ORGANISMS AND THE MYSTERIOUS X: INTERDISCIPLINARY INNOVATION IN EXPERIMENTAL BIOLOGY

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ABSTRACT

Interdisciplinary interaction was an important factor in the growth of radiation genetics in the early twentieth century. During the three decades after the discovery of X-rays in 1895, physicists had been puzzled by their paradoxical behavior: some experiments demonstrated that X-rays were waves, yet others revealed them as particles. At the same time, geneticists studying heredity were struggling to develop a method which could generate artificially induced mutations in the laboratory, thus ridding them of their reliance on infrequent natural mutations. These seemingly unrelated problems in different disciplines were linked by geneticist Hermann Joseph Muller. At a time when most physicists were still confused over the nature of X-rays, Muller harnessed their properties to create the first artificial mutation and thus spawned a new era in the application of physical techniques in experimental biology.

ACKNOWLEDGEMENTS

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ROENTGEN AND THE DISCOVERY OF X-RAYS

On the third day after Christmas, 1895, Wilhelm Roentgen submitted a short paper to the editors of the Physical and Medical Society of Wurzburg. Entitled “A New Kind of Ray--Preliminary Communication,” the text outlined the curious physical properties of a ray Roentgen had discovered six weeks earlier by observing the fluorescence of a photographic plate during electrical discharge experiments. Roentgen had naturally supposed, from their mode of production, that these rays were electromagnetic waves, and set out to measure their wavelike properties. He had performed experiment after experiment, devising ingenious techniques to measure the standard properties of reflection, refraction, and polarization: He failed to detect all three.

In desperation he had dubbed his new discovery as "X-rays," the symbol "X" being traditionally used in mathematics and physics to denote an unknown quantity. He had delayed publication until he had solved the puzzle, but by the end of the year, discouraged and confused, he candidly admitted his uncertainty:

> If one asks oneself what X-rays--which cannot be cathode rays as we have seen--really are, one might first think of ultraviolet light because of their lively fluorescence and chemical effects. But one is immediately confronted with rather serious considerations. For, if X-rays were ultraviolet light. . . one would have to assume that these ultraviolet rays behave entirely differently from the infrared, visible, and ultraviolet rays known at present (Roentgen 1895:317).

Roentgen, however, was not alone in his confusion over the nature of x-rays.[1] Within six months of Roentgen's first paper the scientific literature was swamped by speculations on the new discovery, ranging from conservative to crazy, and including "discharged and uncharged particles, vortices in the ether, and acoustical or gravitational waves of high frequency" (Wheaton 1983:16-17). None of these proposals could adequately describe the mysterious new rays, and in fact the debate over the physical nature of X-rays would last over twenty-five years and would reshape the theoretical structure of modem physics.[2]

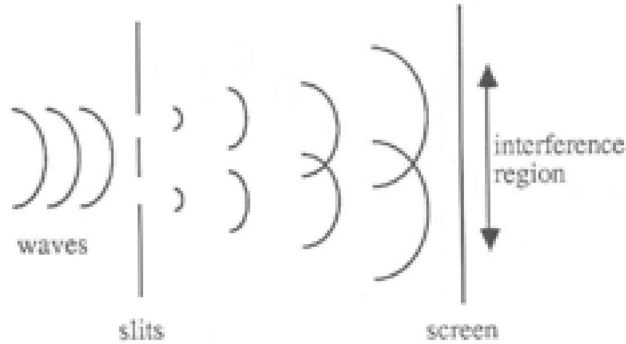


figure 1 a

An interference experiment can illustrate the different localization properties of waves (a) and particles (b). A single wave-front can extend over both of the slits and can therefore be split into two smaller wavefronts which overlap on the screen to produce interference. Particles, in contrast, can only be deflected by the slits and cannot produce overlap phenomena. This point is discussed in more detail in Feynman (1965).

From the start most physicists agreed that Roentgen's rays must be some type of electromagnetic wave, and George Stokes at Cambridge was the first proponent of the popular pulse hypothesis. X-rays, Stokes argued, were spherically shaped electromagnetic impulses which propagated through the ether. In contrast to ordinary waves, which possess an oscillatory character at all times, an X-ray pulse was seen as temporarily localized so that it propagates like a wave but collides with an atom as though it were a particle; this type of pulse would not exhibit the undiscovered interference effects of X-rays but would still demonstrate the curious localized properties which X-ray experiments were beginning to reveal. From its peak of influence in 1907 the pulse hypothesis quickly fell into disrepute: The energy that X-rays pass on to atoms in ionization experiments was more than could be expected from any spreading impulse, and, moreover, only a few atoms in the path of the X-rays emitted an electron. Physicists therefore tended towards a particulate view of the phenomenon, until the demonstration of X-ray diffraction and interference in 1912 confused the issue once again.

