Perspectives

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The Centenary of the One-Gene One-Enzyme Hypothesis

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THE early history of mouse genetics has been recently described by PAIGEN (2003), but one episode in this history perhaps has not received sufficient recognition. In 1900, as soon as Mendel's work was rediscovered, the French biologist Lucien Cuénot decided to see whether Mendel's rules applied to animals as well as plants. After 2 years of work, he reported that the coat of wild mice contains two pigments, *black* and *yellow*, and that crosses between wild mice and albinos and then between the resulting hybrids showed that the absence of either pigment behaves like a Mendelian recessive (CUÉNOT 1902). Within a year, however, Cuénot had found that certain strains of albino mice that had black (or yellow) mice in their ancestry behaved in crosses as if their version of albino was dominant over color. This led him to what, in essence, was the one-gene one-enzyme hypothesis (CUÉNOT 1903).

Cuénot proposed that the two pigments are made from a common *chromogène* as the result of the action of two distinct enzymes (*diastases*, as they were sometimes called in those days). Using the word "*mnémon*" (COUTAGNE 1902) for the inherited entity that holds the memory of how to make something, Cuénot proposed that three kinds of mnémon are responsible for the formation of the chromogen and the two enzymes and that these mnémons are inherited in a Mendelian fashion. In this simple hypothesis, therefore, he was drawing a distinction between the genes that are inherited and the things that the genes determine. At the same time, he was firmly connecting the abstractions of Mendelian genetics to the more down-to-earth realism of biochemistry.

There are many mysteries here. Cuénot's one-mnémon one-diastase hypothesis was published in March 1903, exactly 100 years ago. Why did he himself not make more of his brilliant idea? Why did the hypothesis not become common currency for another half century? Why during that time did so few geneticists, at the very least, try to consider their results in terms of biochemistry?

Cuénot himself may be excused for not pursuing the biochemical corollaries of gene action. The natural extension of his work on the genetics of pigmentation led him into a study of piebald mice, this turned out to be a quagmire. In the process, however, he found the first example of multiple allelism, and he was the first to attribute correctly a distortion of Mendelian ratios to the existence of a lethal allele, and perhaps these clarifications required more mental effort than what we now see as his main contribution.

Also, Cuénot had other excuses. In 1914, he had just started to study the genetics of susceptibility to cancer when World War I broke out, and he had to abandon his mouse colony at the University in Nancy when the German army overran the town (COURRIER 1953). When the war ended, he was over 50, and instead of returning to mouse genetics he retreated into more general physiology and zoology. This was his original field of research late in the nineteenth century, and, in the circumstances, it was a much less contentious occupation. In the first half of the twentieth century, Darwinian evolution and Mendelian genetics were not popular subjects in France (BURIAN *et al.* 1988). A mystical approach to the biosphere was much more the fashion, and a man like Cuénot, who had once planned to write a scathing polemic on "the pseudo-sciences," may well have felt that conformity was the safer course.

British and American scientists had no such excuses. In 1902, William Bateson produced a translation of Mendel's two papers, and it was he who coined the words *genetics* and *allele*. He also invented the words *epistatic* and *hypostatic* to cover results such as Cuénot's where the action of an epistatic gene (for the chromogen) is needed for the detection of the presence of hypostatic genes (for the pigment-forming enzymes). In 1909, not 1902 as STURTEVANT (1965) later claimed (WAGNER

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1989), Bateson himself suggested that certain Mendelian traits were due to the presence or absence of an enzyme but, for some reason, he did not credit Cuénot with being the first to think of this even though he knew about his work (Bateson 1909). Since Bateson was usually punctilious in giving others credit wherever it was due, this suggests that he did not think the one-gene one-enzyme idea was very important.

The fault, however, was partly Cuénot's. Both Mendel and Cuénot chose to describe the genetic constitution of a creature in terms of the traits it could pass on to its descendants, rather than in terms of its own visible traits. Thus, Mendel described the progeny of crosses between the hybrids of plants differing in one trait as (A + 2Aa + a). This is confusing to modern eyes because if the symbolism referred to the genotype of these progeny, we would now write (AA + 2Aa + aa) or (AA + Aa + aA + aa), and if it referred to their phenotype, we would write (A + 2A + a). In his 1903 article Cuénot followed Mendel in describing the hybrids produced in his breeding experiments in terms of the chromogen and enzymes (diastases) that they can pass on to their offspring, rather than in terms of the mnémons they themselves inherited. But his symbolism was awkward and necessarily more complex than Mendel's. He gave the mnémon for the chromogen the uppercase letter C and its absence the uppercase letter A, and the mnémons for the enzymes that make the black and yellow pigments (*noire* and *jaune*) were given the lowercase letters n and j. But because the presence or absence of chromogen determines whether or not the traits for pigment are detected, he wrote the pigment traits as superscripts. Thus the wild, gray mouse was C^{n+j} and an albino mouse with black in its ancestry was A^{n} . For their hybrid progeny he wrote C^{n+j} (A^{n}), where the parentheses indicate that a trait is recessive. Although he had the symbol A for the absence of chromogen, he omitted inventing ones for the absence of yellow and the absence of black, and so he had to show one of the possible progeny from crossing these hybrids as $C^{n+j}(C^{n})$. It was as if he did not wish to break with Mendel by giving symbols to the mnémons, and it may well have been the resulting complexity that stopped many people from trying to understand what he had discovered. Today crosses are described in terms of genotype rather than phenotype and, in many systems, lowercase letters are used to describe nonfunctional alleles. For example, Cuénot's wild-type mice could be written as CNJ/CNJ and the albino mice in his first cross, which lacked both enzymes, would be Cnj/Cnj; in his second article the two kinds of albino mice, with either black or yellow in their ancestry, were albino because they lacked the chromogen, and so they were cNj/cNj and cnJ/cnJ, respectively.

