TIMELINE

Hermann Joseph Muller, Evolutionist

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Abstract | This essay is dedicated to the proposition that Hermann Joseph Muller, widely regarded as the greatest geneticist of the first half-century of the subject, was also one of the greatest evolutionists of this period. His Nobel Prize-winning work, which showed that radiation increases the mutation rate, is in every genetics textbook, and his prescient ideas have influenced almost every aspect of the discipline. Here I emphasize his less well-known contribution to the neo-Darwinian theory of evolution.

Although Hermann Joseph Muller is best remembered for his discovery that X-irradiation induces genetic mutations[1], for which he won the Nobel Prize, he made many influential contributions to evolutionary biology. Muller was the first to emphasize a gene-centred view of evolution, and he made both experimental and theoretical contributions to our understanding of speciation. He also reached insightful conclusions about how genes interact, how they are acted on by natural selection, and how their evolution is influenced by sexual reproduction and population structure. His influence on genetics and evolution was therefore substantial and wide-ranging (for a book-length biography, see REF. 2; for excerpts from his collected papers, see REF. 3). In fact, Muller's interest in evolution pervaded his entire career. As a student, he organized a biology club in which ideas about evolution permeated the discussions. Later on, it was the interest in evolutionary mechanisms that inspired his emphasis on mutation.

In this essay, after a short digression into Muller's colourful personal life, I discuss the many important ways in which he contributed to evolution. More details are given in REF. 4.

A brief biography

Hermann Joseph Muller — Joe to his friends — was born on 21 December 1890, in New York City. His father, also Hermann J. Muller, led his class at City College, New York, and started on a career in international law. Although he was forced to interrupt his studies to take over the family business after the death of his own father, Muller retained his intellectual interests and, in particular, imparted the idea of Darwinian evolution to his young son. He died when his son was 10 years old.

Education and early academic career. Muller's widowed mother was left poor, which meant that young Muller had to work his way through high school. Despite this, he had an outstanding record and showed a remarkable inventiveness: for example, he devised a system of shorthand to speed up note taking. (Late in his life he attached wheels to his suitcase; now we see hardly any other kind.) Being valedictorian of his high-school class led to a scholarship; this partially alleviated his financial difficulties but still required him to work many hours. His undergraduate course in biology at Columbia College was crucial in determining the direction of his career; here, he took a course with Edmund B. Wilson, America's leading cytologist and author of the definitive textbook on cytogenetics[5], which whetted Muller's appetite for more genetics. He started graduate school and, along with Alfred H. Sturtevant and Calvin B. Bridges, became one of the three brilliant students that Thomas Hunt Morgan assembled in the famous 'fly room' at Columbia University[6].

Morgan and his students were building on the foundation laid by Sturtevant's construction of the first chromosome map. It was an exciting time. Everyone worked in the same room and the talk was continuous; ideas were bandied about and progress was astonishingly rapid.

Muller's first faculty position was at the Rice Institute in Houston, Texas, where he enjoyed fellowship with Julian Huxley. After 3 years he returned to Columbia, in the hope of securing a permanent position; however, his stay lasted only 2 years, and in 1920 he accepted an offer from the University of Texas. It was there that Muller made the discovery that made him famous: the production of mutations by X-radiation[2,3,7]. However, his socio-political ideas made his stay in the United States uncomfortable; he became increasingly distressed by racism and capitalist exploitation in the United States, and in 1932 he decided to leave. By then he had also made himself unpopular by sponsoring a left-wing student newspaper.

Germany and Russia. Discouraged, and having burned his bridges in Texas, Muller accepted a fellowship to work in Berlin with Nikolai W. Timofeeff-Ressovsky, who shared his interest in mutation and in applying the principles of physics to genetics. Muller was particularly attracted to Max Delbrück, a physicist in Timofeeff's group, who later became a leader in phage genetics in the United States. But this was 1932; within a year Hitler came to power and Muller's hopes for Germany becoming a leader in genetics research were dashed. He was ready to move on and his deep sympathy for communism induced him to accept an invitation from Nikolai I. Vavilov to move to Leningrad and later to Moscow. This led to a highly productive programme in *Drosophila* genetics, with emphasis on gene structure and mutation, and that made use of the recently discovered giant SALIVARY GLAND CHROMOSOMES (see Glossary). However, this research lasted only a few years.