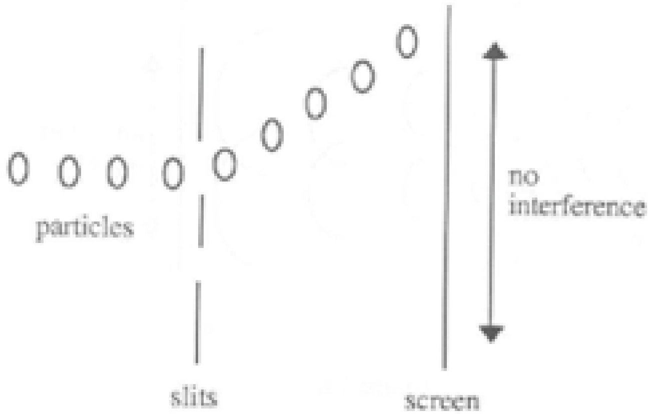
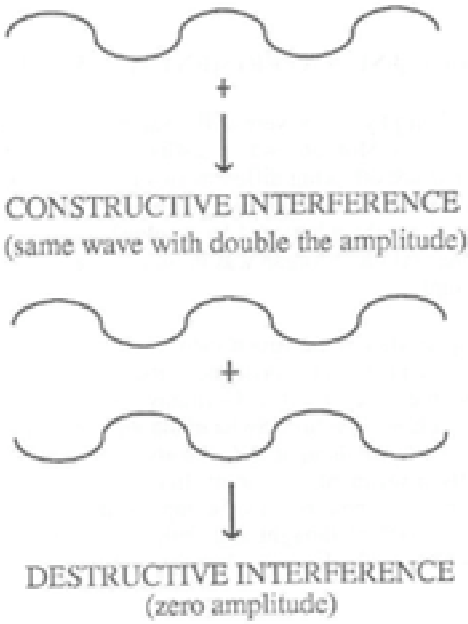


figure 1 b

The most profound difference between particles and waves is that of *localization*: particles are localized in space, whereas waves are continuous over a relatively large interval. The wavelike characteristics of diffraction and interference in fact result from this property of nonlocalization. A simple experiment for ascertaining the existence of diffraction is shown in figure 1. An incident wave can be represented by a wavefront (la) which covers a region in space and which propagates over time, in marked contrast to a stream of particles each of which is localized (lb). The slits can split the initial wavefront into two smaller wavefronts which both propagate towards the screen. Since each wavefront covers a finite *area*, however, it is possible that they can *overlap* to produce a uniquely wavelike pattern of alternating dark and light bands; this phenomenon is known as *interference* (figure 2). The particles can never overlap because of their localization, and consequently demonstrate no interference pattern. The paradox for X-ray behavior was therefore striking: Neither a particle nor a wave description could explain both interference and localization.



The wavelike property of interference results from the relative positioning of the two oscillating wavefronts at the screen. Constructive interference occurs when the peak of one wavefront coincides with the peak of the other, such that the amplitudes add to produce a wave of double the original amplitude. This effect produces a bright band on the screen. At another position, the peak of one wavefront will coincide with the trough of another to give a sum of zero amplitude. Cancelling of the wavefronts is called destructive interference and produces a dark band on the screen. Interference as a whole is therefore characterized by alternating light and dark bands.

figure 2

The influence of the X-ray debate, however, spread far beyond the confines of physics. Whether they were employed to induce organismal mutations or to map the structure of molecules by diffraction techniques, X-rays also became the principle physical tool in early experimental biology.

T. H. MORGAN AND EXPERIMENTAL GENETICS

In 1912, when physicists were still disagreeing over the nature of X-rays, Thomas Hunt Morgan[3] was wrestling with a problem no less fundamental: How are offspring differentiated by sex? Morgan is often seen as the founder of experimental biology, but what was his inspiration? Which methodology did he employ? In 1890, at a crucial stage in his intellectual life, Morgan was invited to the Marine Biological Laboratories in Naples:

> At the Naples station are found men of all nationalities. Investigators, professors, privatdocents, assistants and students come from Russia, Germany, Austria, Italy, Holland, England, Belgium, Switzerland and "America"--men of all shades of thought and all sorts of training. The scene shifts from month to month like the turning of a kaleidoscope. No one can fail to be impressed and to learn much in the clash of thought and criticism that must be present when such diverse elements come together (1896:16).

It was these "diverse elements" which were crucial in the development of a new biological methodology. The mixture of researchers with heterogeneous backgrounds, the arguments over conflicting results, and the interaction between varying intellectual traditions provided a stimulus for Morgan to combine previously disparate areas of biology. The growth of experimental biology was a complex process which cannot be associated with a single influence, but the fusion of different techniques and specialties was a vital component that is too often ignored.

In Morgan's hands this interdisciplinary principle became a powerful tactic, and "the breadth of his interests was such that he always worked simultaneously on several problems, often of a divergent nature" (Allen 1971:517). His approach to the problem of sex-inheritance, a direct precursor to his more general chromosome theories, epitomized this strategy. When Morgan began his *Drosophila* studies in 1910 there existed three different research emphases, but in a few years he reformulated the field:

> his strength lay in his ability to move beyond the three separate research approaches and combine elements of all three. He united strands on the external approach, using population studies and examining ratios of characteristics; the internal, epigenetic approach, emphasizing physiochemical and cytological factors and expression of inherited material; and the hereditarian approach, making reference to inheritance of factors that determine characteristis (Maienschein 1984:479).

Morgan broke with tradition not by overthrowing established doctrine in any one area of research, but rather by perceiving that "biology needed a combination of all three, a convergence of elements from all traditions" (Maienschein 1984:480).

At the inauguration of the new physical laboratory at Vassar College in 1926, Morgan emphasized the need for physical knowledge and techniques in biological work, where

> we realize that only through an exact knowledge of the chemical and physical changes taking place in development can we hope to raise the study of development to the level of an exact science (1927:214).

