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Luis Campos and Alexander von Schwerin (eds.)

**Making Mutations: Objects, Practices, Contexts**



## Table of Contents

*The Making of “Making Mutations”*..... 3

Alexander von Schwerin & Luis Campos

### Identifying Mutation

*Women in Mutation Studies: The Role of Gender in the Methods, Practices, and Results of Early Twentieth-Century Genetics* ..... 11

Marsha L. Richmond

*Mutant Sexuality: The Private Life of a Plant*..... 49

Luis Campos

*Generating Plants and Women: Intersecting Conceptions of Biological and Social Mutations in Susan Glaspell’s “The Verge” (1921)*..... 71

Jörg Thomas Richter

*Non-Evolutionary Mutants? A Note on the Castorrex Rabbit*..... 85

Thierry Hoquet

### Organisms

*Tracing the Totsuzen in Tanaka’s Silkworms: An Exploration of the Establishment of Bombyx Mori Mutant Stocks*..... 109

Lisa A. Onaga

*Supporting the Balance View: Dobzhansky’s Construction of Drosophila pseudoobscura* ..... 119

Matt Dunn

*The First Bacteriophage Mutants: Changing “Genespeak” in the 1930s*..... 127

Neeraja Sankaran

*Commentary on “Organisms”* ..... 145

*Karen Rader*

## **Populations**

*Hermann J. Muller and the Biopolitics of Mutations and Heredity*..... 151

*William deJong-Lambert*

## **Tools**

*Mutations in the Nuclear Age*..... 179

*Soraya de Chadarevian*

*Size and the Centromere: Translocations and Visual Cultures in Early Human Genetics ...* 189

*María Jesús Santesmases*

*Tracing Mutations: Biodosimetry Tools in Post-Cold War Radiation Epidemiology* ..... 209

*Susanne Bauer*

*Commentary on “Tools”: Radiation, Health, and Heredity* ..... 225

*Angela N. H. Creager*

## **Chemicals**

*Medical Physicists, Biology, and the Physiology of the Cell (1920–1940)* ..... 231

*Alexander von Schwerin*

*Making Marigolds: Colchicine, Mutation Breeding, and Ornamental Horticulture, 1937-1950* ..... 259

*Helen Anne Curry*

*The Political Life of Mutagens: A History of the Ames Test* ..... 285

*Angela N. H. Creager*

## The Making of “Making Mutations”

Alexander von Schwerin & Luis Campos

This volume documents a recent workshop on the history of biological mutations in the twentieth century. How could such a seemingly limited topic fascinate twenty-two scholars from seven countries around the world for three days? One reason might be found in the image shown on the front page of our conference program: this image was deliberately presented without any identifying information about the shown plants, making it difficult to distinguish at a glance between “normal” and “mutant” plants. A trained eye — a mutant gaze — is needed. But such an assertion only seems to present still further epistemic challenges: is it ever truly possible to “see” a mutant or a mutation? A gene, conceived in one reductive sense as a stretch of chromosome, is arguably visualizable — at least in principle. A mutation, however, as a process — or as many geneticists might prefer to say, an event — seems still further removed from the phenomenal realm, popular incarnations to the contrary. If mutations are changes between past and present, and can only be inferred from observed phenomena that distinguish a normal organism from its mutated relative, provocative further questions emerge: who is doing the observing and the inferring? How do we know which is the mutant and which the original state? What does it mean to study mutants as the differences that make things visible?

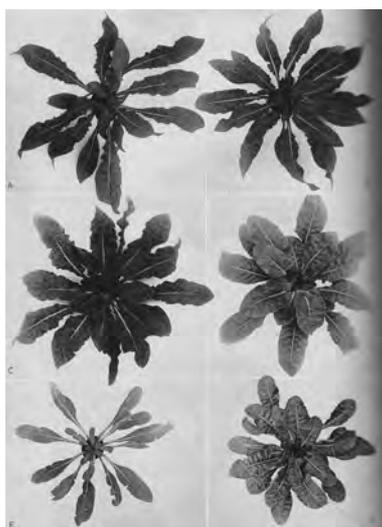


Fig 1: Six rosettes of *Oenothera lamarckiana* and its various mutants – but which is which?  
Photo by G. H. Shull.

Recent scholarship — some of which is included in this volume — reminds us that genetics was understood and practiced in widely different ways among different communities of practitioners, not all of whom were primarily concerned with the gene itself, but many of whom engaged with the study and production of mutants and mutation at various levels and contexts — in the field, the laboratory, and elsewhere. Mutations seem to be at the very heart of the experimental activities as instruments to research genes, chromosomes, or developmental processes. A broad range of practices, activities and institutions extending far beyond geneticists alone sought to produce mutations, to detect mutants and to organize them, to keep them and to distribute them (see Thierry Hoquet’s special volume on “Mutants” in *Critique*, June/July 2006). Mutants functioned as

resources and as valuable objects of exchange.

From ever-transmuting concepts of mutation and shifts in discourse to novel practices in the field and laboratory, to the distribution and regulation of mutagens and broad-scale governmental involvement, mutation thus seemed a particularly fruitful way to explore how the study of heredity in the organism and heredity in society intertwined, from *Die Mutationstheorie* until the dawn of biotech. Engaging with mutations as our focus of study — rather than genes in general — thus opens up promising vistas for exploration as well as new approaches to otherwise familiar material.

### *Imagining Mutants*

This conference had been several years in the making. Almost three years ago now, one of the organizers (Luis Campos) posted an ad on the ISHPSSB bulletin board for a panel at the upcoming meeting in Exeter in 2007, on the topic of “Sports, Freaks, Monsters and Mutants: Toward a History of Mutation.” Along with Igal Dotan, Staffan Müller-Wille, Christina Brandt, and Hans-Jörg Rheinberger as commentator, we ended up with a two-session panel and a packed house. Following the positive interaction generated there, Igal, Alexander, and Luis talked about organizing a full conference on mutation — one that would move beyond what we younger historians, from our own training, viewed as “traditional” histories of genetics that seemed to be overly focused on the history of *Drosophila* or the so-called “century of the gene.” One thing we had begun to realize from previous workshops and from our own work was just how polyvalent the meaning of mutation actually was. Organisms could mutate and so could genes, of course, but no one was really talking about — for example — chromosomal mutations as another intermediate level of mutation. What would the history of genetics look like, we wondered, if we studied the history of genetics as something that was not necessarily coextant with the history of Mendelism? If we took the implications of the mutation theory, broadly understood, seriously? If we moved far away from histories referring to *Drosophila*? What other organisms were being studied, by what other means? How might this relate to larger social and cultural contexts? We also wanted to disarticulate the concept of mutation in genetics from overwhelming attention given to the gene, in order to better explore the place of mutation — and more generally of variations and differences — in the history of biology in its own right. We wanted to broaden the history of mutation as widely as we could within the history of biology.

When Alexander, Igal, and Luis found themselves all at the Max Planck Institute in the fall of 2007, plans went forward. Luis met with Hans-Jörg Rheinberger and proposed that the Institute host a conference on the topic. Hans-Jörg proved receptive to the idea, and so the Cultural History of Heredity group — which had organized other conferences on the history of heredity in recent years — sat down in early 2008 and began to sketch what the conference would look like: what it might cover, how it might be thematized and structured, when it could best be held, and how it might best be run. While earlier conferences in the “Cultural History of Heredity” series had proceeded chronologically, we proposed that this conference take a slightly different approach, by working around a thematic topic rather than taking a strict chronological slice.

A call for papers was soon distributed, announcing a workshop to be held in late January 2009 aimed at investigating genetic mutations as relatively unexplored phenomena of interest in the history of biology. Throughout the twentieth century, we wrote, mutations have been at the heart of the sciences of heredity — from the publication of Hugo de Vries’ *Die Mutationstheorie* in 1901 to the rise of classical genetics, theoretical population genetics, molecular biology and beyond.

It seemed high time to explore that history.



Fig. 2: Hugo de Vries, with his beloved evening primrose, *Oenothera lamarckiana*, at the University of Chicago in 1904.

### *Gathering Mutants*

Since “mutation” itself is a very broad topic, some parameters for the scope of the conference we were called for. We decided to focus on the history of mutation from the publication of the mutation theory by de Vries, a *prima facie* seminal event, up to the advent of recombinant DNA technologies of 1970s when we felt the idea of mutation underwent further interesting transformations. We decided on the subtitle “Objects, Practices, and Contexts” as a sort of structuring device. The analytical approaches to the topic were thus envisioned to include the study of mutations as objects (mutants), as technical and social practices (mutagenesis, models, and networks), and in their many varied political and cultural contexts, from the dawn of genetics through the atomic era. As we wrote in the call for papers:

*Objects:* The place of mutants in the history of genetics has seemed thus far underestimated. Time and again geneticists used mutants to understand heredity: the mutant was that which violated the established order, the unexpected surprising element that was both anathema to conceptual order and yet central to experimental practices producing that order. At first unpredictable in their occurrence and form, attempts were repeatedly made in the first half of the twentieth century to

induce mutants at will, to control evolution, and to harness its power for human ends — with distinctly mixed results. Mutants often remained surprising and were sometimes dangerous, as were frequently the techniques used to produce them. Wily epistemic things, mutants provided always new, and yet always familiar, ways for heredity to jump out again as an unrestrained, unsolved phenomenon. Understanding mutants as objects, we wanted to suggest, can help us begin to more fully explore their central role in the history of biology of this period.

*Practices:* Mutants — and mutations more generally — proliferated throughout the first half of the twentieth century. Understanding the production, amplification, and domestication of mutation in this period entails close study of the varied manners and contexts of practice: from operative concepts and interpretations of mutation to specific techniques and moral economies. Engaging with mutants embedded in such practices, we envisioned, could perhaps help us to begin to unpack the relationships between “mutants” and “mutations” and those who dealt with them — and with each other.

In the study of transmission heredity, for example, the induction of mutations often entailed a mode of inquiry that included altering the environment partly by means of new tools: radium, X-rays, and chemicals. Such new tools existed in complex relationships with practices of characterizing and enumerating mutation: what was a mutation? How could one detect its occurrence? Moreover, the use of such mutation-inducing tools also points directly to relations with larger society: the use of radiation and chemical compounds is inextricable from broader processes of medicalization and industrialization in the first half of the twentieth century. The study of mutation as both object and practice thus also requires paying close attention to the ways in which social institutions, agricultural imperatives, eugenical concerns, clinical hopes, and industrial relations all aligned in particular configurations at particular junctures in time.

*Contexts and Connections:* No longer merely a nodal point in a network of small-scale specialist communities and practices, mutation thus came to embrace a variety of larger social concerns in times of world-historical change, from eugenical worries and matters of social welfare to the development of novel forms of risk assessment able to face a brave new mutagenic world. As the role of state governments proved central to the regulation of toxic mutagens, mutations were inherently part of a broader biopolitics, a situation that became ever more true with the dawning of the atomic age, fears of radioactive fall-out, the emergence of concepts of “genetic load,” and the far-reaching environmental policies of the nineteen-sixties. By mid-century, the environment was no longer merely a tool or a resource for the scientific study of mutation. Rather, broader social and industrial processes that made such novel mutagens available in the first place had turned the environment into an arena of urgent social alarm. But biopolitics operated at more conceptual and simultaneously explicitly “political” dimensions as well: in altering the hereditary substance by changing environmental conditions, for example, the use of mutagens placed dimensions of genetics in a complicated position with respect to questions of Lamarckism and challenges from Lysenkoism. Such macroscale dimensions of the history of mutation also remain in need of their histories.

### *Organizing Mutants*

A number of unusual “mutant” practices were employed in the organization of this conference. After the call for papers had been posted and distributed to several national and professional lists,

over two dozen abstracts were received by the conference organizers. Identifying information — the name and institutional affiliation of each person submitting — was removed from the abstracts, each of which was then circulated under in a numbered list to the members of the Cultural History of Heredity committee. As historians of science we were well aware of the power of networks in maintaining and distributing power in the production of knowledge, the benefits of hybrid vigor, and constructions of objectivity, and so this mechanism of peer review reflected a practical mix of all those insights. It was our hope to hear from — and include — especially the work of promising young scholars whose names were still unknown to us but whose voices would be welcome additions to the scholarly community of mutants. We also envisioned that by not directly inviting already distinguished scholars, but by asking them to likewise submit abstracts for consideration, that established senior scholars would find the conference an opportunity to propose novel (mutant?) takes on what might already be familiar material to them.

Both of these hopes came to be fulfilled. During the course of selecting 16 abstracts, it was abundantly clear to the committee which papers would be a good fit for the program. Work was then done to group the proposed papers into logical panels. When the names of the submitters were at last revealed, it was clear that the process had worked: a rich mix of junior and senior scholars from as far afield as Egypt and Japan, as well as both sides of the Atlantic, were invited to gather together to discuss the making of mutants. One of the committee members mentioned afterward that they thought we probably would have selected the same papers even if we had known the names and institutional affiliation of the submitters, but that the process simply felt better doing it this way. This, too, seems a benefit all around and a potential model for future such conferences.

### *Mutating Mutants*

A final mutation: although initially proposed as "Objects, Practices, Contexts" the conference in its final form reflected the submissions received and was structured around five main themes reflecting different epistemological aspects of the role of mutations. The papers in this volume, *mutatis mutandis*, are ordered so as to reflect the thematic structure used in the conference itself — we included, of course, only those papers and commentaries that the participants themselves ultimately decided to submit for this preprint:

- *Identifying Mutation*: Time and again geneticists used mutants as object to understand heredity but there was often a productive confusion about how to conceptualize mutations and how to speak about them.
- *Organisms*: The choice of organisms as models was crucial: e.g., whether mutations became instructions for a theoretical model of evolution or for changing silk worm industry.
- *Populations*: Eugenics and the visions of medical genetics are the most prominent examples for contexts and connections that were shaped by the history and epistemology of mutations.
- *Tools*: In terms of practice, mutations were at the very heart of the experimental activities of geneticists — but not *only* geneticists, as some of the papers showed.
- *Chemicals*: The invention of chemical mutagens marked a major shift not only in the methodology of inducing mutations, but in the concept and problematization — as somatic events connected to cancer — of mutations, too.

## *Thanking Mutants*

This conference would not have been possible without the magnanimous support of Hans-Jörg Rheinberger, and without the support, advice, and hard work of the Cultural History of Heredity group — namely, Christina Brandt, Bernd Gausemeier, and Staffan Müller-Wille. A special thanks indeed is offered to Antje Radeck, the department secretary, who did most of the administrative and logistical hard work in running the conference and housing and reimbursing our participants. And of course, our deepest gratitude to our fellow mutants, who from afar gathered together in Berlin in early 2009 to make mutations happen.

## *Identifying Mutation*



*Women in Mutation Studies:  
The Role of Gender in the Methods, Practices, and Results of Early Twentieth-  
Century Genetics*

*Marsha L. Richmond*

At the dawn of the twentieth century, biology was at a crossroads. For the past four decades, Darwin's theory of evolution had revolutionized research in many areas of the life sciences, leading to remarkable advances and generating optimism about future developments. Yet ironically the study of evolution was at a crossroads. Since Darwin's death in 1882, there had been intense intellectual wrangling among evolutionists over the efficacy of the central tenet of his theory — natural selection. Divided into a number of different camps, evolutionary biologists upheld various views about the mechanism that fueled evolutionary change.<sup>1</sup> Neo-Darwinists, bolstered by August Weismann's influential theory of the germ-plasm with its assumption of the complete sequestration of the germ-plasm from the somato-plasm, accepted the all-sufficiency natural selection and envisioned evolution much as Darwin had — as a gradual process of selection of small, adaptive variations. Adaptationists, like Ernst Haeckel, ascribed a greater role to the environment in producing advantageous variations, and hence fell more on the side of neo-Lamarckian modes of evolutionary change. Some American paleontologists, led by Edward Drinker Cope, believed in orthogenetic or directed evolution, citing phylogenetic evolution of groups like horses as evidence. Another major camp, the saltationists, began to look internally to the organism seeking the basis for evolution, pointing to the failure to find experimental evidence for either the impact of the environment in producing variation or of gradual evolution. In 1894 William Bateson, one of the most vocal advocates for “discontinuous” variation as the basis for speciation, provided an extensive catalogue of cases supporting this view in his book *Materials for the Study of Variation*.<sup>2</sup> As the new century dawned, it became increasingly clear that only through a better understanding of the nature of variation and heredity would the differences separating these factions be resolved.

Knowledge about the biological basis of heredity, however, had progressed only slightly since Darwin put forward his “provisional hypothesis of pangenesis” in 1868. To be sure, new developments in cytology after 1880 provided a deepening understanding of the cell and especially the nucleus and chromosomes that appeared promising in establishing the material basis for heredity, to which biologists responded by putting forward a variety of hereditary theories.<sup>3</sup> Yet cytologists could offer no experimental means of testing or advancing these theories, contributing

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<sup>1</sup> Peter J. Bowler, *The Eclipse of Darwinism: Anti-Darwinian Evolution Theories in the Decades Around 1900* (Baltimore and London: The Johns Hopkins University Press, 1983).

<sup>2</sup> William Bateson, *Materials for the Study of Variation Treated with Especial Regard to Discontinuity in the Origin of Species*, reprint, 1894 (Baltimore, MD: Johns Hopkins University Press, 1992), On Bateson's early views of variation, see Erik L. Peterson, “William Bateson from *Balanoglossus* To *Materials for the Study of Variation*: The Transatlantic Roots of Discontinuity and the (un)Naturalness of Selection,” *Journal of the History of Biology* 41 (2008): pp. 267–305, and Marsha L. Richmond, “William Bateson's Pre-Mendelian Study of Heredity and Development,” *History of Science Society* (Pittsburgh, 2008).

<sup>3</sup> Gloria Robinson, *A Prelude to Genetics: Theories of a Material Substance of Heredity, Darwin to Weismann* (Lawrence, KS: Coronada Press, 1979).

to the impasse in evolution studies. Only in the spring of 1900, following the rediscovery of Mendel's laws of heredity, did a few biologists begin to express optimism that an experimental approach may be at hand.<sup>4</sup> These hopes were significantly bolstered early in 1901 with the publication of the first volume of Hugo de Vries's *Die Mutationstheorie*.<sup>5</sup> The Dutch botanist believed to have identified a basis for the creation of new species.

Although one of the rediscoverers of Mendel, de Vries believed mutation theory was even more important for evolution studies than were Mendel's laws. Working with the evening primrose *Oenothera*, de Vries found that offspring of *O. lamarckiana* could be identified as new species. This led him to believe that new species could appear suddenly in a single generation by means of "mutation."<sup>6</sup> Recognizing that de Vries's views provided a challenge to Darwinian gradualism, neo-Darwinians attempted to dispute his claims. Nevertheless, de Vries and many other biologists, especially in the United States, viewed his findings as extremely promising in offering the opportunity to study evolution experimentally.<sup>7</sup> As de Vries told an American audience in 1904, "The direct observation of the mutations of the evening-primrose has changed the whole aspect of the problem at once. It is no longer a matter dealing with purely hypothetical conditions. Instead of the vague notions, uncertain hopes, and *a priori* conceptions, that have hitherto confused the investigator, methods of observation have been formulated, suitable for the attainment of definite results, the general nature of which is already known."<sup>8</sup> Finally, after a decades long stalemate and few prospects for mediating opposing philosophical positions over the tempo and mode of evolution, the advent of Mendelism and mutation theory gave early twentieth-century biologists new *experimental* tools to investigate the mechanisms guiding evolutionary change.<sup>9</sup>

Among those who enthusiastically embraced the potential de Vries's mutation theory offered for launching an experimental investigation of evolution was the American zoologist Charles Benedict Davenport (1866-1944). Davenport had long engaged with problems in heredity, and he was among the first biologists to herald Mendel's approach to hybridization studies.<sup>10</sup> While at Harvard and later at the University of Chicago, Davenport had sought an experimental approach

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<sup>4</sup> See, for example, William Bateson, *Mendel's Principles of Heredity: A Defense* (Cambridge: Cambridge University Press, 1902).

<sup>5</sup> Hugo de Vries, *Die Mutationstheorie: Versuche und Beobachtungen über die Entstehung von Arten im Pflanzenreich* (Leipzig: Veit, 1901–1903).

<sup>6</sup> de Vries, *Die Mutationstheorie: Versuche und Beobachtungen über die Entstehung von Arten im Pflanzenreich*. There is a wide literature on de Vries, but see especially the recent biography: Erik Zevenhuizen, *Vast in het spoor van Darwin: Biografie van Hugo de Vries* (Amsterdam and Antwerpen: Uitgeverij Atlas, 2008).

<sup>7</sup> Garland E. Allen, "Hugo de Vries and the Reception of the 'Mutation Theory,'" *Journal of the History of Biology* 2 (1969): pp. 55–87. Peter J. Bowler, "Hugo De Vries and Thomas Hunt Morgan: The Mutation Theory and the Spirit of Darwinism," *Annals of Science* 35, no. 1 (1978): pp. 55–73.

<sup>8</sup> Hugo de Vries, *Species and Varieties: Their Origin by Mutation*, 3d ed., trans. Daniel Trembly MacDougal (Chicago: Open Court Publishing Co., 1912), p. 686.

<sup>9</sup> See, for example, Roswell Hill Johnson's 1903 statement in his proposal to the Carnegie Institution of Washington to fund a Biological Experiment Station to Study Evolution: "Our knowledge of the processes of evolution has been greatly retarded by lack of experimental investigation. Nearly all of the post-Darwinian writing has been either largely deductive or else upon the variation of individuals at a particular time and place, i.e., static. Evolution, above all other things, requires dynamic studies." *Yearbook of the Carnegie Institution* 1 (1903): pp. 274.

<sup>10</sup> Charles Benedict Davenport, "Mendel's Law of Dichotomy in Hybrids," *Biological Bulletin* 2 (1901): pp. 307–310.

to evolution studies as early as the 1890s.<sup>11</sup> With the advent of Mendelism and mutation theory, he believed the time was at hand. Accordingly, in the prospectus he submitted to the Trustees of the newly created Carnegie Institution of Washington, in response to the March 1902 circular soliciting proposals for new scientific research institutes, Davenport proposed establishing a “Station for Experimental Evolution.” This he would erect at Cold Spring Harbor, New York near the site of the Brooklyn Institute’s Biological Laboratory, established in 1890 and under his direction since 1898.<sup>12</sup> Impressed by Davenport’s vision, the Carnegie Institution approved his proposal and provided the funds to create one of the first privately funded biological research institutes in the United States.

Appropriately enough, Davenport invited Hugo de Vries to deliver the scientific address at the opening ceremonies of the new institute on 11 June 1904. Introducing his distinguished guest, Davenport singled out de Vries’s work on mutation, stating, “During the last three years this great work that I hold in my hand has appeared, entitled “Die Mutationstheorie,” the most important work on evolution since Darwin’s “Origin of Species,” a work destined to be the foundation stone of the rising science of experimental evolution.” In his lecture “The Aims of Experimental Evolution,” de Vries referred to the research program on mutation to be carried out at Cold Spring Harbor and focused on advancing knowledge of the basis for mutation in his beloved *Oenothera*:

Ladies and gentlemen, it is a high honor for me that this laboratory has been founded, and that the members of the board and the director have invited me to be its godfather. During a long series of years I have fostered my conception of sudden mutability and cultivated my primroses for myself and for myself only. Some years ago I allowed myself to be induced to betray my secret and to deliver it to the scientific world. It has at once been taken up by your countrymen, and the foundation of this laboratory is the mightiest and most dreadful competition that I could have. I have to give up security and freedom, quietness and calmness, and all that secrecy which I so dearly loved. I have to submit to the prospect of being soon surpassed and largely excelled on the path which until now I considered as my own. I have to yield my much beloved child. But I do it gladly and without regret. It is the interest of the child itself which commands me. It will be better in your hands, Mr. and Mrs. Davenport, and in yours, lady and gentleman officers of the staff. Pray have good care of it and educate it assiduously, that it may become one of the most brilliant parts of your work, a glory to this laboratory and to the institution that founded it, a pride to your country, and a bliss for humanity.<sup>13</sup>

In this ceremonious manner, de Vries thus endorsed the new Cold Spring Harbor Station as a major locus for pursuing a systematic study of mutation.

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<sup>11</sup> His former student during his years at Harvard, Roswell Hill Johnson, in his own proposal to the Carnegie Institution, noted: “I remember that Professor Davenport in his course on evolution at Harvard made a strong plea for experimental work.” *Year Book of the Carnegie Institution of Washington* 1 (1903): p. 275.

<sup>12</sup> John C. Burnham, “The Progressive Era Revolution in American Attitudes Toward Sex,” *Journal of American History* 59 (1973): pp. 885–908.

<sup>13</sup> Hugo de Vries, “The Aim of Experimental Evolution,” *Year Book of the Carnegie Institution* 2 (1904): pp. 39–49, on p. 48, p. 49.

## *Staff of the Station for Experimental Evolution*

The “lady and gentlemen officers” to whom de Vries referred were the three investigators Davenport had appointed to form the staff of the new institute. This included the entomologist Frank E. Lutz (1879-1943), the botanist George Harrison Shull (1874-1954), and the cytologist Anne May Lutz (1871-1938, and no relation of Frank Lutz). All were young researchers Davenport had either known at Harvard or Chicago, and who were eager to advance the experimental investigation of evolutionary problems.

Davenport’s intention to focus on mutation among the expressed research aims of the new Station was clear from the outset. He began collaborating with Daniel Trembly MacDougal (1865-1958), director of the New York Botanical Gardens and also supported by the Carnegie Institution of Washington, who had already commended a taxonomic study of *Oenothera* using seeds provided by de Vries.<sup>14</sup> The first growing season *Oenothera* was sown by George Shull in newly prepared plots at Cold Spring Harbor, while Frank Lutz investigated the fruit fly *Drosophila* as well as the field cricket *Gryllus*, and Anne Lutz, also charged with helping Davenport with administrative correspondence, surveyed a number of different organisms with an eye to finding a suitable object in which to study the cytological basis of variation.

### — Women in Early Genetics —

In selecting a woman as one of the Station’s initial investigators, Davenport reflected social developments that were changing the nature of biological investigation through the entry of women into academic biology. Having gained entrance to higher education beginning in the late 1860s, women by the end of the nineteenth century were graduating from universities around the world with not only B.S. degrees but also advanced degrees in biology. While few women held a Ph.D. in 1900, many had received excellent university training in the life sciences and were qualified to fill open positions in scientific establishments such as that offered by Davenport.<sup>15</sup> Anne Lutz is a good case in point. A native of Shady Grove, Indiana, Lutz had received a bachelor’s degree from nearby Purdue University in 1890 (graduating in only three years) and a master’s

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<sup>14</sup> Davenport noted this collaboration in the first annual report to the Executive Committee of the Carnegie Institution of Washington, stating the intention “to determine the exact relation of the mutants to their parent form and their agreement or disagreement with known laws of variation and heredity.” Michael Gordon, “From Unfortunate Necessity to a Cult of Mutual Orgasm: Sex in Marital Education Literature, 1830–1940,” in *Studies in the Sociology of Sex*, ed. James Henslin (New York: Appleton-Century-Crofts, 1971), pp. 56–67, on 31. See also Sharon E. Kingsland, “The Battling Botanist: Daniel Trembly MacDougal, Mutation Theory, and the Rise of Experimental Evolutionary Biology in America, 1900–1912,” *Isis* 82 (1991): pp. 479–509.

<sup>15</sup> Margaret W. Rossiter, *Women Scientists in America: Struggles and Strategies to 1940* (Baltimore and London: The Johns Hopkins University, 1982). Although in the 1890s “less than 2 percent of American women graduated from college,” this number increased significantly after 1900, with the passing of the “pioneer phase” of women’s education and the reduction of cost associated with expansion in the number of colleges and universities. See Rosalind Rosenberg, *Beyond Separate Spheres: Intellectual Roots of Modern Feminism* (New Haven, CT: Yale University Press, 1982), p. 182, p. 207. Prior to 1900, only about twenty American women had earned a doctorate in botany, zoology, or physiology, primarily from European universities. W. C. Eells, “Earned Doctorates for Women in the Nineteenth Century,” *Bulletin of the American Association of University Professors* 42 (1956): pp. 644–51.

degree in biology the following year.<sup>16</sup> She then transferred to Ann Arbor, where she enrolled in the University of Michigan. Michigan offered a special program in biology that provided a rigorous course of studies designed “for students who wish to devote their time largely to biological work, either as a preparation for the study of medicine or with a view to teaching or engaging in biological research.”<sup>17</sup> Upon graduation in 1893, Lutz was employed as a cytologist, first at Columbia University and then at the newly opened University of Chicago where she assisted William Lawrence Tower, a former student of Davenport’s at Harvard who was hired at Chicago upon Davenport’s recommendation.<sup>18</sup> It was apparently in this connection that Davenport became aware of Lutz’s work.

Davenport interviewed Lutz concerning working at the new Station for Experimental Evolution in December 1903, but she was hesitant about accepting the position. One drawback was its low salary. Certainly one of the reasons Davenport reached out to young, not yet established researchers was because they were more likely to accept the modest salary he could offer. As a single woman, Lutz needed to support herself without requiring outside subsidy. Moreover, as an unmarried daughter with aging parents, she had the social obligation to care for them should their health fail.<sup>19</sup> Davenport, however, satisfied both her concerns. He raised the salary he initially offered slightly and assured her that she could leave at short notice should this become necessary. Lutz thus decided to accept his offer.<sup>20</sup> Certainly she recognized that it was attractive. Other than teaching in one of the women’s colleges, few opportunities existed at the time for a woman to work in science.<sup>21</sup> Thus it was that Lutz arrived at the new laboratory on 1 May 1904, taking charge of all the initial details of its opening in consultation with Davenport, who remained in Chicago completing his final semester of university teaching. Although heavily involved in planning for the

<sup>16</sup> Information provided by Sammie L. Morris, Purdue University Archivist.

<sup>17</sup> *Calendar of the University of Michigan for 1892-93* (Ann Arbor: University Press, 1893), p. 113.

<sup>18</sup> Carnegie Institution of Washington, Archives: Genetics: Director, Charles B. Davenport, 1902-1931, Folder 3: Davenport to R. S. Woodward, President of the Carnegie Institution, 2 August 1917. See also Anne May Lutz to C. B. Davenport, 4 January 1904, and 13 January 1904, Charles Benedict Davenport Papers, Series I: Correspondence, American Philosophical Society (APS), Philadelphia; hereafter “Davenport Papers, APS.”

<sup>19</sup> Martha Vicinus, *Independent Women: Work and Community for Single Women, 1850–1920* (Chicago: University of Chicago Press, 1985).

<sup>20</sup> Lutz’s initial salary was \$750 per annum (Carnegie Institution of Washington Archives, Genetics: Employees, 1904-1916). Davenport described her qualifications in a letter to the Executive Council of the Carnegie Institution: “For the present year it is recommended that Miss Anna M. Lutz, a graduate in Biology in the University of Michigan and some time cytological preparator at Columbia and Chicago Universities shall be appointed to serve from May first at the rate of \$750, for a year’s work with one month’s vacation. Miss Lutz is remarkable as a cytological preparator. She has already been seen with reference to this matter and has promised to give a reply soon.” (Carnegie Institution of Washington Archives, Genetics: Director, Charles B. Davenport, 1902-1931, Folder 3). For details about the negotiations over Lutz’s appointment, see the Charles Benedict Davenport Papers, B: D27, Series I: Correspondence, American Philosophical Society Library, Anne May Lutz correspondence, letters from Lutz to Davenport, 4 January 1904, Davenport to Lutz, 9 January 1904, and Lutz to Davenport, 13 January 1904.

<sup>21</sup> A good case in point is the noted embryologist Julia B. Platt (1857-1935), who despite having received a Ph.D. under August Weismann in 1898 and widespread recognition for her original research on the neural crest undertaken at Wood’s Hole and other marine biological stations, was unable to find a teaching position and was forced to leave science in 1899. Steven J. Zottoli and Ernst-August Seyfarth, “Julia B. Platt (1857–1935): Pioneer Comparative Embryologist and Neuroscientist,” *Brain Behavior and Evolution* 43 (1994): pp. 92–106.

elaborate opening ceremony in early June, she also set up her workspace with the new equipment she requested, including “two compound microscopes and two dissecting microscopes, one Minot microtome, paraffin bath, the necessary glassware for cytological work, and a full laboratory equipment.”<sup>22</sup> By the fall of 1904, Lutz and the other researchers at the Station for Experimental Evolution were well underway pursuing their research at Cold Spring Harbor.



Anne May Lutz (1871-1938)

### *Research Program of the Station for Experimental Evolution*

Davenport laid out his vision of the research to be carried out at the new institute in the proposal he submitted to the Carnegie Institution Trustees in May 1902.<sup>23</sup> Although not mentioning them by name, he aimed to carry out an experimental study of evolution using the new techniques offered by both Mendel and de Vries:

1. AIMS. The aims of this establishment would be the analytic and experimental study of the causes of specific differentiation, — of race change.
2. METHODS. The methods of attacking the problem must be developed as a result of experience. At the present the following seem most important:

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<sup>22</sup> Lutz’s initial job description included “the cytological phenomena of heredity and partly keeping the administrative records of the correspondence of the station”; see *Year Book of the Carnegie Institution*, 3 (1904), p. 27. Charles Benedict Davenport, “First Report of Station for Experimental Evolution under Department of Experimental Biology,” *Year Book of the Carnegie Institution of Washington* 3 (1904): p. 26.