Figure 1 | **Hermann Joseph Muller with a student, Dale Wagoner, at Indiana University.**

Muller had gone to Russia with high idealism, as he thought that in a classless society, social and economic justice would prevail and genetic research would thrive. Alas, the idealistic social aims were far from fulfilled and genetics was completely corrupted by Trofim Lysenko's naive lamarckian ideas, which had found favour with Stalin.

The war years. By 1937, on advice from Vavilov, Muller decided to leave Russia. It was decided that the best way to avoid harming his remaining colleagues was for Muller to join the Spanish Republican Army. For several months he worked there in a blood bank, before moving to a research position at the University of Edinburgh. Notably, during this time, he discussed with his student, Charlotte Auerbach, the possibility of studying chemical mutagens. Her colleague J. M. Robson, noting the similarity of burns produced by mustard gas and X-rays, suggested that mustard gas might be mutagenic. Auerbach subsequently found this to be the case, but her findings were a military secret. By this time Muller had moved to Amherst College in the United States, where he learned of Auerbach's results, but kept them secret.

Muller spent the rest of the war years at Amherst teaching biology to unappreciative army trainees and doing research with a minimum of equipment and assistance. He knew that this was a temporary appointment, which would end when the war was over. By then we were close friends and I remember being appalled that this man, arguably the world's greatest geneticist, would soon be unemployed.

There were several reasons he was not hired. Having been to Russia, he was branded as a communist, and having spoken out against Lysenko, he was branded as a fascist. With wry amusement, he once said that at least both could not be true. In addition, Muller had the (not undeserved) reputation of being a 'difficult' personality.

At last, in 1945 Muller obtained a permanent position. At the age of 54 he joined the faculty of Indiana University, where he had a well-equipped laboratory, assistants and graduate students (FIG. 1). Except for short stays at other universities, he spent the rest of his life at Indiana. He was awarded almost all the honours that a biologist can aspire to, including the Nobel Prize, which he received in 1946.

Despite the many migrations, setbacks and disappointments, Muller held on to his idealistic views. He also retained his indefatigable work habits: he regularly worked long hours in a 7-day week. At Indiana he taught three courses; one was on evolution, which started with the origin of the solar system and ended with human cultural evolution. During his lifetime he wrote more than 300 papers, several of which were path-breaking. His death came on 5 April 1967 (REF. 3) (TIMELINE).

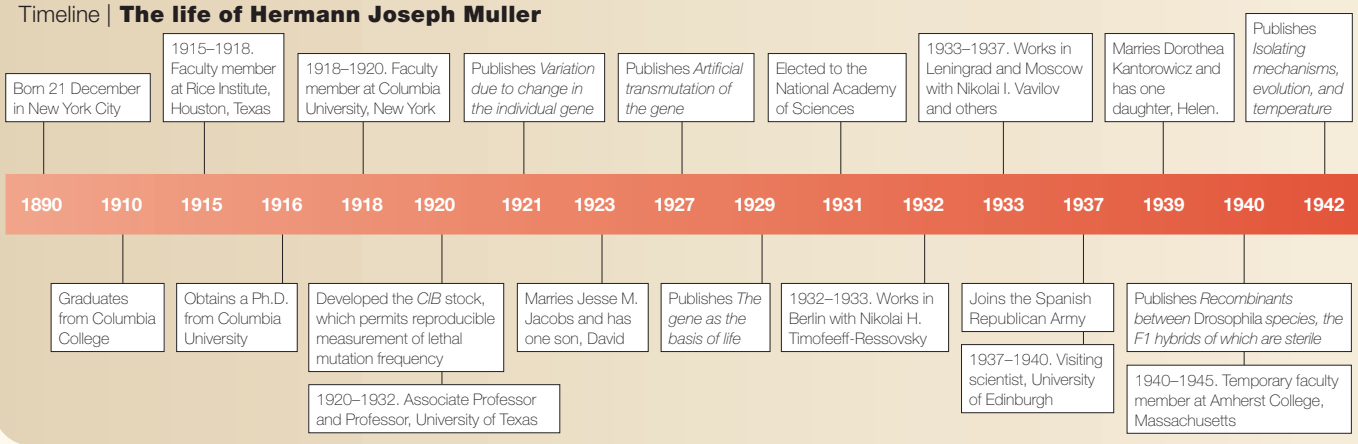
The gene as the basis of evolution

As early as 1921, Muller had developed the idea that the gene was the basis of evolution, and therefore of life[8,9]. By this time the basic phenomenology of mutation was understood, thanks mainly to the Morgan group: the gene is equally stable before and after mutation; mutation of a gene occurs independently of other genes, even its allele; the process is independent of the external environment (of course this changed when Muller himself discovered radiation mutagenesis); and, most importantly, mutations are random with respect to phenotypic effect, and therefore most are harmful.