But Morgan was no naive convert to the omnipotence of physical methods, and he chastised those physiologists who had already studied development but had

> scandalized embryologists by assuming that the egg was little more than a bag of jelly. They spoke in terms of chemistry and physics and quantitative method but made wide guesses as to the kind of jelly they were dealing with. They often showed an appalling lack of concern as to the visible changes in the egg. They were willing, despite their boasted quantitative method, to call an embryo anything that swam, 'round in their finger bowls' (1927:218).

Not physics nor biology but *both* were needed for progress to be made on the fundamental problems of development: "In order to study it our best chance will be to put some physicists in the biological laboratory and some biologists in the physical laboratory" (1927:217).

Morgan's creativity in combining research traditions, however, was limited. He had been trained at Johns Hopkins University as a descriptive embryologist, and although his knowledge of biology was extensive his understanding of the physical sciences was poor. Despite several attempts, Morgan simply did not possess the physical training required to fuse physics and biology into a fruitful symbiosis.

EARLY APPLICATION OF X-RAYS IN BIOLOGY

Morgan's work with *Drosophila* began in 1910, this species first being used as an experimental system around a decade earlier.[4] His work in this area has been well documented,[5] and his primary achievement was to give the first clear demonstration, using the sex-linked inheritance of random mutations,[6] of the association of one or more hereditary characters with a specific chromosome. From this basis, Morgan and his young co-workers, A. H. Sturtevant, C. B. Bridges, and H. J. Muller, were able to argue plausibly in their book *The Mechanism of Mendelian Heredity*[7] that the genes, the units of inheritance, were arranged linearly on chromosomes.[8] For the first time, and by a unification of different specialities, it was possible to provide a mechanistic basis for Mendelian laws.

These studies of heredity, however, were complicated and tedious, for Morgan and his students were completely dependent on the whims of natural mutation. Only by spotting a mis-colored eye, a shriveled wing or a missing antenna could research progress. But mutations were the raw material of experimental genetics, and one desperate need dominated all others in the study of heredity: A method for producing mutations on demand in the laboratory.

Since the beginning of the century numerous attempts had been made to create mutations by high energy radiation or by other physical and chemical treatments.[9] One of Morgan's students recalled that Morgan "began working with *Drosophila* in the hope of inducing mutations. He used wide ranges of temperatures, salts, sugars, acids, alkalis, and radium and X-rays" (Sturtevant 1959:293). Both Morgan (1911) and Loeb and Bancroft (1911) presented reports of their attempts to generate mutations, and the latter paper epitomizes the methods employed, and the difficulties faced, by these experimenters. As Loeb and Bancroft explain:

> the following experiments were undertaken for the purpose of forming a conception concerning the degree of certainty

> with which mutations can be produced experimentally. We have tried the effects of a constant and comparatively high temperature, of radium and of Roentgen rays (p. 781).

This paragraph contains two themes which recurred in the early experimental work. Firstly, the biologists were not guided by any theoretical model which could indicate what type of treatment of the organism would produce a mutation. In many ways, these physical experimental methods were used in a highly speculative manner with little physical sophistication; radiation was just another, little understood, "poison" for the gene. Secondly, there was the problem of sensitivity of the experimental arrangement. In these early papers, we read statements like "In two radium cultures we observed the pink-eyed mutants, but this was also found in cultures not treated with radium" (Loeb & Bancroft:782); in addition, Loeb and Bancroft found that "experiments with Roentgen rays have given us thus far no mutants" (p. 782). In most of the early experiments cited above, a few induced mutants would likely have been generated, but at the time it seemed probable that they were not produced by the treatment since mutation also occurred in the controls (by random effects). The genetic techniques then used were not adequate for the demonstration of an increase in mutation frequency of the magnitude likely to occur (Sturtevant, 1965, chap 11).

Genetic effects of radiation on *Drosophila*, however, were confirmed by J. W. Mavor in 1921. In contrast to Morgan, Loeb, and previous researchers, who looked for standard signs of mutation such as wing size or shades of eye color, Mavor employed the more sophisticated criterion of *nondisjunction*. Occasionally, an unexpected male looking like the male parent is produced, and cytological examination of the chromosomes of this organism reveals that the two X chromosomes of the female parent fail to separate, or disjoin. This process produces a sterile male containing a single X chromosome rather than the usual X and Y chromosomes, which can be easily detected in further breeding experiments (Portugal & Cohen 1971:126). This sensitive mutational criterion, coupled with Mavor's double doses of X-rays (one dose soon after emerging from the pupa and another just before mating), enabled him to claim confidently that his experimental technique had produced artificial mutations. In fact, after white-eyed males were mated with irradiated red-eyed females,

> None of the nineteen control pairs produced white-eyed males. One of the rayed females was sterile. Of the

> fifteen fertile rayed females, twelve produced one or more white-eyed males .... That the presence of these white-eyed males could be due to natural non-disjunction and not to any effect of the X-rays seems extremely unlikely . . . (Mavor 1921:278, emphasis in original).[10]

This 1921 paper shows that X-rays produce a marked increase in the frequency of nondisjunction, and in 1923 Mavor also demonstrated the effect of radiation on the frequency of *crossing over* (1923)[11] E. G. Anderson soon confirmed X-ray induced nondisjunction effects, and in 1925 he reported that one of the exceptional females produced had her two X's physically attached; this was the first induced chromosome rearrangement.