<sup>23</sup> Charles B. Davenport, “Biological Experiment Station for Studying Evolution,” *Year Book of the Carnegie Institution of Washington* 1 (1902), pp. 280-282. Anonymous obituary, 21 February 1944; Cold Spring Harbor Archives, Carnegie Institution of Washington: Davenport, Charles, Biographical Material, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York.

- (a) Cross-breeding of animals and plants to find the laws of commingling of qualities. The study of the laws and limits of inheritance.
- (b) The experimental production of variation — both by internal operations, such as hybridization, or by change of external conditions.
- (c) Study of normal variation, especially as associated with changes in habit and with geographical distribution, — the effects of isolation.
- (d) Experimental study of the effects of selection and of the origin of adaptation in organisms. Does morphological adaptation precede or follow change of habitat?<sup>24</sup>

As was clear in his decision to hire a cytologist among the first staff members, Davenport recognized from the outset the value of combining breeding studies with a study of the cell, as he indicated in his 1907 report to the Carnegie Institution:

Certain portions of that unending stream of reproductive matter which has come down to us from the time when life began on earth and by changes in which all evolution has taken place are now under our careful observation and to a large extent under our control. It is the business of the Department of Experimental Evolution to study the behavior of this germ-plasm and to note its reaction to the conditions we impose. ... Using, with proper care, the soma as the analysis of its germ-plasm, we seek to study the origin of changes in germ-plasms. First, we have paid attention to cases where, it is alleged, the germ-plasm is undergoing a sort of natural, one might say spontaneous, change.<sup>25</sup>

Although Davenport clearly had in mind a study of the basis of mutation, in emphasizing the importance of studying possible changes in the “germ-plasm,” he made the Station the first genetics research institute to combine cytological research with genetic analysis. Moreover, the kind of work he envisioned was not simply descriptive but instrumental, given that any chromosomal changes were to be investigated by following up through controlled breeding experiments.

Because half of her time was initially devoted to secretarial duties, Lutz was unable to launch a focused program of research. She nonetheless well understood the nature of her charge. In the first annual report submitted at the end of 1904, Lutz described her scientific activities of the past eight months, stating, “As a preliminary step to the study of the germ plasms of hybrid plants and animals, it seemed advisable to spend a considerable portion of the present year in making a general survey of the field about us, with a view of discovering such forms native to this locality as might present desirable cytological qualities for future hybridization experiments.” She initially chose insects as her experimental material, a decision that may have reflected both the availability of specimens provided by Frank Lutz as well as the interesting new data coming from cytological investigations underway in the United States.<sup>26</sup> She had rather modest expectations, however, of what the study of chromosomes might portend:

It is naturally to be anticipated that much of the work of the cytologist will apparently come to naught, as it may be presupposed that the chromosomes of closely related forms in the vast

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<sup>24</sup> Carnegie Institution of Washington, Archives, Washington, D. C. Genetics: Director, Charles B. Davenport, 1902-1931, Folder 3.

<sup>25</sup> C. B. Davenport, “Department of Experimental Evolution,” *Year Book of the Carnegie Institution* 7 (1908): p. 86.

<sup>26</sup> The seminal chromosome studies of Nettie Marie Stevens, for example, which led to establishing the existence of sex chromosomes, were done on coleoptera, some of this work having been carried out at the Biological Laboratory at Cold Spring Harbor during the summer of 1906.

majority of cases will be found similar in size, shape, and number; but work will be continued independently and in connection with the experiments being carried on by other members of the staff, and if from among many failures an occasional result may be obtained which will throw new light upon the question of inheritance, the reward will be ample.<sup>27</sup>

She soon discovered, however, that her assumption that chromosome morphology would be similar in closely related forms was quite mistaken. Not only did she arrive at a more complicated understanding of the relationship between chromosome number and variation than either she or anyone else had predicted, but the pursuit of this problem would form the basis of her scientific work for the remainder of her career. Indeed, her findings more than amply rewarded her in throwing new light not only on “the question of inheritance,” but also the nature of mutation.

— *Oenothera* Studies —

The research program carried out on the evening primrose at Cold Spring Harbor was multifaceted. Shull had grown *Oenothera* varieties with the aim of determining “the exact relation of the mutants to their parent form and their agreement or disagreement with known laws of variation and heredity.”<sup>28</sup> In addition to studying whether mutants displayed normal patterns of Mendelian inheritance, Shull focused on another aspect of the de Vriesian research program: investigating different kinds of variation. As he explained, given that “variations are of two kinds, mutations and fluctuations, both of which doubtless have important bearing upon evolution, the study of variation resolves itself into (1) a search for mutations, and (2) the investigation of the causes, modification, and fixation of fluctuating characters.” He thus cultivated 48 different pedigree-cultures of *Oenothera*, including *O. gigas*, *lamarckiana*, *lata*, *nanella*, and *rubrinervis*. Combining this with a biometrical analysis of heredity, Shull’s research centered on trying to determine “whether or not there is any tendency on the part of the mutants to regress toward the parental condition.”<sup>29</sup> Regression would indicate that mutation was not, as de Vries suggested, a permanent condition, but rather a phenomenon produced through hybridization.

Lutz did not initially join in Shull’s study of *Oenothera*. In her report of 1905, she stated that she was continuing to “search for the interpretation of the laws of heredity in the germ glands of various plants and animals,” primarily studying insect material provided by Frank Lutz. In 1906, having been relieved of her secretarial work, she devoted herself “wholly to investigation,” primarily studying infertility in buckwheat.<sup>30</sup> The following year, however, she began focusing on

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<sup>27</sup> *Year Book of the Carnegie Institution* 3 (1904): pp. 32-33.

<sup>28</sup> George H. Shull, Report, *Year Book of the Carnegie Institution* 3 (1904): p. 31.

<sup>29</sup> George H. Shull, Report, *Year Book of the Carnegie Institution* 4 (1905): p. 98. As Davenport indicated to members of the Carnegie Institution Executive Committee in 1904, he intended to appoint to the staff “a Biometrician who shall study Variation quantitatively and measure the results of experimentation,” and that Frank Lutz had applied for this position. Carnegie Institution of Washington Archives, Genetics: Director, Charles B. Davenport, 1902-1931, letter to the Executive Committee, 2 January 1904.

<sup>30</sup> Charles B. Davenport, “Biology, Experimental. Department of Experimental Evolution, Cold Spring Harbor, New York,” *Year Book of the Carnegie Institution of Washington*, 5 (1906): p. 96. The significance of Lutz’s early researches is provided in the publication celebrating twenty-fifth anniversary of the Station’s founding: “Miss Anne M. Lutz was able to give only a part of her time to cytology since she served as secretary to the Director. She made important contributions to the problem of the intersterility of types of buckwheat having different forms of flower. She also discovered that the eggs of the insect *Gastroidea* would develop without fertilization.” See “Research Contributions of the Staff of the Department of Genetics, Carnegie Institution of Washington, During Twenty-five Years,” (1929);

what Davenport noted was “most important definite question to answer,” namely, “How may the course of the stream of germ plasm that has come down to us from remote ages be controlled in its onward course?”<sup>31</sup> She did so by focusing on the cytology of *Oenothera* species and varieties.

### *Lutz's Study of Oenothera*

An early description of Shull's and Lutz's work on *Oenothera* was provided in a newspaper article written by one of Davenport's former students at Harvard, John Hiram Gerould, who particularly noted the Station's focus on mutation studies — its de Vriesian origins and the challenge this theory posed to Darwinian evolution:

But De Vries, working upon the evening primrose in the fertile fields and rich gardens of Amsterdam, did not exhaust the possibilities of its mutation when grown on other soils, under other climatic conditions, so Dr. Shull and Miss Lutz of the Carnegie Laboratory have planted here seed of several of De Vries' young species or mutants, and by the crossing of one form with another, or by spontaneous mutation of the parent form, have obtained still other novelties. Miss Lutz, applying the latest methods of microscopic anatomy to the cells of the root-tips and to the pollen grains of the young species, has discovered that even the contents of the cells have been sensibly changed by the process of mutation, and have taken on new and easily recognized characteristics.<sup>32</sup>

It is not clear what prompted the decision, but Lutz began working on *Oenothera* cytology in January 1907, using cultures grown in 1906.<sup>33</sup> Lutz first examined somatic cells, intending to become familiar with *Oenothera* chromosomes before examining the germ cells. However, finding that she could count the number of chromosomes more easily in root-tips of pot-bound plants in the rosette stage than from germ cells, as she noted in her annual report for 1907, this had “proven a subject of such unexpected interest ... that work will be continued, for the present at least, upon

Carnegie Institution of Washington Archives, Washington.

<sup>31</sup> C. B. Davenport, “Department of Experimental Evolution,” *Year Book of the Carnegie Institution* 6 (1907): p. 76.

<sup>32</sup> See John H. Gerould, “To Improve the Race. Aims of the Carnegie Laboratory on Heredity. The Remarkable Institution at Cold Spring Harbor Now First Described--The Principles of Evolution Being Observed from Plants, Animals and Human Beings--All with the Object of Deducing Laws to Eliminate Defectives from Our Race--A Wonderfully Thorough Study Being Made of the Theories of Eugenics” (p. 4); the clipping is not dated, nor is the newspaper identified, but from the reference to Lutz's work, it must have been written after 1907. See Charles Benedict Davenport Papers, Series II: Station for Experimental Evolution, Folder: History, American Philosophical Society, Philadelphia. On Gerould's scientific work, see Kale S. Bongers, “Eugenics at Dartmouth College: John Hiram Gerould and Human Heredity,” *Dartmouth Undergraduate Journal of Science* (2007): pp. 24–26.

<sup>33</sup> After Lutz began to be recognized for her discovery of polyploidy, Reginald Ruggles Gates claimed that she began her work only after learning about his own investigations on *Oenothera* chromosomes late in 1906. As Gates told Davenport in a letter of 9 March 1921, “I think the world knows that I was the first to make this discovery [announced at the New York meeting of the American Association for the Advancement of Science in December 1906] ... and it was only *after this* that Miss Lutz at your suggestion germinated seeds of *Oenothera* & examined the seedling root-tips in various forms, as a result of my prior discovery.” Davenport Papers, APS, R. Ruggles Gates correspondence. From a letter Lutz wrote to Davenport in October 1907, however, it appears that her first cytological slides were prepared from cultures grown in 1906, presumably by Shull. Shull was actively participating in *Oenothera* research along with MacDougal and may have encouraged Lutz to make a cytological study of this material. See D. T. MacDougal, A. M. Vail, G. H. Shull, and J. K. Small, J. K., *Mutants and Hybrids of the Oenotheras* (Washington, D. C.: Carnegie Institution of Washington, 1905).

somatic tissue exclusively.”<sup>34</sup> In October 1907 Lutz spent a month at the New York Botanical Garden helping Charles Stuart Gager, who, like MacDougal, was an ardent supporter of de Vries’s mutation theory. In this context he was carrying out a study of the impact of radiation on changing the germ plasm.<sup>35</sup> He asked Lutz to analyze the germ cells of the *Oenothera* plants he was treating.<sup>36</sup> By the end of 1907, then, Lutz was completely engrossed in an investigation of the chromosome numbers of various species of *Oenothera* and the attempt to link these to external morphology, a subject that dominated her attention for the next decade.

Lutz’s first publication of this work came in early August 1907, when a preliminary note appeared in *Science* announcing the finding of double chromosome numbers of *Oenothera gigas* compared to *O. lamarckiana*. As she noted, “The exceptional opportunities offered at this station for a study of inheritance as manifested in the germ cells of the *Oenotheras* led me to undertake a study of the chromosomes of *Oenothera Lamarckiana*, its mutants and hybrids.”<sup>37</sup> While she hesitated to state definitely what the number of each form was, her counts indicated that *O. Lamarckiana* had “fourteen or fifteen” and *O. gigas* “twenty-eight or twenty-nine.” In addition to this interesting finding, she noted that, “Other points of interest are coming to light, particularly in connection with the hybridization of mutants, and will be mentioned in a later note.”<sup>38</sup> The “unexpected interest” noted in her annual report thus came from finding that *Oenothera gigas* had double the number of chromosomes found in *O. lamarckiana*, the first public recognition of polyploidy in *Oenothera*. This was a notable discovery indeed. For one thing, it sensitized biologists that cytology may soon offer insights into the nature of mutation as in some way connected with chromosome number or chromosomal changes.

A couple of weeks after this notice appeared, Lutz and other staff members attended the Seventh International Congress of Zoology held in Boston. At this meeting a section on heredity was organized for the first time, and Lutz presented a paper summarizing her work to date. In the published version, entitled “A Study of the Chromosomes of *Oenothera Lamarckiana*, its Mutants and Hybrids,” Lutz pointed out the exceptional conditions the Station for Experimental Evolution offered for undertaking such a study, given that “pedigreed cultures derived from pure bred seed obtained from de Vries and McDougal, had been grown ... for three generations.”<sup>39</sup> Stating she had undertaken this work “with no ambition to confirm or overthrow any preconceived ideas concerning the behavior of the chromosomes,” Lutz noted that one of the most interesting points discovered to date was the “*indication of variation in the number of chromosomes found within*

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<sup>34</sup> Anne M. Lutz, “Cell-studies in Heredity,” *Year Book of the Carnegie Institution* 6 (1907): p. 78. To determine chromosome number, she primarily used metaphase figures, “the only satisfactory stage for the determination of chromosome number in root tips of *Oenothera*” (Anne M. Lutz, “*Oenothera* Mutants with Diminutive Chromosomes,” *American Journal of Botany* 3 [1916]: p. 513).

<sup>35</sup> On this work, see Kingsland, “The Battling Botanist: Daniel Trembly MacDougal, Mutation Theory, and the Rise of Experimental Evolutionary Biology in America, 1900–1912”; David Magnus, “Theory, Practice, and Epistemology in the Development of Species Concepts,” *Studies in the History and Philosophy of Science* 27 (1996): pp. 521–545; and Luis A. Campos, “Radium and the Secret of Life” (Ph. D. diss., Harvard University, 2006), chap. 3.

<sup>36</sup> C. B. Davenport, “Department of Experimental Evolution,” *Year Book of the Carnegie Institution* 6 (1907): p. 83.

<sup>37</sup> Anne M. Lutz, “A Preliminary Note on the Chromosomes of *Oenothera Lamarckiana* and One of Its Mutants, *O. Gigas*,” *Science* 51 (2 August 1907): p.151; italics in original.

<sup>38</sup> *Ibid.*, 152.

<sup>39</sup> Anne M. Lutz, “A Study of the Chromosomes of *Oenothera Lamarckiana*, Its Mutants and Hybrids,” in *Proceedings of the 7th International Zoological Congress, 1907* (Boston: Harvard University Press, 1912), p. 352.

*different plants of the same species.*<sup>40</sup> Such a finding was totally at odds with her initial expectations, and was a point she intended to follow up in future work.

Having ventured into cytological *terra incognita* with her discoveries, Lutz was relieved to hear the renowned Columbia cytologist Edmund Beecher Wilson mention similar points in one of two papers he gave at the congress. Wilson, too, cited recent findings indicating that “nearly related species or even varieties of the same species may show marked differences in the number and size-relations of the chromosomes.” Reflecting on this, Wilson noted that such “a difference in the chromosomes must involve some kind of constitutional difference between the two forms, and it seems possible that sufficiently careful observation may reveal corresponding physiological if not morphological differences.”<sup>41</sup>

Lutz interpreted this as support for the provisional hypothesis that chromosome number may not be an essential feature defining a species after all. As she told Davenport, “I am coming more and more to realize that our knowledge concerning the behavior of the germ cells in even the best known groups of the animal kingdom is far too meager to warrant the deductions and conclusions we are attempting to make. Some one collects a number of beetles from a restricted locality and reports the number of chromosomes for the species which these few specimens represent to be a certain definite number; but what light has he had, for example, upon the range of variability within the species — if his collection has been so limited? From the evidence continually coming to light in my own work — and from the grudgingly admitted evidence of other workers I am finding that we may find chromosome number as variable a character as any other when our knowledge upon this subject becomes more extended; at any rate this question is of first importance and must be looked into before any conclusions concerning the behavior of the germ cells can be of value.”<sup>42</sup> Although technical difficulties in determining the precise number of chromosomes in *Oenothera* species no doubt promoted such a supposition, that Lutz could entertain such an idea indicates how fluid was her notion about the significance of the chromosomes at the time. She did, however, find evidence to associate chromosome numbers with particular morphological characteristics. Indeed, she even noted that the presence of particular chromosomes could be used to predict certain morphological features, a finding of practical import since it provided a means of predicting chromosome numbers in various *Oenothera* forms without having to carry out a time-consuming and tedious cytological analysis.

Lutz’s publications delighted Davenport, not only from an intellectual but also from an administrative perspective. He well understood that the Station’s annual budget largely depended upon a steady stream of results to justify the outlays from the Carnegie Institution’s endowment. In his annual reports to the Trustees, Davenport did a masterful job trying to place the work carried out at the Station in a historical and disciplinary perspective understandable by non-biologists. Lutz’s discoveries along with Shull’s breeding work prompted him to wax eloquent on the importance of focusing on the “germ-plasm” as part of the overall research program of the Station:

Using, with proper care, the soma as the analysis of its germ-plasm, we seek to study the origin of changes in germ-plasms. First, we have paid attention to cases where, it is alleged, the germ-

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<sup>40</sup> Ibid., p. 353; italics in the original.

<sup>41</sup> Edmund Beecher Wilson, “Differences in the Chromosome-Groups of Closely Related Species and Varieties, and Their Possible Bearing on the ‘Physiological Species,’” in *Proceedings of the 7th International Zoological Congress, 1907* (Boston: Harvard University Press, 1912), pp. 347–348.

<sup>42</sup> Lutz to Davenport, 5 September 1907, Davenport Papers, APS.

plasm is undergoing a sort of natural, one might say spontaneous, change. The most famous case of this is that of the evening-primrose, to which de Vries called attention. We are breeding evening-primroses extensively, and some of the results of our work have been published in conjunction with studies made by Dr. MacDougal. The capacity of this wonderful plant for inciting investigations upon itself seems unlimited. We have only begun an era of investigation into its germ-plasm; and in this plant the structure of the germ-plasm of different species exhibits peculiarities that can readily be seen with the microscope. Miss Anne M. Lutz has devoted much time to the study of the stainable bodies (chromosomes) of the various species and has found the number to vary greatly, as, e.g., 14, 15, 28, 29, 30. When a species with 15 chromosomes is crossed by one having 30 the hybrid offspring have 22, being half-way between the parental numbers, but a few show the ancestral group numbers of 15 and 30 again. *The structures in the germ-plasm are thus inherited exactly like the somatic characters; and this is the first time that such parallelism has been traced.*<sup>43</sup>

This line of work, in other words, suggested a connection between chromosomes and de Vriesian mutational events, and thus was precisely the kind of advance Davenport encouraged, and indeed pressed for, among his staff members.

Davenport wasn't the only one to express great interest in Lutz's results. William Bateson, who had heard Lutz's paper at the Boston Congress and talked to her when he visited Cold Spring Harbor afterwards, was quite interested in the association of different chromosome numbers and alternative characters. He wrote his student Nora Darwin (following her famous grandfather by studying the genetics of heterostylism in the primrose *Oxalis*) from the United States, suggesting that the different lengths of styles might likewise be associated with differing chromosome numbers. "You ought at once to get on to the cytology," he advised Darwin. "Probably you will find the chromosome number of the mids higher than (? double) that of the longs. I have seen wonderful cases of this in *Oenothera* here prepared by Miss Lutz (*Science* or *Bot. Gaz.* about June or July '07). Also *Gates. Bot. Gaz.* Feb. '07 Try the root-tips. ... If you can't do it I will ask Miss Lutz to try, but I think you ought to do it. I shall have plenty of seed, & probably we could raise plants any time in green house."<sup>44</sup>

De Vries was also quite excited by Lutz's work. He wrote Davenport in December 1907, stating, "Please tell miss Lutz that I enjoyed the discovery of the double number of chromosomes in *Oenothera gigas* immensely. You know that, to my mind, the origin of the *gigas* is the one absolutely typical case of species-formation in all my cultures."<sup>45</sup> The following year he publicly recognized this work, stating, "The hybrids of *Oenothera gigas* have since gained an entirely special interest through the discovery of Miss A. Lutz in Cold Spring Harbor," and noting that her findings had since been confirmed by R. Ruggles Gates and his own student J. M. Geerts.<sup>46</sup> It is

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<sup>43</sup> C. B. Davenport, "Department of Experimental Evolution," *Year Book of the Carnegie Institution* 7 (1908): p. 86, pp. 87-88; emphasis mine.

<sup>44</sup> William Bateson to Emma Nora Darwin, 24 August 1907, Darwin Family Papers, Add. 8904.1: 1701-1750, Manuscripts Room, Cambridge University Library, Cambridge. For Bateson's direction of the work of geneticists at Cambridge, including that of Emma Nora Darwin (later Barlow), see Marsha L. Richmond, "Women in the Early History of Genetics: William Bateson and the Newnham College Mendelians, 1900-1910," *Isis* 92 (2001): pp. 55-90, and Marsha L. Richmond, "The 'Domestication' of Heredity: The Familial Organization of Geneticists at Cambridge University, 1895-1910," *Journal of the History of Biology* 33 (2006): pp. 565-605.

<sup>45</sup> De Vries to Davenport, 31 December 1907, Davenport Papers, APS. De Vries in fact believed that *gigas* was the only true "progressive" mutation in *Oenothera*. See Hugo De Vries, "Mutations in Heredity [1912]," in *The Rice Institute Pamphlet*, vol. 1 (Houston: Rice Institute, 1915), pp. 518-570, on p. 557; for the German edition, see also Hugo de Vries, "Die Mutationen in der Erblchkeitslehre," in *Hugo de Vries Opera e Periodicis Collata*, vol. 7 vols. (Utrecht: The Netherlands: A. Oosthoek, 1912), pp. 515-50.

<sup>46</sup> Hugo de Vries, "Bastarde von *Oenothera gigas*," *Berichte der Deutschen Botanischen Gesellschaft* 36a

evident, then, that Lutz's discovery caused a considerable stir among geneticists, prompting them to think about the connection between chromosome numbers and mutation as well as other phenomena associated with variation.

Lutz continued this line of work the following year, investigating polyploidy in *O. gigas* by studying "the behavior of chromosomes in inheritance by crossing *gigas* with a form having the smaller number." The results, however, were somewhat disappointing. She was only able to obtain three offspring from a cross between *O. gigas* and *O. lata*. Nonetheless, these plants showed "such remarkable combinations of chromosomal and vegetative characters that it was decided to repeat the cross upon a larger scale the following season."<sup>47</sup> Despite the considerable difficulty involved in artificially pollinating the *gigas* x *lata* hybrid owing to low pollen count, she collected enough seeds to be able to analyze the second generation in 1909. In addition to her cytological work, she also carried out observations of a more purely botanical nature, following up suggestions de Vries made in his opening address of 1904 that the "mutable strain itself" needed to be studied. Given that not all seeds produce new species, "Thence the question, Which seeds mutate, and by which causes are they elected to do so? The location of the mutating seeds within the fruit, the position of the preferred fruits on the spikes, the influence of the individual strength of the sundry branches, and many other points have to be investigated."<sup>48</sup> Accordingly, Lutz attempted to correlate a plant's cytological makeup with its morphological characters, carrying out measurements of buds, flowers, and leaves, and tracing the plant's branching configuration. Such work, however, was tedious. She claimed that she recorded observations of "vegetative characters" continuously between 5:00 am until 7:30 pm for two months during the summer flowering season.

### *Lutz's Exchanges with R. R. Gates*

Despite Lutz's claim that she came to this topic with no theoretical preconceptions, this was not exactly true: she interpreted her results through the lens of de Vries's mutation theory. This allegiance is particularly revealed in the manner in which she analyzed her own results as well as those of the Canadian botanist Reginald Ruggles Gates (1882-1962). While working on his Ph.D. at the University of Chicago, Gates initiated a cytological study of *Oenothera* during the summer of 1905 while at the Marine Biological Laboratory at Wood's Hole and with the encouragement of the botanist Bradley Moore Davis.<sup>49</sup> He subsequently continued this work both at the MBL and Chicago.<sup>50</sup> Unlike Lutz, Gates preferred working on the germ-cells, finding somatic chromosomes to be "much smaller and less satisfactory to deal with than in the germ cells." At the 1906 Christmas meeting of the American Association for the Advancement of Science in New York,

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(1908):pp. 754–62.

<sup>47</sup> Anne M. Lutz, "Cell Studies in Heredity," *Year Book of the Carnegie Institution of Washington* 7 (1908): p. 95.

<sup>48</sup> Hugo de Vries, "The Aim of Experimental Evolution," in *Year Book of the Carnegie Institution of Washington*, vol. 3 (Washington, D.C.: Carnegie Institution of Washington, 1904), pp. 39–49, on p. 48.

<sup>49</sup> Davis had written to Davenport in July 1904 to inform him about his intention "to deal chiefly with the wild forms and their relationships. I do not intend to publish anything this summer but thought I should like to get a few men whom I know interested in the work." B. M. Davis to Davenport, 14 July 1904, Davenport Papers, Series I, American Philosophical Society. Davis apparently interested Gates in this work.

<sup>50</sup> J. A. Fraser Roberts, "Reginald Ruggles Gates. 1882–1962," in *Biographical Memoirs of Fellows of the Royal Society*, vol. 10 (London: Royal Society of London, 1964), pp. 83–106.

Gates's adviser, John Merle Coulter, excitedly reported his student's preliminary finding of a difference in chromosome numbers in specimens of *O. lata*. As the first discovery of its kind, Gates, in the words of his biographer, "found himself famous almost overnight."<sup>51</sup> The next year, in a paper he presented at the 1907 Boston International Zoological Congress, Gates gave the chromosome number of *Oenothera Lamarckiana* as 14 and noted that when *Lamarckiana* was crossed with *O. lata*, the progeny resembled both parental forms. In those resembling *Lamarckiana*, he expected to find 21 chromosomes, assuming they resulted from "a union of three nuclei having 7 chromosomes each," yet he counted only 20 chromosomes. Seeking to explain this seemingly anomalous result, he suggested that "the persistence or 'genetic continuity' of the chromosomes, lead to variations in the chromosome counts of different individuals of the same race."<sup>52</sup>

Lutz heard Gates's talk but was skeptical of his claims. Afterwards she discussed his findings with a Dutch biologist who told her that one of de Vries's students disagreed with Gates's count, but had not yet published his results. This news bolstered her confidence. After leaving Boston, Lutz went home to Indiana and continued her cytological analysis. As she wrote to Davenport,

You will be interested to know that I have had an opportunity to work up a few of the preparations of the hybrid offspring of *O. lata* x *O. Lamarckiana* — which I brought with me. You will recall that Gates reported 20 chromosomes for the germ and somatic cells of this hybrid (having studied two plants in successive seasons). As far as I have gone, I have found what I expected I should find, 14-15. *Never more!* I have worked on but 2 tips from one plant so far, but each showed a number of figures: I have material from a half dozen plants of 1906 culture still to be gone over and a pan full of 1907 seedlings which I hope will be ready for me as soon as I get back. This ought to furnish sufficient evidence to straighten the matter out one way or the other.<sup>53</sup>

While previously she believed to have found variation in the number of chromosome numbers of related forms, she now believed this was due to the inherent technical difficulties of this work, not to chromosomal variation itself. Preparing slides in which the chromosomes were all clearly visible and individually delineated was always extremely difficult, and so she compensated for this by examining as many different specimens as possible.

At the December 1907 meeting of the Botanical Society of America in Chicago, Gates and Lutz were both invited to give papers on *Oenothera*. Perhaps implicitly criticizing Lutz's methodology, Gates emphasized that his work was based on a study of germ cells due to "the well-known variation in chromosome numbers in root-tips."<sup>54</sup> He too reported that the pollen mother cells of *Oenothera gigas* have 28 chromosomes and a reduced number of 14. He believed, however, that "all the mutants do not originate in the same way," pointing to offspring arising from a cross between *O. lata* x *O. gigas*, some of which had 21 chromosomes and others with 20 chromosomes. To account for these differences, he suggested that the variation arose from pairing mistakes at meiosis. Occasionally "one chromosome passes to the wrong pole of the spindle, making the reduced numbers nine and twelve."<sup>55</sup> As his biographer pointed out, this was the first mention of

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<sup>51</sup> Roberts, "Reginald Ruggles Gates. 1882–1962," on p. 86.

<sup>52</sup> R. Ruggles Gates, "The Chromosomes of *Oenothera* Mutants and Hybrids," in *Proceedings of the 7th International Zoological Congress, 1907* (Boston: Harvard University Press, 1912), p. 356.

<sup>53</sup> Lutz to Davenport, 13 October 1907, Davenport Papers, APS.

<sup>54</sup> This was a point he expressed on several occasions. See, for example, R. Ruggles Gates, "A Study of Reduction in *Oenothera Rubrinervis*," *Botanical Gazette* 66 (1908): p. 1–34.

<sup>55</sup> R. Ruggles Gates, "Further Studies on the Chromosomes of *Oenothera*," *Science* 27 (1908): p. 335.

the phenomenon later identified by Calvin Bridges as nondisjunction of the chromosomes.<sup>56</sup> It also was a finding that deviated from the expectations of de Vriesian mutation theory in that it pointed to abnormalities in meiosis, not mutational changes in the pangenes prior to fertilization, as the source of mutation and variation.

For her part, Lutz noted in her paper that despite the fact that her own chromosome counts were not conclusive, she could not agree with Gates's report of 20 chromosomes in the hybrids of *O. lamarckiana* x *lata*. Rather, she had found "each plant to have 14 chromosomes in the cells of the root tips," and *O. lata*, *oblonga*, and *nanella* to have 14, 15, or 16.<sup>57</sup>

Gates's opinion notwithstanding, Lutz continued to work with the root tips of plants, believing somatic tissue provided a better means of determining precise numbers of a plant's somatic chromosomes. She explained her reasons for working with this material in a 1907 letter to Davenport, "In working up the germ cells of the *Oenotheras* for Dr. Gager," she wrote, "I am impressed with the advantages I have in the study of the root tips. Such quantities of material must be sectioned to obtain ever so little of the right stages of the former that there might be danger of reaching conclusions from very limited observations. As yet we have found no such beautiful figures in the germ cells as I have repeatedly seen in the root tips. This work is very instructive and I do not consider it time lost to me at all, but I shall be very glad to get to work on the root tips once more."<sup>58</sup> Another advantage to working with root tips was that it was easier to correlate somatic cells with morphological characters from the same plant. Lutz was always as concerned with connecting her cytological work to biological problems — perhaps a good early illustration of a "cytogenetical" approach as well as the de Vriesian research program.

Lutz published her analysis of the chromosomes of the first generation progeny of the cross between *O. lata* and *gigas* in a short paper in *Science* in 1908. Her aim, she noted, was to throw "some light upon the behavior of chromosomes in inheritance and of determining, if possible, whether number, size and shape of chromosomes are regularly associated with the inheritance of certain definite external characters."<sup>59</sup> She found the offspring of this cross to be divided into three classes: *lata*, *gigas*-like, and intermediate. The numbers of chromosomes appeared to be closely associated with external morphological characters in the first and last group, and "probably also in the second group." This included the shape of pollen, in which she found that parental pollen grains differed in the number of lobes and that these differences were inherited.<sup>60</sup> Her suspicion was that chromosome number influenced the morphology of pollen itself, and if this were true, examining the pollen might provide a good guide to estimating the plant's chromosome number.

— Lutz's Criticism of Gates —

In carrying out this work, Lutz increasingly found her observations to be at odds with those of Gates. Writing to him after the Boston meeting, Lutz inquired whether they might possibly be working on different forms, which might possibly explain the discrepancy in their respective chromosome counts.<sup>61</sup> For his part, Gates worried about establishing his priority and the

<sup>56</sup> Roberts, "Reginald Ruggles Gates. 1882–1962," p. 86.

<sup>57</sup> Anne M. Lutz, "Chromosomes of the Somatic Cells of the *Oenotheras*," *Science* 27 (1908): p. 335.

<sup>58</sup> Lutz to Davenport, 13 October 1907, Davenport Papers, APS.

<sup>59</sup> Anne M. Lutz, "Notes on the First Generation Hybrid of *Oenothera Lata* x *O. Gigas*," *Science* 29, no. 737 (12 February 1909): p. 264.

<sup>60</sup> *Ibid.*, p. 267.