Muller emphasized the information-carrying capacity and self-replicating ability of the gene, but he added a third property, the ability to replicate mistakes. He argued that it is this ability that makes evolution possible: once an entity exists that can faithfully replicate its rare errors, even if only a small fraction are favourable, then natural selection can operate to produce ever-higher levels of adaptation. Needless to say, Muller was greatly excited by the Watson–Crick model, which all but shouted the mechanistic basis for what he had thought the gene must do.

Muller made one of his most prophetic statements in a lecture in Toronto in 1921 (REF. 8). He told his audience that the recently discovered d'Herelle bodies, now called bacteriophages, offered the possibility of studying genes by direct chemical means. He famously said: "Must we geneticists become bacteriologists, physiological chemists, and physicists, simultaneously with being zoologists and botanists? Let us hope so." Indeed, shortly after the end of the Second World War, bacterial and virus genetics led the way to a much finer resolution in genetic analysis. At the same time, chemical manipulation of large molecules, such as proteins and nucleic acids, had become feasible. The stage was set for what Muller in his Pilgrim Trust lecture called 'the coming chemical attack on the gene'[10].

Timeline | **The life of Hermann Joseph Muller**

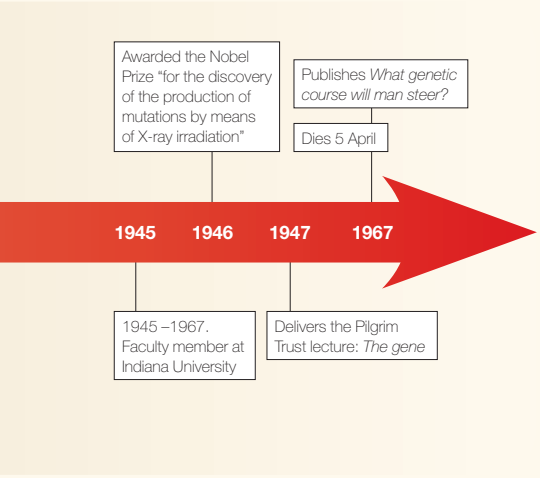


Evolutionary significance of 'difficult' and complex traits. In the early decades of the twentieth century there was lingering doubt as to the evolutionary role and Mendelian basis of complex traits, some of which seemed to defy genetic analysis. Muller was convinced that evolution depends on genetic variation of all sorts: major genes as well as their modifiers.

Two traits, *Beaded* and *Truncate* wings were particularly troublesome. In a masterful genetic analysis, by far the most detailed at the time, Muller and Edgar Altenburg[11,12] identified the individual units that affected these traits and found how they interacted. They pointed out that variability was sometimes environmental and sometimes the effect of modifying genes. They argued that because these minor variants segregate in the population, and are often maintained as balanced heterozygotes, they could provide the variability on which natural selection acts.

Where do new genes come from?

If a gene mutates to produce a new function, it necessarily loses the old one. But if the gene has somehow duplicated, then one copy can mutate to produce the new function while the other retains the old one. Muller had long been aware of this process and had suspected, from its unusual crossover behaviour, that the *Bar* eye mutant in *Drosophila melanogaster* was a duplication. This idea was eventually confirmed when the duplicate nature of *Bar* was directly observed in salivary gland chromosomes[13]. Calvin B. Bridges[14] had reached the same conclusion and also noticed that many chromosomal regions contain double bands; indeed, many of these were later confirmed by genetic analysis to be duplications.



Box 1 | **Muller's ratchet**

This theory describes the accumulation of deleterious mutations in a small population in the absence of sexual reproduction.

Every population — sexual or asexual — contains deleterious mutations, and individuals totally lacking such mutations are uncommon. In a small population, every individual might have at least one deleterious mutation in any one generation. This is not a problem if the species is sexual, as an individual with no deleterious mutations can be created by recombination.