"ON SUNDAYS THEY SIMPLY PRAYED":

FURTHER STAGES IN THE X-RAY DEBATE

Geneticists in the 1920's achieved some empirical success with artificially induced mutations but made no progress towards understanding the physical basis for these effects. This is hardly surprising, however, since physicists had not yet formulated a satisfactory theory for radiation-matter interactions. These years therefore witnessed a resurgence in the X-ray debate; the problem of the mysterious rays was not yet solved.

After the observation of X-ray diffraction, which seemed to provide conclusive evidence of the wave picture, H.G.J. Moseley at the Cavendish Laboratories in Cambridge constructed an X-ray spectrograph using a crystal as a grating. This device relied on the wave properties of X-rays for its operation, but Moseley's experiments revealed that they are absorbed locally, just as if X-rays were particles.[12] By physical insight, coupled with experimental prowess, Moseley had exposed the inadequacies of current theory.

C. G. Darwin, who had been Moseley's colleague at Cambridge, also fought in the Great War, but after his discharge he was eager to make up for lost time. In 1919 he wrote to Neils Bohr, creator of the quantum mechanical atom and an old friend from their time together at Manchester University before the war. The central problem, Darwin perceived, was the quantum mechanical description of the interaction of radiation, which included both visible light and X-rays, with matter: Combining Bohr's atom with Maxwell's equations for electromagnetism *should* yield a solution to the X-ray dilemma. Yet quanta, as Darwin bemoaned, were still new and strange to most physicists:

> I am doing my inadequate best to talk to people about quanta; everybody accepts them here now (which is better than it was in 1914 at any rate), but I don't think that most of them realize their fundamental importance or have studied the arguments in connection with them (1919).

This reluctance to study quanta was not mere ignorance. The "old quantum theory," as the work in this period is now called, was plagued with severe difficulties and inconsistencies; the most serious, which soon became a crisis, was its complete failure to provide an adequate description of radiation-matter interactions.

Once again we return to the same problem, infecting the description of all types or radiation. It appeared as if both light and X-rays sometimes behaved as waves and sometimes as particles. A solution had already been proposed, but it appeared so outrageous that few took it seriously. Albert Einstein, in 1905, had composed a paper entitled "On a Heuristic Viewpoint Concerning the Production and Transformation of Light," and when writing to an old school friend the same year he succinctly described his work: "It deals with radiation and the energy characteristics of light and is very revolutionary . . ." (Klein 1963:59). Einstein was not exaggerating. His paper had suggested an explanation for the puzzling localization; Light, in fact, did not act continuously in interactions with matter but rather in the form of discrete energy quanta. The photoelectric effect, in which the number of electrons emitted depends not on the intensity of the incident light but only on its frequency, was one example of a puzzling phenomenon which was perfectly explained by Einstein's new hypothesis, but other difficulties still remained. Not only did the proposal attack Maxwell's equations for electromagnetic wave propagation, one of the finest achievements of nineteenth century physics, it also seemed incompatible with simple optical effects. How could diffraction and interference, perfectly explained by the wave theory, be described in terms of "light particles"? And how should the working physicist calculate using such a strange theoretical tool? Even after Einstein extended his quantum theory of radiation in 1917, introducing conservation of energy and momentum, he gained few converts (Einstein 1917).

Also in difficulty were physicists using Bohr's atomic model, based primarily on classical mechanics, coupled with Maxwell's equations.

There seemed only two options, both of which required rejecting an aspect of classical physics: either one kept the classical mechanics of the Bohr atom and rejected Maxwell's equations in favor of the light quantum, or one retained the wave theory and abandoned conservation principles in mechanics. Bohr, convinced that Einstein was brilliant but misguided, unequivocally stated his support of the latter course in his reply to Darwin:

> as regards the wave theory of light I feel inclined to take the often proposed view that the field in free space ... is adequately described by Maxwell's equations and that all difficulties are concentrated on the interaction between the electromagnetic forces and matter .... On the quantum theory conservation of energy seems to be quite out of the question . . . (1919).

Bohr's conviction of the validity of his own atomic model waxed and waned over the next five years, but he steadfastly rejected all attempts to introduce the light quantum into physics.

In late 1923, however, Bohr faced his most serious challenge. Arthur Compton, a young professor at the University of Washington, had proposed the same hypothesis for X-rays as Einstein had for light: X-ray interactions occur not continuously but by discrete energy quanta. In an elegant derivation he demonstrated that Einstein's quanta, together with conservation of energy and momentum, fully explained his experiments with X-ray scattering and absorption (Compton 1923).[13] Compton was not without dissenters, and debates raged for several months, but the result had come at a time when many physicists were becoming disillusioned with Bohr's problematic version of quantum theory. Success in explaining the 'Compton effect' sparked renewed interest in Einstein's original proposals, and slowly a few papers appeared using the new light quantum to calculate optical phenomena.

Bohr's position appeared precarious, and during 1924 he dedicated all his effort to answering Einstein. His reply, written with two junior colleagues and entitled "The Quantum Theory of Radiation," was a final attempt to save the wave theory of light by abandoning both the Bohr atom and strict conservation principles for energy and momentum (Bohr et at. 1924).[14] Today such rejection of the foundational structure of classical mechanics may seem extreme or even ridiculous. Yet at a time of utter confusion, when the standard laws of classical physics were failing miserably in the atomic realm, such a move was in fact conservative rather than revolutionary. If classical mechanics had needed slight modification in the Bohr atom, why not challenge its foundations further? As Martin Klein explains:

> If we ask *why* Bohr and his co-workers were willing to give up the validity of the conservation laws, I think the answer is clear: it was to save physics from an alternative they considered even less acceptable--the admission of light quanta (Klein 1970:3).