<sup>61</sup> Reginald Ruggles Gates (1882-1962) Papers, King's College London Archives (hereafter: Gates Papers,

competition in this area of study Lutz represented. Early on the two apparently discussed potential conflict in their research programs and arrived at a mutually acceptable agreement about publishing their results. In a letter of August 1909, for example, Lutz wrote, "While I very much appreciate your courtesy in writing me concerning your mention of observations of somatic chromosomes in the *Oenotheras*, I do assure you it was entirely unnecessary. I should not have considered it an infringement, no matter how much you had had to say on the subject. Even tho' we did have an understanding, I took it to mean only that each for the present needs keep to this own line in the main. I do not have any "comer" in somatic chromosomes, and I hope you will feel entirely free to report upon them as much as you like. It will be very helpful to me to compare my own observations with those of yours."<sup>62</sup> Despite such a disclaimer, it is apparent that both viewed each other as a rival, not simply in terms of their findings and publications but also in regard to their differing methodologies and theoretical interpretations. Whereas Lutz pursued her work using interpretative lens of de Vries's mutation theory, Gates did not find de Vries a good guide and preferred his own "chromosome-centered" approach.<sup>63</sup> He began to think of mutation as a consequence of "germinal instability" rather than the mutation of a pangene, and associated mutation events with irregularities in the pairing of chromosomes. As he explained this concept in 1911, "Mutation in *O. Lamarckiana*, therefore appears to be a condition of germinal instability and not a simple process of hybrid splitting, although this condition of instability has probably been brought about through previous crossing in the ancestry. ... Mutation, whether or not always preceded or accompanied by crossing (of which it is probably a result), will thus account for much species formation, and for the polymorphism of many genera."<sup>64</sup>

Gates was keenly interested in establishing his priority in *Oenothera* discoveries and especially sought recognition for his independent discovery of tetraploidy in *O. gigas*. He began to lobby geneticists, laying out his claims, early on. In July 1909, for example, he wrote to William Bateson to object to his statement about polyploidy in *Oenothera* published in the new edition of *Mendel's Principles of Heredity*, stating:

I have been much interested in your recent book on Mendelism wh. is such a clearly written and complete account of Mendelian work. It will certainly be of great value to investigators. So perhaps you will be glad if I call your attention to p. 271. The impression is that Miss Lutz' work preceded mine. My work was begun in 1905 and I am quite certain that she began in Jan. 1907 after the presentation of my first paper on the subject at the New York meetings. The two papers mentioned in your footnote, in wh. I gave the counts in *O. Lamarckiana* and *O. lata*, were both published before her first article. I merely mention this because you will wish to know the facts, and I certainly have no desire to detract credit from Miss Lutz' work in any way.<sup>65</sup>

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King's College). Folder 7/1: Correspondence 1903-1908, Anne Lutz to Gates, 14 November 1907, and 27 November 1907. I thank Luis Campos for sending me extracts from the Lutz-Gates correspondence.

<sup>62</sup> Gates Papers, King's College, Folder 7/2: Correspondence 1909-1912, Anne Lutz to Gates, 16 August 1909.

<sup>63</sup> In a letter to Bateson, 17 July 1911, Gates noted that whereas he previously did not see how his findings could fit in with Mendelian heredity, he could now do so by applying Edith Rebecca Saunders's system of analyzing doubleness in petunias. He also noted that de Vries was not very helpful: "I believe that most of the behavior in *Oenothera* can now be explained on this basis, but I wish I had your help in applying to some of the details. De Vries has been too unanalytical in the treatment of his results." Bateson correspondence, Cyril Dean Darlington Papers, Bodleian Library, Oxford University.

<sup>64</sup> R. Ruggles Gates, "Mutation in *Oenothera*," *American Naturalist* 45 (1911): pp. 605-6.

<sup>65</sup> Cyril Dean Darlington Papers, Bodleian Library, Oxford University, D.33: Bateson Letters, R. R. Gates to Bateson, 8 July 1909. In the passage to which Gates refers, Bateson mentioned both Lutz and Gates in the discussion of "Chromosomes as the possible Bearers of Factors," stating: "Again, Miss Lutz, and,

He was no doubt unhappy with de Vries's various statements lauding Lutz's work prior to mentioning Gates's papers.<sup>66</sup> Gates clearly believed he deserved priority since he had begun working on this topic before she had. Gates laid out the chronology of the early work in 1908, noting he had begun work "on plants grown at Woods Hole, Mass., from seeds of De Vries, in 1905," which was first reported on at the December 1906 New York meeting of the American Association for the Advancement of Science. "After my first announcement of results Miss Lutz germinated seeds of several forms and examined the root-tips of the seedlings, finding about 14 chromosomes in *O. Lamarckiana*, as already stated, but 28 or 29 in *O. gigas*."<sup>67</sup> He also used his own publications as a vehicle to establish priority.<sup>68</sup> Certainly by the end of his life, some gave him full credit for discovering polyploidy in *Oenothera*.<sup>69</sup>

While Gates was correct that Lutz began working on *Oenothera* in January 1907, whether this was prompted by her learning about his work in December 1906 is not clear. *Oenothera* cultures had been grown at Cold Spring Harbor since 1905, and she was well familiar with Shull's collaboration with MacDougal and Gager.<sup>70</sup> Moreover, having heard de Vries's address in 1904 and read Davenport's annual reports, she was well familiar with the importance of *Oenothera* for mutation studies. Later, Lutz addressed Gates's claims of priority, stating that in Gates's first paper, he did not discuss any mutant having a chromosome number different from *Oenothera Lamarckiana*, while the "first mention of a mutant with a chromosome number differing from that of *O. Lamarckiana* was published by the writer 6 months later."<sup>71</sup> In any event, there is no doubt that Lutz and Gates viewed each other as competitors. Rather than being a negative, however, such a situation may have been beneficial in serving to stimulate their mutual studies and sharpen their focus.

Competition aside, however, Lutz became increasingly skeptical about Gates's scientific credibility, privately questioning his determination of chromosome numbers in different *Oenothera* species and hybrids, as well as his understanding of the meiotic events producing varying chromosomal counts, methodological practices, and theoretical views.<sup>72</sup> Publicly she

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independently, Gates, have found remarkable diversities in *Oenothera*, especially that *gigas* has 28, while *lata* has 14. Obviously this doubling means something definite, but it is not suggestive of the determination of specific difference." (p. 271). William Bateson, *Mendel's Principles of Heredity* (Cambridge: Cambridge University Press, 1909), p. 271. In the second edition of this work (1913), Bateson modified the footnote to which Gates referred, stating: "Important evidence as to variations in chromosome numbers has been published by R. R. Gates, *Botanical Gazette*, July, 1908."

<sup>66</sup> See, for example, de Vries, "Die Mutationen in der Erblchkeitslehre," vol. 6: p. 542.

<sup>67</sup> R. Ruggles Gates, "The Chromosomes of *Oenothera*," *Science* 27 (1908): pp. 193–195

<sup>68</sup> R. Ruggles Gates, "Polyploidy," *British Journal of Experimental Biology* 1 (1923): p. 156.

<sup>69</sup> In his obituary of de Vries, however, Sir Daniel Hall gave Gates full credit for this discovery, stating that "among the mutations, Gates found the first polyploid." See A. D. Hall, "Hugo de Vries. 1848–1935," in *Biographical Memoirs of Fellows of the Royal Society*, vol. 1 (London: Royal Society of London, 1932–1935), p. 373.

<sup>70</sup> Lutz relied on Shull's material for her initial study. See Anne M. Lutz, "Cell Studies in Heredity," *Year Book of the Carnegie Institution* 8 (1909): 93, and Anne M. Lutz, "Triploid Mutants in *Oenothera*," *Biologisches Centralblatt* 32, no. 7 (1912): pp. 387–435, on p. 389 n.8. Lutz states that she grew her own plants in 1909 and 1910. Shull had collaborated with D. T. MacDougal in hybridization studies in *Oenothera* and was a co-author of D. T. MacDougal, et al., *Mutants and Hybrids of the Oenotheras* (Washington, D. C.: Carnegie Institution of Washington, 1905).

<sup>71</sup> Lutz, "Triploid Mutants in *Oenothera*," p. 432.

<sup>72</sup> Lutz was not the only one to notice Gates's backtracking. The Ph.D. student of De Vries's former student and successor Theo Stomps, J. Adolphina Leliveld, noted of Gates in her historical survey of early cytological work on *Oenothera* that "a number of his statements were soon recanted by himself or contested by other investigators," although many "facts contained in his work deserve special attention."

pointed out discrepancies and misleading statements in his papers, and also the sloppiness in his genetic analysis. In addition, she responded to his criticism of her use of root-tip chromosomal figures, noting that over the years she had examined at a minimum “8000 metaphase figures, and probably many more.”<sup>73</sup> Any variability in her chromosome counts, she noted, was due to the technical difficulty of identifying individual chromosomes in multiple sections taken from a plant’s root tips, not to any inherent methodological limitations. Privately, she felt Gates wanted to exclude others from the field. As she told Bradley Davis in 1912, “I was much pleased to receive a copy of your last publication. It was quite interesting to find two papers on the same subject in this number of the *Annals of Botany*. Dr. Gates seems to be very thoroughly convinced that there is but one infallible authority on primrose cytology!”<sup>74</sup>

Perhaps as a reaction to Gates’s approach, in presenting her own findings Lutz was careful not to overreach her data and to qualify her statements.<sup>75</sup> For example, in defining her usage of *mutant* as distinct from a *hybrid* form, she explained that the “term ‘mutant’ is used throughout this paper and others to follow, in the de Vriesian sense, and does not necessarily imply that the offspring of the plant in question will reproduce the characters of the parent throughout later generations.”<sup>76</sup> In addressing how to distinguish a mutant on the basis of external characters, she stated, “A mutant of the *Lamarckiana* group is distinguished from the parental form and other mutants, not so much by some particular character — for few characters are peculiar to any one type alone — as by the combination of characters which is peculiar to itself.”<sup>77</sup> It was for this reason, she admitted, that it was sometimes difficult to identify an individual plant as belonging to one species or another. Otherwise, however, she became adept at predicting chromosome numbers by examining external characters, consistently finding that plants exhibiting certain traits throughout their life cycle had a particular chromosome number. The converse, however, was not true: plants with the same number of chromosomes might not always be morphologically similar

J. Adolphina Leliveld, “Cytological Studies in Some Species of the Genus *Oenothera*,” *La Cellule* 40 (1931): pp. 195–256, on p. 196.

<sup>73</sup> Lutz, “Triploid Mutants in *Oenothera*,” p. 422; see also p. 408, n. 21.

<sup>74</sup> Ralph E. Cleland Papers, Lilly Library, Indiana University, Lutz to Davis, 19 April 1912.

<sup>75</sup> Lutz’s scientific method may have been influenced by her professor of botany at Michigan, Volney M. Spaulding. In his botany textbook, Spaulding included a note to students about how to conduct botanical work, stating: “Do not be hasty in drawing conclusions. Make a constant practice of comparing the object you are studying with others of the same kind. Note differences and resemblances. Learn by the actual process what it is to acquire a general conception. ‘Honesty in science means, first, facts well proved, and then conclusions slowly and painfully deduced from facts well proved. In all your work stop and think.’ The mere accumulation of facts, if nothing is done with them, is of little consequence. Constantly ask the question, what does this fact mean? You may or may not be able to answer the question, but that is no reason for not raising it.” Volney M. Spaulding, *Guide to the Study of Common Plants: An Introduction to Botany* (Boston: D. C. Heath and Co., 1894), x.

<sup>76</sup> Lutz, “Triploid Mutants in *Oenothera*,” p. 389 and n.9. De Vries’s understanding of mutation was complex. Generally he considered a mutation to be a change in a pangene that resulted in new characters in the offspring, and such changes would be reproduced in subsequent generations. Such mutations he believed occurred prior to the formation of the germ cells. However, whether a mutation would appear in later generations depended on the type of the mutation—progressive, retrogressive, or degressive—and also on whether the mutation might simply be associated with “fluctuating variability,” that is, reflect the presence of different numbers of active or latent pangenes. For a summary of de Vries’s views, and especially how they changed after the rediscovery of Mendel, see Ida H. Stamhuis, Onno G. Meijer, and Erik J.A. Zevenhuizen, “Hugo de Vries on Heredity, 1889–1903: Statistics, Mendelian Laws, Pangenes, Mutations,” *Isis* 90 (1999): pp. 238–267, and especially Zevenhuizen, *Vast in het spoor van Darwin: Biografie van Hugo de Vries*.

<sup>77</sup> Anne M. Lutz, “Fifteen- and Sixteen-Chromosome *Oenothera* Mutants,” *American Journal of Botany* 4 (1917): p. 71.

since they might have different combinations of chromosomes.

Another problem of particular interest to Lutz and other *Oenothera* workers was how chromosomal mutations arise, in part to test de Vries's mutation theory. In a 1909 paper, Gates disputed the possibility of a triploid mutant, which would be expected according to de Vriesian theory. As Gates noted, "De Vries describes the appearance of a mutation as resulting from the union of a 'mutated' germ cell with an ordinary germ cell. However this view can scarcely apply in this case, since, although it is possible that germ cells may occasionally be produced with the unreduced number of chromosomes, fertilization with such a germ cell would produce an organism with 21 instead of 28 chromosomes. The possibilities of two such unreduced germ cells — an egg and a sperm — getting together in fertilization are very remote. Moreover, no instances of this sort are known, and if this were the method of origin one would also expect to find mutants occurring with 21 chromosomes."<sup>78</sup> In her 1912 paper, Lutz countered Gates's challenge by explaining how such triploids could arise in keeping with de Vries's notions, that is, that triploids could be produced by mutation. To explain the origin of tetraploidy in *Oenothera gigas*, for example, Lutz pointed to what she initially called the "de Vries-Stomps theory" and later referred to as the "Stomps-Lutz" theory. This held that tetraploidy was the product of the "union of two germ cells each having the diploid number of chromosomes." This theory could also explain the origin of triploid mutants through the "union of a haploid and a diploid germ cell."<sup>79</sup> Such a view was compatible with de Vries's conception of mutation in its implicit assumption that a "mutational event" occurred that prohibited egg cells from undergoing a reduction division. Of all the *Oenothera* mutants, only *gigas*, de Vries believed, was a "progressive mutation." To account for tetraploidy, he assumed, stretching his previous interpretations, that a change in a pangene caused the double chromosome numbers to form in the germ cell prior to fertilization. Hence he was pleased by Lutz's discovery of triploid mutants. This finding well explained the finding of a "half-hybrid," *Oenothera biennis semi-gigas*, in a cross between *O. biennis* and *O. gigas*, explained as arising from haploid germ-cells with 7 chromosomes (*biennis*) and 14 chromosomes (*gigas*). He viewed this as a kind of transitional case.<sup>80</sup>

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<sup>78</sup> R. Ruggles Gates, "The Stature and Chromosomes of *Oenothera Gigas* De Vries," *Archiv für Zellforschung* 8 (1909): pp. 525–552.

<sup>79</sup> Lutz, "Triploid Mutants in *Oenothera*," p. 421. Lutz later referred to this theory as the "the Stomps-Lutz theory of the production of tetraploid forms by means of the union of two unreduced cells (14+14)." As Erik Zevenhuizen notes, this is probably more accurate: "It seems to me that Stomps was a better partner to Miss Lutz to discuss matters like these than De Vries. Stomps, although as staunch a defender of the mutation theory as De Vries, mainly considered mutations from a cytological point of view while De Vries was very much focused on the outside appearance of a plant. During the 1870s and 1880s De Vries was almost exclusively involved in physiological research (reducing plant growth from a physical phenomenon to a chemical and eventually a biological-genetical thing) and the microscope was his chief instrument. But after 1890, while still teaching microscopic techniques to his students, he seems to have hardly ever looked through a microscope again. When writing about the chromosomes of *Oenothera* De Vries (as far as I know) always refers to the research of others (among them several of his pupils: Stomps, Geerts, Van Overeem, Boedijn)." (personal communication, 11 August 2005). For a fuller explication, see Zevenhuizen, *Vast in het spoor van Darwin: Biografie van Hugo de Vries*.

<sup>80</sup> De Vries discussed this issue, pointing to Lutz's experimental confirmation, in Hugo de Vries, "Mutations in Heredity," *Rice Institute Pamphlet* 1 (1915): p. 518–570 (esp. pp. 552–553), the talk he gave in 1912 at the opening of the Rice Institute (now Rice University). See also Zevenhuizen, *Vast in het spoor van Darwin: Biografie van Hugo de Vries*, pp. 427–430.

The Stomps-Lutz theory could not, however, well account for the production of 21-chromosome offspring of *O. lata* (15 chromosomes) when self-pollinated or when crossed with *Lamarckiana* (14 chromosomes). To explain pairing irregularities, Lutz cited the views of Victor Grégoire, the highly respected Belgian cytologist, rather than Gates. Grégoire suggested that irregularities in the division of male and female germ cells might arise if the reduction division in *Oenothera* were arrested at different stages of “heterotypic prophase” (prophase of the first reduction division) or, more rarely, at metaphase of the homotypic division.<sup>81</sup> Arrested development seemed preferably to a de Vriesian than Gates’s alternative theory of germinal instability, which viewed mutation as a product of chemical changes in the germ plasm and not simply mistakes in chromosome pairing.<sup>82</sup>

Like Gates, Lutz increasingly focused on pairing mistakes at both the homotypic and heterotypic stages of meiosis to explain the variation in chromosome numbers in *Oenothera* mutants. Lutz thought that irregularities in chromosome distribution were primarily restricted to male germ cells, in which “one chromosome occasionally passes to the wrong pole of the spindle at the reduction division.” Thus *lata* pollen mother cells, with a diploid chromosome count of 15, could form germ-cells with 6 and 9 chromosomes, and *Lamarckiana* germ-cells with 6 and 8 chromosomes. It appeared to be a general rule, however, that “*offspring never result from the union of two germ cells whose combined number of chromosomes is less than the diploid number for O. Lamarckiana,*” that is, fewer than 14 chromosomes.<sup>83</sup> In short, Lutz regarded all mutants of *O. Lamarckiana* as forms that generally have “a chromosome number differing from that of the parent” and persistently display Lutz never referenced changes in the chromosomes themselves, only differences in their number.<sup>84</sup>

Gates, for his part, used public as well as private channels to lobby for his views. For example, in opposition to de Vries, he told Bateson that he had “much evidence that the mutation phenomenon in *O. Lamarckiana* are the result of crossing, but it is not probable that *O. Lamarckiana* is a simple hybrid as Davis suggests.”<sup>85</sup> He also explained his notion of germinal instability, which resulted “from crossing or from any other cause. It may lead to the doubling of the nuclear content in one case (*gigas*) or the duplication of one chromosome in another case (*lata*), the loss of something which determines tallness in another (*nanella*) or a change in cell chemical-structure which leads to greatly increased pigmentation in another (*rubricalyx*).”<sup>86</sup> In addition to his published papers, these views were presented in greater detail in his 1915 book, *The Mutation Factor in Evolution, with particular reference to Oenothera*.<sup>87</sup>

Lutz’s paper on triploid *Oenothera* mutants attracted considerable interest among biologists. De Vries’s former student and *Oenothera* cytologist Theo Stomps praised her work in 1916.<sup>88</sup> Shull, for example, corresponding with the Berkeley zoologist E. B. Babcock, stated, “I am glad you called Professor Kraus’s attention to Miss Lutz’s work upon ‘Triploid Mutants’. When you familiarize yourself with her work you will see that she has found not only one, but many of these triploid

<sup>81</sup> Lutz, “Triploid Mutants in *Oenothera*,” pp. 425–426.

<sup>82</sup> R. Ruggles Gates, *The Mutation Factor in Evolution, with Particular Reference to Oenothera* (London: Macmillan, 1915), pp. 301–303. He claimed his “chromosome hypothesis” could be regarded “as supplementary, and not contradictory, to the pangen hypothesis of de Vries.” (303).

<sup>83</sup> Lutz, “Triploid Mutants in *Oenothera*,” p. 424; italics in the original.

<sup>84</sup> Lutz, “Triploid Mutants in *Oenothera*,” p. 433.

<sup>85</sup> C. D. Darlington Papers, Bodleian Library, Bateson Letters: R. R. Gates to Bateson, 17 July 1911.

<sup>86</sup> C. D. Darlington Papers, Bodleian Library, Bateson Letters: R. R. Gates to Bateson, 28 February 1914.

<sup>87</sup> Gates, *The Mutation Factor in Evolution*.

<sup>88</sup> Theo J. Stomps, “Über den Zusammengang zwischen Stature und Chromosomenzahl bei den *Oenotheren*,” *Biologisches Centralblatt* 36 (1916): pp. 129–160.

forms. In the single season of 1910 she identified 8 of these triploid forms, of all of which definite chromosome-counts were made. Dr. T. J. Stomps (*Berichte d. Deutsch. Botanischen Gesellschaft* 30: 406, 1912) has also found triploid mutants. There can be no doubt of the correctness of Miss Lutz's statement that these will probably be found to occur with comparative frequency."<sup>89</sup> De Vries was also pleased, mentioning the paper in his lectures and publications.<sup>90</sup> It is ironic, then, that after having established herself as a leading *Oenothera* worker, Lutz was dismissed from her position at the Station for Experimental Evolution.

### *Lutz's Departure from Cold Spring Harbor*

The three-year gap in the dates of Lutz's publications reflects scientific as well as personal issues impacting her work. Not only was *Oenothera* cytology subject to inherent technical difficulties, but it also moved workers into unexplored scientific terrain. As Adolphina Leliveld noted in her historical survey of the field published in the early 1930s, "*Oenothera* was practically the first object subjected to a genetic and cytological investigation going hand in hand, with the preconceived idea of obtaining an insight into genetic relations by means of cytological data."<sup>91</sup> Moreover, the peculiar nature of the data compounded the challenges. Normal modes of explanation used in cytology and genetics, both of which were relatively new, simply did not seem to apply to *Oenothera*. It is no wonder, then, that Lutz was unsure about how to interpret her results. She admitted that after publishing the 1909 paper on crosses between *O. lata* and *O. gigas*, "it became apparent that no logical explanation of many of the curious combinations of chromosome number and vegetative characters found in these hybrids could be offered," since geneticists were ignorant "of the normal behavior of *O. lata* when self-pollinated or crossed with another of its kind" and cytologists knew little about "the range of variation of chromosome number among the different types of *O. gigas*."<sup>92</sup> She thus decided to explore these questions before publishing further results.

On top of these concerns, she also faced problems in the workplace. Over the years, a growing strain had developed in Lutz's relationship with Davenport, and judging from their correspondence they increasingly found themselves at loggerheads over a number of issues. There were minor things like her request for an assistant so she could accelerate her progress, and more major ones such as her complaints about her work environment. More serious still, however, was the extreme disappointment she felt when Davenport turned down her request to spend the 1909 growing season at her family home in Indiana. Although she pointed out the benefits to be gained from growing her plants in the rich Indiana soil, Davenport countered that her results required continuity in the growing conditions. Putting science aside, Lutz admitted that her request stemmed from the psychological toll of living year-round in the small and insular community at Cold Spring Harbor:

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<sup>89</sup> American Philosophical Society, University of California Department of Genetics: Shull to Babcock, 14 April 1914.

<sup>90</sup> For example, see Hugo De Vries, "Mutations in Heredity [1912]," in *The Rice Institute Pamphlet*, vol. 1 (Houston: Rice Institute, 1915), pp. 518–570.

<sup>91</sup> Leliveld, "Cytological Studies in Some Species of the Genus *Oenothera*," on p. 196.

<sup>92</sup> Lutz, "Triploid Mutants in *Oenothera*," pp. 413, n. 24.

I cannot deny that the proposed plan offered some attractions to me as a welcome change after 5 years of village life. Perhaps, since your duties in connection with the station call you out among new faces and fresh ideas so many days of each week, you are not in a position to realize how degenerating is the effect of the changeless life among the lazy ambitionless inhabitants of this village. It is conducive to mental stagnation. The occasional visitor who comes to the Station we see but for a minute or two at best, and but little help and inspiration can come from that source. Dr. Shull is away half of each year, and Dr. Harris has been, and doubtless will continue to be away several months of each year. Dr. Lutz & Mr. Johnson who remained in continuous residence gave as the chief reason for the final change the uninterrupted monotony of the life in this community.<sup>93</sup>

But Davenport's further assertion that she needed to remain at the Station to be able to assist other staff members as needed particularly incensed her. She responded with ill-concealed resentment:

I was considerably surprised at your reference to my obligations to be here in order to be ready to assist other members of the staff with cytological work. This agreement, like the Secretary's work *was a temporary arrangement*, and *I had the understanding from you later that I was released from all obligations other than that pertaining to my cytological work*. On one occasion in staff meeting when I mentioned a piece of cytological work which I had planned to do for Dr. Shull, you opposed to members of the staff making any larger demands upon my time for such assistance. You added that you thought members of the staff had been too free in the past in making such requests, and it must be distinctly understood in the future that I must have all of my time for my own research work.

I am willing and very glad indeed to assist yourself and any members of this Staff as *friend to friend*, just as each and all have helped me on many past occasions. But *I will not continue under any contract at this Station which binds me to greater obligations to other members of the Staff (with the exception of yourself) than that which each bears to me.*<sup>94</sup>

There is a gendered dimension to these remarks. Certainly Lutz begrudged the secretarial duties she was initially assigned, when nothing was required of the male researchers. Likewise, she interprets Davenport's comment about her availability to serve the needs of other researchers as applying to her a different standard than that expected of the male staff members. Her sharp reply makes clear her insistence that her research work be considered on a par with that of the male investigators. Finally, her reference to the tedium of day-to-day work at the station — relieved for those (males) able to escape it from time to time — resembles the complaints of feminists about the monotony and insularity of women's daily domestic duties. On the other side Davenport was no doubt angered by Lutz's rather insolent and somewhat disrespectful reply and lack of proper deference customarily accorded to a supervisor and senior (male) colleague.

Tensions between the two continued to simmer over the ensuing months. Ill-feelings again erupted several months later, when Davenport reprimanded Lutz for having entertained guests in her laboratory late at night, causing him disturbance. Lutz apologized. To his implicit suggestion of sexual impropriety in entertaining a gentleman so late at night, she carefully pointed out that there was another woman present as well. Yet once again she referred, in defending her actions, to the monotony at the Station:

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<sup>93</sup> Davenport Papers, APS, Lutz to Davenport, 23 April 1909.

<sup>94</sup> *Ibid.* The underlined phrases were apparently from the hand of Davenport, who also made marginal annotations on the letter.

I am just in receipt of your note. It is the first *unkindness* I have received at your hands, and this was so unexpected, I do not know how to explain it.

I presume you refer to last evening when Miss Cagwill came to sit with me because she was alone at Mrs. Wylie's. She had work to do, and so had I, otherwise it would have been pleasanter to have staid [*sic*] in her room. The "late supper" you mention consisted of a bowl of hot soup at 10 o'clock. There was no one present but Miss Cagwill, Mr. Stephenson, and myself. Until 10 there was no one in my room but Miss Cagwill and myself for Mr. Stephenson — as you probably know, was in his room at work. He afterwards went back to his work and continued until 15 of 12 as did I — when we all went home. ...

We have been repeatedly told by workers from other institutions that they do not consider it possible to accomplish the best results in a place where there is nothing to freshen or divert one's mind. Your business takes you out 3 or 4 times a week among new surroundings — and you are unconsciously freshened for your work. I do not think you are in a position to realize how stable and stagnant one becomes who has no change of thought. ... There are so few diversions and pleasures here, that it never occurred to me but that you would be glad of any simple diversion we might find. I have never worked in an institution where such things were at all unusual for people living in boarding houses and working long hours in the laboratory.<sup>95</sup>

With her thinly veiled criticism of how he ran his "institution," it is clear that the two were destined to have a final confrontation, which came in August 1910 after an explosive series of events.

— Lutz's Firing —

Lutz was not the only member of staff who was dissatisfied with Davenport's leadership style. Shull, too, had long resented the preferential treatment Davenport showed each summer to members of the Biological Laboratory. Both complained, for example, about the exclusion of staff members from Laboratory events and especially the lectures, despite the fact that the summer participants had full access to Station facilities such as the library, as well as jealousy over the accommodations provided to Biological Laboratory participants, whereas staff members had to secure their own housing in the village. It was not unusual, then, that in writing to Shull, who was working in Santa Rosa studying Luther Burbank's horticultural techniques, Lutz repeated such complaints. Unwisely, Shull enclosed Lutz's letter in the critical missive he wrote to the President of the Carnegie Institution, R. S. Woodward, in July. Woodward was naturally disturbed by these charges and in turn informed Davenport, sending him both letters.

Davenport was livid at what he viewed as a transgression. Moreover, given that his association with the Biological Laboratory was extramural to his direction of the Station for Experimental Evolution, he may also have been concerned about the bad impression these aspersions cast on his direction in the eyes of President Woodward.<sup>96</sup> He immediately called Lutz into his office, confronted her with the charges, and asked for her resignation. Blind-sided by the allegations, Lutz immediately wrote to Woodward, stating, "I have been notified by Prof. Davenport today of my dismissal from the Staff of the Station for Experimental Evolution on the charge of 'insubordination and disloyalty to the Director.'"<sup>97</sup> She asked Woodward to send her a

<sup>95</sup> Davenport Papers, APS, Lutz to Davenport, 2 December 1909. Again, this letter includes marginal annotations and underlining apparently made by Davenport.

<sup>96</sup> Carnegie Institution of Washington Archives, Genetics: Employees, 1904-1916, Folder 2: Davenport to Woodward, 23 August 1910; Woodward to Davenport, 24 August 1910; Woodward to Davenport, 25 August 1910.

<sup>97</sup> Carnegie Institution of Washington Archives, Genetics: Employees, 1904-1916, Folder 2: Lutz to Woodward, 23 August 1910.

copy of Shull's letter, claiming she had not written anything to him that she would not have wanted Dr. Davenport to read. Woodward, however, demurred, informing her that "In accordance with this view you should have address [*sic*] your complaints or criticisms in the first instance directly to Dr. Davenport. There should have been no chance to have your views reach me indirectly," and under the circumstances it was his duty to "sustain the Director in this matter." Woodward did, however, subsequently warn Davenport about the danger of permitting internal dissension within his institute and brought the matter up at the next meeting of Carnegie heads of departments.<sup>98</sup>

Davenport was again shaken two weeks later when he received Shull's resignation. As the most prolific and scientifically recognized staff member at the Station, Davenport well recognized that Shull's "resignation would be the greatest blow the Station could receive."<sup>99</sup> Accordingly, he tried to convince Shull to remain, mentioning his belief that it was owing to the Lutz affair. In reply, Shull readily admitted that his resignation was tendered owing to his embarrassment at having unintentionally provoked Lutz's firing. Yet Davenport sought to assure him that the decision to fire Lutz was based on more than this incident. As he explained, he had doubts about her scientific competence:

I shall not discuss the events that have led me to take this action; the whole matter is exceedingly painful to me. It is the first time in my life that I have asked for the resignation of any subordinate of any grade and nothing but the profoundest conviction of, and the clearest insight into, my duty to the Department and the Institution have led me to this step. ... If ever it is your lot, in the exercise of official duty, to do any distasteful task you will realize how a burden will long be borne in silence until some slight addition to it renders it intolerable.<sup>100</sup>

Shull nonetheless attempted to plead on Lutz's behalf, "Miss Lutz's resignation is a serious blow to one side of my own scientific work at the Station. *She is now the most critical and best trained student of the *Oenotheras* in America*, and she has at all times shown the greatest willingness to be helpful to those with whom she has been association. I feel that it will mean an unfortunate loss to science if some way is not found in which she can continue her work."<sup>101</sup> Davenport, however, stood his ground, suggesting that Lutz's failure to publish more reflected poorly on her scientific abilities:

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<sup>98</sup> Carnegie Institution of Washington Archives, Genetics: Employees, 1904-1916, Folder 2: Woodward to Lutz, 25 August 1910; Woodward to Davenport, 27 August 1910.

<sup>99</sup> Carnegie Institution of Washington Archives, Genetics: Employees, 1904-1916, Folder 2: Davenport to Woodward, 9 May 1914.

<sup>100</sup> Davenport Papers, APS, Series I: Correspondence. Shull Correspondence, Folder 3: 1909-1911, Shull to Davenport, 27 August 1910; Davenport to Shull, 3 September 1910.

<sup>101</sup> Davenport Papers, APS, Shull to Davenport, 12 September 1910; emphasis mine. There is evidence that Lutz did indeed blame Shull for her firing. In arranging with Harley H. Bartlett, secretary of the Botanical Society of America, for someone to read her paper at the 1915 meeting, Lutz stated: "I shall be every glad to have you read my paper at the Christmas meetings, and if not convenient for you, Dr. Davis or anybody, EXCEPT DR. SHULL." H. H. Bartlett Papers, Bentley Historical Library, University of Michigan, Lutz to Bartlett, 17 September 1915. In her published papers, however, she referred cordially to Shull, as in 1916, when she noted: "During the years in which this work was conducted at the Station for Experimental Evolution, Dr. G. H. Shull kindly gave me the privilege of studying all forms of interest which appeared in his cultures of *Oenothera*." Lutz, "Oenothera Mutants with Diminutive Chromosomes," p. 519.

Permit me to say that, despite the intimacy of your acquaintance with Miss Lutz (I might almost say *because* of it) you are perhaps less in a position than I to know the real Miss Lutz and to judge of the advisability of her continuing here. You write of feeling that I have misjudged Miss Lutz. But in forming my judgment I relied on no hearsay but only on things that I had seen with my own eyes, heard with my own ears and realized of my own knowledge.