In an asexual population, however, deleterious mutations cannot be removed (except by reverse mutation, which would be improbable, especially in a small population). In the following generation the best individual in the population has one mutation. In a later generation there may be no individual that has only one deleterious mutation, so the best individual in the population has two mutations. And so on. The number of mutations increases in a stepwise manner and there is no turning back. And so, in a ratchet-like manner, a small asexual population gradually accumulates an increasing number of deleterious mutations, and may become extinct. Muller's ratchet constitutes an important argument for the evolution of sex, although the importance of the effect depends mainly on the population size and the mutation rate.

Muller and Bridges thought that duplications might arise as mistakes in crossing over, or a similar process, and recognized their great evolutionary importance: organisms of greater complexity would arise as the gene number is increased and new functions are acquired. The idea that new genes come from old genes presaged the wholesale finding of new functions arising by gene duplication, for example in homeobox and globin clusters.

Mutation as a human problem

As Muller was aware that most mutations are harmful, he regarded mutations as a mixed blessing: too high a mutation rate could lead to an increased number of disabilities, or even to extinction. Not content with only verbal discussion, Muller tried a quantitative approach. He reached the remarkable conclusion that the MUTATION LOAD is proportional to the mutation rate, not to the deleterious effect of individual mutations. In particular, if the measure of well-being is Darwinian fitness, then the load is not just proportional but is in fact equal to the diploid mutation rate divided by the number of mutant alleles that are eliminated with each death or failure to reproduce[15,16]. This conclusion had been reached earlier by J. B. S. Haldane[17], although Muller was the first to use it to estimate the impact of mutation on the human population[15,18].

Value of sexual reproduction

The value of recombination. Muller shares with Ronald A. Fisher the credit for producing the first convincing argument for the evolutionary advantage of recombination[19,20]. Muller argued that the advantage lies in putting together, in a single individual, favourable mutations that arise in different individuals. In an asexual species, mutations can be incorporated only in series — a new mutation in a descendant of an old one — whereas with sex they can recombine and evolve in parallel, thereby greatly accelerating the evolutionary process.

Although this was a good idea, Muller's mathematics were rather elementary and were easily improved[21], notably by Joe Felsenstein[22]. Fisher also realized that even a single favourable mutation would have a much better chance of prevailing in a sexual population than in an asexual one[20]. In an asexual population, the fate of a mutation strongly depends on the genotype in which it arises, whereas in a sexual population it can be selected on its own merits by being tried out in many genetic combinations.

Another argument for the evolutionary advantage of sexual reproduction is that it allows organisms to keep up with an ever-changing and usually deteriorating environment; rapidly evolving parasites, for example, create a particularly malevolent and unpredictable environment[23]. A third argument, strongly advocated by Alexey Kondrashov[24], is that sexual reproduction, together with QUASI-TRUNCATION SELECTION[25], provides an efficient way to eliminate harmful mutations at minimum cost. Another of Muller's ideas, called 'Muller's ratchet'[26], is based on the fact that in a small population there may be no individual that is free of unfavourable mutations. In a sexual population, a mutation-free individual can arise by recombination, but in an asexual population there is a permanent loss of fitness (BOX 1).

The advantage of diploidy. Diploidy is so widespread in higher organisms that it must have an evolutionary advantage. A species that changes from haploidy to diploidy has an immediate advantage by hiding the effect of recessive deleterious mutations. The advantage is short-lived, however, as a new equilibrium is reached when the doubled number of loci doubles the overall mutation

rate and the fitness is reduced correspondingly. But there is no going back, as a return to haploidy would entail all the deleterious effects of intense inbreeding.

Another argument, which I suggested, is that diploidy provides an obvious protection from the deleterious effects of somatic mutation[21]. In this case, selection is more direct, as the mutation affects the individual in which it occurs, rather than its descendants. Not surprisingly, Muller had also thought of this and characteristically wanted others to know it; he found it in some old lecture notes but it was not published.

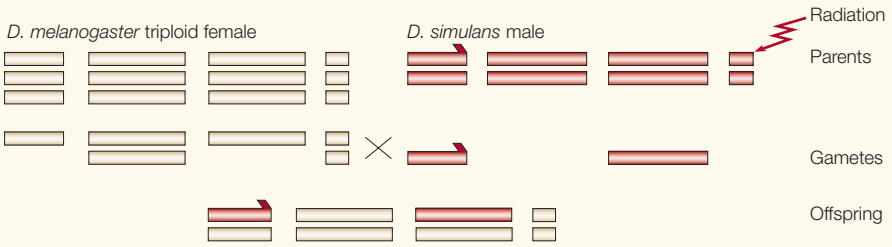


Figure 2 | **Bypassing hybrid sterility.** A triploid *Drosophila melanogaster* female is mated to a heavily irradiated *Drosophila simulans* male. The gametes are unbalanced, but complementary; when combined, these gametes produce a balanced diploid offspring. This cross is the equivalent of a backcross, which would be possible if the hybrids were fertile.