Paul Dirac, an astute physicist who received the Nobel Prize for his work in quantum mechanics, had no qualms over rejecting classical mechanics:

> There was the excitement of the Bohr-Kramers-Slater theory. That provided a new outlook, and it seemed to me to be a very reasonable outlook. With the backing of Bohr behind it, it seemed to me that here was a theory that was certainly worth considering. It meant giving up detailed conservation of energy, but I did not especially mind that. Conservation of energy had only been proved statistically. Here was a way that did seem to provide an escape from some of the fundamental difficulties concerned with understanding radiation (1977:117).

Little wonder that, almost thirty years after Roentgen's original discovery of X-rays, confusion still abounded over the physical description of electromagnetic radiation. Physicist Banesh Hoffman well remembered the difficulties:

> The same entity, light, was at once a wave and a particle. How could one imagine its possible size and shape? To produce interference it must be spread out, but to bounce off electrons it must be minutely localized .... It is well that [we] should appreciate ... the agony of the physicists of the period. They could but make the best of it, and went around with woebegone faces sadly complaining that on Mondays, Wednesdays, and Fridays they must look on light as a wave; on Tuesdays, Thursdays, and Saturdays as a particle. On Sundays they simply prayed (1959:42).

The year 1925 was eventful for physics. Precision experiments with X-ray scattering demonstrated that strict energy conservation was valid in radiation-matter interactions, thereby ending the short life of the Bohr-Kramers-Slater theory. Instead ot modifying classical mechanics, Heisenberg conceived of a new type of mechanics for quanta, or "quantum mechanics," which offered an escape from the earlier tension between classical and quantum concepts. Yet this was a quantum analysis only of mechanics and not of electrodynamics; in fact, a full theory of quantum electrodynamics was only formulated a quarter of a century later in the 1950's.[15] After the demise of Bohr's attempt to retain classical electrodynamics, physicists tentatively turned to light quanta. But there existed no detailed quantum theory of radiation, and those physicists who accepted light quanta often did so hesitatingly and reluctantly. Besides, Heisenberg's new quantum mechanics, and especially its formal elaboration in the following years, used a physically unvisualizable description of the atomic realm together with unfamiliar mathematical techniques. Physicists spent the remainder of the decade in becoming familiar with the new theoretical tools.

MULLER AND X-RAY INDUCED MUTATIONS

It was against this background, therefore, that Hermann J. Muller achieved his fundamental breakthrough in X-ray induced mutation.[16] Muller was a member of the first generation of biologists to have been trained solely within the framework of the new experimental biology, and he had no experience, unlike researchers of Morgan's generation, of any type of morphological study. In contrast, he studied for a Master's degree in physiology (1912), receiving a thorough training in quantitative experimentation; his thesis research employed the latest electrical methods to study transmission of nerve impulses. But genetics remained his primary interest, originally stirred by an undergraduate course given in chromosomes and heredity by E.B. Wilson at Columbia,[17] and he was accepted into Morgan's lab for doctoral studies. His major contribution to *Drosophila* genetics was to develop the first rigorous experimental method for analyzing mutations. Previous results were mainly qualitative, as the mutational frequencies were often too low for an accurate quantitative study and analysis of mutants depended highly on subjective judgement. Muller used the so-called "C1B" chromosome, an X chromosome carrying a lethal mutant gene, to improve experimental accuracy. By crossing other *Drosophila* with this mutant, certain expected classes of males would then fail to appear: Comparing the theoretically expected results with the experimental observations enabled Muller to detect sex-linked inheritance with minimal observation error.

Muller, together with the rest of the genetics research community, realized the need for a technique to create artificial mutations. He also knew the methodology he would employ. Muller was well aware of, and prepared for, the necessity of interaction between the biological and physical sciences. Speaking at a 1921 symposium of the American Society of Naturalists in Toronto, several years before his work with X-rays, he discussed the physical basis of the gene:

> Hence we cannot categorically deny that we may be able to grind genes in a mortar and cook them in a beaker after all. Must we geneticists become bacteriologists, physiological chemists and physicists, simultaneously with being zoologists and botanists? Let us hope so (Judson 1979:49).

Muller's diversity was characteristic of a change in experimental biology. In his experimental studies Morgan "was inclined to use simple techniques and equipment" (Sturtevant 1959:298), but his student, by contrast, was willing to learn sophisticated methods from several fields and use them wherever he could. When he harnessed X-rays for biological research, Muller became one of the first geneticists to introduce the techniques and methodology of the physical sciences.

Muller also had the diverse training needed to implement his aims. At high school he had been interested in all sciences, but he especially "had a flair for the physical sciences and mathematics" (Carlson 1981:23). He applied to Columbia University Engineering school to work in electron physics; too young at sixteen to be admitted, he enrolled instead in Columbia College. Although converted to the biological sciences by E.B. Wilson's lectures, he tried

> "to get as good an understanding in biochemistry and physiology as possible, the better to attack general biological and genetic problems later." He planned his undergraduate work to give himself a broad background in the sciences. He also "retained an interest in physics, but had no time to satisfy it, except as attending as a visitor . . . Prof. Pegram's graduate course on radiation (X-rays, radioactive substances, etc.)" (Carlson 1981 ;33).[18]

Muller, like Morgan before him, had interest and ability in diverse areas of the natural sciences.