I am enough of a student of animal behavior to pay attention to reactions and have had enough experience with people to judge of the internal significance of reactions. However, as a student of psychology I am slow to accept the evidence of my own senses unless confirmed by sundry independent witnesses. Judged by all these tests Miss Lutz had fallen so far short that I had long ago decided that we could not work together. However, I am nothing and the scientific work of this Department is everything. Had Miss Lutz in the past six years showed marked evidence of ability to carry out independent investigation and to get results she could have remained on salary as the reputation of the Department was not being seriously damaged. But, despite remarkable opportunities, the result of her work has been slight. Some weeks ago she laid before me a plan of completing before she leaves five of the investigations out of the "14" she had under way — I have urged that she attempt not too much. As a matter of fact, unless I am greatly mistaken, she will hardly finish more than one. This inability to push to completion a research (in striking contrast to her energy in daily work) is fatal to her scientific career and does not justify further expenditures of funds on her which might be devoted to the support of a more productive worker. ... It had come to a point where Miss Lutz or I must leave the Department, and I had to conclude that it must be she.<sup>102</sup>

In the end, Shull withdrew his resignation, although he left the Station in October 1915 to become professor of zoology at Princeton University.

Davenport clearly did not credit Lutz for the important discoveries she had already made. His dire opinion of 1910, moreover, contrasts sharply with the laudatory views he later expressed of her accomplishments. This suggests that Davenport's negative opinion may have been connected with his concern to bolster the Station's reputation in the eyes of the Carnegie Institution's Trustees. Her aversion to publishing results she was unsure of or that she judged to be incomplete or sloppy may have hindered her productivity, but she believed it made her a better scientist. Indeed, she criticized other *Oenothera* workers, not only Gates but also Davis, for publishing too hastily.<sup>103</sup> But this, along with her abrasive rapport with Davenport, brought an end to the institutional support for her scientific work.

### *Lutz's Research Trip to Europe*

Lutz's resignation became effective on 1 February 1911, and in June she left for Europe, telling Davenport, "The chief object of my visits to Holland and Belgium is to work up the cytology of

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<sup>102</sup> Davenport Papers, APS, Davenport to Shull, 12 October 1910.

<sup>103</sup> To de Vries, for example, she criticized Davis as follows: "Professor Davis's statements concerning the herbarium specimens of Lamarck which *he had never seen* certainly cannot be regarded as reliable. Still, his statements would carry convictions to many casual readers, if not corrected, as I am glad to know that they will not be allowed to stand unchallenged." Hugo de Vries Archive, Centrale Facultaire Bibliotheek, University of Amsterdam, Inv. no. 170: Lutz to de Vries, 22 December 1913. To Stomps, she criticized Gates: "I have enjoyed reading your two exceedingly interesting papers very much indeed. I was especially pleased to find that you had counted 21 chromosomes in "Hero-Individuen." I wonder what Dr. Gates can say in reply to the evidence for 21-chromosome mutants now! That has certainly knocked the "props" from under his argument against the DeVries-Stomps theory of the origin of the 28-chromosome condition in *O. gigas*." Theo J. Stomps Archive, Centrale Facultaire Bibliotheek, University of Amsterdam, Inv. no. 331: Lutz to Stomps, 3 February 1913. I thank Erik Zevenhuisen for sending me photocopies of the Lutz letters in the de Vries and the Stomps archives.

Professor de Vries mutants,” spending time with him in Amsterdam.<sup>104</sup> In Belgium, she was given a place in Victor Grégoire’s cytological laboratory, becoming the first female student registered at the Catholic University of Louvain. Over the course of a year, she was able to work out “the majority of the details of special cell-study connected with these investigations (exclusive of chromosome counts).”<sup>105</sup>

Grégoire confirmed her results, which greatly bolstered her confidence in the validity of her *Oenothera* interpretations. With obvious satisfaction she reported her results to Davenport in May 1912, “I am happy to state that my results have all come out *in strong confirmation of the mutation theory*. I didn't tell Professor de Vries until Professor Grégoire and I had gone over every inch of the ground and made sure of the evidence. Then I wrote him — just a few days ago. He was naturally very much pleased, as most of the primrose cytologists have been doing their best to scrape up evidence to discredit the theory. Professor Grégoire paid me the compliment to say that no such a comprehensive piece of cytological work as the Cold Spring Harbor studies had heretofore been accomplished on any group of plants.”<sup>106</sup> She also felt vindicated in her decision not to publish prematurely, “It has been hard to hold all on and work while others published, but I felt confident in the larger gains to be obtained by this method, and the results, I feel, have justified the course I pursued. Gates and Davis have committed themselves to a good many erroneous conclusions as result of limited observations and hasty publications.” Davenport, despite his personal animosity, was pleased by these developments.

Lutz’s reference to the “strong confirmation of the mutation theory” her work provided referred to de Vries’ call in *Die Mutationstheorie*, “I hold that all the new characters of a mutant are manifestations of a single change that has taken place within it. Morphological proof of this thesis can as yet hardly be produced, but physiologically it follows of necessity, in my opinion, from the fact that these characters are always associated and, so far as our experience goes, cannot be separated.”<sup>107</sup> In showing that mutation was associated with chromosomal changes prior to fertilization, and hence not simply a product of the mixing of factors in hybridization, she provided “morphological proof” through identifying the gametic constitution of triploids in support of de

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<sup>104</sup> Davenport Papers, APS, Lutz to Davenport, 10 August 1911. Lutz met de Vries in 1904, when he spoke at the opening of the Station for Experimental Evolution, and again in 1906 when he again visited the Station during his tour of the United States (personal communication, Erik Zevenhuisen, 2005). In Davenport’s report published in the *Year Book of the Carnegie Institution*, 10 (1911): p. 86, he noted: “Miss Anne M. Lutz, who has been associated with our work from the beginning, first as secretary and later as cytologist, resigned in February and is continuing her studies on the cytological differences of the *Oenotheras* in Belgium. A full report of her prolonged studies here has been nearly completed.” Lutz visited de Vries in July and September 1911 and again in June 1912, in order “to be assured of the correct identification of the Cold Spring Harbor mutants supposed to duplicate the characters of forms which de Vries had described and named.” Lutz, “*Oenothera* Mutants with Diminutive Chromosomes,” p. 503.

<sup>105</sup> Paul Débaissieux, “Victor Grégoire (1870–1938),” *Revue Des Questions Scientifiques* 116 (1939): pp. 349–69; Lutz, “*Oenothera* Mutants with Diminutive Chromosomes,” p. 504. De Vries considered Grégoire one of the most eminent botanical cytologists in Europe; Hugo de Vries, “Modern Cytological Problems,” *Rice Institute Pamphlet* 1 (1915): pp. 596–614, on p. 596.

<sup>106</sup> Davenport Papers, APS, Lutz to Davenport, 9 May 1912. With respect to Lutz’s confirmation of the mutation theory, de Vries’s biographer Erik Zevenhuisen remarked: “[Lutz] is very important in De Vries’ life story because it was she who discovered that *Oenothera gigas* is a tetraploid and several of the other *Oenothera* mutants are the results of trisomy. So there were no mutating pangenes as De Vries had stated, attacking in this way the very essence of his mutation theory.” (personal communication, 2005).

<sup>107</sup> Hugo de Vries, *The Mutation Theory: Experiments and Observations on the Origin of Species in the Vegetable Kingdom*, trans. J. B. Farmer and A. D. Darbishire (Chicago: Open Court Publishing Co., 1909), vol. 1: p. 403.

Vries's conception of mutation. Triploids, she proved, could result from a union of a gamete that through mutation (a change in pangenes) contained the double number of chromosomes (14) and a normal haploid gamete with 7.<sup>108</sup>

Lutz continued working on *Oenothera* after returning home to Indiana, and was no longer obligated to credit the Station for Experimental Evolution for supporting her work since, as she told Davenport, "the work must nevertheless be continued wholly at my own expense and through the courtesy of other Institutions."<sup>109</sup> Future papers expressed her gratitude to botanists at nearby Purdue University, who provided laboratory facilities to enable her to carry out cytological analysis.<sup>110</sup> There was a limit, however, to continuing to work in science without institutional support.

### *The Final Papers*

After publishing the paper on triploidy, Lutz continued with her attempt to correlate chromosome number with the external morphological characteristics. In 1917, she published a short paper on pollen shape in tetraploids, a point of special interest in connection with the well-known recognition that large numbers of *Oenothera* seeds failed to germinate.<sup>111</sup> While she agreed with Gates that sterility appeared to depend "upon the compatibility, or incompatibility of the chromosomal combination which the number represents," she continued to be critical of his wider conclusions.<sup>112</sup> In two papers of 1916 and 1917, Lutz thoroughly critiqued an important 1914 paper by Gates and Nesta Thomas of King's College London, stating that her "primary object" was "to discuss, in the light of the Cold Spring Harbor and Louvain studies of somatic chromosome number in *Oenothera Lamarckiana* and its derivatives, certain theories and conclusions which Gates and Miss Thomas have based upon the results of their investigations."<sup>113</sup> Studying *Oenothera lata* and *O. semilata* — 15-chromosome mutants derived sporadically from crosses between 14-chromosome *O. Lamarckiana*, *biennis*, and *rubricalyx* — Gates and Thomas focused on the meiotic divisions. As expected, they found daughter cells with 7/8 or sometimes 6/9 chromosome distribution. They followed the fate of the "extra" chromosome, believing it generally divided longitudinally in half and then degenerated or broke into fragments.

Lutz used the principle she had previously formulated — namely, that "all forms having identical somatic characters throughout all stages of their development invariably have the same number of chromosomes" — to guide her analysis of different morphotypes having the same

<sup>108</sup> See de Vries's acknowledgement of Lutz's results: de Vries, "Modern Cytological Problems," on p. 553.

<sup>109</sup> Davenport Papers, APS, Lutz to Davenport, 20 May 1911.

<sup>110</sup> Lutz thanked Professors J. C. Arthur and Stanley M. Coulter, and Mr. George N. Hoffer for "innumerable courtesies and many privileges enjoyed in the botanical laboratories of Purdue University during the past three years." Lutz, "Oenothera Mutants with Diminutive Chromosomes," p. 504.

<sup>111</sup> Anne M. Lutz, "Characters Indicative of the Number of Somatic Chromosomes Present in *Oenothera* Mutants and Hybrids," *American Naturalist* 51 (1917): pp. 375–377 Lutz discussed this work with Harley Harris Bartlett, professor of botany at the University of Michigan. See Harley Harris Bartlett (1886-1960) Papers, Bentley Historical Library, University of Michigan, Ann Arbor, Lutz to Bartlett, 17 September 1915. I thank Luis Campos for directing my attention to this correspondence.

<sup>112</sup> Lutz, "Fifteen- and Sixteen-Chromosome *Oenothera* Mutants," p. 74; italics in original.

<sup>113</sup> R. Ruggles Gates and Nesta Thomas, "A Cytological Study of *Oenothera* Mut. *Lata* and *Oe. Mut. Semilata* in Relation to Mutation," *Quarterly Journal of Microscopical Science* 59 (1914): pp. 523–71. See Anne M. Lutz, "The Production of 14(+)-Chromosome Mutants by 14-Chromosome *Oenothera Lamarckiana*," *Science* 63 (1916): pp. 291–92, and Lutz, "Oenothera Mutants with Diminutive Chromosomes," p. 504.

chromosome number.<sup>114</sup> She disputed Gates and Thomas's claim that the extra chromosome degenerated, suggesting that they were rather observing "merely whole chromosomes with clear spaces, or unstained regions." She also identified a small, "extra" chromosome in crosses between *O. lata* x *Lamarckiana* and speculated that mutations arose through the occasional production of 8-chromosome ovule fertilized by a normal pollen mother-cell with 7 chromosomes, suggesting it was the female, not the male gametes as Gates and Thomas believed, that carried the extra chromosome. The diminutive "extra" chromosomes, she emphasized, furnished strong evidence to support the theory of chromosomal individuality given that both *O. rubrinervis* and *O. aberrans* had diminutive chromosomes, and yet were morphologically very different.<sup>115</sup>

In 1917 Lutz again focused on Gates and Thomas's "theories and conclusions." Whereas Gates had previously claimed that all forms with 15 chromosomes would either resemble *O. lata* or would be *lata*-like, he now believed a form's external appearance depended on "various circumstances ... the most important of these factors is probably the peculiar combination of chromosomes received."<sup>116</sup> After years of careful study, Lutz believed she had established "that each combination of somatic characters is constantly associated with a certain number of chromosomes; in other words, that each type of plant has a definite, fixed number of chromosomes."<sup>117</sup> However, she well recognized that chromosome number alone could not explain the peculiarities in *Oenothera* mutants: those who attempt to do so "finds his pathway beset with many obstacles."<sup>118</sup> Indeed, she began to look not only to "unbalanced chromosome numbers and the meiotic irregularities" for the answer, but also to other factors to explain the phenomena.<sup>119</sup> For example, she now thought that meiotic irregularities may themselves be correlated with whether seeds were produced by early flowers or by late flowers on the same branch of a particular plant, or came from a terminal versus a basal bud, that is, environmental factors.<sup>120</sup>

Lutz, however, could go no farther in trying to solve the problem of mutation in *Oenothera*. Although it is clear that she was planning to publish several more papers, in the end these did not materialize.<sup>121</sup> She continued to live at her family home in Shadeland, Indiana to the end of her life.

<sup>114</sup> Lutz, "Oenothera Mutants with Diminutive Chromosomes," p. 502.

<sup>115</sup> Anne M. Lutz, "Oenothera Mutants with Diminutive Chromosomes," *American Journal of Botany* 3 (1916): p. 516, p. 520, p. 524, p. 511. In her 1917 paper, Lutz speculated that the "diminutive" chromosomes may not actually be a "chromosome, but merely a detached fragment of a whole chromosome, or a remnant of a degenerating chromosome." Lutz, "Fifteen- and Sixteen-Chromosome Oenothera Mutants," p. 57.

<sup>116</sup> Lutz, "Fifteen- and Sixteen-Chromosome Oenothera Mutants," pp. 54–55.

<sup>117</sup> Lutz, "Fifteen- and Sixteen-Chromosome Oenothera Mutants," p. 56.

<sup>118</sup> Lutz, "Fifteen- and Sixteen-Chromosome Oenothera Mutants," p. 56, p. 78.

<sup>119</sup> Lutz, "Fifteen- and Sixteen-Chromosome Oenothera Mutants," p. 94.

<sup>120</sup> Lutz, "Fifteen- and Sixteen-Chromosome Oenothera Mutants," p. 97.

<sup>121</sup> Lutz intended to publish a final paper in a three-part series in the *Journal of Botany*, as she mentioned in a letter to Davenport: "I am under obligations to send the third paper of the mutant series to the Journal of Botany. The Naturalist has a two-page note and another under way, dealing with "Pollen conditions in somatic chromosome number and *Oenothera Lamarckiana* and its derivatives considered in relation to the question of gametic impurity." I thought I would send to the Naturalist also, as it will not be of great value. It will contain no new facts, but will deal with the facts bought [*sic*] out by de Vries, Gates, Lutz, etc., in relation to this question. Following this, there will be three or four papers of the hybrid series which will contain new evidence. When I have them together, I will ask the Journal of Botany to release me from my agreement with them, and considering the certain length of at least one of them, it is quite possible that the editors will be glad to do so. I feel obliged to add however, that I cannot afford to do this unless assured of the same favors generously granted by the Journal of Botany. If the Station for Experimental Evolution is willing to assume responsibility for any charges that may be made for extra pages or illustrations, in case such charges were necessary, or will guarantee me that no such charges will

Although she was offered a job at Harvard and with the U.S. government during World War I, she turned these down owing to poor health. She earned an income through making and selling microscopic slides on biological subjects, one of the first women to create such a business. Like other university-educated women at the time who were not employed outside the home, Lutz sought out socially useful activities on which to focus. She became active in several area civic groups, including the Indiana State Tuberculosis Association, the Tippecanoe County Historical Association, and the League of Women Voters. In 1932, Lutz was recognized for her scientific work by Purdue University, becoming the first woman to receive an honorary Doctor of Science degree from the university. She died at the age of 67 in 1938.<sup>122</sup>

### “An Unfortunate Loss to Science”

As Shull realized in 1910, Lutz’s firing from the Station for Experimental Evolution effectively brought her scientific career to an end. Although she continued to work for a number of years and publish her results, the lack of consistent institutional support — particularly laboratory facilities for cytological study and help with plant cultivation — eventually brought an end to her work in botanical cytogenetics.

Nonetheless, her accomplishments continued to draw attention. Her papers were cited by her peers, and even singled out for praise. In 1920, in his annual report to the Carnegie Institution, Davenport reflected on the last fifteen years of the Station for Experimental Evolution, admitting that the research program had not lived up to all of “our highest hopes.” Nonetheless, there had been some breakthroughs, focusing on Lutz’s *Oenothera* work, “Thus at this Station was made the first discovery of the variation of chromosomes associated with, and inducing, a corresponding mutation of a species (the evening primrose). This lead has opened up great advances made by Professor Morgan and his colleagues. By discoveries made at this Station we see clearly that there are two types of mutations — the one due to irregularities of assortment of chromosomes and the other to changes in the chromosomes themselves; there are inter-chromosomal mutations and intrachromosomal mutations.”<sup>123</sup> The following year, addressing the topic of “Interchromosomal Mutation,” Davenport recalled de Vries’s address of 1904 in which “he expressed the hope and expectation that his *Oenothera* work would be continued by this department.” As he noted, “We tried for some years to do this through the work of Dr. G. H. Shull and Miss Anne M. Lutz. Many others took up the work and, with the departure of Dr. Shull, it was for a time abandoned here.

be made for accepted manuscript, I shall be glad to ask the Journal of Botany to release me from my agreement with them. Following the hybrid series I hope, ultimately, to have a very comprehensive pollen paper and another on somatic mitosis in *Oenothera*. These can be arranged for later.” Davenport Papers, APS, Lutz correspondence, 23 May 1917. She also wrote to H. H. Bartlett trying to arrange to give two papers, on “Dimorphic Mutants of *Oenothera Lamarckiana*” and “Characters Indicative of the Number of Somatic Chromosomes Present in *Oenothera* Mutants and Hybrids,” at the December 1916 meeting of the Botanical Society of America that she intended to publish. (Lutz to Bartlett, 10 December 1916, Bartlett Papers, Bentley Historical Library, University of Michigan.)

<sup>122</sup> Anne May Lutz biographical data, Purdue University Archives, Lafayette, Indiana. I thank Sammie L. Morris, archivist, for her assistance. On the enthusiasm for reform work among educated women in the late nineteenth and early twentieth centuries, see Rosalind Rosenberg, *Beyond Separate Spheres: Intellectual Roots of Modern Feminism* (New Haven, CT: Yale University Press, 1982).

<sup>123</sup> C. B. Davenport, “Department of Experimental Evolution and Eugenics Record Office,” *Year Book of the Carnegie Institution of Washington* 19 (1920): 107. By 1920, Davenport’s understanding of chromosomal mutations had been enriched by the findings coming from Albert Francis Blakeslee’s work on *Datura*. See

With the coming of Dr. A. F. Blakeslee the search for genetically simpler mutating plant material has been continued, and has now been rewarded by finding it in *Datura stramonium*.<sup>124</sup> Mentioning Albert F. Blakeslee's and John Belling's discovery of chromosome irregularities in *Datura*, Davenport noted that the behavior of the jimson weed "is like that discovered by Miss Lutz in the primroses at this Station 13 years ago, which was the starting-point for the great development of our knowledge of the relation between somatic mutations and chromosome variation."<sup>125</sup>

Davenport's historical reconstruction elicited a rejoinder from Gates, who believed Davenport gave too much credit to Lutz for early *Oenothera* cytological discoveries and failed to recognize his own contributions. To this Davenport replied:

My memory on this matter is not perfectly clear. All that I remember is that one summer Miss Lutz came to me and told me of her discovery of the differences in the number of chromosomes between *gigas* and, I think, *lata*. I am sure that my reaction at the time was that it was absolutely new and exceedingly important, if correct. Of course, I looked over her slides carefully after that and confirmed her conclusion. I think it must have been in the summer of 1906, altho it may have been 1905. Miss Lutz started in in [*sic*] 1904 and we had *oenotheras* from the very beginning and Miss Lutz, besides certain office duties, devoted herself exclusively to certain cytological studies, chiefly upon them.

Miss Lutz was always exceedingly slow about publishing and I remember that on the occasion mentioned she resisted my suggestions to publish and desired to wait for further information.

Another thing that was quite strongly in my mind, after all these years, is Miss Lutz coming to me in some excitement, stating that you had at a scientific meeting described the things that she had found and she felt that she had been forestalled in actual publication. It is my recollection that her work had been done so long before she told me of your paper as to warrant my saying that she discovered the variation first, even tho she had never published about it.<sup>126</sup>

Gates, however, again pressed Davenport to print a retraction. To this Davenport demurred, offering as justification for supporting Lutz's claims, and echoing her criticism of the caliber of Gates's scientific work:

Your earliest paper, read at the Christmas meetings, tells of your finding of an *oenothera* with 20 chromosomes but you are misled in its interpretation or at least the plant did not have the origin that you supposed it had. You did suggest that mutation in *oenothera*, perhaps, originated from irregularities in the chromosomes but this belief seems to be regarded by others as not being a discovery. Thus I think that Miss Lutz must be credited first as associating the number of chromosomes with a particular mutation, as she did when she associated the 24 chromosomes with the form, *gigas*. That is what I had in mind in my statement. Certainly in your book on the "Mutation Theory" you bring out very clearly the role of abnormalities in the number of chromosomes in mutations but at that time we did not have so clearly in mind the locus of what we may call Mendelian mutations in the genes of the chromosomes, as this is a matter which has been worked out in detail since your book was printed.<sup>127</sup>

Gates was incensed by Davenport's criticism of his work, and in reply Davenport did admit he

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Campos, "Radium and the Secret of Life," chap. 3.

<sup>124</sup> C. B. Davenport, "Department of Genetics," *Year Book of the Carnegie Institution of Washington* 20 (1921): p. 103.

<sup>125</sup> *Ibid.*, p. 110.

<sup>126</sup> Davenport Papers, APS, Gates to Davenport, 9 March 1921; Davenport to Gates, 25 March 1921.

<sup>127</sup> Davenport Papers, APS, Gates to Davenport, 11 April 1921; Davenport to Gates, 14 May 1921. See also Gates to Davenport, 30 May 1921.

probably should not have addressed matters of priority in this report, but did so because “it is important to show the Trustees that our work has been useful.”<sup>128</sup> His constant concern to highlight the significance of work conducted at the Station may account for his memory lapse in suggesting that Lutz began work on *Oenothera* in 1905 rather than in early 1907.

At the festivities marking the 25th anniversary of the Station for Experimental Evolution (since renamed the Department of Genetics) held in 1929, the Princeton embryologist Edwin G. Conklin singled out Lutz’s contributions to *Oenothera* studies, calling her recognition of polyploidy in *Oenothera* an “epoch-making discovery” that “established that mutations may be due to changes in the number of chromosomes as well as to intrachromosomal mutations.”<sup>129</sup> Yet despite this contemporary recognition, Lutz’s contributions to *Oenothera* genetics were soon obscured. Subsequent surveys made no mention of her publications, and Ralph Cleland, whose seminal discovery of ring chromosomes in *Oenothera* in 1922 opened the way to unraveling the basis for the odd morphological variation in the group, mentioned her work only in passing in his seminal book, *Oenothera: Cytogenetics and Evolution*.<sup>130</sup> Indeed, Cleland effectively dismissed her work in comparison with that of other early pioneers of mutation in the evening primrose, noting that “Lutz’s papers dealt primarily with chromosome numbers, but the other authors also attempted to describe meiotic behavior.”<sup>131</sup> Certainly Cleland would not have found Lutz’s focus on somatic cells of great interest at the time he ushered in a new era in *Oenothera* studies. Increasingly, the “mutational events” in *O. Lamarckiana* came to be understood as the product of the peculiar chromosomal mechanics involving ring formation with crossing-over during meiosis.<sup>132</sup> Not only did such work require techniques and equipment not available to Lutz, but also a mode of conceptualization that was far beyond the de Vriesian understanding of mutation and methodical approach to the problem that had held sway for two decades.

In this regard, however, Lutz provides an insightful window into early approaches to mutation studies. She also well exemplifies the experiences of some of the first women to work in genetics. She was no anomaly: women were well represented in both genetics and cytology in the first two decades after the rediscovery of Mendel, not only in the United States but also in Britain and Germany.<sup>133</sup> Entering genetics after completing advanced university training in biology, she

<sup>128</sup> Davenport Papers, APS, Davenport to Gates, 14 May 1921.

<sup>129</sup> See “Address by Professor Edwin G. Conklin at Cold Spring Harbor,” in the “Report of the President, 1929,” *Year Book of the Carnegie Institution* 23 (1929): p. 31.

<sup>130</sup> J. Adolphina Leliveld, “Cytological Studies in Some Species of the Genus *Oenothera*,” *La Cellule* 40 (1931): pp. 195–256; R. Ruggles Gates, *Taxonomy and Genetics of Oenothera: Forty Years Study in the Cytology and Evolution of Onagraceae* (The Hague: W. Junk, 1958); Ralph E. Cleland, *Oenothera: Cytogenetics and Evolution* (New York: Academic Press, 1972).

<sup>131</sup> Ralph E. Cleland, *Oenothera: Cytogenetics and Evolution* (New York: Academic Press, 1972), p. 43.

<sup>132</sup> Ralph E. Cleland, “The Reduction Divisions in the Pollen Mother Cells of *Oenothera Franciscana*,” *American Journal of Botany* 9 (1922): pp. 391–413. For an overview, see James Schwartz, *In Pursuit of the Gene: From Darwin to DNA* (Cambridge, Mass. and London: Harvard University Press, 2008), chap. 11. For a contemporary recognition of the importance of Cleland’s new cytogenetic approach, see Leliveld, “Cytological Studies in Some Species of the Genus *Oenothera*,” pp. 200–202.

<sup>133</sup> Marsha Richmond and Ida Stamhuis, *Women in the Early History of Genetics* (In preparation); Marsha L. Richmond, “Women in the Early History of Genetics” (2001): pp. 55–90; Helge Satzinger, “Women’s Places in the New Laboratories of Genetic Research in Early 20th Century: Gender, Work, and the Dynamics of Science,” in *Women Scholars and Institutions. Proceedings of the International Conference (Prague, June 8–11, 2003)*, eds. Ida Stamhuis, Soňa Strbáňová, and Kateřina Mojsejová (Prague: Studies in the History of Sciences and Humanities, 2004), 13A: pp. 265–94; Ute Deichmann, “Frauen in der Genetik, Forschung und Karrieren bis 1950,” in *‘Aller Männerkultur zum Trotz’: Frauen in Mathematik und Naturwissenschaften* (Frankfurt am Main: Campus Verlag, 1997).

benefited from the absence of significant competition from male workers and the marginality of the new field.<sup>134</sup> She appears to have encountered no significant hindrance, either in her research, attending conferences, publishing papers, or in gaining recognition for her work both at home and abroad. Indeed, gender posed little barrier, even though she was often the first woman to achieve certain milestones, as when she was granted admission to the Catholic University of Louvain at a time when women were not readily admitted into European universities.

Nonetheless, a more nuanced focus on Lutz's career reveals less clearly discernible constraints. Using her relationship with Davenport as a guide, she appears to have been subject to a different social standard than male researchers, and the consequences for any digression were more severe. Those who did not adhere to social expectations — either in terms of expected demeanor and, in Lutz's case, steady scientific productivity — were subject to dismissal. Owing to women's more restricted employment opportunities, termination of their position threatened their ability to continue working in science. Males, on the other hand, had greater opportunities to secure another position, especially through university employment.

Moreover, the circumstances surrounding Lutz's firing indicate the kind of "gender politics" operating in early twentieth century science. While there is no indication that Lutz was a feminist, she appears to have been a woman who freely spoke her mind around males. As such, she may have transgressed the boundaries of expected female decorum, applicable in institutional as well as domestic settings, of showing proper deference to male superiors. In charging her with "insubordination," Davenport implied that she was a gossip, a characteristic more associated with women than men.<sup>135</sup> Certainly, her correspondence indicates she could sometimes be duplicitous: while adopting a cordial tone in corresponding with individuals, she could turn around and make disparaging comments about them to others. Yet, she may have had genuine grievances to provoke such actions. As the events behind her firing reveal, it was the female victim who was severely punished while the transgressions of the male, Shull, were overlooked. Davenport also failed to countenance her repeated mention of the loneliness and isolation she (and others) experienced at the Station, despite the widespread attention Charlotte Perkins Gilman brought to such feelings in her 1892 story "The Yellow Wall-Paper" and later publications.<sup>136</sup>

Davenport may also have harbored gendered assumptions in interpreting Lutz's reticence to publish as a poor reflection of her scientific abilities. Others shared her belief that scientists should be confident about their results and interpretations before publishing. Nonetheless, it is true that women may have been more hesitant to publish than men. Women in science, sociologists note, tend to be more conservative in their publishing strategies — waiting to make their findings public until they are confident about their validity. The preference for a strategy of "quality" over "quantity" may relate to the greater pressures women feel in establishing the reliability of their results.<sup>137</sup>

In the path-breaking and complicated field of *Oenothera* genetics, as Davenport illustrates, Lutz's conservative tendencies may have been considered more a vice rather than a virtue. In this

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<sup>134</sup> It is interesting to note, for example, that the next two cytogeneticists hired at Cold Spring Harbor were both men: Charles W. Metz in 1916 and John Belling in 1920.

<sup>135</sup> Patricia Ann Meyer Spacks, *Gossip* (New York: A. A. Knopf, 1985).

<sup>136</sup> See Charlotte Perkins Gilman, *Women and Economics: A Study of the Economic Relation Between Men and Women as a Factor in Social Evolution*, reprint, 1899 (Berkeley, Calif.: University of California Press, 1998).

<sup>137</sup> Jonathan R. Cole, *Fair Science: Women in the Scientific Community* (New York: The Free Press, 1979). See also the discussion of this point from a perspective of status in science rather than gender in Robert K.

highly competitive field of study, the publication of novel observations and interpretive analyses were quickly rewarded. Women in such fields may have faced greater pressures as well as more uncertainty. Such a matrix of complex institutional, social, intellectual, and psychological factors may all have played a role in the rise and fall of Lutz's scientific career, as well as in why her work has received little historical acknowledgement.

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## *Mutant Sexuality: The Private Life of a Plant*

Luis Campos

The mutant sexuality of the evening primrose *Oenothera lamarckiana* was central to de Vries' mutation theory. In this article, I suggest that historians should pay more attention to the primacy of scientific observation and what I call "the mutant gaze" in the study of mutation. I suggest that we have in the gloriously complex case of *Oenothera* — and its role in the fate and legacy of the mutation theory in the first decades of the twentieth century — a new analytical tool for doing the history of science that to my knowledge has not yet been fully theorized or systematically employed in an empirical example. This tool, I will argue, can help us better understand and appreciate the central place of the mutant gaze in what has sometimes been called "Oenotherology" — as well as the place of gaze in science more generally.

To begin, we all know that there is much more to the history of genetics than the classic story of *Drosophila* genetics. As stimulating and important as this work was, a dominating attention to this narrative — from the Columbia "fly boys" stories to Muller's later radiation genetics — has tended to eclipse a tremendous variety of non-genically oriented experiments by other top geneticists in this period concerned with understanding the phenomena of mutation. In other work I have delved into this richer history of experimental mutagenesis in the period prior to Muller and orthogonal to the primary interests of the drosophilists,<sup>1</sup> and I also have suggested other new ways of rethinking the history and legacy of de Vries' mutation-theory. In seeking to recover the ways in which a number of scientists saw themselves as inspired by or working along a primrose path first charted by de Vries, I have argued that we need to rethink the mutation-theory more as the vibrant and sometimes eclectic research tradition it was — we might call it "Oenotherapy" (and "Oenopractice," of course) — than the static and "disproven" theory that it certainly wasn't.<sup>2</sup>

The question of mutation in de Vries' beloved plant, *Oenothera*, proved to be intimately related to what was recognized from fairly early on as its "queer" mode of reproduction, a complex set of mysterious interactions that took cytogeneticists decades to unravel. It is worth noting that an intermediate realm of mutation between gene and organism — a third sect commonly known to contemporaries in the first third of the century as "chromosomal mutation" — was widely apparent in the literature of the 1910s, 1920s and 1930s, and consisted of phenomena such as polyploidy, trisomy, reciprocal translocation, and more. Chromosomal mutations — resting on the number, arrangement, and interconnections of chromosomes — were widely understood to be an important mechanism of evolutionarily significant variation completely independently of any changes known to have occurred in genes. Artificially induced chromosomal mutations, such as Blakeslee's efforts in the 1920s and 1930s, were even referred to as early examples of "genetic engineering."<sup>3</sup> Oddly, however, for all their commonplace existence in the literature of the period, references to chromosomal mutations are almost entirely absent from the *historiography* of genetics, which has been largely focused on genetics as an enterprise about genes. It is imperative that we understand what genetics meant to geneticists of all stripes, and that we venture beyond the

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<sup>1</sup> Campos 2006.

<sup>2</sup> Campos 2010.

<sup>3</sup> For more on Blakeslee, see Campos 2006, and Campos 2008.

straight confines of familiar stories of “drosophilism.” To aid in this, I make an important distinction between genics (the genocentric tendency also common to most histories of genetics) and genetics (the more pluralistic practices that actually co-existed in this period), in order to try to capture how mutation meant multiple things in this period. It is of critical importance to pay attention not only to the way that disciplinary distinctions (zoology, botany, genetics, karyology) may have affected the production of genetical knowledge, and what counted as a mutation in which field, with what skill, or to whose eyes — but also to other more personal distinctions as well.

