive cycle (about 10 days), abundant progeny (100 to 400 per mating), and the fortuitous property that meiosis in males is not accompanied by the usual exchange of chromosome segments, made the results of matings readily interpretable. At Columbia University, T. H. Morgan and his colleagues A. H. Sturtevant, C. B. Bridges, H. J. Muller, and their students had seized on these advantages to initiate one of the most intense periods of discovery in genetics. It had taken them only five years to establish that (i) genes occur in linear arrays along each chromosome, (ii) pairs of homologous chromosomes exchange parts (cross over) in meiosis during maturation of eggs, and (iii) many genes can be assigned to individual chromosomes and their positions can be mapped relative to one another.

Until 1935, exploration of the role of genes in development was impeded by the lack of a suitable experimental organism, one whose genetics and embryology were well enough understood. Then G. W. Beadle and B. Ephrussi at the Institute de Biologie in Paris devised a way to use *Drosophila* to examine the developmental fate of genetically defined embryonic tissues. This led to their discovery that the fly's eye pigments are formed by pathways whose individual steps are controlled by genes. However, *Drosophila* proved inadequate to pursue that lead. Instead, the common bread mold *Neurospora crassa* would provide the bridge. Adopted as an experimental tool by B. O. Dodge at the New York Botanical Garden, its genetics had been worked out by C. Lindegren, a student of Morgan. Beadle and E. Tatum recognized that *Neurospora* could be used to determine whether induced mutations create specific nutritional deficiencies. It was an inspired choice. Working in basement laboratories at Stanford, they obtained literally hundreds of mutants, each readily associated with a specific nutritional requirement. They surmised, and later established, that each gene was responsible for one enzyme required for the synthesis of a particular cellular constituent. These early 1940s discoveries became the basis for the one gene–one enzyme hypothesis or, as we know it today, the one gene–one polypeptide paradigm.

Yet the gene-enzyme relationship had already been inferred 30 years earlier by the British physician Archibald Garrod, who had, in 1902, noted that alcaptonuria, a human defect producing black urine, had an unusual pattern of inheritance. William Bateson, who played a critical role in promoting Mendel's work soon after its rediscovery around 1900 and introduced the term "genetics," recognized that alcaptonuria was inherited like a recessive mendelian trait. In the succeeding 10 years, Garrod extended the mendelian paradigm to the characterization of other human metabolic maladies. Eventually he suggested that each was the consequence of the loss of a different metabolic step, presumably because of a particular enzyme deficiency. But human disease was largely the province of physicians and physiologists, who did not appreciate the significance of Garrod's insight, and geneticists were generally unfamiliar with the medical literature. Consequently, Garrod's ideas languished for decades until *Neurospora* provided Beadle and Tatum with the appropriate model to transform Garrod's inferences into verifiable evidence.

By the late 1940s, Tatum had adopted an even more attractive system for examining the relation between genes and cellular functions. The common intestinal bacterium *Escherichia coli* has simple nutritional requirements and divides every 20 to 60 minutes, yielding billions of cells per milliliter of growth medium.

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Moreover, a large number of readily measurable physiological characteristics are genetically controlled, allowing for the isolation and characterization of mutants that are defective in specific cellular functions. When J. Lederberg and Tatum discovered that *E. coli* strains can participate in sexual exchanges, they opened the way to a more formal genetic analysis and the construction of a map of the bacterium's single circular chromosome. The extensive genetic characterization of *E. coli* made it ideal for elucidating the genetic code and the principles governing gene expression and regulation.

E. coli's utility as an experimental system was even more pervasive because it is host to a variety of bacterial viruses (bacteriophages) that also contain organized genomes. Today, bacteria and bacteriophages provide a vast collection of genotypes with specific phenotypes that serve for specialized genetic and functional analyses. Bacteriophages were critical in confirming earlier experiments with pneumococci demonstrating that DNA alone is the genetic material. The study of bacteriophages stimulated Watson and Crick's effort to determine the structure of DNA.

Since the rediscovery of Mendel's work nearly a century ago, nothing has contradicted the assumption that all genetic systems, regardless of organism, work in fundamentally the same way and through the same set of molecules. The unity of genetic mechanisms across the enormous variety of life forms has extraordinary ramifications in that it allows us to use information acquired from one organism to explore others; the function of a gene isolated from one organism can be tested in another. For example, certain yeast genes that are essential for survival and human genes implicated in cancer are exchangeable with virtually no difference in function. Genes from bacteria are even capable of curing a genetically defective human cell. The small but significant differences between the molecular structures of diverse organisms have provided a new and powerful tool for the study of evolutionary biology. Perhaps the most profound example of this has been the use of ribosomal RNA gene structure to demonstrate the existence of Archaebacteria, a vast branch of microbes whose discovery has changed the way we think about the early stages of life.