Muller's presence at the course on radiation proved especially useful. We have seen that Morgan's and Loeb's attempts to induce artificial mutations were characterized by a lack of appreciation for the physical variables in the system. In 1927, however, Muller was directing a laboratory at the University of Texas in which he worked closely with physicists. In the light of his training, previous statements, and current contacts, it is very likely that Muller kept up to date with important advances in physics, of which the most widely discussed was the debate over radiation. In fact, in the 1920's the most cited paper in prominent physics journals was Compton's 1923 study of X-ray scattering as a localized phenomenon.[19] In all his communications Muller seemed well aware of the physics of X-ray interactions. When he announced the first rigorous evidence for large-scale X-ray induced mutations in 1927, he explained that

> *on theoretical grounds*, it has appeared to the present writer that radiations of short wave length should be especially promising for the production of mutational changes... (p. 84, emphasis added).

Here Muller is being tantalizingly vague: What were the "theoretical grounds" on which he based his experiments? In this short initial communication he did not elaborate, but in a longer paper of the following year Muller spoke of the localized action of X-ray absorption, in which

> the transmuting action of X-rays is thus narrowly circumscribed, being confined to one gene even when there are two identical genes close together (Muller 1928:717).

He then talks comfortably in the language of the physicist about the mechanism producing gene mutation, where

> the secondary or [beta]-radiation, the released electrons, may be the effective agent, and the chance position of the gene in relation to the course of the electron may be a deciding factor in the production of the mutation. That the mutations are thus caused by chance *absorption of individual quanta*, such as may take place in the line of these secondary rays, is further suggested by the lack of relation between the amount of the X-ray dose and the character of the mutations produced: their number varies with the X-ray dosage, but it seems that the "degree" or

> nature of the individual mutations themselves does not vary with the dosage (pp. 717-718).

This passage is interesting in three respects: first, Muller suggests a rigorous and novel physical explanation of mutation; second, he explicitly refers to the light quantum, a concept that was only just being assimilated into the structure of physics and was totally alien to biology; and third, Muller talks of the "degree" of mutation as being independent of the intensity of the X-ray dosage, a situation analogous to the physical characteristics of the photoelectric effect.

In his Nobel speech almost twenty years later, Muller reiterated, admittedly in hindsight, his specific reasons for turning to X-rays as an experimental tool:

> the nature of the individual mutation process, which sets it in so different a class from most other grossly observable chemical changes in nature, led naturally to the expectation that *"point effects"* brought about by high-energy radiation like X-rays would also work to produce alterations in the hereditary material. For if even the relatively mild effects of thermal agitation can, some of them, have such consequences, surely the energetically far more potent *point changes* produced by powerful radiation should succeed (1946:29, emphasis added).

This statement and Muller's other quotes above are illustrated schematically in figure 3.

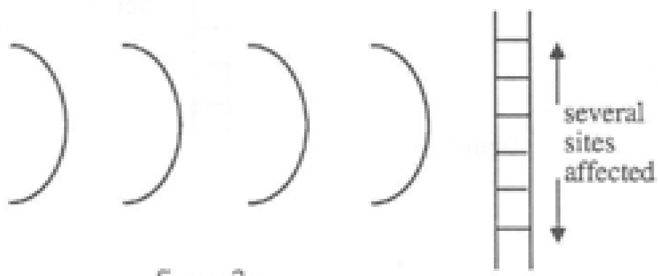


figure 3a

> As a consequence of their different localization properties, waves and particles produce different effects on a linear array of genes in a chromosome. A wavefront (a), spread over a finite area, would induce mutations in several adjacent sites. Only a particle (b) could create the highly localized and single-site "point effects" observed in X-ray induced mutations.

As discussed earlier, a propagating wave can be viewed in terms of a delocalized wavefront; such a wavefront impinging on a linear array of genes would affect a large number of sites (3a). In contrast, a small localized particle would influence only one site (3b), thus explaining the highly specific point mutations observed in *Drosophila* genetics. By understanding the intricate debate over the nature of X-rays, and indeed of radiation in general, Muller was able to exploit their physical characteristics to revolutionize the study of genetic mutation at a time when many physicists were still struggling with the new concepts.[20] The process had taken over thirty years, but Roentgen's mysterious rays had now passed from being an enigma in theoretical physics to constituting a powerful experimental technique in genetics.

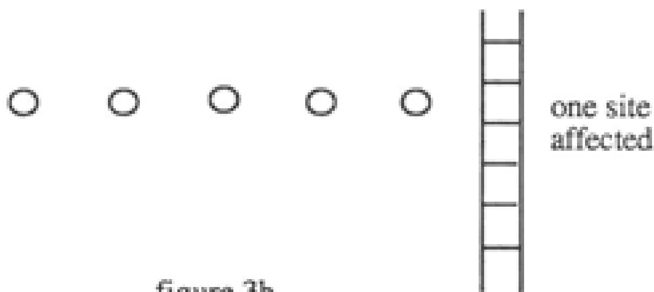


figure 3b

CONCLUSION: INTERDISCIPLINARY INTERACTION AND SCIENTIFIC INNOVATION

In a paper entitled "Radiation and Genetics," delivered to a special meeting of the American Society of Naturalists on "Radiation and Life," Muller praised the technique of induced mutations:

> Radiation and genetics is my title, but I cannot do it justice, for the field of radiation genetics is, in a sense, coextensive with that of genetics itself--it affects or induces crossing over, non-disjunction, chromatin displacements, gene mutation and even, as Patterson has recently found, somatic segregation. And it produces these things in quantities, under determinate conditions. If you are ever *ennuied*, just try rubbing the Alladin's lamp of the X-ray tube or the radium needle, and pretty soon you will be flooded with a "superfluity of riches," in the midst of which the chief question becomes what to ignore (1930;246).