Onward to *Oenothera*. I have been concerned in recent years to trace the impact and legacy of Hugo de Vries’ mutation theory on a number of geneticists in this period. One insidious phenomenon has been the dominant Whiggish narratives that we have all been told (or told ourselves) of the “disproof” of de Vries’ mutation theory — a consequence of a primarily genic account of the history of genetics. The standard narrative here is that *Oenothera* turned out to be a bizarre plant, with an extraordinarily unusual system of heredity, and one that was not representative of heredity “in general” (whatever that might mean). The received view of the fall of de Vries’ mutation theory holds that de Vries’ theory began to come into disrepute during the second decade of the twentieth century as it was discovered that the plant he had been studying, *Oenothera lamarckiana*, had odd chromosomal dynamics. Careful genetical breeding work is held in this view to have been instrumental in determining that something unusual was going on with *Oenothera*’s mode of reproduction, just as careful cytological work was required to establish the behavior of its chromosomes during meiosis.

*Oenothera* is definitely one queer plant. The “mutants” that de Vries had discovered and that bred true generation after generation, and which many had held to be proof of his theory, were argued by Otto Renner in the first decade to be the result of a system of two complexes deduced genetically that he labeled *velans* and *gaudens* (accounting for what would later be known as a sort of balanced lethal). These were cytologically “confirmed” by Bradley Davis, Reginald Ruggles Gates, and Ralph Cleland in the 1910s, 1920s, and 1930s to be the result of chromosomes linked together end-to-end in rings rather than the homologous pairs separating and pairing during meiosis, thus leading to the unequal distribution of chromosomes into daughter cells and to differing phenotypic effects persisting through generations. Masterful synthetic accounts by the 1940s were held to have cleared things up. *Oenothera* was shelved, ironically perhaps, as a bit too freakish for much use in proper genetics.

In order to understand how the study of chromosomal mutations was a central enterprise in genetics and the major legatee to de Vries’ mutation theory, I headed off to Amsterdam to read my way through Hugo de Vries’ surviving papers. These were kept in a small concrete closet of the biological library on the science campus of the University of Amsterdam on the outskirts of the city. From the papers kept tucked away in this closet, I learned many interesting things about de Vries’ practice and the development of the mutant gaze. I learned some fascinating things about the private life of *Oenothera* — and about de Vries himself. And from similar explorations of the papers of some of the staunchest supporters and proponents of the mutation theory from 1900 to 1930 — men such as Theodoor Stomps, Reginald Ruggles Gates, and Harley Harris Bartlett — men who clearly saw themselves in the research tradition of the mutation theory de Vries had inaugurated, I began to see a pattern of the mutant gaze coming out for further analysis. This paper is my first attempt to point to those connections and to offer a possible new reading of the private life of *Oenothera* — and those who studied it.

## Queering the History of Science

“New & queer things continue to turn up in the chromosome business,” E. B. Wilson wrote to Bateson as early as 1905, “there seems to be no end to the kinds of combination, couplings and doubling up that they can do... I can’t doubt that we are on the track of something. –What is it?”<sup>4</sup> From early on, the problem of *Oenothera* was clearly the problem of its chromosomes and their odd behavior. Throughout the teens and into the twenties and beyond, cytological investigators struggled to come to grips with *Oenothera*’s “normal” karyokinetic idiosyncrasies, and the sheer complexity of the phenomena it presented: polyploidy, trisomy, aneuploidy, and arguments over the nature and meaning of “hybridism.” Many argued that the “extensive sterility” of the pollen was the best indicator that *Oenothera lamarckiana* was in fact a hybrid species. But it is generally agreed to be genetical work of Otto Renner and the cytological work of Ralph Cleland on *Oenothera*’s complicated hereditary behavior and structures that brought new facts to light. As Cleland later summarized:

One of the striking characteristics of the *Oenotheras* is the existence of very extensive complexes of linked genes. In fact, in the various wild strains now under cultivation, all or almost all of the known genes belong apparently to a single linkage system. It is as though practically all of the genes were situated in a single chromosome pair, or as though the *Oenotheras* had but one pair of chromosomes, instead of 8. These plants are then homozygous or heterozygous, not for limited groups of genes, but for the whole complex.<sup>5</sup>

In other words, *Oenothera*’s chromosomes did not pair up with each other for conjugation and division; rather, they joined in alternative ways, ending up forming rings and thereby creating a radically different type of hereditary mechanisms that not only preserved otherwise lethal genes against selection, but in fact created what were phenotypically distinct new species in the space of one generation simply by this chromosomal rearrangement and reattachment — with no genic change necessary. (This complicated hereditary system took decades to figure out.)

Interesting historical work needs to be done on the remarkable patterns of chromosomal anthropomorphism in this period. The history of associating natural and social orders is centuries-long; the association of the behavior of plants with that of humans and their own sexual lives, while of more recent vintage, is already well-established in the literature: I need only mention Londa Schiebinger’s “The Private Life of Plants” to suggest that undoubtedly the history of the term “conjugation” as applied to chromosomes has a longer history predating the study of *Oenothera*.<sup>6</sup> And indeed, this association of conjugating chromosomes with heterosexual pairing continues over decades (there are examples in Bateson, Darlington, and Dobzhansky — even Herbert Spencer Jennings early on warned against the “haphazard mating” of chromosomes).<sup>7</sup> There is rich material here for an analysis of chromosomes and their pairings much as Emily Martin has done for the egg and the sperm.<sup>8</sup> The inability to conceive of chromosomes that did not, would not, could not pair

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<sup>4</sup> Wilson, E. B. to W. Bateson, April 2, 1909. Darlington Papers, Oxford University, D.32.

<sup>5</sup> Cleland 1929, pp. 329-330.

<sup>6</sup> Schiebinger 1991. The subtitle of my article pays homage to Schiebinger’s pathbreaking readings.

<sup>7</sup> Jennings, H. S. to Reginald Ruggles Gates, January 22, 1910. Gates Papers, King’s College London.

<sup>8</sup> Martin 1991, pp. 485-501.

during meiosis — the centerpiece of sexual reproduction — proved a major obstacle to deciphering *Oenothera*'s sexual behavior. Indeed, for most of their existence, chromosomes are not paired — but in many species like *Oenothera* they are not paired even at meiosis or mitosis. A free Martin-style reading of scientific accounts of *Oenotheran* reproduction might point out a further heterosexist bias: an implicit heteronormativity of chromosome pairing that was presumed in the case of *Oenothera*'s reproduction, and consonant with work done in *Drosophila*. This presumption may well have helped to enshroud *Oenothera*'s cytonuclear bedroom in mystery even as it led to the later characterization of *Oenothera*'s reproductive system as “aberrant,” “degenerate,” or “subsexual.”

The accomplished cytogeneticist Cyril Darlington pointed out that these chromosomal rings constitute genetic complexes in *Oenothera*, behave “as a unit in inheritance,” and “affect the whole habit and structure of the plant.” As such, Darlington argued, “[i]n these respects they resemble the sex difference in animals.”<sup>9</sup> Rings of chromosomes were not just reflecting *Oenothera*'s weird sexual habits — they could themselves be conceptualized as *sexual elements*. In a quick turn of phrase and a flash of insight, Darlington here explicitly transformed an understanding of what had previously been understood by most *Oenotherologists* up to then to be *chromosomal mutants* into perhaps nothing less than new and queer *sexes* writ large. But many others insisted on calling such a form of reproduction “subsexual reproduction,” demarcating it as queer, even among plants well known for their polymorphous perversity. Such investigators pointed out how this system of reproduction must be evolutionarily “degenerate” when compared with reproductive systems uncovered in other species. And yet, the wide ecological range and rich evolutionary history of *Oenothera* demonstrate that even this queer form of sexual reproduction produced viable mutants. The question is therefore something of an epistemic challenge for the historian: is there a way in which using sexuality as an analytical lens can help us understand something of the dynamics of these discursive twists and turns in *Oenotherology*? Is there more to the mutant gaze than meets the eye?

While it may not have been Darlington's authorial intent to consolidate a convincing account of “subsexual” reproduction where the interaction of the chromosome complexes themselves counted as a queer form of sexual reproduction — and where the identity of the complex as a sex “megachromosome” depended on the alternative behavior and multiple queer pairings of chromosomes — what is clear is that careful cytogenetical work did not so much *disprove* the mutation-theory, as our current historiography suggests, as *expose* the biases that “closeted” such queer forms of reproduction. Paying careful attention to the private life of this plant can only help to give a more accurate understanding of the history of mutation; it may also make possible a rich new “queer” reading for historians of genetics. Drawing on feminist scholarship in our field, and the insights into the role of gender in genetics, I want to suggest that sexuality and sexual orientation can be more for the history of science than an *object* of study; just like sex and gender, sexuality and sexual orientation can be fruitfully used as *tools of analysis* in understanding the construction of scientific knowledge. That, at least, is the experiment I am trying here.

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<sup>9</sup> Darlington 1932, p. 339.

Is this a “legitimate” reading? The fact that the actors themselves were aware of the multiple and sometimes problematic colloquial resonances of the scientific terms and theories in play, and the intercalation in their personal narratives in their correspondence of personal (hetero)sexual histories and genic or chromosomal discoveries — one thinks most notably of the colorful correspondence between Darlington and Pio Koller — should make us at least open to interpretive possibilities that a fine-grained analysis of the history of genetics using sexuality as an analytical lens can provide. Highlighting heterosexist biases in the study of reproduction at the chromosomal level may even be scientifically productive. But first and foremost, the proper answer to such an undoubtedly well-intentioned question is to ask why this kind of interpretive lens has not yet been attempted before.

In his book *A World Without Women*, David Noble has described early modern science as a monastic tradition that produced knowledge in a space that, as Steve Harris has paraphrased the argument, “was itself deliberately and self-consciously crafted to exclude women... Their nature as women was somehow antithetical to the homosocial bonds necessary for the production of scientific knowledge.” Mario Biagioli has similarly pointed to the purpose and function of homosociality in early scientific academies.<sup>10</sup> Historians of science have thus already well begun to explore the possible implications of the homosocial development of science in the early modern age; we have paid a great deal of attention in the history of science to the role of homosocial environments and the exclusion of women in the formation of modern science. We have also studied homosexuality as a historical concept and form of emergent biopolitics, an epistemic thing with a particular historical trajectory and construction all its own. We have curiously not, however, linked these two strands of analysis together with an empirical case actually suggesting how such rampant homosociality and relatively unremarked-upon homosexuality in science may be related — and more interestingly, how they may be related to the production of modern genetical knowledge. The (confirmed) bachelor is a curiously frequent figure in the history of science — Copernicus, Galileo, Descartes, Boyle, and Newton were all bachelors for most if not all of their lives — and yet these sorts of things all historians of science know about have gone largely unanalyzed using sexuality as a lens. *Why?*

Many scholars interested in the connections of gender and science have been concerned to trace the intercalation of women into science, and what some have termed “the introduction of sex into the laboratory.” I want to suggest today, however, that sex was probably always already in the laboratory — or the field, the academy, or any other homosocial environment, for that matter. There were surely more cases of homosexual scientists and the connection of this to the production of scientific knowledge than the zero uncovered so far. With apologies to J. B. S. Haldane, while the history of genetics may be queerer than we have thus far supposed, it ought not be queerer than *we can* suppose — or than we can least ask about.

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<sup>10</sup> “In order for the male philosopher’s pure love for ideal forms to survive and beget knowledge, his desire should be redirected from corrupting material objects of desire — i.e., women, toward a purer form of love: one with another man.” Biagioli 1995, p. 141.

## *The Private Life of People*

We know something now about the immensely complicated private life of *Oenothera* — what about the private life of the Oenotherologists? I focus here on four men central to the story: Hugo de Vries, Theodoor Stomps, Reginald Ruggles Gates, and Harley Harris Bartlett. I want to suggest that there is a link between the so-called permanent structural hybrids of *Oenothera* known as complex heterozygotes, and the complex and heretofore unremarked-upon role of heterosexism in early genetics.

— Hugo de Vries —

It was evidently an open secret that Hugo de Vries, the inventor of the mutation theory, though married, was something other than “straight.” (As the saying goes, “even Oscar Wilde had a wife.”) Moreover, it is striking to see no fewer than three of his most knowledgeable contemporaries in the study of *Oenothera* mutations, and often among his strongest supporters, also possibly shared a queer sexual orientation.

The social meaning of the mutation theory was of prime importance to de Vries, as a number of scholars have already demonstrated.<sup>11</sup> Onno Meijer, in particular, has noted that for de Vries this was partially a way of explaining how it was possible “that humans have sometimes useless or even harmful characteristics” that could possibly be controlled or improved. And as Bert Theunissen noted, “de Vries’ *Mutationstheorie* was not only intended as an exposition of his scientific insights into the phenomena of heredity and evolution, but also to give articulate expression to his position in the Dutch debate on the reform of society at the turn of the century.”<sup>12</sup> Theunissen has noted:

In the long run, De Vries also expected biology to provide solutions for many other social problems, such as the problem of human intellectual (in)equality and its consequences for education and the social order, of the rights and wrongs of social Darwinism, of racism, etc. For De Vries, scientific progress and social progress went together.<sup>13</sup>

...Besides adding substance to his claim regarding the practical value of science, De Vries believed that the laws of heredity provided direct insights in the nature of society itself: “[they] open up perspectives for a social biology that is extremely attractive.”<sup>14</sup>

...De Vries concluded, the important point to be made was that the application of the laws of fluctuating variability to society ‘will doubtless bring about a milder judgment [of one’s fellows] and greater mutual respect and thus contribute to the increase of the happiness and contentment of humanity. And in this way our knowledge of nature not only enhances our material, but also our intellectual well-being. Knowledge is power; may it always be used to the good!’<sup>15</sup>

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<sup>11</sup> I am indebted here to the extraordinary assistance in this project rendered by Erik Zevenhuizen, Archivist of the de Vries Papers at the time of my visit and who has recently completed a biography of Hugo de Vries, in Dutch.

<sup>12</sup> Theunissen 1998, p. 476.

<sup>13</sup> Theunissen 1998, p. 480.

<sup>14</sup> Theunissen 1998, p. 485.

<sup>15</sup> Theunissen 1998, p. 487.

Or elsewhere: “It is indeed the aim of all branches of science to promote the happiness of one’s fellow-men.”<sup>16</sup>

It was in Meijer’s 1986 article, “Hugo de Vries and Johann Gregor Mendel: The History of a Denial,” that Meijer committed to print the first scholarly interpretation that Hugo de Vries was gay, thereby implying that there might be a deeper significance to his claims for the societal implications of the mutation theory than may at first have seemed.<sup>17</sup> Meijer has passed along other information about de Vries to scholars in the field that has yet to make it into scholarly publications — for example, that “of course de Vries was gay,” or that there were various “boys” who had helped organize and were running around at de Vries’ 80<sup>th</sup> birthday party, and that de Vries clearly enjoyed the company of younger men working around the house. But Meijer is not the only source for such stories. Others in 1996, ten years later, spoke with de Vries’ old housemaid who told how de Vries and his wife slept in separate rooms, and how de Vries had photographs of naked men and women decorating the mantle of his bedroom. Questionable evidence, surely, but other intriguing evidence comes from the historian Peter van der Pas in the early 1970s. In the midst of research for writing a biography of de Vries for his degree, van der Pas wrote to his advisor to say: “That Hugo de Vries would have been homosexual is a widely distributed story. Even American geneticists are coming with this story to appear in the daylight.” One of Van der Pas’ advisers wrote back: “You don’t need to doubt the correctness of the suspicion; it was here generally known among friends and colleagues [people who surrounded him] although they were silent about it. [*i.e.*, it was an open secret] ... Probably this is the explanation for his unfeigned aversion of female students and at the same time his friendly attitude towards several of them, for instance, those who were engaged or married to the male students he was good friends with.”<sup>18</sup>

Other accounts also exist that de Vries had a “younger friend” (in his late teens) by the name of “Willem de Jager” who helped with the housework at the de Vries home in Lunteren in the 1920s while going to secondary school, and who would take trips abroad to Paris and London with de Vries when de Vries was in his 70s while Mrs. de Vries stayed at home. De Vries was evidently very open about his special “friendship” with Willem de Jager and other male youths.<sup>19</sup> In another letter from de Vries dated December 1921, for example, de Vries even noted that he was intending to spend Christmas and New Year’s Eve in Davos, Switzerland, “to keep my young friends company” (this may have referred to the younger brother of Stomps).<sup>20</sup>

At the very least, basic details about Hugo de Vries’ sexuality seem to have been well known to his contemporaries as well as to a relatively small cadre of de Vries researchers in recent times. But the real question is: how this is relevant for Hugo de Vries’ science? Or is this just another fact about his life, like his doting mother?<sup>21</sup>

<sup>16</sup> Theunissen 1998, p. 479; citing de Vries 1899, “Eenheid in veranderlijkheid.” Rectorial Address, Amsterdam University, 1898. In H. de Vries: *Zaaien en planten*, Tjeenk Willink, Haarlem, pp. 3-25. Compare with a similar sentiment: “Voorwaar een schoon ideaal! Bij te dragen tot de bevordering van het levensgeluk der mensheid is het grote doel van alle wetenschap.” De Vries 1898, pp. 65-80.

<sup>17</sup> Meijer 1986, pp. 69-90.

<sup>18</sup> Heimans to van der Pas, April 10, 1972. Hugo de Vries Papers, University of Amsterdam.

<sup>19</sup> According to Erik Zevenhuizen, a staff member at the University of Amsterdam whose father had worked with de Vries in his experimental garden in Lunteren, had been cleaning his house and found things belonging to his father. These included a letter written by de Vries to the man’s father, saying “I’ve been on holiday with Wilhelm die Jäger...”

<sup>20</sup> de Vries to Palmer, December 1921. Hugo de Vries Papers, University of Amsterdam.

<sup>21</sup> As Betty Smocovitis has asked: “Is detail about personal matters — marital relationships, family etc., all that important, especially in the biography of a scientist? How much light does it shed on chromosomal botany to know details about reasons that Stebbins’s first marriage failed?” V. B. Smocovitis, “Living with

— Theodoor Stomps —

We don't hear much about de Vries' children in his correspondence, but we do hear about Theodoor Stomps, one of his favorite students — though, interestingly, not his brightest — and the two maintained a close connection ever since Stomps first arrived at the University of Amsterdam in 1903. Eighteen years old, Stomps' start at the university owed much to de Vries' intervention after Stomps' father died shortly after Stomps had matriculated. De Vries ended up financially sponsoring Stomps' education. Decades later, when Stomps was going through hard times — after years of living with his mother, she had finally died — he reached out to de Vries for support, declaring the “terrible emptiness” he felt, and noting “I can understand people who commit suicide who are in the same conditions.”<sup>22</sup> Stomps apparently had a reputation for being a bit eccentric, naïve, and a bit childish, leading another of de Vries' former students, van Leeuwen to note: “This time Stomps was I think rather down and complaining about all kinds of things. I think he is getting very old but there is not much to do against it. I can't send a woman to him and neither will I give her a recommendation of Stomps to any woman I know.”

It was this period of intense loneliness, this sense of family-lessness, that came to be reflected in a speech that Stomps later gave expanding on de Vries' own interests in the broader implications of the mutation theory for society. On January 8, 1935, Stomps made a public statement on a matter of fundamental interest to science, to Dutch politics, and to his own life. In a speech given as the Rector Magnificus of the University of Amsterdam entitled “The Mutation Theory and Its Significance for Our Society,” Stomps declared (in a passage worth quoting at length):

I want to close my discussion of this part with a few words about something that happens, that means an enormous tragedy for a large part of our fellow people, namely, homosexuality. ... For a biologist that has been trained in heredity, it is a very simple fact that were it not known, we would be advised to search for it because it can be found. I will try to give you a feeling of the essence and may refer to one of the ground principles of the mutation theory, namely, that pangenes can behave with a different force or intensity. There is not only the active and latent condition but also intermediate grades of activity. With several species which have been studied more closely, one has discovered this principle. Erwin Baur, for instance, got from the dark red flowering large snapdragons through continuous retrogressive mutations in one pangene not less than eight constant races with different shades of color varying from pale red to ivory. Also Morgan discovered with the fruit fly several series of unilocal factors, for instance a number of eleven eye colors from the dark red of the wild flies to the white. Several researchers with plants and animals that especially also the pangenes that determine the sex which can occur in different states are easily changed by mutation. When we follow Richard Goldschmidt's material of a butterfly, collect them at several places, then we will find males and females of different places together very often give a very peculiar offspring, with all possible intermediate forms between males and females, so-called intersexual individuals. The crossing of a European female with a Japanese male gave Goldschmidt only male offspring. With this the problem of homosexuality, that is intersexuality, in man is of course completely understood. It is improbable that by all people the factors that determine the sex are working with the same force, and the experiments of Kniep, Vanden Dries, and others, with fungi

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Your Biographical Subject: Special Problems of Distance, Privacy and Trust in the Biography of G. Ledyard Stebbins Jr.,” Smocovitis 1999, p. 429.

<sup>22</sup> Stomps to de Vries, December 11, 1934. Hugo de Vries Papers, University of Amsterdam.

justify this claim, that mutations can cause at the most unexpected moments homosexuality. There is about homosexuality nothing secretive, nothing shameful, and we can only have pity with those people that are struck by it and who mostly must lack the most beautiful thing that can give value to life, that is, the raising of a family. ... So I hope that His Excellency, the Minister of Justice, will decide to amend the famous article 248bis, which makes a great difference in the treatment of rights between the homo- and heterosexual! As I am informed, it is not even true that a larger percentage of the homosexuals are brought to court than the heterosexual population! [i.e., that homosexuals are not more criminal than heterosexuals] And speaking about punishments may this be all the time a medical treatment that with heterosexual offenses might castration, while with a homosexual offense we should rather think of the very interesting experiments of Steinach, etc., with frogs, guinea pigs, rats, and chickens, that prove that the transplantation of the sexual glands literally can bring to light all traits of the other sex, or, when time permits by syringe injection of the hormone of the desired sex.<sup>23</sup>

One anonymous postcard sent in response to the lecture simply said “Praise!” [“Hulde!”] Another, more complete letter came from D. Hoogendijk, the director of arts and advertising for a publishing company in Amsterdam:

Dear sir,

Your beautiful lecture on January 8<sup>th</sup> has had for me personally many important effects. That I feel a very strong urge to thank you. It gave several people in my environment who are very dear to me the unseen opportunity to speak out about a subject that otherwise in the company of homosexuals is not mentioned or only in a very negative way. When one is nevertheless liking a homosexual, in spite of himself, one tends to keep silent and a silence that very often is even harder to bear and that gives him the feeling of living on a deserted island. It is indeed very sad. But now yesterday, it appears to me as if a dark cloud that clouded the sun for a very long time was disappearing. The world became lighter and warmer. People looked different, more friendly... [he tells a story that sometimes he was sent away and had to wait in corridor, until his father said you are a good boy now, you can come back inside... that it was like a wonderful feeling that you were a part of the family again, and he could even cry]. And this almost-forgotten feeling came yesterday again to me although it was only for one day I thank you very sincerely for that, I was part of the world again.<sup>24</sup>

What Stomps must have thought was a stroke for sympathy for homosexuals, some newspapers of the day attacked as a form of naïve materialism concerning mutations and human nature. Although not top rank, Stomps was still a serious scientist, however — a man in a position of power, as well as a lonely man who had just lost his only family. Whether he was struggling with his own sexuality or at home in it, his conflation of homosexuality with intersexuality reflects a dominant conceptualization of the time that equated the two in the category of a “third sex,” making the call for a study of what we would today call intersexuality also a call for the study of the genetics of homosexuality for his contemporaries. What’s more, according to historian Theo van der Meer, “Since the University of Amsterdam, at the time was the so-called City or Municipal University Amsterdam, many local dignitaries including the mayor were present, as well as the university professors and the like: most of them were deeply offended and some would refuse to shake hands with Stomps ever again. Not surprisingly, the rumor spread that Stomps himself was homosexual,

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<sup>23</sup> Stomps 1935.

<sup>24</sup> D. Hoogendijk to Stomps, 10 January 1935. Hugo de Vries Papers, University of Amsterdam.

which he vigorously denied... In 1947 Stomps would give a lecture on mutation theory at the recently (1946) founded Shakespeare Club, the forerunner of the COC, still the national gay and lesbian organization. When asked about his rectoral address in the previous decade, he said he had been moved then by a recent arrest of one of his assistants for trespassing 248bis.” A letter from another contemporary was recently uncovered by Van der Meer that noted not only that Stomps was indeed homosexual, but a further tale of de Vries himself: that de Vries had been forced to quit his job as a high school teacher in Amsterdam because of unspecified “sexual contacts with some students.”<sup>25</sup>

— Reginald Ruggles Gates —

Two of de Vries’ other staunchest early defenders, the Canadian Reginald Ruggles Gates and American Harley Harris Bartlett, also seem to have been a bit queer. As one newspaper described Gates later in life:

... he has scarcely a line in his forehead and few gray hairs in his head. He looks as if he could shoot a snappy 75 on the golf links any afternoon, or paddle a canoe for miles on great Slave Lake, where he studied the Eskimos, without fatigue ... travelling was never irksome to him and, indeed, was his sole recreation.<sup>26</sup>

Another stated that he was a “brown-haired, cheerful, boyish-looking scientist” who first started “wresting... secrets from the evening primrose in 1907 as a pure botanist, but by 1922 he had convinced himself that his discoveries about the microscopic chromosomes within its germ cell were true also of human beings.” (This was published in an article entitled: “Parents Can Learn from the Evening Primrose: Human Heredity Lessons from Plants.”<sup>27</sup>) A third article noted that his “experiment in Regent’s Park began seven years ago. An acre of evening primroses is hidden behind banks of shrubs and flowers, and from those primroses Professor Ruggles Gates and his London University assistants have wrested secrets of heredity, which are fundamental also for man.”<sup>28</sup>

Whatever other wresting Gates may have been doing in an acre of primroses hidden behind banks of shrubs and flowers in Regent’s Park is not stated — but perhaps that is only because it did not have to be. As Graham Robb has noted in his *Strangers: Homosexual Love in the Nineteenth Century*, “Balletic beating about the bush was both a precaution and a ritual” in biographical accounts of known homosexuals. “Some entries are so coy as to appear insulting, but this was not necessarily the intention. The idea, sometimes, was to convey the precious information as it were under the counter... secret vocabularies were more a celebration than a practical device. Even today, some of the most interesting and curiously Victorian circumlocutions can be found in

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<sup>25</sup> Theo van der Meer, personal communication, August 12, 2009.

<sup>26</sup> “Finds Life’s Secret in Evening Primrose,” *Windsor Daily Star*, August 29, 1935.

<sup>27</sup> *New Chronicle*, 10 September 1936. Another article was entitled “Seeking Clue to Heredity: World-Wide Inquiry”; “Queer Family Traits”; “Odd Toes’ & ‘Odd Eyes,” *Paris Daily Mail*, May 25, 1936. Pages 73 and 68 of Gates archives newspaper clipping album. Gates Papers, King’s College London.

<sup>28</sup> “The Primrose Path with Professor R. Ruggles Gates,” *Evening Standard*, April 6, 1939.

obituaries and literary companions written by heterosexual or closet gays... ‘intensely private,’ ‘complex personality,’ ‘enigmatic,’ etc...’<sup>29</sup> Another description of Gates seems to fit this known art:

... As a colleague he was difficult to get to know and to be friendly with, but from time to time his wry smile and twinkling eyes expressed a sense of humour not displayed to all and sundry. He was almost effeminate in his gentleness but he had a core of resilience and when occasionally he became involved in unworthy controversies, sometimes on the wrong side, he rarely admitted to error or retracted any statement previously made. In many ways he was a strange man, but with his prolific writings he was not without influence on the scientific thought of his day. / His first wife was the well-known botanist and pioneer advocate of birth control, the late Dr. Marie Stopes. This marriage was annulled.<sup>30</sup>

The double-speak seems suggestive enough: “difficult to get to know” “wry smile” “twinkling eyes” showing a “sense of humor not displayed to all and sundry” “almost effeminate” “core of resilience” “a strange man” with an annulled marriage.

In fact, it seems almost as if Gates gave up his sex life to devote himself to properly eugenical causes — or used eugenical theory to justify his evident lack of sexual attraction to his wife. “Human aspirations directed along the line of the improvement of mankind will, in the course of time, lead a man to select his mate, not because he loves her or desires her money,” the *Daily Mail and Empire* reported Gates as saying, “but because the union will result in a superior type of children.”<sup>31</sup> In a lecture on “Heredity in Plants, Animals, and Man,” Gates was said in another article to have declared that “What applies to plants applies to persons... Of course you can’t draw an antithesis between love and ideas of heredity.” Gates’ “expressed opinion” was that “[a] couple of young persons who begin to feel heart palpitations when they meet might well spend an evening studying each other’s pedigrees instead of holding hands under the family snapshot album.” An interlocutor asked: “But do you really think a man would study a girl’s pedigree before deciding whether or nor not to ask her to marry him?” “Why not?” queried Dr. Gates. “There is no reason why love should not be intelligent, is there. If you have a knowledge of heredity, it naturally will be a factor in determining whom you love.”<sup>32</sup>

It seems both quaint and tragic, then, to reflect on Gates’ circulation of a photograph of his new bride, Marie Carmichael Stopes, to some friends in 1911. William Woodbury responded to say: “Judging from the young lady’s photo I should certainly not pick her out as an authority on fossils. No doubt however this feature is only a ‘mutant’ — ”<sup>33</sup> (The irony here being that Gates, not his wife, turned out to be more the mutant.) Even de Vries wrote to Gates in 1911 to congratulate him on his marriage to “Miss Stopes.”<sup>34</sup>

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<sup>29</sup> Robb 2004, pp.149-150.

<sup>30</sup> “Prof. R. Ruggles Gates” *London Times*, August 13, 1962.

<sup>31</sup> “Marriage for love may result in happiness but it cannot result, except by accident, in the improvement of the human race, Professor R. Ruggles Gates, Canadian-born professor of botany at the University of London, declared today in an interview.” “Marriage for Love Viewed Critically: May Bring Happiness But only Accident if Human Race Improved” *Daily Mail and Empire*, Toronto, October 5, 1932.

<sup>32</sup> “Study of Human Pedigrees is Urged for Love Makers,” “Press Cuttings, Volume 2, 1931-1936” Gates Papers, King’s College London.

<sup>33</sup> William Woodbury to Gates, March 11, 1911. Gates papers, King’s College London.

<sup>34</sup> De Vries to Gates, March 29, 1911. Gates papers, King’s College London.

Their sexless marriage was preceded by Gates' correspondence with friends on the possibility of apogamy as a consequence of the mutation theory. As early as 1905, following his first readings of the *Mutation-theory*, one of Gates' friends, William Lawrence, wrote from the University of Chicago to say: "The more I read about mutations the more plausible is the theory that apogamy might exist." This idea of asexual reproduction was a curious but understandable possible implication of the mutation theory — sex was not needed for novel variety.

Mrs. Stopes, however, needed sex, and she made sure the world knew — and knew that it needed it, too. The mild-mannered wife rapidly became dissatisfied with her married life, and educated herself on what a woman might reasonably expect in a marriage, having entered it with virtually no idea herself. The result of her self-education — and frustration with (and by) Gates — led her to an affair with a Japanese lover, a demand for a separation from Gates and an annulment on the grounds of impotence, and finally to a public stage where she continued to rail against her husband in print, using thinly veiled references to her sexless marriage and undersexed husband as a springboard for her sex activism manual *Married Love* (1918) and her eugenical family planning efforts. (Gates' second marriage also ended in divorce, again for "impotence," and he did not remarry until old age — happily, that time.)

Even as Stopes publicly attacked her impotent ex-husband, Gates was already explaining by 1915 how mutants of *Oenothera* with chromosomes that did not properly "pair up" with "partners" during "conjugation" could nevertheless be responsible for viable phenotypically distinct mutant species in *Oenothera*. And Gates was insisting — even as he and Stopes were getting an annulment in 1916 — that even if the pairing of chromosomes did not work out, such queer mutants could get along just fine, reproduce in their own way, and be evolutionarily significant.

Gates claimed to have caught the fire from de Vries' own remarkable findings. As he wrote to de Vries in 1928, on the occasion of de Vries' 80<sup>th</sup> birthday:

[T]he blaze of your *Oenothera* research had so recently burst forth when I reached the point of taking up research, that it not only determined the direction of my earliest investigations, but has been the main factor in the development of my work ever since. / I well remember how fortunate I felt in reaching the research stage just at the time when you were producing such a flood of new conceptions and results. In many respects it was the most important development since Darwin, and I have never forgotten the enthusiasm with which I seized the opportunity of investigating the cytological side.<sup>35</sup>

Gates' first investigations into the cytological phenomena of *Oenothera* — leading to the discovery of polyploidy in *gigas* in 1907<sup>36</sup> — led him to uncover a possible mechanism: that "two simulta-

<sup>35</sup> Gates to de Vries, Feb 7, 1928. 587: 816 Hugo de Vries Papers, University of Amsterdam.