Species differences

Until the coming of molecular techniques it was not possible to study genetic differences in species that could not be crossed. In particular, the hybrids between *D. melanogaster* and *Drosophila simulans* are sterile, frustrating genetic studies.

While he was at Edinburgh, Muller and his student Guido Pontecorvo undertook a study of the genetic differences between these two species[27]. To bypass the block posed by hybrid sterility, they devised an ingenious procedure. They mated triploid *D. melanogaster* females with heavily irradiated *D. simulans* males. The radiation led to ANEUPLOID gametes, which sometimes combined with complementary aneuploids from the triploid *D. melanogaster* females to produce diploid progeny (FIG. 2). Most of these backcross progeny were sterile and had low viability, but those with only the Y and fourth chromosome from *D. simulans* were fertile and could be analysed.

I do not know whether such experiments convinced many sceptics of the chromosomal basis of species differences. A demonstration of genetic similarities and differences between mice and rats, or humans and yeast, came only later, after DNA sequence comparisons became feasible.

Isolating mechanisms and speciation

The 1930s was a period of much discussion of speciation, and particularly of ISOLATING MECHANISMS. Muller's main interest was how evolution proceeds to more complex, better-adapted states, not the relatively simple problem of splitting into separate species. Nevertheless, he wrote several articles on the latter subject.

Muller's 1942 paper[28] is a classic. I read it at the time, having just finished a thesis on isolating mechanisms. I was enormously impressed by the number of ideas that were new to me. Muller had always emphasized partial dominance and INTER-LOCUS ADDITIVITY, as opposed to complete dominance and EPISTASIS. But he realized that the speciation process must depend on epistatic interactions.

Muller thought, as was also generally held, that most speciation was ALLOPATRIC. If a species is split into two or more isolated groups, each will follow its own evolutionary path. Newly isolated groups can evolve new structures and processes but, as is equally important, they will evolve different methods for doing essentially the same thing. Each population will evolve its own harmonious set of genes. But in the hybrids, harmony becomes discord. For example, Muller noted that *D. melanogaster* and *D. simulans* have identical thoracic BRISTLE arrangements, but the hybrids have an irregular pattern[29].

Theodosius Dobzhansky[30] had developed essentially the same idea, so this method of allopatric speciation is usually referred to as the Dobzhansky–Muller theory (although William Bateson's ideas came very close[31]). Recent decades have brought many putative examples of SYMPATRIC SPECIATION, a subject on which Muller had little to say and that is still controversial.

Dosage compensation

Muller was the first to emphasize that most mutant genes that are linked to the X chromosome have the same phenotype in males and females despite the presence of twice as many X chromosomes in females. For example, in *D. melanogaster* an eye that is mutant for the X-linked *apricot* mutation has the same colour in males and females. But females that are heterozygous for *apricot* and *white* (and therefore have the same number of copies of *apricot* as *apricot* males) have eyes that are only half as dark. To explain this curious phenomenon Muller imagined a system of compensators; that is, of genes that equalize the dosage effect in males and females[29]. This mechanism has turned out to be wrong: compensation in *D. melanogaster* is brought about by greater transcriptional activity on the male X chromosome[32]. This is in contrast to dosage compensation in mammals, which is accomplished by inactivating one of the two X chromosomes in females. Remarkably, the

Glossary

ALLOPATRIC SPECIATION
Formation of separate species in geographically isolated populations.

ANEUPLOID
Having an unbalanced number of chromosomes.

BRISTLE
Hair-like structures in Drosophila; in particular, those on the thorax.

EPISTASIS
An interaction between non-allelic genes, such that the joint phenotype differs from the one that would be produced if the two genes were acting independently.

INTER-LOCUS ADDITIVITY
Additive, or independent, effects of genes at different loci.

ISOLATING MECHANISM
Any mechanism (for example, sterility, inviability, refusal to mate) that prevents the exchange of genes between species that live in the same locality.

KIN SELECTION
Perpetuation of some of an individual's genes by aiding the survival and reproduction of near relatives.