The title of the presentation was apt, for Muller's work had indeed been innovative both in radiation and genetics, but especially in his combination of the two. By fusing an understanding of the difficult issues in X-ray absorption with his techniques for accurate genetics experiments using the C1B lethal mutant gene, he was able to introduce advanced physical techniques into biology.[21]

Muller was a unique individual, professionally, personally, and politically, and his contribution to radiation genetics was uniquely his own. Yet interdisciplinary interaction is a recurring theme which characterizes much innovative science. Morgan had perceived its importance back in 1907:

> Good judgement and accurate observation may lead to fine work, but constructive imagination seems to be required for the highest order of *original* work … ; the man who sees *new and overlooked combinations* may open fields of research that will set to work an army of able "investigators" (p. 10, emphasis added).

For example, Muller's "superfluity of riches" was no idle boast. By demonstrating the need for physical techniques in the life sciences he had encouraged a novel approach to biology, and the late 'twenties and 'thirties witnessed a new type of geneticist who was rigorously trained in the physical sciences and interested in the problems of describing life (Fleming, 1968). Foremost amongst these was Max Delbruck, theoretical physicist and student of Neils Bohr at Copenhagen before turning to biology, who aimed to explain the fundamental problem of radiation genetics: What was the physical process by which gene mutation occurred?[22] Muller's visions stimulated Delbruck, and the young physicist sought to emulate his mentor's interdisciplinary strategy:

> Delbruck continued to pursue the connection between physics and genetics. His research, appearing as a section of the 1935 joint paper entitled "On the Nature of Gene Mutations and Gene Structure," offered for the first time a physical explanation of gene action. This study, in collaboration with Timofeef [a geneticist] and K.G. Zimmer, a physical chemist, was based on Muller's 1927 discovery of artificial mutations using the *Drosophila* as a model and X-rays as a tool for studying alterations in the gene structure. Zimmer studied dose response curves with different radiation intensities and wavelengths, Timofeef performed the genetic analysis of mutations, and Delbruck constructed the theoretical model for gene structure. Joint publications in biology, chemistry, and physics were relatively uncommon in the 1930's, and the 1935 paper ... signalled a trend that would later become a pattern for publication in molecular biology (Kay:219-220).[23]

Delbruck's model, in turn, became the focus of Erwin Schroedinger's essay *What Is Life? The Physical Aspect of the Living Cell* (1955), an influential exposition which encouraged many physicists to turn their interests to biology.[24]

Such creativity in discovering "new and overlooked combinations" is not confined to radiation genetics. N.C. Mullins, in a detailed study of Delbruck's phage group, has analyzed how extra-disciplinary input from physics to biology was crucial for the growth of molecular biology (Mullins 1971). In another case, physicists of the late nineteenth century developed an interest in the physical basis of organic chemistry; from this source, rather than from the traditional university chemistry laboratories, sprung the research field of physical chemistry (Dolby, 1976). A study of the growth of X-ray astronomy has shown that it was physicists with peripheral interests, not those actively engaged in optical astronomy, who generated the fundamental innovations. In fact,

> in several respects the development of physical chemistry is similar to that of radio astronomy. In both cases the new ideas began on the margins of the established disciplines and, as with the phage group, these first stages were associated with the movement of physicists into areas of investigation for which they had not been trained (Edge & Mulkay 1976:380).

Writing from a sociological perspective J. Ben-David discovered that, for certain nineteenth century innovations in medicine,

> "revolutionary" inventions are usually made by outsiders, that is by men who are not engaged in the occupation which is affected by them and are, therefore, not bound by professional custom and tradition (1960:557).[25]

The same interdisciplinary strategy so successfully used by Muller has often produced innovations which arise from introducing influences from another specialty.

Historians, however, often appear reluctant to exploit the same strategy, and analysis of interdisciplinary interaction has primarily been the province of sociologists and philosophers. It is time to remove the blinkers of disciplinary autonomy and to search for "new and overlooked combinations" in the history of science.[26] For example, how were the physical paradoxes of the X-ray debate finally resolved? It was Bohr, at the 1927 Como conference, who proposed the principle of *complementarity* in which the wave and particle behavior of X-rays were mutually exclusive yet complementary properties of the same entity. Here the influences were reversed, for his father was a reknowned physiologist and Bohr's philosophy was profoundly influenced by methodological arguments between supporters of reductionism and holism in biology.

But that's another story.[27]

Notes

[1]For a useful summary of changing views concerning the physical nature of X-rays, see the introduction to Wheaton (1983). Chapters 1 and 2 of Steuwer (1975) offer an alternative interpretation of the early history of X-rays.

[2]Roentgen presented three different reports concerning his original discovery, but after 1896 he published nothing further on X-rays.

[3]For a detailed account of Morgan's life and research in *Drosophila* genetics see Allen (1976,1969) and Manier (1969).