<sup>36</sup> Of course, whether it was Gates or Anne Marie Lutz who had actually discovered this phenomenon became a matter of dispute at the time. Gates was extraordinarily keen to declare his priority in matters of research and often found himself embroiled in priority disputes. One wonders whether this is due more to his personality, his short stature, the injustices actually done him, or some other cause. At the same time as his dispute with Lutz (1921), Gates was also claiming priority over Blakeslee in identifying chromosomal mutation as being due to events in meiosis (Davenport to Gates, Davenport to Gates, March 25, 1921: "I have overlooked your statement of the subject in your book in 1915. I read the entire report to our staff and nobody made exception to it, and it must be, therefore, that Dr. Blakeslee had forgotten the statement you made in your book in 1915. Dr. Blakeslee has just brought me a copy of your book. Though you clearly state that mutation is, inter alia, due to meiosis; yet the contrast does not seem to be stated as we have stated it.") Two years, Gates was in a dispute with Shull (1923) regarding *rubricalyx*, and would later most famously become involved in disputes with Darlington over parasynapsis and telosynapsis. Gates Papers, King's College London.

neous mutations may occur,” as the *Times Literary Supplement* described his work in 1915, “through mismating of the chromosomes in two pairs, so that each germ-cell receives both members of one pair.”<sup>37</sup> Chromosomes were arguably once again stand-ins for heterosexual relations — at least for the readers for the *TLS* — even when “mismating” to produce a mutant.

Ever since Renner’s delineation of two complexes and his claim, on genetical grounds, that *Oenothera* was a effectively a complex hybrid, de Vries had been happy enough with those who martialed cytological evidence to support the position that *Oenothera* was in fact a mutant (this despite the fact that de Vries held — at least initially — that his mutation theory stood independently of any claims of the chromosome theory). Gates had rapidly become one of de Vries’ most accomplished supporters experimentally justifying in *Oenothera* this distinction between hybrids and mutants.

Bateson seemed to think that de Vries was queer in a number of ways, whether it was his English or his goings-on: “I have thoroughly revised the English of his paper — queer stuff it was”<sup>38</sup> and “[t]here is something very queer about De Vries’s goings on and I wonder if he will not get us all into trouble some day, and discredit our mystery.”<sup>39</sup> Even his experiments were showing queer phenomena).<sup>40</sup> But Gates opposed Bateson in characterizing the behavior of *Oenothera* as something entirely queer: “I cannot agree that the changes in *Oenothera* are ‘utterly irregular.’ On the contrary, many of them have been shown to be very orderly indeed, only the... ‘order’ is not that of Mendelian recombination (as I take it you now agree) but of a different kind.”<sup>41</sup>

Gates’ 1915 book, *The Mutation Factor in Evolution* was his attempt to show this “different kind” of order, and to solve the question of determining whether the variants of *Oenothera* were the result of hybridization or mutation proper. He concluded: “Mutation and hybridization are distinct processes,”<sup>42</sup> and Gates’ “great achievement,” according to J. Arthur Thomson in 1920, was thus “[t]o have established a correlation between peculiarities in the chromosomes and peculiarities in the body of the plant.”<sup>43</sup> This was indeed a high achievement at a time when the number of chromosomes in humans was itself a matter for speculation — and the belief that there might even be a difference among the races, a serious research question. Gates eventually published scores of articles, including two major books on the question of mutation, the second being *Mutation and Evolution* (1921).

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<sup>37</sup> “New Departures,” *Times Literary Supplement*, July 29, 1915

<sup>38</sup> William Bateson to his wife Beatrice, 8 July 1899. G3G56/G8E22, Bateson Papers, John Innes Centre.

<sup>39</sup> Bateson describing de Vries’ visit to Burbank and its relationship to the politics of the Carnegie Institution, Bateson to Bea, 24 August 1907, Bateson Papers, John Innes Centre.

<sup>40</sup> “De Vries has an important paper in *Biol. Centrablatt* for Feb. 15 on differences between characters carried by [male] and [female] cells of same plant... It is, I think, possible that the mother or father respectively may be incapable of transmitting certain qualities, and even probable that there may be some queer forms of sex-limitation and that therefore productions should be made with great caution in Equidae.” 651 Bateson to C. C. Hurst, March 13, 1911. John Innes Centre.

<sup>41</sup> R. R. Gates to Bateson, 28 Feb 1914, Darlington Papers, Oxford University.

<sup>42</sup> Rept Royal Soc 1914, Dec 17, 1914, Grant. Gates Papers, King’s College London.

<sup>43</sup> J. Arthur Thomson regarding Gates, Feb 23, 1920. Gates Papers, King’s College London.

— Harley Harris Bartlett —

In May 1914, Gates received a letter saying:

I am very glad to see you come out flatly with your assertion that hybridization and mutation are independent phenomena. I agree with you, — cannot understand the Mendelian attitude at all. One of my papers is called ‘additional evidence of mutation in *Oenothera*.’ I have obtained beautiful mutations from several species, and am not bright enough to explain them *myself* in accord with the hypothesis of multiple factors or anything else. It may be that the Mendelians will be equal to the emergency, however.<sup>44</sup>

Harley Harris Bartlett was nothing if not a fascinating character. An expert on the taxonomy of *Oenothera* from a very young age, he had worked as an assistant at the Grey Herbarium at Harvard for three years, and was a graduate student for one year before moving to work at the Bureau of Plant Industry until 1915. Throughout these early years, Bartlett was in correspondence with a host of botanical luminaries interested in unraveling botanical complexities, from George Shull and Bradley Davis to Edmund Sinnott and John Coulter, and later he even became a friend of Sewall Wright. One student newspaper account described Bartlett as being “the only American ever adopted by a tribe of cannibals,” who was made “deputy of dead spirits” after having learned the tribe’s language while botanizing in Sumatra, “heart of world’s rubber supply” in 1918.<sup>45</sup> He became an assistant professor, then full professor in 1925, and managed to become the head of the Botany department at the University of Michigan from 1923 until 1947, without ever having completed a PhD. In 1928 alone Bartlett indicated that he grew 35,000 plants — “a very fine showing” — in his ongoing study of “the mutation problem in *Oenothera*.”<sup>46</sup>

Indeed, Bartlett seems to have kept forever busy — busy enough for his sister to say: “I hope that the machinery is getting oiled and will soon be running smoothly. Don’t run *your* own personal, *private* machinery too hard.”<sup>47</sup> And he seemed busy enough for his correspondents to frequently complain that he seemed a “confirmed bachelor” and to wonder why they never heard a word of his personal life. One friend wrote: “I should be glad to... have some word of you personally.”<sup>48</sup> Another took him to task saying, “When you write your ‘decent personal letter’...”<sup>49</sup> and another time saying “You tell very little of yourself & doings. I hope matters are improving.”<sup>50</sup> Other colleagues didn’t seem capable imagining that Bartlett wasn’t married: “One or two personal questions which please don’t overlook. *Are* you married? I have[?] heard rumors to that effect.”<sup>51</sup>

Even Edmund Sinnott, who referred to Bartlett as “a confirmed old bachelor,” tried to entice Bartlett away from the primrose path: “I want to... to assure you that married life is the acme of human happiness. Come on in, the water’s fine!”<sup>52</sup> Published biographical accounts also often emphasize Bartlett’s marital status as well, but try to explain the anomaly away: “Although unmarried, he was intensely fond of children, who often delighted in his famous beefsteak parties

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<sup>44</sup> Bartlett to Gates, May 12, 1914. Gates Papers, King’s College London.

<sup>45</sup> “Report written by Martha Papo for journalism class, January 7, 1953” Box 6, H.H. Bartlett Papers, University of Michigan.

<sup>46</sup> Bartlett to de Vries, September 4, 1920; 140: 576. Hugo de Vries Papers, University of Amsterdam.

<sup>47</sup> Hazel [his sister] to Bartlett, November 18, 1915. Bartlett Papers, University of Michigan

<sup>48</sup> Edwin to Bartlett, March 17, 1915. Bartlett Papers, University of Michigan

<sup>49</sup> Davis to Bartlett, Sept 22, 1916. Bartlett Papers, University of Michigan

<sup>50</sup> Davis to Bartlett, April 10, 1916. Bartlett Papers, University of Michigan

<sup>51</sup> Robert Vincent Cram to Bartlett, April 27, 1921. Bartlett Papers, University of Michigan.

<sup>52</sup> Sinnott to Bartlett, May 3, 1916; Sinnott to Bartlett, November 27, 1916.

and equally famous stories, and to whom, as to his students, he was affectionately known as ‘Uncle Harley.’<sup>53</sup> Another source described him as “ruddy faced” and “stocky,” and living with his second cousins twice removed, the grandchildren of his sister Hazel.

De Vries the established botanist and Bartlett the enterprising youth (described by one correspondent in 1915 as a “young upstart” and by another as “little bear”) became friends from very early on in Bartlett’s life and career. Ironically, it was none other than Bradley Davis of “*Oenothera-is-a-hybrid*” infamy, who had introduced the two in mid-September 1912, telling de Vries “you will enjoy meeting him. He is making, as you doubtless know, the most critical taxonomic studies in America upon the *Oenothera*.”<sup>54</sup>

In fact, already in 1913, at age 27, Bartlett had written to de Vries describing, with a series of exclamation points ever-increasing in size, his excitement over his new results of “a *fine, completely fertile, progressive* mutation” in wild seeds.<sup>55</sup> He delivered an address on “the status of the mutation theory, with especial reference to *Oenothera*,” at the American Society of Naturalists in 1915, and wrote to de Vries to say “I *will do as good a job as I can*.... I shall try to prepare my paper very carefully so that the mutation theory will not suffer because of a poor presentation. If you should visit us then, I’ll surrender my place to you!”<sup>56</sup>

Bartlett was nothing if not one of de Vries’ strongest supporters — stronger even than Gates. Already by the spring of 1914, he wrote: “The more I see of the *Oenotheras* the more convinced I become of the truth of the mutation theory.” Aware of the criticism that many were making that so many of the progeny were not fertile, Bartlett continued: “Have you run across any *Oenotheras* in which the germination is good, and most of the progeny are *mutations*? I have such a case, which is so remarkable that I have not dared to say anything about it publicly.” Again, a proponent of the mutation theory sensed a need to be cautious and careful about his claims. But this was the beginning of Bartlett’s work on what he called “mass mutations.” He wrote to de Vries: “Please do not think that I have gone crazy. I shall not publish anything on this case of apparent *mass mutation* while I am absolutely sure of it. The data in the paper which I now have on hand are of the conventional *Lamarckiana* type. ... I like to let you know occasionally that I am still active, and still a de Vriesian! With very highest regards.”<sup>57</sup> And yet, he reported in June the following year, “I find that in progenies showing mass mutation in *Oe. Reynoldsii* only about 5% of the seeds have germinated!” demonstrating a remarkable level of sterility.” This is not the case, however, with *Oe. pratincola* Strain E which shows a similar phenomena.”<sup>58</sup> One correspondent, amazed at Bartlett’s puzzles and experiments, declared “I think you have a life long work before you in trying to straighten these erratic plants out, and then some!”<sup>59</sup>

Whether straightening out or making things ever more inverted, Bartlett remained for years a staunch defender of the mutation theory against all comers. And both Bartlett and de Vries repeatedly expressed affection for each other following a joint collecting trip they took through the American South. It is rare to see a portrait of de Vries in a casual mode, much less happy. Most of the photos that we have of de Vries come from him later in life, after he had made a name for himself, and generally after his theory was already coming into question, while he was respected as

<sup>53</sup> Vertical file for Bartlett, Bartlett Papers, University of Michigan.

<sup>54</sup> Bradley Davis to de Vries, July 15, 1912. 382:751. Hugo de Vries Papers, University of Amsterdam.

<sup>55</sup> Bartlett to De Vries, 4 November 1913. 170: 1147. Hugo de Vries Papers, University of Amsterdam.

<sup>56</sup> Bartlett to de Vries, 22 June 1915. 170: 1151. Hugo de Vries Papers, University of Amsterdam.

<sup>57</sup> Bartlett to de Vries, April 28, 1914. 170:1164. Hugo de Vries Papers, University of Amsterdam.

<sup>58</sup> Bartlett to de Vries, 22 June 1915. 170: 1151. Hugo de Vries Papers, University of Amsterdam.

<sup>59</sup> Charles A. Davis to Bartlett, August 21, 1915. Bartlett Papers, University of Michigan.

a statesman of science. So it is especially striking that the only surviving photos of him with a smile come from this trip he made with Bartlett to Mobile and Castleberry, Alabama, in October 1912 to gather further samples of *Oenothera* in the wild — a walk down the primrose path in Dixie, and a trip that Davis seems to have arranged.<sup>60</sup> (See Figures 1 and 2.)

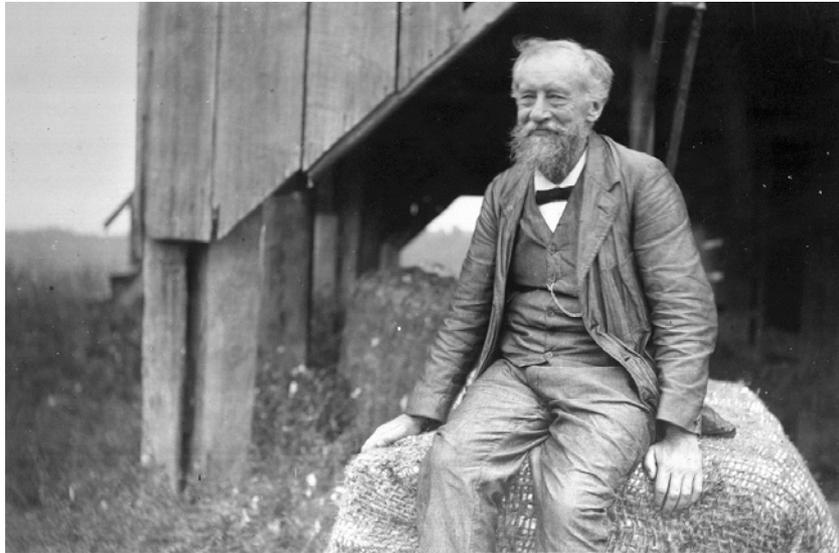


Fig. 1: Hugo de Vries, somewhere in Dixie (near Castleberry, Alabama).



Fig. 2: H. H. Bartlett and Hugo de Vries, during a break from collecting, somewhere in Dixie (near Castleberry, Alabama).

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<sup>60</sup> “You will I am sure be much interested in seeing *Oe. grandiflora* at its stations in Alabama. I am confident that this species holds the key to many of the puzzles among the herbarium sheets of *Oenothera* of the late 18<sup>th</sup> and early 19<sup>th</sup> centuries.” Bradley Davis to de Vries, July 15, 1912. 382: 751. Hugo de Vries Papers, University of Amsterdam.

This trip proved not only to be central for de Vries' later theorizing, but emotionally significant as well. Already by September 1915 de Vries wrote to Bartlett saying how long it had been "since I had the pleasure of getting [a letter] from you." And even five years later, overjoyed to learn of Bartlett's recent results with mass mutation, he wrote: "I want to thank you most cordially for taking me with you to Castleberry and sharing the seeds, we collected there, with me. They have been, for me, the means of elucidating all the difficulties, arising from Renner's study of the empty seeds."<sup>61</sup>

But *Oenothera* was not just at the heart of disputes over what counted as a mutant or a mere hybrid, and what such data and positions could affirm as to it being native to one continent or another — such collecting trips were also probably part of de Vries' own quest for personal sexual expression, just as his other trips with Wilhelm die Jäger to Paris and London had been. It is clear that de Vries derived great pleasure from his trips to the field, to America, and to other places where he could be with his boys — and often without his wife — whether that was in Alabama, Cold Spring Harbor, or Davos. Bartlett, like de Vries and Gates, was also an inveterate traveler, and enjoyed his travels with de Vries immensely: "I cannot tell you how much I have enjoyed and appreciated the opportunity to be with you these last two weeks. I wish only that the time might have been longer. Now I can only look forward to visiting you in Amsterdam and accompanying you on a primrose tour in Europe!"<sup>62</sup> A fast homosocial bond had formed between the two men, de Vries even taking the liberty to complain to Bartlett about the shortage of good able men in his laboratories and their replacement by women: "All our valid students will be called on for the army this year. We shall have only some unable men (for military service!) and quite a number of women. I do not like this prospect."<sup>63</sup>

We know that at least one compromising photo of de Vries probably taken during this trip was very carefully guarded and probably later destroyed. Bartlett wrote: "Only one pose, (A very undignified one for which you stipulated *a very limited distribution*) was a failure. I am deeply grieved, but presume that you will execute an Indian war dance for very glee."<sup>64</sup> For his part, reconnecting with Bartlett years later, de Vries remarked: "Your beautiful photograph reminds me that I owe you a letter since a long time. I Thank you most heartily for sending it, it recalls those most delightful days, which we spent together at Mobile and Castleberry, and which I consider to be the best part of my last trip through America. How I long to cross the sea once more! But that is impossible now."<sup>65</sup>

## Openings

So perhaps the title of this article should have been: "Mutant Sexuality: The Private Life of A Plant (and Those Who Studied It)." Whether he was hanging out with the boys or with his *Amorphophallus titanus* (see Figure 3 — history is queerer than fiction), de Vries was part of a small brotherhood of researchers both exploring and defending the mutation theory who themselves had

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<sup>61</sup> De Vries to Bartlett, February 10, 1917. 328:321. Hugo de Vries Papers, University of Amsterdam.

<sup>62</sup> Bartlett to de Vries, October 2, 1912. 383:321 Hugo de Vries Papers, University of Amsterdam.

<sup>63</sup> De Vries to Bartlett, 18 September 1915. Bartlett Papers, University of Michigan.

<sup>64</sup> Bartlett to de Vries, November 2, 1912. 383: 349 Hugo de Vries Papers, University of Amsterdam.

<sup>65</sup> De Vries to Bartlett, September 19, 1917. Bartlett Papers, University of Michigan.

some connection with the queer mutants they studied, and who questioned the dominant, gene-centered, Mendelian, “drosophilist” approach to try to understand how reproduction *actually* took place in *Oenothera*. Perhaps we can conclude, then, that a queer reading would recognize a plurality of modes of reproduction and evolutionary mechanisms — a freedom from Mendelian gene-centered genetics, which cannot and does not encompass the diversity of ways in which reproduction *actually* takes place, and which in fact stifled a proper understanding of *Oenothera* for such a long time and contributed to tremendous confusions over the nature and meaning of “hybrid” and “mutant.”

Most geneticists understood the mixing and matching of chromosomes and parts of chromosomes to be a “mismating” of parts, an “aberrant form of reproduction.” But queer as it may be, it was *in fact* how reproduction worked in *Oenothera*. Botanists today have calculated that such a flexible form of reproduction produced literally billions of combinations: 135,135 combinations of 14 chromosomes arranged in seven chromosomes in a “hypothetical Renner complex,” with the combination of complexes in diploids, could lead to some 9,130,801,680 different possible combinations.<sup>66</sup> Far from furtive, *Oenothera* might be one of the most oversexed genera in the world.<sup>67</sup> Or as Cleland summarized in 1949:

*Oenothera* is a widespread and very successful genus. This is due, in part at least, to the fact that certain characteristics which by themselves would have been deleterious have been combined in such a way that increased survival value has been imparted to the genus. Reciprocal translocations tend to reduce fertility in individuals heterozygous for the translocation. Lethals tend to kill individuals homozygous for these lethals or to eliminate whole categories of gametes. Self-pollination tends to reduce hybrid vigor. In *Oenothera*, however, translocations have produced large circles which, when they possess balanced lethals, result in the permanent heterozygosity of all chromosomes and consequent maximal heterosis. Self-pollination cannot reduce heterosis under these circumstances, but it does have the beneficial effect of increasing the certainty of seed set and thus overcoming the sterilizing effect of the lethal. / The combination of all three characters, therefore, has led to increased survival value.<sup>68</sup>

Seemingly degenerate, not self-evidently *as* heterosexual as other hereditary systems, this mode of reproduction was something unto itself. From the mutant that was really a hybrid to the mutant that was really a degenerate to the mutant that simply emerges in probable combinations from a nontraditional group of organisms with fascinatingly complex chromosomal behavior and that do not fit classical definitions of species but that are hardy, widespread, and diverse — *Oenothera*’s mode of reproduction has served it well. As if Renner’s earlier choice of terms for the chromosome-complexes of *Oenothera* were not suggestive enough — *gaudens* (“gay,” or happy in Latin) and *velans* (“closeted,” or concealing).

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<sup>66</sup> Harte 1994, p. 73-74.

<sup>67</sup> As Harte concludes: “the whole scenario looks like a major quiz problem: How can you combine the contents of a big bag full of unfavourable characters to achieve at low cost a high probability of survival for the species and, at the same time, keep the way open for evolution? *Oenothera* has solved this problem. The genus should be awarded a large prize for it. But, instead, it is given a bad name as a collector of exceptions with the sole purpose of creating difficulties for biologists” (222).

<sup>68</sup> Cleland 1950, pp. 7-8.

So an argument here might draw on the polymorphously perverse and polysexual nature of *Oenothera*'s mode of reproduction: perhaps their producing sterile pollen that cannot serve in reproduction is a form of queer sex — sex without reproduction as its aim. Or perhaps the very lack of pairing of the chromosomes, which is held to be responsible for sterile pollen, is an example of queer behavior. Or perhaps it is the existence of chromosome complexes that function as sex chromosomes in their own right, according to Darlington's view, presenting another mode of reproduction labelled "subsexual" reproduction that permits and has permitted *Oenothera* to reproduce itself for millennia, to generate novel combinations of phenotypic traits for selection, and to accumulate lethal genes that nevertheless do not harm the organism. These sorts of queer reproduction are certainly viable, although they only faintly resembles the classic genetic idea of how two sexes reproduce. Or perhaps these chromosome complexes just thoroughly queer the idea of sex in the first place — are plants with different complexes different species? Or different sexes? Did de Vries discover new species, or a remarkable number of possible new sexes in one plant? Is the mutation theory simply an elaboration of how novelty emerges beyond the gene in a basically heterosexual Mendelian system? Or, when properly understood and the mysteries of the plant more fully explored, was the mutation theory a potential way of destabilizing a heteronormative conception of reproduction dominant in *Drosophila*-centered Mendelian genetics? These are some of the ways we might envision a queer reading.

Might not Mendelism in its very approach to genetics have helped define and maintain views opposed to the more pluralistic approaches possible in the research traditions of the *Mutations-theorie* — de Vries' labile pangen explanation, Gates' chromosomal explanation, and finally Bartlett's mass mutation hypothesis, which finally convinced de Vries to leave the pangen theory behind? Might not the predominant heteronormativity of cytologists at the time and their initial inability to understand alternative chromosomal arrangements as novel and viable evolutionary forms, rather than merely "haphazard mating" or "mismatching" demonstrate a distinctive blindness of a particular kind that we might now perhaps identify as a hallmark of, to coin a phrase, "heterosexist genetics"? Organismic mutation — what de Vries started with. Genic mutation — what genetics (and the history of genetics) largely became. And as to this third sect of the multiple effects of "chromosomal mutation": perhaps this third sect has something to do after all with what was called the "third sex."

So how *does* a scientist's sex life — actual or desired — relate to their production of scientific knowledge? Perhaps an investigator's love life might have something to do with his ability to discern other viable and evolutionarily significant patterns of chromosomal arrangements (Gates). Perhaps it comes from an investigator's delivering a politically oriented speech drawing on insights from both his scientific work and personal life (Stomps). Perhaps it might be by envisioning (and scientifically confirming) radically different possibilities of reproduction while carrying out and leaving behind sparse but suggestive clues to a life well-lived (Bartlett)? Perhaps the sexuality and sexual orientation of scientists — and not just their sex or gender — has something more to do with studies of heredity than we might at first imagine.

The case of *Oenothera* is thus queer in more ways than one: its mutants demonstrated a form of reproduction that widely recognized as being queer (revealed by "the mutant gaze"); its mutants were studied by scientists who were in at least several instances themselves probably queer ("the mutant gays"); and the queer phenomena *Oenothera* demonstrated were mobilized as both perso-

nal and public resources in battles to recognize the full extent of natural variation among chromosomes and their behavior, among plants, and among people. How fascinating that this should all unexpectedly come out of a closet in Amsterdam.

My only question, when we look at a photo of de Vries standing next to *Amorphophallus titanus* or his own beloved *Oenothera lamarckiana* is: which one is the mutant?



Fig. 3: Hugo de Vries with *Amorphophallus titanus*, in Wageningen, 1932.

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## *Generating Plants and Women: Intersecting Conceptions of Biological and Social Mutations in Susan Glaspell's "The Verge" (1921)*

Jörg Thomas Richter

Susan Glaspell, one of the early and highly influential exponents both of modern American Realist and Expressionist drama, is mostly read today for the radical feminist positions she adopted in many of her works. These are valid readings. It is significant, however, that her feminist critique every so often finds expression in dramatic explorations of biological theory.<sup>1</sup> Early in her career, while still working as a journalist in Davenport, Iowa, she had joined the Monist Society, a religio-scientific group that was loosely modelled on the ideas of the German naturalist Ernst Haeckel and saturated with evolutionary ideas of Darwinian and Nietzschean origin. As Tamsen Wolff has convincingly shown, this biological background is particularly significant for her experimental drama *The Verge* (1921).<sup>2</sup> Zooming in on the mechanisms of biological heredity, and staged within a laboratory-like, tightly controlled cultural context, the drama features a female botanist who, by breeding a new species of plants, tries to break natural mechanisms of heredity. The drama shows how the botanist finally mutates into a new kind of woman herself that leaves behind the social (and linguistic) constraints of her times. And more than that, it also confronts the audience with the hazards of social unintelligibility involved in the chance process of mutation.

The central motif of the three-act drama is the botanist Claire Archer's struggle with the social conventions of her time. On the symbolic level, this struggle is shown through the repeated emphasis put on patterns and acts of pattern-breaking. Thus, the first act is set in Claire's experimental greenhouse where, according to the set description, "*The frost has made patterns on the glass as if — as Plato would have it — the patterns inherent in abstract nature and behind all life had to come out, not only in the creative heat within, but in the creative cold on the other side of the glass. And the wind makes patterns of sound around the glass house.*"<sup>3</sup> Against the backdrop of the patterned set design, the first act shows how Claire's seemingly secluded life as a horticultural scientist is invaded by domestic life. Deprived of heating at their living quarters during a stormy winter morning, her three male companions, her friend Tom, her lover Dick, and her husband Harry as well as her daughter from a previous marriage, Elizabeth, seek their way to the greenhouse to have breakfast, for it is there where all the heat has been ordered by Claire. During the turbulent breakfast in the over-heated greenhouse, full of slapstick scenes and often absurd comedy, Claire successively rejects the intruders' claims in regard to her roles as a woman, lover, wife and mother with references to her horticultural work. In the second act, set in her study in the family mansion that is also marked by a "*a marvellous pattern on the curved wall*" (*The Verge* 78), Claire is presented again in defense against similar demands. This time it is her sister Adelaide who wants her to appreciate the satisfaction of being part of "the main body" and "having one's roots in the big common experiences" (*The Verge* 82). Adelaide's intervention, however, fails, so that Claire is eventually introduced to a neurologist who but affirms the suspicion of her insanity that has already been brought up by both her sister and husband. The final act returns to the greenhouse to

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<sup>1</sup> Here I follow Papke 2006.

<sup>2</sup> Wolff 2002, esp. chapt. 4. Wolff is particularly informative on the background of eugenic theory to the drama.

<sup>3</sup> Glaspell 1978, p. 58. All further references to *The Verge* are cited parenthetically within the text.

show the success of Claire's plant experiments. When the Breath of Life, Claire's mutated plant, ultimately proves its stability as a new species, Claire, instead of celebrating her success, kills Tom, the one male to whom she has been able to confide her unconventional ideas. She does so because he had just pledged his love to her, and this is precisely what Claire rejects as a last captivating emotion that would tie her to the social sphere. The drama ends then with Claire singing the Puritan hymn "Nearer My God to Thee" in the presence of the remaining, flabbergasted men.

In the following, I will argue that Glaspell's *The Verge* draws on Hugo de Vries' mutation theory as a means to reflect on cultural reform. In so doing, I will first discuss the significance that Glaspell gives to patterns and pattern-breaking. I will secondly sketch the popular discussion of the de Vriesian theory in the United States in the first two decades of the twentieth century before commenting on how Glaspell integrates this notion in *The Verge*, especially in regard to contemporary feminist ideals. I will conclude by pointing out some of the aesthetic concerns that are brought about by Glaspell's use of mutationist theory, turning to, if you like, mutationist poetics.

## I. Patterning

The whole play is pervaded by pattern motifs both on the visual and the verbal level. A few examples out of roughly twenty throughout the play should suffice to illustrate this core motif. I have already indicated how Glaspell's set description both of the greenhouse and her study require visual patterns as background for the action. Likewise the stage action again and again foregrounds this motif. In act one, for instance, Claire explains the purpose of her work in plant breeding:

Out there — (*giving it with her hands*) lies all that's not been touched — lies life that waits. Back here — the old pattern, done again, again and again. So long done it doesn't even know itself for a pattern — in immensity. But this — has invaded. Crept a little way into — what wasn't. Strange lines in life unused. And when you make a pattern new you know a pattern's made with life. And then you know that anything may be — if only you know how to reach it. (*The Verge* 77)

Later, she wonders, "Yes, but why does the fabric of life have to — freeze into its pattern? It should (*doing it with her hands*) flow" (*The Verge* 86).

Added to her fear that anything new will relapse yet again into patterns is Claire's obsession with language.<sup>4</sup> Towards the end of the second act, she unwittingly breaks into free verse:

Stop doing that! — words going into patterns;  
They do it sometimes when I let come what's there.  
Thoughts take pattern — then the pattern is the thing.  
[...]  
I want to lie upon the earth and know.  
But — scratch a little dirt and make a flower;  
Scratch a bit of brain — something like a poem  
(*covering her face*). (*The Verge* 88)

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<sup>4</sup> See Hinz-Bode 2006, esp. pp. 165-177. Cf. also Wolff 2002, p. 186. Hinz-Bode who has described in great detail how Claire's transformation is expressed in a speech style that slowly disintegrates in the process of the play.

Like life, language structures what to Claire's mind should refrain from structure. Patterns, then, are accentuated in the play, and in many cases they highlight a familiar epistemological paradox: the recognition of the new occurs within the format of already customary knowledge, the latter being modified and perhaps transposed to a different level in the process. Through such a radically modernist epistemological desire for the ultimately new, Claire is truly bound to become a tragic figure. Though her creations eventually develop into new forms, their very newness will again lapse into a structure, a dilemma staged in her destruction of a 'weak' mutation, the Edge Vine. Change is only honoured for change's sake; in her radical understanding of science, "Beauty is that only living pattern — the trying to take pattern" (*The Verge* 97). In this emphasis on pure potentiality, dramatic tension is most pronounced in Claire's efforts to break and forge patterns on biological, social, linguistic and aesthetic levels.

Claire's strife for the new appears most openly in her efforts to create a new species of plants: she attempts to trigger mutations through various means such as hybridization or the use of environic stress; she is cross-pollinating, experimenting with fertilizers or subjecting her plants to lice.<sup>5</sup> Indeed, Glaspell heavily utilizes biological theory. More specifically, she draws on the then-popular idea that life does not develop along gradual processes, but in those sudden jumps and leaps Hugo de Vries had then described as mutations.<sup>6</sup> At least this is the cultural significance Claire Archer attributes to her plant experiments. Explaining her experiments to the three stereotypical males featured in the drama, to Tom, Dick and Harry, towards the second half of the first act, Claire alludes to the First World War, that in her eyes "was a stunning chance" but "didn't help," and was just "Showing our incapacity for madness." The war was, as Claire argues,

Not the madness that — breaks through. And it was — a stunning chance! Mankind massed to kill. ... Is there one ounce of energy has not gone to this killing? Is there one love not torn in two? Throw it in! Now? Ready? Break up. Push. Harder. Break up. And then—and then—But we didn't say — 'And then — ' The spirit didn't take the tip.

HARRY: Claire! Come now (*looking to the others for help*) — let's talk of something else.

CLAIRE: Plants do it. The big leap — it's called. Explode their species — because something in them knows they've gone as far as they can go. Something in them knows they're shut in to just that. So — go mad — that life may not be prisoned. Break themselves up into crazy things — into lesser things, and from the pieces — may come one sliver of life with vitality to find the future. How beautiful. How brave. (*The Verge* 70)

To be sure, the First World War had often been used at the time for exemplifying the working of natural selection in the cultural realm. Even eminent authors and naturalists such as John Burroughs had argued that the struggle between the Prussian, the French, the English and the American "*Kultur*" was "attended by the same contingencies, the same law of probability, the same law of the survival of the fit, as are organic bodies." Yet what Burroughs deems "the blind, wasteful

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<sup>5</sup> Hybridization and environic stress were common methods among many researchers beginning to work with de Vriesian mutation theory. So did, to name but two examples Daniel Trembly MacDougal, the American translator of Hugo de Vries *Species and Varieties*, mainly by using chemical substances that altered protoplasm (see (see Harding 1905); or F.N. Duncan (1915) in his experiments not with plants, but animals (*drosophila*).

<sup>6</sup> Though the term mutation does not appear once in the drama, Glaspell still refers to the more common notion of the evolutionary leap that is also used in the American translation of de Vries' *Species and Varieties*. "The theory of mutation assumes that new species and varieties are produced from existing forms by sudden leaps," writes de Vries. See Vries 1904, p. vii. De Vries' *Die Mutationstheorie* (1901) was first published in English translation as late as 1909, making his *Species and Varieties* for five years his authoritative text in the US.

fury of the elemental forces”<sup>7</sup> on the basis of his sociobiological analogy would actually represent just another failed moment of cultural crisis in Claire's eyes, failed, because it did not bring about the desired social change.

