Hermann Muller on Measuring Mutation Rates

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The Measurement of Gene Mutation Rate in *Drosophila*, Its High Variability, and Its Dependence upon Temperature

Hermann Joseph Muller

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The task of actually counting mutations [...] to compare their frequencies of occurrence [...] would have seemed almost like that of counting needles in haystacks, to compare their frequencies, or like making graphs to show the rates of occurrence of gold pieces on streets of different types. H. J. Muller (1928)

For the pioneers of genetics, mutants were precious. Although they were extremely useful, mutants with readily detectable phenotypes were so rare that it was as impractical to measure mutation rates as to measure the average number of needles in a haystack.

But Hermann Joseph Muller (with contributions from Edgar Altenburg) developed a reliable approach for assaying mutation rate. Muller's methods, published in *GENETICS* in 1928, helped to uncover crucial clues about the nature of mutation. Those methods also led to Muller's winning a Nobel prize for showing that X rays increased mutation rates.

The trick, Muller found, was to look for a more plentiful type of needle. He focused his efforts on lethal mutations, which he and Altenburg had shown to be much more common than the morphological mutants commonly studied at the time. The first major test of their methods was to compare mutation rates in *Drosophila* at different temperatures. Muller found a small but statistically significant increase in mutation rate at higher temperatures. This was the first demonstration that mutation rates could be altered by an external influence.

As Muller was writing up a comprehensive account of these experiments, he started testing the effects of X rays on muta-

tion rates. It became immediately apparent that radiation exposure massively increased mutation rates. And Muller's quantitative methods put hard numbers on the increase.

Muller raced off a cursory note to *Science* to establish priority, and the *GENETICS* article describing the methods development and temperature result was published the following year. As well as marking a new era in mutation studies, the *GENETICS* article kick-started this journal's long tradition of publishing foundational work that uses mutation rates to investigate the mechanisms of inheritance and evolution.

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