By the beginning of the twentieth century the pathways for the breakdown of certain amino acids had been worked out by the biochemists and, perhaps under Bateson's influence, in 1908 the physician Archibald Garrod suggested that certain rare conditions such as alkaptonuria are caused by failure to carry a breakdown pathway to completion owing to a lack of one of the necessary enzymes and that these deficiencies are inherited as Mendelian recessives (Garrod 1908). Nowhere did Garrod refer to Cuénot, and it is plain that he was more interested, as befitted a doctor, in the diseases due to "inborn errors of metabolism" than in the light they shed upon the mechanisms of genetics (Bearn 1994). We, who are more accustomed to a modest level of interchange between science and medicine, may wonder why more attention was not paid to his work. But at that time medicine was regarded as an art rather than a science, both by doctors and by everyone else. For example, even late in the 1930s an investigation in the United States of the likely impact of future technological inventions did not consider possible advances in medicine, presumably because even then medicine was not thought of as a technology (National Resources Committee 1937).

So the link between genetics and biochemistry had to wait another 30 years until George Beadle and Boris Ephrussi (1936), working partly at the Pasteur Institute in Paris and partly at the California Institute of Technology, investigated, by grafting experiments, the steps and genetics that lead to the eye color of Drosophila. Because of his Marxist principles, Ephrussi was perhaps hoping to establish the importance of cytoplasmic inheritance (championing the proletarian cytoplasm as opposed to the capitalist nucleus), and Beadle wanted to find out whether genes are expressed all the time. But their experiments were the direct precursor of Beadle and Tatum's work with Neurospora and the one-gene one-enzyme hypothesis (Beadle and Tatum 1941). (It was not until after World War II that Boris Ephrussi succeeded in becoming the first professor of genetics ever to be appointed in France, and this alone shows why Cuénot was wise to retreat into the safety of general zoology.)

At first sight, it seems strange that Cuénot did not represent the results of genetic crosses in terms of genotypes rather than phenotypes. What is the point of having a lovely word like mnémon if you do not then use it to clarify your thoughts? But we have to remember that Mendel had set the precedent and had already established a reliance on abstractions when he invented the adjectives "dominant" and "recessive." At the time, these words were not understandable, and their ready acceptance tended to be a barrier to further thought about possible underlying mechanisms. And when Bateson invented the adjective "epistatic," he was following Mendel's example in choosing an abstraction rather than the kind of explanation offered by Cuénot's results. Every branch of science, even physics, has its mystics, as witnessed by Ernst Mach's refusal well into the twentieth century to believe in the existence of atoms (Nye 1972).

The reluctance to accept the one-gene one-enzyme hypothesis persisted until the 1950s and 1960s. Beadle (1966) recounted how the status of the idea "dropped to an all-time low at the Cold Spring Harbor Symposium of 1951." The problem arose mainly because of "position effects." It was hard to see why transposition of a gene to a new location should make it unstable or no longer able to generate its enzyme. The opening talk at that symposium was given by Richard Goldschmidt. Although in his own early work (Goldschmidt 1916) he had followed Cuénot and Garrod, he explained why he now inclined to a much more abstract notion of genes (Goldschmidt 1951). The level of obscurity was further increased with the second talk, by Barbara McClintock (1951), in which she wrote that her experiments with the transposable dissociation factor (Ds) "do not constitute evidence that Ds is composed of a material substance." Indeed, when she was asked sometime in the 1960s whether she thought of such elements as actual physical entities she replied "Certainly not!"

Such were the problems of an earlier age, and we may now ask what morals can be drawn from this history. One obvious thought is that we should never let complex phenomena (such as the genetics of hybridization in Hieracium, the genetics of piebald in mice, and position effects in maize and Drosophila) divert our attention from simpler truths, as perhaps happened for Mendel and certainly for Cuénot and many others. Equally, we should remember that abstract words such as "dominant" and "recessive" are like the jargon of a religion, comforting but essentially a dead end and never to be thought of as actual explanations. Perhaps the final word should be George Beadle's: "Do not discard an hypothesis just because it is simple—it might be right" (Beadle 1966, p. 32).

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