## II. *Cultural Evolution by Revolution*

Claire's theory that evolution does not proceed gradually, but in sudden leaps and jumps by way of mutation, responded to many of the cultural aspirations at the core of the Progressive Era between 1890 and 1920. At the time Glaspell was writing her drama, however, Progressivist aspirations were increasingly called into question. The play was staged at the time when the United States, after signing the peace treaties with Germany, Austria and Hungary that formally ended the First World War, began to withdraw from foreign politics. It was also written in the face of a new conservative turn proclaimed in the new president Warren G. Harding's famous “return to normalcy,” a campaign platform that had met strong popular support and eventually effected Harding's landslide election. In Harding's turn away from foreign politics to a renewed conservative politics of the interior, previous middle-class activism had come to an end, indicated last but not least in the contemporary reactions to leftist anarchic movements, the so called Red Scare.

Glaspell's focus on sudden change draws up a stark contrast to such cultural backlash. Claire's attempts to “explode” the species, to “break up” and “break through” in order to accomplish the “big leap” in speciation allude to the saltationist and mutationist explanations spread in contemporary biology and propagated by botanists as different as Hugo de Vries and Luther Burbank.<sup>8</sup> Burbank, for instance, holds that “It is only when some one breaks absolutely away from all precedent and rule and carves out a new place in the world that any substantial progress is ever made.”<sup>9</sup> Equally important for Glaspell would have been also Henri Bergson, for whom the de Vriesian notion of an inherited “tendency to change” was a clear point of departure from contemporary neo-Darwinism. In his bio-philosophical synthesis, biological mutation helps explain the missing link between human and animal culture, the “sudden leap from the animal to man.”<sup>10</sup> Glaspell's drama, as I wish to argue here, utilizes botany as a conceptual system that is somewhat more promising in regard to evolutionary dynamics than contemporary social culture which, for Claire as well as for many other progressivist reformers, has fallen back to a static condition in the Harding era. In this light, plants, at least in Glaspell's drama, are simply the better creatures in that they are more open to potentiality, in that they possess more vitality than normalcy-suspect human beings, the latter being always already caught up in established social and cultural conventions. Last but not least, the mutated exemplars are singularities: Claire's assistant Anthony, for instance, is convinced, “There's a million people like you ... There is just one Edge Vine” (*The Verge* 60).

In staging biology as a social and political force Glaspell utilizes the nagging debate between gradualism and mutationism for poetic purpose. At the time both mutationism and saltationism

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<sup>7</sup> Burroughs 1915a, pp. 250-251.

<sup>8</sup> A host of critics has already remarked on the de Vries and Burbank references in the bylines of their arguments. See Waterman 1966; Bach 1979, p. 166; Gainor 2001, pp. 160-161; Wolff 2002, pp. 168-169.

<sup>9</sup> Burbank 1907, p. 20

<sup>10</sup> Bergson 1911, pp. 86, 186. On Bergsonian ideas in Glaspell see the short references in Papke 2006, pp. 32-33. In regard to Burbank and de Vries, Bach (1979, especially p. 166) has sketched out thirty years ago in how far her contemporary audience reacted to the horticultural allusions of the play.

had become challenges to more customary gradualist theories of evolution.<sup>11</sup> Indeed, just before *The Verge*, Glaspell had explored the idea of gradual bio-cultural change in her drama *Inheritors* by focussing on the long term development of a midwestern family across five generations.<sup>12</sup> *The Verge* can be seen as a conceptual counterpart to the earlier drama in its exploration of cultural reform through biological imagery. Though Glaspell here picks up on the concept of mutation some years after the concept had lost its force in biological discourse, it was still suited well enough to strike off cultural conservatism, or, as Wolff has argued, to qualify contemporary eugenic thought. For despite its difficulties in the biological arena,<sup>13</sup> de Vriesian thought continued to enjoy an immense popularity in the broader American culture. De Vries was eagerly embraced by Darwinians and Lamarckians alike, by eugenicists and sociologists, even by literary scholars who saw in de Vries an alternative to Darwinian and Spencerian explanations of the development of literary forms. For John Manly, writing in 1907, “Certain literary forms [such as the miracle play] ... must come by a single, simple mutation, for the entirely sufficient reason, that their very existence depends upon the presence of an absolute unit.”<sup>14</sup> For Manly, and for many others throughout the humanities, mutation theory offered a viable way out of having to account for historical discontinuities and change, even if the argument would run in danger of stating hardly more than the simple claim that cultural phenomena might just have suddenly appeared without cause, without end, or without warning.

At first, of course, mutation was only hesitatingly applied to human physical evolution. It was used to explain the formation of racial distinctions, but increasingly also to explicate mental evolution and the human expression of emotion. These were phenomena that for some could no longer be explained by their “serviceability” in natural or sexual selection or by the proverbially missing links between animal and human culture.<sup>15</sup> Ellsworth Huntington, in his book *World-Power and Evolution*, claimed in de Vriesian manner that “the commonest cause of mutations and thus of the origin of species is germinal change due to the action of extremes of heat and cold upon the organism in its early stages of growth,” a hypothesis that for him explained the development of human culture (and, as to the biological symbolism in *The Verge*, this hypothesis also sheds a light on the frequent shifts of dramatic action from the over-heated greenhouse to the sub-zero exterior). Huntington could elegantly extend to the eugenic demand that “we learned how the highest of all animals is being changed and how his future evolution may be directed along the right path.”<sup>16</sup> In this vein, the editorial of the second issue of *The Journal of Heredity* in 1911 quite boldly held that “Evolution in a republic, as in plant and animal organisms, in part comes by

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<sup>11</sup> For a survey on evolutionary theories around the time see Levit / Meister / Hoßfeld 2008.

<sup>12</sup> On this reading of *Inheritors*, see Richter 2008, pp. 221-231.

<sup>13</sup> In regard to the increasing scepticism of biological researchers towards de Vries after 1913 see Allen 1969.

<sup>14</sup> Manly 1907, p. 14. See also the follow-up article by Hoskins 1909. Manly, one might argue, would even today be a useful source for all those, who believe in Dawkin's theory of the meme as transmitter of literary information.

<sup>15</sup> Cf. Thompson 1905. In like manner, Thorstein Veblen saw in the development of the “dolicho-blond” race a clear instance of mutation, brought about at a time “when the parent stock was exposed to notably novel conditions of life, such as would be presumed (with de Vries) to tend to throw the stock into a specifically unstable (mutating) state.” Qtd. from Veblen 1912/1913, p. 495. For mutated emotions see Pierce 1906. For an application of de Vries to mental evolution see, aside from Thompson, also Alexander 1913, p. 676: “the human mind itself is no augment of arborescent faculties, but a sudden and unpredictable mutation [...]”

<sup>16</sup> Huntington 1919; qtd. from Popenoe 1920, pp. 143-144. Popenoe duly notes that Huntington's idea of climatic change causing for mutation rests on experiments by W.L. Tower with potato-beetles, P. Kammerer with toads, F.B. Sumner with mice, and A.H. Clark with crinoids. Cf. Popenoe 1920, p. 142.

sudden mutations” and that “Human heredity, like heredity in plants and in lower animals, changes by means of occasional wide mutating leaps followed by slow evolutionary adaptations a small step at a time.” The same editorial intertwined transcendentalist notions of poetic and moral force with biocultural dynamic, claiming that “When a genius and a new idea are in combination a general mutating movement occurs.”<sup>17</sup> Just for the record: Well before mutation had become a catch-word, Henry David Thoreau had made famous a quotation from Confucius, writing that “The virtues of a superior man are like the wind; the virtues of a common man are like the grass; the grass, when the wind passes over it, bends.”<sup>18</sup> If set against a transcendentalist background, popular mutation theory seemed to have offered a new version of nineteenth-century explanations of cultural superiority and genial exceptionality.

Thus, noting that mutations occur when a species is in a state of mutability, Maynard M. Metcalf from the Orchard laboratory in Oberlin, Ohio, somewhat frustrated with the eugenic ideal to just bring “mankind as a whole nearly to the level of the present best,” posed the question most radically, “Is man mutating today? Does he present stable variations which may be utilized to secure his evolution to a higher condition?”<sup>19</sup> Of course, one of the answers to Metcalf’s question has always been a blunt: No. For, as to human physical and mental capacities, the embryologist Edwin Grant Conklin already then concluded that “the peak has been reached.” Conklin, however, still believed in mutability within the social realm, for “social evolution is proceeding at a rate which is amazing, if not alarming.” He found that “The present seems to be a mutation period in the evolution of human society,” and he insisted in his theory of biological democracy that “There is such a thing as evolution by revolution.”<sup>20</sup>

It is amazing to see in how far such comprehensive social theorizing arose from the rather narrow field of experimental botany, making the analogy between botany and social life a common theme in the 1920s. Perhaps the most important voice in this regard was Luther Burbank who had claimed in his popular book *The Training of the Human Plant* that “Man has by no means reached the ultimate. The fittest have not yet arrived.” Burbank did not so much worry about the survival of the fittest than he did about the arrival of the fit. He believed that humanity will eventually reach a “different order of being”;<sup>21</sup> and he was convinced that “The transcendent qualities which are placed in plants will have their analogies in the noble composite, the American of the future.”<sup>22</sup> Of course, the extension from horticulture to human culture might have been suspect from a biological point of view already then. Still, his synthesis underscores that the idea of horticultural mutation helped interlink a broad variety of cultural concepts.

Thus, even if my selection of quotations from contemporary sources may be somewhat blurry, exactly this is my point: What de Vriesian mutation theory eventually came to cover in the United States in the first decades of the twentieth century was, at best, a fuzzy field of meaning spread out across various social, including but not limited to biological discourses, the common denominator in most cases being only the potential suddenness of radical change and the vague sense that sudden change occurred in moments of instability, of crisis. Mutation had attained the status of a collective symbol in that it linked a variety of specialized cultural discourses in an

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<sup>17</sup> “Imperialism in Democracy” 1911, p. 63.

<sup>18</sup> Thoreau 1966, p. 116.

<sup>19</sup> Metcalf 1916, pp. 362-363.

<sup>20</sup> Conklin 1921, pp. 72, 74. See also the review of Conklin’s book “Man, the Captain of His Fate” 1921, p. 44. As Kathy Cooke (2002) has shown, Conklin in fact held a moderate position towards eugenics.

<sup>21</sup> Burbank 1907, p. 73.

<sup>22</sup> Burbank 1907, p. 75.

interdiscursive knot.<sup>23</sup> The appeal to the collective symbol of mutation signified a potential break in hereditary determinism, or, analogously, in the deterministic forces of cultural tradition. Fittingly, the great philosophical synthesizer Henri Bergson, who was so well received at the time in the United States, ventured to reunite mutationists and gradualists, arguing that if mutations be accidental, the tendency to mutate at all is effected by gradual developments.<sup>24</sup>

### III. Feminist Mutationism

In such a collective symbolic light, Claire Archer's tinkering with the plants takes on particular significance in regard to contemporary gender roles. Exploiting the symbolic potential of mutationism, Glaspell makes Claire the prototype of a contemporary, Progressivist Era feminist ideal. As numerous critics have remarked, with Claire, there is a character on centre stage, who paradigmatically represents the New Woman. The stage presents a highly trained female professional, who is spiritually independent, who feels unbound by conventional — that is: male — assumptions about marriage, who openly admits her sexual desires, and who has inherited enough funds to be economically independent as well. Many of the social comedy scenes in the drama show how the men around her have trouble in arranging themselves with such a personality, and Glaspell takes pains to mark this issue. A female creator/scientist, Claire openly confronts the role expectations attributed to her by the other characters of the play: Dick Demming calls her “so fascinating a hostess” (*The Verge* 62), while in fact she is denying her guests even the heating; Harry Archer appeals to her as a “refined woman” (*The Verge* 64), while she calls herself a “strumpet” (*The Verge* 64); and when her daughter Elizabeth, one of Claire's already “finished” experiments (*The Verge* 72), steps on the scene to cast her in the role of a mother, Claire attempts to strike her daughter with the Edge Vine and cries out, “To think that object ever moved my belly and sucked my breasts” (*The Verge* 78).

Consequently, both Claire's scientific pursuit and her social attitudes seem to concur in a sort of feminist messianic message that has often been acknowledged in contemporary theatre criticism as well as in recent Glaspell scholarship.<sup>25</sup> For many, Claire is a female Doctor Faustus pursuing her way to superhuman mastery. And true, what both Glaspell and her husband, George Cram Cook, for a time subscribed to was their belief in “our biologic Jesus,” a theological creature that hybridised both messianic expectation and evolutionary power. Cook wrote in a late poem:

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<sup>23</sup> For collective symbols and interdiscursivity see Link 1988. In fact, one of the appeals de Vriesian theory had for the interested amateur was that it could be reproduced in the home garden. In this spirit, George Cram Cook, Susan Glaspell's later husband, maintained an experimental greenhouse. Glaspell writes in her Cook biography *The Road to the Temple* (1926), p. 154: “Jig built a greenhouse; the greenhouse celebrates itself in song, and this is the marriage song of the two who come to it.” The often quoted passage from the greenhouse's song is on pp. 154-155: “No mere Wordsworthian guest of Nature be / Spectator and not sharer of her life, / But her co-worker, with selective art / Prescribing form to her wild energies: Saying, 'Thou shalt be!' and 'Thou shalt not be!'”

<sup>24</sup> See Bergson 1911, p. 86.

<sup>25</sup> Hinz-Bode 2006, chapt. 8, is especially good in discussing the feminist bias in Glaspell scholarship.

For if the speck,  
In us, its inheritors,  
Does not finally make that turn  
With our latest, somewhat discredited god,  
Our biologic Jesus,  
It would have been better  
And much more beautiful  
For the earth  
On its long way through heaven  
To have remained peopled  
By the significant silence of its stones.<sup>26</sup>

From act one to act two, Claire's development similarly appears to bear out Burbank's dictum that "we must break away from the mere petrified word-pictures of others and cultivate the still 'small voice' within by which we become strong in individual thought and quick in action, not cropped, hedged and distorted by outward trivial forms, fads and fancies." Burbank eventually crowns such development with the prospect of American "imperial dominion."<sup>27</sup> In contrast, Glaspell deliberately exaggerates the analogy between mutated plant and social change in the further course of the play, for Claire turns from feminist messiah to female manslayer when she kills her friend Tom in a fit of ecstasy just because he had pledged his love to her. Tom, who represented a last tie to the conventional social world in the symbolic rather than causal structure of the play, is to be given up in Claire's world for an unknown evolutionary future. Destruction and death are, as Claire pronounces again and again, a gift in preparation of evolutionary future. The drama does thus not only show how the botanist finally mutates into a new kind of woman — it similarly confronts the audience with the hazards of social unintelligibility involved in the chance process of mutation: Claire's speech turns into incoherent, fragmentary stammer at the latest after the murder of Tom. The superfeminist has become a killer on the edge of sanity; and by leaving open whether Claire has become insane or whether indeed she has succeeded in "breaking through" to a sort of Nietzschean superfemininity,<sup>28</sup> the play's ending is a plea for the impossible: an endless continuation of social evolution rather than its fixation in any stable social utopia.

The drama, then, oscillates between a feminist agenda on the one hand, and a larger socio-evolutionary concern on the other hand. Such oscillation is also underscored in the symbolic properties of Claire's mutated plant, the *Breath of Life*. The name seems to be carefully chosen, it alludes to a plant in "Rappaccini's Daughter," a short story by Nathaniel Hawthorne published in 1844, and to an essay collection by the late transcendentalist naturalist and essayist John Burroughs, published under the very title *The Breath of Life* in 1915. Most of Burroughs' essays show his growing discontent with the mechanistic and economical explanations of biological and evolutionary processes.

In the tradition of Ralph Waldo Emerson, Friedrich Nietzsche and Henri Bergson, Burroughs argues for a hybrid conception of vitalism and creative evolution, "The push of life, of the evolutionary process, is back of all and in all. We can account for it all by saying the Creative Energy is immanent in matter, and this gives the mind something to take hold of."<sup>29</sup> Surely Claire

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<sup>26</sup> Cook qtd. in Glaspell 1926, pp. 272-273.

<sup>27</sup> Burbank 1907, pp. 98-99.

<sup>28</sup> Margit Sichert (1997) has exhaustively shown the Nietzschean dimension within the play.

<sup>29</sup> See Burroughs 1915b, p. 9.

likewise affirms such evolutionary potential. Her plant, the Breath of Life, seems to embody the optimistic belief in creative energy immanent in cultural evolution, and her break with conventional gender roles is certainly part of the drama's symbolic argument. Yet in regard to the feminist agenda of the play, one needs to be cautious since, aside from Burroughs and contemporary mutationist discourse, Glaspell's *Breath of Life* also plays upon yet another intertextual reference.

In Nathaniel Hawthorne's classical story "Rappaccini's Daughter" — like *The Verge* mostly set in an experimental garden, "an Eden of poisonous flowers"<sup>30</sup> — the "breath of life" is associated with a scientist's daughter. Part of one of her father's medical experiments, she is raised and sustained on plant poisons, so that, in turn, she becomes poisonous to all who encounter her.<sup>31</sup> To her father/creator, Prof. Rappaccini, she embodies a scientific breakthrough, she is the "daughter of [his] pride and triumph" who "now stands apart ... from ordinary women."<sup>32</sup> Such apartness, though, as it is also maintained throughout Glaspell's play, ultimately leads to her social exclusion. As Hawthorne has it, it is "the effect of my father's fatal love of science — which estranged me from all society of my kind."<sup>33</sup> The scepticism towards manipulative biology is already voiced in the narrator's description of the experimental garden where "there had been such commixture, and, as it were, adultery of various vegetable species, that the production was no longer of God's making, but the monstrous offspring of man's depraved fancy, glowing with only mockery of beauty."<sup>34</sup> Even more, Rappaccini's daughter herself becomes the object of male scientific rivalry that finally kills her in complete denial of her human emotions. Thus, Glaspell's *Breath of Life* may certainly represent the liberation of the female subject from male scientific fantasy, for now it is a female scientist who breeds the revolutionary Breath of Life. But one is still left to wonder in how far Claire's feminist experimental strife does not also indicate that she is just reproducing a male scientific fantasy on a feminist basis. After all, one needs to consider in how far Glaspell actually looks beyond the limits of feminist reform to achieve a broader, evolutionary significance. And finally, as the Hawthorne reference also indicates, the drama is also tinged with doubt towards a manipulative biology that intervenes with "natural" evolution. Read against the background of Hawthorne's tale, Glaspell's feminist Faust, Claire Archer, would, in the words of Hawthorne, be just another "poor victim of *man's* ingenuity and of thwarted nature, and of the fatality that attends all such efforts of perverted wisdom."<sup>35</sup>

#### IV. *Aesthetics of Shock*

For Glaspell, I suspect, it is dramatic art rather than feminist politics that has the potential to effect cultural change, and, arguably, it is on the aesthetic level where Glaspell would subscribe to mutationist theory. In de Vriesian logic, one of the preconditions for mutations to happen is the instability of the species. Mutations occur only if the species is, as de Vries calls it, in a "state of

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<sup>30</sup> Hawthorne 1974, p. 115.

<sup>31</sup> As Rappaccini's daughter exclaims, the poisonous flower is but a "sister, my splendor, it shall be Beatrice's task to nurse and serve thee; and thou shalt reward her with thy kisses and perfume breath, which to her is as the breath of life!" (Hawthorne 1974, p. 97)

<sup>32</sup> Hawthorne 1974, p. 127.

<sup>33</sup> Hawthorne 1974, p. 123.

<sup>34</sup> Hawthorne 1974, p. 110.

<sup>35</sup> Hawthorne 1974, p. 128, emphasis added.

mutation” or in a “condition of mutability,” like, in his opinion, the famous evening primrose was at the turn of the century.<sup>36</sup> Glaspell’s *The Verge* appropriates this idea in a poetic way, shaping a dramatic format that seeks to destabilize the expectations of her theatre audience by confronting them with the monstrous, the mutable. Tamsen Wolff has commented on the “messy compositions” that result from “Glaspell’s aim to create a new dramatic hybrid, unfixed in its form yet rooted in a charged contemporary debate.”<sup>37</sup> Indeed, *The Verge* needs to be read in the context of the then developing, avant-garde expressionist theatre, a non-mimetic dramatic form that focuses on the subjective experience of a single character, for other than in the then conventional well-made plays, Glaspell’s focus is entirely upon a “monagonist” rather than on the conflict between protagonist and antagonist.<sup>38</sup> As I wish to argue in conclusion, the messy composition is a device in an aesthetics of shock, that, according to Herbert Grabes, was fundamental to the rise of modernist aesthetics and always went together with a heightened emphasis on alterity, on otherness, and defamiliarization expressive of the avantgarde’s search for the radical new.<sup>39</sup> Dramatic art seeks emotional appeal, and it was again Bergson who had claimed in his then-influential essay on laughter that “emotion can be utilized for breaking down old customs and establishing new ones.”<sup>40</sup> As I have tried to show, Glaspell draws on the collective symbolic potential of biological theory at the time. Yet transporting the theory onto the stage adds a further level of aesthetic indeterminacy to the open — and thus to some extent also poetically trivial — biological allusions. Aside from the reference to the proverbially obscure symbolism of the Hawthornian tale, indeterminacy is fostered by a multiplicity of interrelations between the symbolic level and the level of dramatic action. A brief section from the breakfast scene in the first act may illustrate the point, blending in the image of the egg Claire’s explanation of her biological theory, her husband Harry’s wish for an untroubled breakfast (and marriage), and Tom’s ultimately unfulfilled desire for Claire, or, to say it with Harry: her ovum.

CLAIRE: ... I want to break it up! I tell you, I want to break it up! If it were all in pieces, we'd be  
(*a little laugh*) shocked to aliveness (*to DICK*) — wouldn't we? There would be strange new  
comings together — mad new comings together, and we would know what it is to be born, and  
then we might know — that we are. Smash it. (*her hand is near an egg*) As you'd smash an egg.  
(*she pushes the egg over the edge of the table and leans over and looks, as over a precipice*)  
HARRY: (*with a sigh*) Well, all you've smashed is the egg, and all that amounts to is that now  
Tom gets no egg. So that's that. (*The Verge* 64-65)

The scene follows the principles set out in Bergson's concept of “reciprocal interference,” meaning that a “situation is invariably comic when it belongs simultaneously to two altogether independent series of events and is capable of being interpreted in two entirely different meanings at the same time.” For Bergson, the resulting laughter is “a mechanism superposed upon life” that “indicates a slight revolt on the surface of life.”<sup>41</sup> Against this background of the destabilizing power of the

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<sup>36</sup> de Vries 1904, *Mutations*, p. 521, p. 539.

<sup>37</sup> Wolff 2003, p. 215.

<sup>38</sup> See Müller 2006, p. 51. In American drama this process began in particular with the adaptation of expressionist forms as developed by August Strindberg.

<sup>39</sup> See Grabes 2004, pp. 23-24 and *passim*.

<sup>40</sup> Burgess 1916 and Knight / Peters / Blanchard 1921, p. 291.

<sup>41</sup> Bergson 1921, p. 45, p. 200.

comic and the absurd, Glaspell's curious blend of social comedy, of slapstick, of melodrama, of science play and tragedy could thus be seen as a venture to create mutationist instability on a receptional level. This would be also quite similar to what George Cram Cook, her husband, saw in drama, "The shock of new forms, and hence awareness of all form, the adventure of the great new chance for expressing what has not been formed."<sup>42</sup>

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<sup>42</sup> Glaspell 1926, p. 167.

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## *Non-Evolutionary Mutants? A Note on the Castorrex Rabbit*

Thierry Hoquet

Throughout the twentieth century, from Henri Bergson to Pierre-Paul Grassé, French evolutionists have acknowledged both the fact of the transformation of species and the fact of mutation, but they have often refused to amalgamate the two into one single theoretical framework. This sort of French “resistance” to evolutionary mutants has often been linked to a persistent “(Neo)Lamarckism.” It is supposedly only because French evolutionists believed in the inheritance of the acquired characteristics — in other words, because of their incorrect theory of heredity — that they were unable to understand the basic tenets of the theory of evolution by mutations.

I’d like to show that the situation has always been more complex. I will go through some objections raised against the mutationist account of evolution, following, like Alice in Wonderland, a rabbit. Except that my rabbit will not be a white one, but a strange mutant called the Castor-Rex or Castorrex. The Castorrex mutation was first documented in the 1920s and much discussed in the 1920s and 1930s. I will use this animal, as presented in a 1928 book by Jean Rostand, *Les chromosomes*, as an entrance point into the maze of French evolutionary thought. The Castorrex and Rostand’s reference to it will be a good opportunity to reassess the status of the various mechanisms of evolution — be they “Darwinian,” “Lamarckian,” or “de Vriesian” — among evolutionary theories during the first quarter of the twentieth century.

### *I. The Castorrex and its Interpretation*

— The Story of the Castorrex —

In 1919, in Coulongé, a small town in the Department of Sarthe (France), a new mutation was documented on the farm of Désiré Caillon. Among his adult rabbits, some remained totally naked, with wrinkled skin and no hair at all. Caillon shared his discovery with the Abbé Amédée Gillet, the priest of his parish, who started breeding the rabbits and produced a new variety, whose hair was short and whose color was *castor* (beaver). In 1913, a rabbit skin was presented at a fair held in the Grand Palais in Paris. And in 1924, Castorrex (or King Beaver) made its *grand début* at the *Salon international d’aviculture de Paris (International Show of Poultry Farming)*, where Gillet presented six of his rabbits under that name. The main feature of the Castorrex was the shortness of the long rigid hair called “directional hair” (in German: *Leithaar*; in French: *poils de direction*, *poils recteurs* or *jarres*). But Gillet, lacking any background in genetics and totally ignorant of the laws of inheritance, produced only rabbits that showed the clearest signs of congenital degenerescence and were often sterile.

The new rabbits drew a great deal of public attention. Among others, John C. Fehr, a U.S. rabbit raiser, promptly purchased some of those rabbits at a very expensive price and introduced the breed to the United States. Many breeders, amateurs, and scientists came to Coulongé to see Father Gillet’s rabbits and to buy specimens from him. Although the abbot was something of a conman,<sup>1</sup> the breed quickly spread across Europe, especially in Germany, where similar mutations

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<sup>1</sup> See for instance the testimony of Alex Wiltzer, published in the *Revue Avicole* and reproduced on the web:

had been observed and selected for.

— The Castorrex in Debates —

The Castorrex rabbit played a significant role in at least four different and tightly entangled directions: breeding, genetics, *Erbpathologie*, and evolution.

First of all, the Castorrex was an event in breeding. Yves Olivier, from the Faculté des Sciences in Nancy, devoted a 96-page book to this new breed (*L'Élevage du Castorrex*, 1929). Eugène Kohler, Professor of Spanish at the Faculté des Lettres de Strasbourg and rabbit-fancier, had bought some of the Abbé Gillet's rabbits. He crossed Rex rabbits with ordinary breeds, creating Rex of various colors (Fauve, Noir, Chinchilla, Herminé...). Kohler published a paper on the Castorrex in the April 1925 issue of the important German rabbit breeders' journal, *Der Kaninchenzüchter*; the paper's impact was immediate and huge.

Hans Nachtsheim (1890-1979), at the *Institut für Vererbungsforschung der Landwirtschaftlichen Hochschule*, in Berlin, Dahlem, obtained a special grant from the Prussian Ministry for Agriculture to acquire an expensive male rabbit (*Rammler*), in June 1925 (see figure 1).

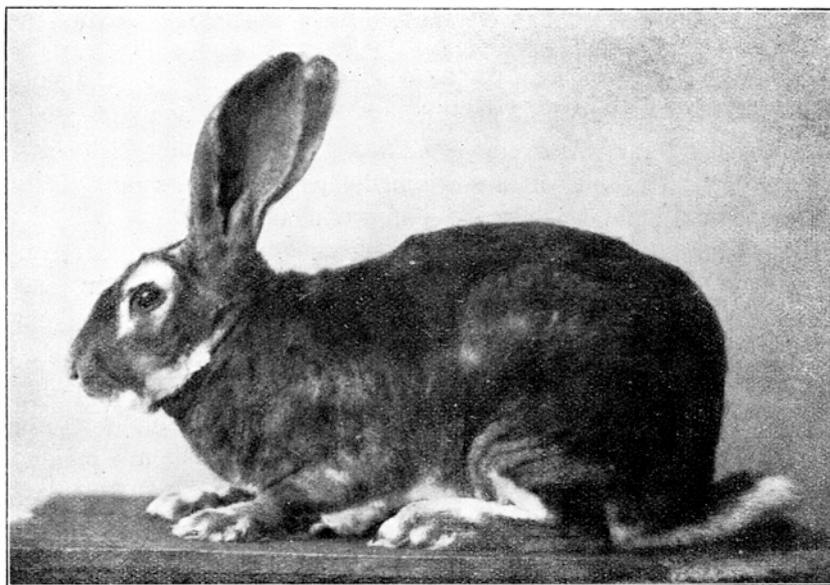


Fig. 1: Hans Nachtsheim asked to the Prussian Ministry of Agriculture a special grant to acquire a Castorrex sire from E. Kohler. (Nachtsheim 1929, p. 4)

Nachtsheim's interest in the rabbits was both theoretical and practical: his numerous conferences and publications include both technical tables and insights on the economic importance of the Rex rabbit.<sup>2</sup> In the context of the Weimar Republic, rabbit breeding offered an alternative to the

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<http://lapinrex.free.fr/historique.html#kolher>.

<sup>2</sup> Nachtsheim (Rexkaninchen) 1928, Nachtsheim (Zukunft) 1928; Nachtsheim (Entstehung) 1929; Nachtsheim (Rexkaninchen) 1929; Nachtsheim (Genetik) 1929, see in particular the section, "Die wirtschaftliche Bedeutung des Rexkaninchens," pp. 46-49.

expensive importation of fur, and also a means to feed people with cheap meat. As Alexander von Schwerin has shown, German breeders aimed at transforming the French's "serendipitous product" (*Zufallsprodukt*) into a methodical and standardized production system, through "the breeders' German industriousness" (*durch deutschen Züchterfleiß*), with mottos such as: "rabbit meat: the people's food" (*Kaninchenfleisch: Volksnahrung*) or "breeding for fur is key" (*Pelzzucht ist Trumpf*) (see figure 2).<sup>3</sup>



Fig. 2: To German breeders, the introduction of the Castorrex signified the hope of independence from costly importations. (from Schwerin 2004, p. 81)

From April 1926 to July 1927, Nachtsheim was in the United States, where he imported a pair of rabbits to New York. During this time, Nachtsheim's assistants were carrying on the studies in Berlin; C. Kosswig was taking care of the German breeds, while O. Thiel was studying the coat color of the Rex<sup>4</sup>. In the States, the Castorrex was met with great interest by those who were working on the Mendelian factors for the pigmentation of the fur, including William E. Castle (1867-1962), at the Bussey Institution in Harvard.<sup>5</sup> Both Castle and Nachtsheim went on to work

<sup>3</sup> Schwerin 2004, pp. 68-79 and 94-103; Zimmermann 1925, p. 785; Kleinhaus/Orphel 1927, p. 94.

<sup>4</sup> See Thiel 1928.