But not everything about gene structure and function can be learned by studying bacterial systems. Bacteria cannot reveal uniquely eukaryotic attributes such as the transactions between the DNA in a cell's nucleus and the translational machinery in its cytoplasm, or the developmental processes that transform a single fertilized egg into a complex multicellular organism with a uniquely specified architecture and nervous system. Although our driving curiosity is to understand ourselves, humans remain a difficult subject for biological research. Until quite recently, studies of human genetics were restricted to observations of diseases caused by mutations. Model systems that can serve as genetic surrogates for humans are, and will continue to be, needed.

Yeast, a single-celled eukaryote, has proven to be more like human cells in its molecular structures and functions than anyone imagined. *Drosophila* is once again central to biological research. Another invertebrate, the nematode *Caenorhabditis elegans*, has revealed unexpected attributes of the developmental process: Some cells differentiate during development only to suffer programmed death once they have served their purpose. That program, called apoptosis, is directly relevant to human cells and the process of tumorigenesis but it is best understood, for now, in the nematode.

Genetic analysis of the special aspects of vertebrate biology takes advantage of decades of work on mutant mice. In more recent times, genetically altered mice have provided special tools for studying gene replacement, very early development, and disease pathology. But mice are relatively large and, as those studying transgenic animals have learned, very costly to maintain. Moreover, early embryogenesis and fetal development are hidden from view inside the mother. Perceptive biologists recognized that using the tiny zebra fish can overcome these drawbacks because its embryos are transparent and inexpensive to rear, and it has been possible to generate large collections of mutants.

The emphasis on simpler and simpler genomes from about 1950 to 1970 pushed plant genetic research to a back seat, and a convenient experimental plant was slow to emerge. That changed about two decades ago when *Arabidopsis thaliana*, with its small genome and rapid life cycle, was recognized as an ideal model organism. Taking a cue from the history of *Drosophila* research, the *Arabidopsis* community organized the isolation, cataloging, and storage of mutants and made them readily available to all. Efficient methods for transferring genes among plants followed rapidly. Findings with *Arabidopsis*, besides yielding fundamental knowledge about this organism, are directly transferable to agriculturally important species because of the similarity of genes and genomes among all plants, and will help meet the challenge of feeding our planet's ever-growing human population. Also important, this new knowledge can be applied to ameliorate environmental degradation as we learn to use plants for direct conversion of solar energy into essential products such as plastics and oils.

"LOOKING OVER THE PAST 150 YEARS—AT THE TINY GARDEN AT BRNO, THE FILTHY FLY ROOM AT COLUMBIA, THE LABS OF THE NEW YORK BOTANICAL GARDEN, THE BASEMENT LAB AT STANFORD, AND THE SUN-DRENCHED EARLY GATHERINGS AT COLD SPRING HARBOR—IT SEEMS THAT THE FRINGES, NOT THE MAINSTREAM, ARE THE MOST PROMISING PLACES TO DISCOVER REVOLUTIONARY ADVANCES."

What began as an effort to map and sequence the human genome now has a broader scope and includes comparable goals for the worm, fly, and mouse genomes. The sequence of the yeast and several bacterial genomes are already known and the *Arabidopsis* genome is well underway. If the past yields any lessons, these projects will be the foundation for understanding our own biology and that of the plants on which all other animals and we depend.

Molecular genetics has revealed a wealth of detail about many biological systems. Still, current ignorance is vaster than current knowledge. Nothing in the human-made world rivals the complexity and diversity of living things. There are, in nature, concepts that no one has yet imagined. Looking over the past 150 years—at the tiny garden at Brno, the filthy fly room at Columbia, the labs of the New York Botanical Garden, the basement lab at Stanford, and the sun-drenched early gatherings at Cold Spring Harbor—it seems that the fringes, not the mainstream, are the most promising places to discover revolutionary advances. Attempts to program the direction and tools of genetic research could not have foreseen the diverse sources from which progress resulted. The lesson is that those who attempt to program future fundamental research, however well motivated by medical, agricultural, or social needs, are likely to divert researchers from the fringes where the most promising discoveries are often made.

ILLUSTRATION: TERESE WINSLOW