MUTATION LOAD
The deleterious effect of mutation on the well-being of a population.

QUASI-TRUNCATION SELECTION
An approximation to 'truncation selection' (see Glossary definition) in which the threshold between the selected and non-selected trait is not sharp.

SALIVARY GLAND CHROMOSOMES
Giant, multiple-stranded chromosomes that are found in the salivary glands of the Drosophila genus.

SYMPATRIC SPECIATION
Species formation between populations in the same location.

TRUNCATION SELECTION
Selection in which all individuals with more than a certain number of mutations are eliminated, whereas those with fewer are retained.

same end result in many species is attained by different means — a principle that is evident throughout evolution.

Muller was particularly insightful in realizing that if wild-type genes were completely dominant there would be no need for dosage compensation. Surely compensation did not evolve simply to take care of rare mutants such as *apricot*. So Muller concluded that normal genes are not fully dominant. This far-reaching conclusion has since been abundantly confirmed; there is hardly ever a completely recessive gene.

These insights into allelic interactions are examples of Muller's most striking intellectual gift: the capacity to see far beyond the immediate and obvious consequences. From the observation that most X-chromosome-linked mutant genes produce the same phenotype in males and females, he reached the seemingly unrelated conclusion that normal genes are only partially dominant.

Muller and human evolution

Muller attributed much of what is unselfish, noble and even altruistic in human behaviour to the tribal nature of our ancestral populations, and invoked the idea of KIN SELECTION to explain this behaviour. This idea, which originally came from Fisher[20] and Haldane[33] and that was developed in detail by Bill Hamilton[34], proposes that an individual perpetuates some of its own genes by preserving relatives. Because in a small tribe, everyone is related, kin selection can lead to cooperation and unselfishness. However, Muller believed that recognition is probably based on group membership rather than kin identification (for an initial attempt to quantify this idea, see REF. 35).

According to Muller, it is 'human nature' to be friendly and cooperative with members of one's own group. It is equally 'human nature' to be unfriendly to members of other groups. Muller believed that we need the mollifying effects of a developing civilization to expand the former tendency and to reduce the latter.

The future of humankind

A discussion of Muller's evolutionary ideas would be woefully incomplete without his uninhibited views on future human evolution. From early on, Muller was an ardent eugenicist, a position that was expressed forcefully and colourfully in his book *Out of the Night*[36]. But he soon became discouraged, realizing that the social and economic inequities in the 1930s would make any fair genetic assessment unrealistic.

Muller objected to the early eugenics movement as being not only intrusive, but simplistic and ineffective. He was not content for our species simply to stay in place by getting rid of harmful genes. Instead, he hoped for really big improvements: he envisaged the possibility of combining desirable traits, now in different individuals, into the same one, so that the average person could enjoy an easy understanding of relativity and quantum mechanics, the complexities of Bartok and Stravinsky, and the enigmatic poetry of Rilke.

Muller suggested that this could be achieved through the judicious use of artificial insemination. He argued against the use of sperm from any person until 25 years after his death, in case late-life deficiencies or defects in the children were discovered. He argued against any form of compulsion; women should make the choice, and he believed they would do so eagerly. People, he said, should be inspired rather than coerced, to adopt what he called 'germinal choice'. He emphasized the desirability of both intelligence and cooperativity.

Needless to say, Muller's programme generated opposition or, perhaps worse from his standpoint, indifference and ridicule. Hardly anyone shared his view that humans would behave as idealistically as he assumed. I marvel that his remarkable mind, which led to frequent mistrust of individual humans, could be so confident of the idealistic behaviour of the larger society.

Artificial insemination is now routinely practiced, but the purposes are humanitarian, not eugenic. One wonders, of course, how Muller would have modified his ideas in light of the powerful molecular and cellular techniques that are now becoming available.

Conclusion

Although Muller is best known for his genetic research, he also made seminal contributions to evolution. He argued for the gene as the basis of life, and therefore of evolution. He noted that new gene functions and therefore greater complexity could arise from gene duplication. He emphasized mutation as the basic element of evolution. He pointed out the evolutionary advantages of sex and diploidy. He discovered dosage compensation, which equalizes the expression of X-linked genes in the two sexes. He demonstrated the chromosomal basis of species differences and he showed how isolating mechanisms can evolve during speciation. For these and other reasons Muller is entitled to a place among the greatest students of evolution.

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Competing interests statement
The author declares no competing financial interests.

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