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Hermann Joseph Muller's Study of X-rays as a Mutagen, (1926-1927) [1]

By: Gleason, Kevin M. Keywords: X-rays [2] Radiation [3] Genetics [4] Mutation [5]

Hermann Joseph Muller conducted three experiments in 1926 and 1927 that demonstrated that exposure to x-rays, a form of high-energy radiation [6], can cause genetic mutations, changes to an organism's genome [7], particularly in egg [8] and sperm [9] cells. In his experiments, Muller exposed fruit flies (*Drosophila* [10]) to x-rays, mated the flies, and observed the number of mutations in the offspring. In 1927, Muller described the results of his experiments in "Artificial Transmutation of the Gene" and "The Problem of Genic Modification". His discovery indicated the causes of mutation and for that research he later received the Nobel Prize in Physiology or Medicine [11] in 1946. Muller's experiments with x-rays established that x-rays mutated genes [12] and that egg [8] and sperm [9] cells are especially susceptible to such genetic mutations.

Muller studied genetic mutations and the structure of chromosomes in fruit flies during the early twentieth century. From 1910 to 1915, Muller worked with Thomas Hunt Morgan [13], a scientist at Columbia University in New York City, New York, who researched the role chromosomes play in heredity. Chromosomes are structures that consist of DNA, the genetic material of the cell, and are found within a cell's nucleus [14]. While working in Morgan's fly lab, Muller helped discover a class of genes [12] called marker genes [12], also called genetic markers, that enabled scientists to identify specific places in the genome [7], even after making changes to particular chromosomes or genes [12]. Muller used genetic markers in his later x-ray [15] experiments that identified mutations in the genome [7]. In the 1920s, Muller studied the role of temperature as a possible mutagen, or cause of genetic mutations. He showed that high temperatures had the capability to mutate genes [12]. Through his work studying the effects of temperature on genetic mutations, Muller developed a method to quantify the number and frequency of mutations which he used in his later experiments with radiation [6].

In the early 1900s, professionals used x-rays, a form of high-intensity radiation [6], in the medical, dental, and industrial fields, though they knew little about the long-term effects of exposure to radiation [6]. Many researchers studied how x-rays affected living cells. In 1907, physician Charles Russell Bardeen showed that toad eggs fertilized with sperm [9] he exposed to x-rays resulted in embryos with developmental abnormalities that prevented toad larvae from developing into tadpoles. Experiments like Bardeen's supported Muller's hypothesis that mutations involved changes to individual genes [12]. Muller hypothesized that he could induce genetic mutations using x-rays. Muller performed a series of three experiments in 1926 and 1927 exploring the role of x-rays as a mutagen.

Muller began his first experiment testing x-rays as a mutagen in 1926 while at the University of Texas in Austin, Texas. In his first experiment, Muller bred flies whose genomes contained particular genetic markers on the X-chromosome, which enabled him to identify mutations. In normal flies, female flies have two X-chromosomes. Male flies, however, have only one X-

chromosome and one Y chromosome which does not contain those particular genetic markers. Muller used male flies that contained the X-linked gene, meaning it was located on the X-chromosome, for bobbed bristles (*bb*) as a genetic marker. The *bb* gene, led to offspring with noticeable differences in the shape of the flies' sensory bristles compared to normal flies. Muller also used female flies that were homozygous for the X-linked gene *sc v f*, meaning that both X-chromosomes contained the *sc v f* gene. The *sc v f* gene led to offspring with a difference in eye color and distinguishably different sensory bristles. Before mating the male and female flies, Muller exposed the flies to x-ray [15] radiation [6] in an attempt to induce genetic mutations in them. Following the x-ray [15] treatment, he mated the flies to produce offspring consisting of heterozygous females, meaning that each female offspring had one X-chromosome with the *bb* gene and one with the *sc v f* gene, and male offspring had the *sc v f* gene. The *bb* genetic markers were recessive, so the heterozygous females displayed the physical traits associated with the *sc v f* gene, but still carried the *bb* gene and, any mutations induced by the radiation [6] in that chromosome.

To determine whether genetic mutations were induced in a parent exposed to radiation [6], Muller mated the heterozygous female offspring, which had both *bb* and *sc v f* genes [12], with their *sc v f* brothers. The male offspring of that cross (grandsons of the irradiated male or female parent) revealed whether or not the x-rays had induced any mutations. Rather than looking for abnormal body parts, Muller determined whether or not mutations had occurred by studying lethal mutations, types of mutations that cause the offspring to die before being born. To identify the lethal mutations, Muller observed the ratio of *bb* male and *sc v f* male offspring. If the offspring lacked *bb* males and only *sc v f* males were present, Muller reasoned that exposure to radiation [6] induced lethal mutations in the *bb* genes [12] of male grandparents. Alternatively, if only *bb* males were present, he reasoned that exposure to radiation [6] induced a lethal mutation in the *sc v f* female grandparent.