[4]The advantage of using *Drosophila* was its extremely short life span of around fourteen days; results of breeding experiments could therefore be obtained rapidly.

[5]See in particular the account by the participant A. H. Sturtevant (1965, Chaps. 6-7).

[6] These mutations were often subtle and their detection not simple. For a comprehensive list of mutations, with accompanying diagrams, see Bridges (1944).

[7]This book (Morgan *et al.*, 1915) is the standard account of the chromosomal theory of inheritance, but a more detailed discussion of the chromosomes themselves is given in Morgan (1919).

[8]Morgan's conception of genes on chromosomes can best be described in terms of beads on a string, but beads that could nevertheless cross between strings under the right conditions. A discussion of Morgan's experiments in the language of modern genetics is given in Klug & Cummings (1983), and a more technical account can be found in Watson (1976, pp. 153-157).

[9]Oscar Hertwig was among the first to attempt artificial production of mutations, but I have not treated his work in this account.

[10]The occurrence of white eyes in the phenotype is characteristic of *Drosophila* possessing only the X-chromosome.

[11]*Crossing over* is a process occurring between two chromosomes. Following the formation of pairs, both chromosomes occasionally break at the same point and rejoin crossways. This allows the formation of recombinant chromosomes containing some genes determined from the paternal chromosome and some from the maternal one; crossing over greatly increases the amount of genetic recombination. For further details see Watson (1976, pp. 151-156).

[12]Moseley began a very promising career as a physicist but was tragically killed at the age of twenty-seven in the 1915 Gallipoli campaign. For an account of Moseley's life and work see Heilbron (1974).

[13]For a history of the Compton effect and its importance to quantum physics see Steuwer (1975), Chapters 6 & 7.

[14]This paper, which contained only one short equation, was essentially a conceptual discussion of how to tackle the radiation issue; it combined Kramers' theory of matter, Slater's approach to the electromagnetic field, and Bohr's rejection of the light quantum. For a discussion of the intricacies of the theory see Hendry (1981).

[15]For historical essays by two creators of quantum electrodynamics see Dirac (1983) and Weisskopf (1983). A detailed and technical account of Richard Feynman's contributions is given in Schweber (1986).

[16]The historical study of H.J. Muller has mainly been the work of E.A. Carlson. This first reference should be Carlson (1981), but shorter articles are Carlson (1967, 1971, 1972). Carlson has also edited a selection of Muller's essays (Carlson, 1973). A sketch of Muller's scientific contributions with full bibliography is given in Pontecorvo (1968), whereas Muller's personal life and views on human genetics are treated by Sonneborn (1968).

[17]Muller probably used as a textbook Wilson's influential *The Cell in Development and Inheritance* (Wilson, 1896).

[18]The passages in quotation marks are selections from the autobiographical data submitted by Muller at the request of the National Academy of Sciences.

[19]Small, H.D.: *A Citation Index for Physics: 1920-1929*, Final Report on National Science Foundation Grant SOC77-14957, p. 24. Compton's paper was cited 82 times, and is closely followed by Einstein's "On the Quantum Theory of Radiation" which is cited once less. These two

papers, both concerned with the quantum description of radiation, easily beat the third most cited article, on non-polar molecules, which is mentioned only 67 times.

[20]I am aware of the fact that much of the evidence I have presented in favor of Muller's understanding of physics is circumstantial, and in a search of his published papers in the 1920's I have found no passage which explicitly states that Muller was led to his discovery by the raging debate over the nature of X-rays. Yet I believe that the timing of his work, together with Muller's training in physics and association with physicists, lends strong support to my argument, and the omission of any discussion of strange physical paradoxes would not be unusual in communications addressed primarily to geneticists. Further research on this topic is currently in progress.

[21]Muller, of course, did not stop his radiation experiments in 1927, and compendium of his research papers in radiation genetics has been edited by Pontecovoro (1962). For the progress of genetics research after Muller's original X-ray discoveries, written by the researchers themselves, see Dunn (1951).

[22]Despite the qualitative success of radiation genetics, early experiments were performed with little knowledge of the exact physical process by which X-rays induced gene mutations. These mutations are now understood to be the result of nucleotide ionization on the DNA strand.

[23]This is one of a few historical articles which attacks the fundamental questions of interdisciplinary interaction. Delbruck later became founder of the "phage group," a small band of researchers who used bacteriophage rather than *Drosophila* for mutational experiments. For a general history of bacteriophage research see Stent (1963), and for a personal account by another prominent member of the phage group see Luria (1984).

[24]For a study of Delbruck's influence see his *Festschrift* volume, Cairns et al. (ed.) (1966), and also the analysis by Mullins (1971).

[25]See also his discussions in Ben-David (1964) and Ben-David & Collins (1966).

[26]There is a subtle but important distinction between studies of scientific disciplines, usually viewed as discrete entities, and interdisciplinary interaction, which requires comprehension of the simultaneous development of two or more specialties. The classic study of the interactive trident of research in molecular biology is Olgy (1984). The

former approach, however, is far more common, and examples in the history of the life sciences include Kohler (1982), Geison (1978, 1981), and more pertinent to this study, Law (1976).

[27]T. Morgan, "Physics or Biology?: The Priority Dispute for Complementarity," unpublished paper delivered at the History of Science Section, Canadian Learned Societies Meeting, Hamilton, Canada (May 1987).

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