Muller created over 1,000 cultures of first generation flies whose parents had been subjected to x-rays and a similar amount of control cultures, cultures in which the flies' parents were not subjected to the radiation [6]. By comparing the results of his x-ray [15] experiments with control cultures, Muller confirmed that x-rays caused the genetic mutations and that the mutations did not spontaneously arise, or arise from normal cell function.

After examining the cultures, Muller observed that there were a high number of lethal mutations in the offspring of the x-ray [15] treated flies (88 lethal mutations in 758 cultures). The control group showed a lower frequency of the lethal mutations (1 lethal mutation in 947 cultures). Muller concluded that the x-ray [15] exposure caused the lethal mutations in the offspring of the x-ray [15] treated flies. He also found that mutations occurred in both the male and female flies when exposed to x-rays, indicating that both sexes were vulnerable to radiation [6]-induced mutations.

Building on the results from his first experiment, Muller conducted a second. In the second experiment, Muller used a different type of genetic marker. He used a group of X-linked genes [12] called *ClB* genes [12] which were lethal to male fruit flies. Through controlled mating, Muller bred a generation of fruit flies in which the male offspring could inherit one of only two kinds of X-chromosomes: ones that had the lethal *ClB* gene, or ones that had been exposed to radiation [6] in earlier generations. If parent flies radiated in earlier generations had developed lethal mutations in the x chromosomes of their gametes, then mating the files would fail to produce any living male offspring. By counting the number of male and female offspring, Muller inferred the results of mutations caused by radiation [6]. He determined that x-ray [15]

exposure caused 150 times more flies to die through a lethal mutation compared to the spontaneous rate of mutations that occurred in the control group.

Muller then developed a third experiment in the spring of 1927 that specifically looked for visible mutations in the offspring of radiation [6] exposed fruit flies. Muller used females with two X-chromosomes fused together as well as a single, separate Y-chromosome to mate with males with the *bb* gene that he had also exposed to x-rays. Mating females with fused X-chromosomes leads to an unusual mode of inheritance. Unlike typical sex inheritance, where males inherit their X-chromosome from their mother and their Y-chromosome from their father, mating a female with fused X-chromosomes leads the opposite. Instead, males inherit their X-chromosomes from their father and their Y-chromosome from their mother. Consequently, any non-lethal mutation induced in a male parent can be identified in their sons because their sons inherit their fathers' X-chromosome. By that method, Muller noted that many visible mutations caused by radiation [6] were the same as visible mutations that occurred spontaneously, such as white eyes, small wings, and bobbed bristles. Furthermore, he found that the mutations occurred more frequently in flies exposed to radiation [6] than they did in the untreated flies.

In his 1927 article "Artificial Transmutation of the Gene," Muller published his conclusions that exposure to x-rays could cause genetic mutations. However, Muller failed to include complete data and methods of his prior experiments. According to Elof Carlson, a student of Muller, the paper grabbed the attention of geneticists, but many questioned Muller's findings because of the missing data. Later that year Muller released the paper "The Problem of Genic Modification" at a genetics conference in Berlin, Germany. His second paper detailed his 1926 and 1927 experiments and provided clarifications that "Artificial Transmutation of the Gene" lacked. A year after the conference, other scientists confirmed Muller's claims that x-rays led to mutations in both plant and animal chromosomes.

Muller's discovery that x-rays caused genes [12] to mutate had many different implications in various fields. In the field of radiology, Muller's work illuminated previously undocumented dangers of x-rays. His findings showed that x-rays could be particularly harmful to humans [16] in their reproductive years. Radiologists began taking precautions to shield patients from radiation [6] that could cause genetic mutations to sperm [9] and egg [8] cells, possibly affecting later embryo development. In the field of genetics, Muller's work showed that environmental factors like radiation [6] affected heritable characteristics. Furthermore, his discovery enabled scientists to directly induce genetic mutations instead of waiting for mutations to occur spontaneously. For his experiments on the mutagenic effects of x-rays, Muller received the Nobel Prize in Physiology or Medicine [11] in 1946.

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Subject

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