<sup>5</sup> Castle 1928, pp. 192-199; Castle 1929, pp. 53-60; Castle 1930.

in close cooperation and co-author articles on the Castorrex (see figure 3).<sup>6</sup>

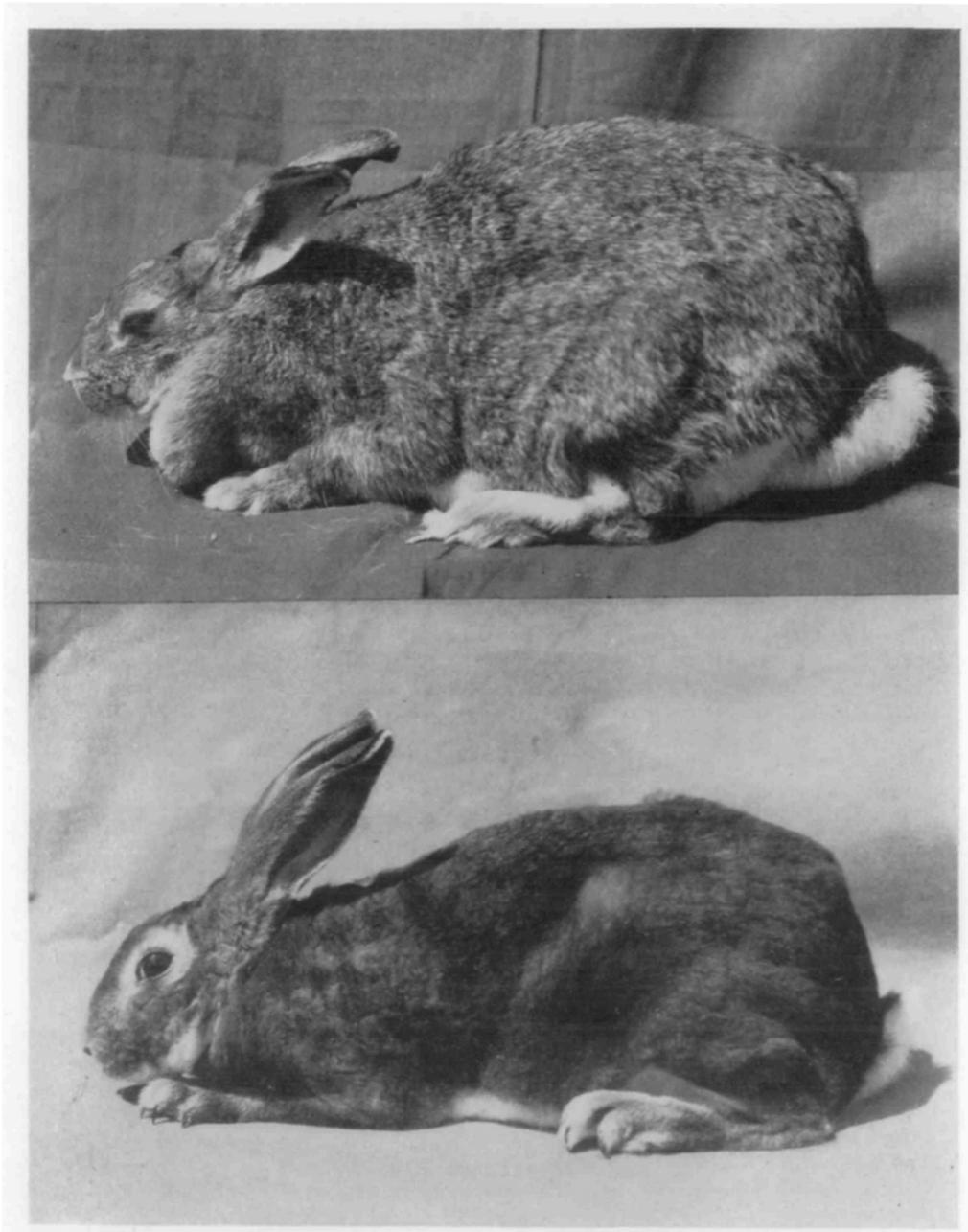


Fig. 3: William Castle knew about the Castorrex from Walter Landauer from the Storrs Experiment Station. He then started a tight cooperation with the German geneticist Hans Nachtsheim on the genetic factors of the coat color of the Rex Rabbits. When Nachtsheim visited the United States in April 1926, he brought two Rex rabbits with him. (Castle 1928, p. 192)

The Castorrex is a good case study to understand how the interests of the breeder community were reflected in the research of various naturalists on the variation in the coat color, such as Lucien

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<sup>6</sup> Castle/Nachtsheim 1933, pp. 1006-1011.

Cuénot's studies on the Mendelian rules of inheritance.<sup>7</sup> Evolutionary studies on coat colors are also relevant to this issue, including the selectionist mechanism in Wallace's work on mimicry, and orthogenetic laws in Theodor Eimer's study of the formation of color pigments in the skin of lizards.<sup>8</sup> Mutations were also interpreted, in the de Vriesian framework, as a mechanism for evolution, competing from the Darwinian or Lamarckian frameworks. Mutations were soon to occupy the page left blank by Darwin in his *Origin of Species*, as they turned out to be the *variations* used as raw material by natural selection. From Darwin to de Vries, evolutionary theory endured a twist from continuous to discontinuous variation. Those mutations that Darwin had rejected as sports returned to the evolutionary picture, and de Vries's mutations came to be identified with what Albert von Kölliker had called "*sprungweise Veränderungen*" (1864) and what Charles Darwin himself called "bud-variation" or "sports."<sup>9</sup> The question of the compatibility between Darwinism and de Vries's mutations was a topic much discussed, despite de Vries's own claim that his theory was in full accord with the principles laid down by Darwin.<sup>10</sup>

The fact that the main example used by de Vries was a plant named "*lamarckiana*," might seem something of an irony.<sup>11</sup> Much has been said about the pertinence of the choice of the *Oenothera l.* as a model organism; Thomas Hunt Morgan's choice of *Drosophila ampelophila* (also known as *melanogaster*) was far less disputed. If mutants were soon to find application in evolutionary theory, for what kind of evolutionary mechanism did they provide evidence? According to M.M. Metcalf in 1913, *Oenothera l.* supported orthogenetic conceptions of evolution, since its variations are never completely random but follow determined tendencies.<sup>12</sup> Evolutionists expected that the mutation theory would bring new insights, not only to the question of the support for heredity or on the nature of the gene, but also on the question of the mechanism for the origin of species.

In fact, both hybridism (the science of the effects of crossing) and mutationism (the fact of the sudden appearance of sports) had evolutionary impact, but the two questions have to be treated distinctly. De Vries's allegiance to Mendelism has been much discussed.<sup>13</sup> Mendelism, strictly speaking, is a theory of the laws or mechanisms of variation and heredity along the lines of various crosses; whereas mutationism was, from the start, a claim on the nature of variations and, more importantly, a new theory of the origin of species by means of discontinuous variation. But hybridism turned out to also be considered as a means for the origin of species, especially in the work of the Dutch botanist Johannes Paulus Lotsy (1867-1931) for whom hybridization offered an alternative and a complement to the theories of the origin of species based on variability.<sup>14</sup>

But it is probably wrong to speak of the role of mutation in the evolution theory without also stating that mutations are often detrimental. Most strikingly, it is noteworthy that the *Castorrex* originally suffered from different diseases: sterility, alopecia (or spot-baldness), chronic

<sup>7</sup> See among numerous articles, Cuénot 1902, pp. 27-30; Cuénot 1903, pp. 33-41.

<sup>8</sup> See for instance Wallace 1889; Eimer 1874; Eimer 1881, pp. 239-517.

<sup>9</sup> Kölliker 1864, pp. 174-186; Darwin 1868, ch. XI.

<sup>10</sup> See for instance, for an analysis of the competing *verae causae* to evolution, Nutting 1921, pp. 129-131, especially p. 131: "In conclusion it seems to me that we are justified in maintaining that Mendelism and the mutation theory, while forming the basis of the most brilliant and important advances in biological knowledge of the last half century, have neither weakened nor supplanted the Darwinian concept of the 'origin of species by means of natural selection'."

<sup>11</sup> The name comes from the fact that this plant was first known in 1797, when it was described in Paris, from specimens grown at the *Muséum d'histoire naturelle*.

<sup>12</sup> Metcalf 1913, pp. 67-68. See also Sturtevant 1924, pp. 579-580.

<sup>13</sup> See Meijer 1985, p. 189-232.

eye infections (cataracts, keratitis, atrophie of one of the eyes). In his study of the case of the Castorrex, Nachtsheim classified this variation as a degenerative mutation.<sup>15</sup> In France, Mendelian characters were popularized as “chemical diseases or diatheses,” in the works of the prolific and influential biologist and theoretician of biology Félix Le Dantec (1879-1917).<sup>16</sup>

Robert D. Lienhart (1884-1972), working at the Faculté des sciences in Nancy, suggested that the Castorrex form was the accidental product of treponematosi, a nonvenereal syphilis resulting from a spirochete (*Treponema cuniculi*). Lienhart thus infected a population of rabbits in a rabbit hutch with spirochetosis: this infection resulted in several kinds of dystrophiae, many of which were heritable. The Castorrex mutation was just one of those disorders, artificially selected by the breeder.<sup>17</sup>

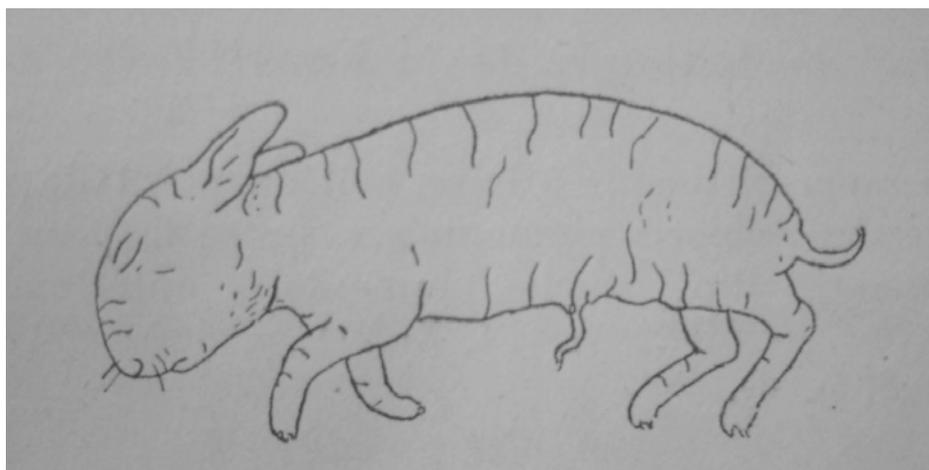


Fig. 4: Robert Lienhart, from the Faculté des sciences in Nancy underlined the fact that the Castorrex, not only lacks the “jarres” (or directional hair), but also the “vibrisses” or what is commonly called “moustache” (tactile hair located on the upper lip and the cheeks of Rabbits). (Lienhart 1928)

The question asked by Lienhart bears on the nature and causes of mutations (see figure 4). The specific features of the Rex are considered to be *mutations*, *sudden variations*, or *sports*. But what is the cause of those variations? Ultimately for Lienhart, the so-called mutations were mere recombinations of various genetic factors; Mendelian laws of assortment of alleles were sufficient to explain the various phenotypes observed.<sup>18</sup> But other naturalists, who might not have mastered

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<sup>14</sup> See Lotsy 1916.

<sup>15</sup> Nachtsheim (Zukunft) 1929, p. 54: “Das Rexkaninchen ist eine ganze typische *degenerative Mutation*. Die Lebensfähigkeit ist ... stark herabgesetzt.” (quoted in Schwerin 2004, p. 84) See also Nachtsheim (Wandlung) 1929, p. 326: “Aufgrund unserer Untersuchungen müssen wir also sagen, der Züchter seidigweicher Rexe hält seine Tiere für um so besser, je kranker das Haarkleid ist, um so stärker machen sich auch die sonstigen schädigenden Wirkungen des Rexfaktors bemerkbar.” (quoted in Schwerin 2004, p. 100, who comments: “the economically oriented speech is immediately intermingled with medical and eugenical considerations.” — “Der ökonomisch ausgerichtete Diskurs vermischte sich unvermittelt mit medizinischen und eugenischen Bezugspunkten.”)

<sup>16</sup> See Le Dantec 1904, pp. 513-517; Le Dantec 1909.

<sup>17</sup> Lienhart 1927, p. 386; Lienhart 1928, pp. 413-416.

<sup>18</sup> See R. Lienhart’s study of the “genetic formula” of the Castorrex: Lienhart 1930, pp. 523-524, esp. p. 524: “Les prétendus mutants de Lübeck, de l’Eure, d’Alsace et de Moselle, signalés par différents auteurs, ne sont nullement des mutations nouvelles, mais de simples combinaisons à phénotype castorrex provenant de l’introduction insoupçonnée, dans les élevages ordinaires, de Lapins d’aspect normal, mais hétérozygotes...”

the Mendelian laws with Lienhart's expertise, were persistently asking what caused the differences in phenotypes. For instance, Etienne Létard (1890-1983), Professor at the Ecole nationale vétérinaire de Lyon, an active participant in the story of this rabbit, asked in 1930:

Why, with no apparent reason, does an individual present with an important difference, whether morphological or physiological, with its offspring? Such a question remains, most of the time, unanswered, but it is legitimate to attempt to discover the cause.<sup>19</sup>

Such a shift in interpretation between Lienhart and Létard also indicates how traditional practices might have led breeders to resist Mendelism. The Mendelian segregation of characters was considered by many breeders as contrary to their practices: "Mendelizing is oscillating" (*Mendeln heißt Pendeln*), the German breeders, for instance, claimed.<sup>20</sup> If the Darwinian concept of selection was of course closer to the actual practice of the breeders, it seems that breeders were in general hostile to theory, as was clearly shown by Jean-Louis Fischer in the case of the Abbé Germain Vieules. Vieules, who founded a *Revue internationale de génétique* and authored *Histoire génétique pédigrée d'une famille de haricots*, in 1916, addressed the Darwinians with the following challenge: "montrez-nous une espèce nouvelle de votre fabrication M. Charles Darwin et nous serons tous darwinistes." For traditional practitioners such as Vieules, only empirical truth mattered, and it bore the name of no one.<sup>21</sup>

— Rostand and the Monstrosity of the Castorrex (1928) —

In his 1928 book, *Les chromosomes*, the young biologist Jean Rostand (1894-1977) gave a good account of the state of mind of French biologists.<sup>22</sup> The son of playwright Edmond Rostand, Jean Rostand had a bachelor's degree in science (*Licencié ès-sciences*) from the Faculté de Paris. In 1916-1917, he studied the reproductive cycle of the larvae of the *Miastor* fly at the Laboratory for the Evolution of Organized Beings (*Laboratoire de l'évolution des êtres organisés*), under Professor Maurice Caullery. But as early as 1919, right after his father's death, Rostand retired from Caullery's laboratory and became an independent writer.<sup>23</sup>

*Les chromosomes* (1928) is not, strictly speaking, a scientific publication but more of a popular science book. Especially for that reason, the book gives a good snapshot of French attitudes with respect to mutations at the time. Rostand's conception of "mutations" was that chemical changes occur in the structure of the chromosomal particles, for example, rearrangement of atoms, transformation of an albumin molecule into one of its isomers... For Rostand, mutations could be defined as a factorial alteration of the hereditary components of the sex cells. The causes of mutations remained mostly unknown, although they included exposure to certain chemical substances (esp. in food) or to radiation as in H. J. Muller's experiments.

Rostand listed the strengths and weaknesses of this theory of evolution by mutations. In

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<sup>19</sup> See Létard 1930, republished on-line, <http://lapinrex.free.fr/letard.html>. Létard gave several lectures on the Castorrex, see for instance, "La race Castorrex, conférence donnée au cercle militaire de Namur, le 14 octobre 1928," republished in *La Vie Rurale*.

<sup>20</sup> See Schwerin who contrasts Nachtsheim's genetic point of view with the breeders' opposition to Mendelism (Schwerin 2004, pp. 56-83). Compare Nachtsheim 1922, p. 635-640 and Sustmann 1923, p. 469.

<sup>21</sup> See Fischer 1990, pp. 43-64.

<sup>22</sup> Rostand 1928.

<sup>23</sup> See Fischer 1978.

favor of this theory, he referred to the case of the Castorrex rabbit and drew the following conclusion: new breeds frequently appear by mutation and mutations are immediately heritable, although ordinarily recessive. Nonetheless, problems remained with the mutationist account of evolution. First, advantageous mutations are rare and, in general, mutations are “absolutely ordinary, and deprived of any hereditary value (*absolument quelconque et dénuée de valeur héréditaire*).”

Accordingly, Rostand suggested that, if mutations have ever played a role in evolution, then “those mutations must have been very different from those that we observe or provoke today.”<sup>24</sup> It seemed that twentieth-century mutants did not provide new features; their mutations were only detrimental, even destructive and never progressive or really innovative. If the Castorrex was the ultimate paradigm for mutants, today’s mutations equated to what were previously known as monsters or excess — in other words *sports* such as the shortness of legs of the Ancon sheep or hexadactyly.<sup>25</sup> But Rostand’s doubts concerning evolution by mutations were also related to his conception of the role of selection: does natural selection act mostly as a sieve, sorting out variations and eliminating the less favored ones, or is it also creative?

The mutationist account of evolution would amount to the following: that species vary in one way or the other, in any possible direction, because, from time to time, the sex cells of some organisms go through a modification in their chromosomes. Mutants with the worst conformation disappear, others survive.<sup>26</sup>

But all sorts of mutants, and not only the “fittest,” survive. As he put it in 1931:

Life is a certificate of viability, not of excellence. There is no bonus for the best adaptation.”  
 (“Vivre est un brevet de viabilité et non d’excellence. Nulle prime à la meilleure adaptation.”)<sup>27</sup>

Surely Rostand was no original thinker for the time. This is what makes him especially relevant to a general inquiry on the French ideas about evolution in the 1920s and 1930s, especially in the wake of the Castorrex rabbit. It seemed that most of the mutations, far from being beneficial, were often lethal monstrosities, so that their role in evolution should not be asserted without special care.<sup>28</sup> If mutations played a role in the course of past organic evolution, then they most probably were of a different kind and nature. And even so, the idea that mutations could build the whole diversity of living organisms remained a very doubtful one. A common theme is easy to identify in the various criticisms: mutations do not create new plans of organization, but they rather “embroider” along preexisting patterns. Most of the mutations are only a matter of excess or want, deprived of any real creative (i.e., evolutionary) power.<sup>29</sup>

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<sup>24</sup> Rostand 1928, p. 266.

<sup>25</sup> See a similar list of mutations in Rostand 1931, pp. 120-121.

<sup>26</sup> Rostand 1928, p. 265: “La théorie mutationniste de l’évolution se réduirait donc à ceci: les espèces varient d’une manière quelconque, dans n’importe quelle direction, parce que, de temps à autre, les cellules sexuelles de certains organismes subissent une modification dans leurs chromosomes. Les mutants trop mal conformés disparaissent, les autres survivent.”

<sup>27</sup> Rostand 1931, p. 111.

<sup>28</sup> Rostand 1928, p. 264: “Pour ceux qui tiennent que les mutations sont des espèces naissantes, la création expérimentale de nouvelles espèces serait dès maintenant chose faite. Mais la grosse question que nous ne pouvons qu’effleurer à cette place, est précisément de savoir si les mutations sont les espèces naissantes.”

<sup>29</sup> For a popular account on this ornamental nature of mutations, see Le Dantec 1909, “Première Leçon.”

## II. Which Mechanism for Evolution? Darwinism, Lamarckism, Mutationism: the Search for Alternative Solutions

Rostand's account of mutations and of the *Castorrex* suggests that the French resistance to evolutionary mutants was partly due to "local" factors, among which Lamarck's influence on French biologists probably ranks first. Immediately following comes the incredible influence of the philosopher Henri Bergson (1859-1941). Several other important references come to the fore when considering Rostand's French sources: his Parisian mentor Maurice Caullery (1868-1958), as well as the Nancy geneticist Lucien Cuénot (1866-1951) and the Geneva-based zoologist Émile Guyénot (1885-1963). However, the question remains open, as to whether those references constitute a typically French context, or whether they simply are the French local version of a more general resistance among the communities of biologists to the theory of evolution by means of mutations. In this latter case, French resistance would be due to general problems in the theory of evolution by mutation itself and not to some idiosyncratic misunderstandings.

— Dissatisfaction with the Mechanisms of Evolution —

During the first quarter of the 20<sup>th</sup> century, many biologists considered that evolution was a fact in search for explanatory mechanisms. The 1909 celebration of the centenary of Charles Darwin's birth and the fiftieth anniversary of *On the Origin of Species* proved sufficiently that various schools and personal agendas were competing around the evolutionary theory.<sup>30</sup> At least three different rival systems were competing, each of them with its own merits and limits: Darwinism or the theory of natural selection was considered completely insufficient but fully established (for instance, it was considered proven by the "fact" that "nature is at war"); Lamarckism was desperately trying to establish its very basis: the inheritance of acquired characteristics; as for mutationism, it was considered too limited in its range. With each system being impaired by the things it failed to explain, the time was ripe for syncretism — despite the previous attempts of the Neo-Darwinians, such as August Weismann, to demolish an earlier phase of syncretism.

Typical of this ecumenical attempt is the book of A.L. and A.C. Hagedoorn, published in 1921 under the title *The Relative Value of the Processes Causing Evolution*.<sup>31</sup> According to the two geneticists, three completely different theories offered an account of evolution in nature and each found adherents. Among biologists, a minority supported Lamarck's theory of the inheritance of adaptive changes induced by the environment. Some inclined to the views of Darwin and Weismann, that species gradually changed by means of natural selection on small, individual variations. Others believed with de Vries that new species sprung into being spontaneously by mutation or saltation.

The disparity among those theories was so big that many biologists believed that "theories of evolution must always be essentially speculative." Biologists shared some "unconscious recognition of the one-sidedness of the above-named theories," that each tries to explain all evolution by one omnipotent agency to the exclusion of all other causes. Darwin, far from being rejected, was praised as singular among biologists for his "broadness of vision." Only a few biologists indeed attempted to reach a new synthesis; in most cases, they considered that their results had value in themselves but they failed to consider to what extent those results could be considered as building

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<sup>30</sup> See Richmond 2006.

blocks.

There is one point in common to all the theories of evolution, excepting Darwin's, and that is, that each theoretician has always over-emphasized one point, one single link in the chain of processes which goes to the making of the species, and has brought out this point as 'the' cause of evolution.<sup>32</sup>

Lamarck, Weismann, and de Vries were all considered as "extremists" who had "been very useful in bringing adaptation, selection, and mutation to the fore, and so stimulating discussion of the importance and the relative role of these different processes in the making of species." But "their striking theories" had had their day, and among them, "genetics ha[d] been tamed."<sup>33</sup> It was therefore time, so the Hagedoorns claimed, that the biologists see the forest of evolution behind all the trees of isolated mechanisms.

That is why, when Johannes Paulus Lotsy claimed that crossing explains the origin of new species, he added immediately:

To save another kind of critic unnecessary trouble, the author is fully prepared to admit unhesitatingly that his theory explains but part of the problem of evolution, so that there is ample room for them to take part in the exploration of this most interesting field of investigation; but he may be permitted to remark that the rest, left unexplained by theories based on variability, is not smaller than that left unexplained by his theory.<sup>34</sup>

Lotsy's mechanism made no claim to be the underlying secret of nature, but rather to offer a sufficient explanation for a few cases of speciation. The book pays a due tribute to Darwin (if not to natural selection), starting with the following dedication:

To the memory of Charles Darwin, this sketch is dedicated by the Author as a tribute to his character and to his work which led to the general recognition of the principle of evolution.

And the introduction ends with the following remarks:

But notwithstanding all our stooping, we who try to reveal the underlying secret of nature, feel, even in the midst of our defeats, that the fundamental idea on which all our efforts are based, that the conception of continuity in all that happens, that the Principle of Evolution, which owes so much to Charles Darwin, is correct that, as he expressed it, the 'ordinary succession by generation has never once been broken'.<sup>35</sup>

In fact the search for additional mechanisms of evolution has always been the favorite game of evolutionary thinkers: Moritz Wagner with his *Migrationgesetz* in 1868 and George Romanes with his physiological selection in 1886 are but two examples among many attempts to describe the laws of evolution that followed in the wake of the "Darwinian revolution."<sup>36</sup> American naturalists were also looking for some "unknown factors in evolution." As H.F. Osborn put it: "If acquired

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<sup>31</sup> Hagedoorn 1921.

<sup>32</sup> Hagedoorn 1921, p. 3.

<sup>33</sup> Hagedoorn 1921, p. 4.

<sup>34</sup> Lotsy 1916, p. VII.

<sup>35</sup> Lotsy 1916, p. 10.

<sup>36</sup> To the point that Peter Bowler even coined the expression "the Non-Darwinian revolution." See Bowler 1988; see also Wagner 1868; Romanes 1886, pp. 314-316, 336-340, 362-365; accompanied by several letters to the editor: "Organic Evolution," pp. 360-361; "Physiological Selection and the Origin of Species," pp. 407-408; Romanes 1888, pp. 173-175.

variations are transmitted, there must be some unknown principle in heredity; if they are not transmitted, there must be some unknown factor in evolution.” Herbert W. Conn also made perfectly clear that he saw the two evolutionary paradigms (Lamarckism and Darwinism) as having been exhausted and that he felt the need for new forces and alternative theories. If, on the one hand, Darwinism was considered clearly established on its bases, but not sufficient; and if, on the other hand, Lamarckism struggled in vain to establish inheritance of the acquired characteristics, then, Conn argued, evolutionists had to look for a third solution, which he coined “orthoplasy.”<sup>37</sup>

I don’t think that the French evolutionists were an exception here. They were trying to overcome the opposition between Darwinism and Lamarckism, feeling the need for a general and unified evolutionary framework and feeling the lack of it. Far from developing general frameworks or offering metaphysical hypotheses, French biologists generally referred to under the name “Neo-Lamarckians” were working in the field of experimental transformism. They were in fact true disciples of the methods and spirit of Claude Bernard’s physiology and Louis Pasteur’s microbiology, fields to which one can add causal embryology, and particularly the experimental teratology of Camille Dareste.<sup>38</sup> Of course, Lamarckian inheritance certainly played an important role in their resistance to evolution by mutations. But a closer look at French accounts on Lamarckian inheritance clearly suggests that this model was already contested and dismissed by the turn of the twentieth century. Lamarckism was a paradigm in crisis in France in the 1920s and 1930s.<sup>39</sup>

For instance, Rostand, basing his claim on the study of the *Castorrex*, doubted that mutations are the true mechanism of evolution, but his doubts also applied to the two other conceptions of evolution — the Darwinian and the Lamarckian. It seemed to him that Lamarckism has incontestable qualities: it could easily explain how webbed feet evolved in aquatic birds or how calluses developed on camels’ knees; but Rostand was also conscious that the problem of the inheritance of acquired characteristics was an unsolved knot of problems. The issue with Lamarckism was the relationship between *soma* and *germen*. Whereas a mutation affected the *germen* insofar as it was a modification of the immortal germ-line, a *somation* was a modification that merely affected the (mortal) body of the adult organism. Could it then be transmitted to the offspring by hereditary means?

For Rostand, the somation or modification of the general state of the adult individual could possibly affect the general state or condition of its offspring, without any definite character being transmitted. Contemplating the idea of a Lamarckian inheritance but finally rejecting it as contrary to the facts, Rostand refused to decide in favor of one or the other alternatives:

We are presently facing a dilemma, in which we are trapped and we are not even on the edge of finding a way out. The evolution of species, is, without acquired inheritance, very difficult to conceive; and as to acquired inheritance, not only is it very difficult to conceive but it also comes that facts are frankly contrary to it.<sup>40</sup>

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<sup>37</sup> Osborn 1895, quoted by Weismann 1896, p. 267. See also Baldwin 1902.

<sup>38</sup> See the seminal paper of Gayon/Burian/Zallen 1988, pp. 357-402; and, expanding along those lines, the work of Laurent Loison, a first-class study on French “Neo-Lamarckians”: “Les notions de plasticité et d’hérédité chez les néolamarckiens français (1879-1946), *Eléments pour une histoire du transformisme en France*,” PhD Thesis defended on December 3, 2008, at Nantes University under the direction of Stéphane Tirard. On Dareste, see Fischer 1994.

<sup>39</sup> See for instance how Émile Guyénot portrayed the situation in 1921 (Guyénot 1921), pp. 598-606.

<sup>40</sup> Rostand 1928, p. 277: “nous sommes présentement enfermés dans un dilemme, dont il ne paraît pas que nous soyons près de sortir: l’évolution des espèces est, sans l’hérédité acquise, très difficilement concevable; et quant à l’hérédité acquise, non seulement elle est très difficilement concevable, mais les

Nonetheless, “we’ve never been as sure of the evolution of living forms.”<sup>41</sup> However mysterious the *mechanism* of evolution remained, the *fact* of evolution had never been so certain.

— Bergson’s *Élan* and the Spring of Nature —

The French attitude towards mutations cannot be understood without a look at the most influential book by Henri Bergson (1859-1941), *Creative Evolution* (1907).<sup>42</sup> This book largely continues along the lines of Bergson’s own philosophical stance, but it might also be read as an answer to the view of evolution conveyed by thermodynamics and expressed in *La Dissolution*, by his fellow philosopher André Lalande (1867-1963).<sup>43</sup> Whereas the principle of entropy seems to imply the continuous degradation of energy, Bergson developed a view of evolution as a glorious stampede, a series of explosions, and a process of development.

Published soon after the studies of deVries on the *Oenothera lamarckiana*, *Creative Evolution* devotes a section to the role of mutations in the process of evolution. Relying on a very up-to-date knowledge of the biological literature, Bergson distinguished and discussed four main evolutionary mechanisms: the Darwinian (variationist), the Batesonian-DeVriesian (mutationist), the Eimerian (Theodor Eimer’s orthogenesis), and the so-called Lamarckian conception of the inheritance of acquired characteristics. Bergson refuted each of them and ended up proposing his own conception of evolution by a vital or creative “*élan*.” The operators of evolution, he claimed, were not to be pictured as an accumulation of blind mutations or acquired characteristics, but as dynamic explosions.

Bergson was specially interested in “parallel evolution,” the fact that an organ — for instance the eye — appeared several times during the course of evolution. This case seemed especially relevant to Bergson who wondered how such a fact could be accounted for by the mutationist theory, whether mutations were micro or macro. He developed two different objections:

- He objected to the variationist (Darwinian) account that it required too many steps, so that the occurrence of the same output (an eye for instance) was rendered improbable. The construction of a complex and coherent design was deemed highly improbable in the course of multiple and uncoordinated minute operations.

- The same objection did not apply to the mutationist account, since the number of intermediary steps was by far less numerous. Macro-mutations or sports could produce complex designs in only one or a few massive changes. The drawback of this account is that the size and range of variations may compromise the coherence of the organism.

Bergson’s account of evolution came to be very influential in the French context and was regularly quoted by French biologists throughout the twentieth century. For instance, Rostand took up two arguments from Bergson. First, his whole argument against Lamarckian inheritance:

There might be *an inheritance of the variation*, according to Bergson, but not of the *character*. Any *somation* might, theoretically, induce a mutation in the descent, but an indefinite mutation.<sup>44</sup>

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faits lui sont franchement contraires.”

<sup>41</sup> Rostand 1928, p. 277: “jamais nous n’avons été aussi certains de l’évolution des formes vivantes.”

<sup>42</sup> See Gayon (Annales), pp. 175-189.

<sup>43</sup> Lalande 1899.

<sup>44</sup> Rostand 1928, p. 270: “Il peut y avoir *hérédité de l’écart*, suivant le mot de Bergson, mais non pas du caractère. Toute *somation* peut, théoriquement, induire une mutation dans la descendance, mais une mutation quelconque.”

Earlier in his text, facing the yet unsolved if not unsolvable dilemma of Darwinian vs. Lamarckian evolution, Rostand had evoked Bergson's *élan* as a possible (although improbable) third way:

Are we to suppose that such mutations [i.e. mutations of a different amplitude] did occur in the past? that the evolutionary force of the chromosomal substance is nowadays dried up? that the *élan vital* is exhausted?<sup>45</sup>

No doubt there is a hint of irony in Rostand's sentence. Bergson's *élan* offers a new version of the ancient theme of the exhaustion of nature.<sup>46</sup> But ancient as it may sound, this theme, once reactivated by Bergson and, later, by the works of the Jesuit priest and paleontologist Pierre Teilhard de Chardin, had an enormous appeal to French evolutionists during the twentieth century. They solidly believed that the mutations of the past should differ essentially from today's mutations, since evolution seemed to have lost all strength and ability to build new designs. As Rostand put it, "Life is no longer evolving and building, it has given all it could give."<sup>47</sup> At the end of the 1920s, Maurice Caullery (Rostand's mentor) expressed a similar point in a conference held in Padova: that Lamarckism was an appropriate description of the ancient times, since adaptive somatic variations had existed at the time, but such was no longer the case.<sup>48</sup>

Bergson's influence would be relayed by many French evolutionists, throughout the twentieth century. Louis Vialleton's *L'origine des êtres vivants* (1929) is a good example of a biologist taking up Bergson's claim that mutants can't explain the construction of the macro-taxa.<sup>49</sup> Another example is another student of Maurice Caullery, Albert Vandel (1894-1980), who was Professor at the Faculté des Sciences in Toulouse. In his 1939 book, *L'homme et l'évolution*, he asked whether the "spring of nature" had lost its resilience, since the mutations of the day seemed to be of too narrow a scope. Vandel criticized the general philosophy underlying the mutationist account of evolution as giving an excessively anthropocentrist (and individualist) approach: only in the human species do individual variations really matter.<sup>50</sup>

The question of the "spring of nature" was very vivid in the French (Bergsonian) context, but, as with other themes in the critique of the mutationist account of evolution, it was not unique to the French. The same kind of arguments can be found in H.W. Conn's *Limits of Organic*

<sup>45</sup> Rostand 1928, p. 266.

<sup>46</sup> A similar assumption had been made in a general Epicurean framework by Denis Diderot in his *Letter on the Blind for the Use of Those Who See* (1749), and Fontenelle had asked in 1680 "Where have they gone, those vigorous and stiff souls, the Périclès and the Socrates?" To which his answer was that nature might be exhausted. See Fontenelle, *Nouveaux dialogues des morts, Œuvres complètes*, Corpus des œuvres de philosophie en langue française, Fayard, tome I, p. 85. Charles Naudin similarly expressed, in 1852, that nature had lost its power of plasticity. For Naudin, two opposite forces were in balance in nature: plasticity and atavism. When breeders wanted to create a new breed of domestic animals or plants, they had to play with those two forces, exactly as nature did in the past. But, Naudin added, nature worked under more favorable conditions, since she took "the primitive types, somehow, *in their native state*, when the forms still had all their plasticity and were not chained, but weakly, by the force of atavism." (Naudin 1852, p. 104) See also Félix Le Dantec, *Stabilité de la vie* (1910).

<sup>47</sup> Rostand 1931, p. 153: "la vie n'est plus évolutive, construisante, elle a partout donné ce qu'elle pouvait donner."

<sup>48</sup> Quoted by Rostand 1931, p. 154.

<sup>49</sup> Vialleton 1929.

<sup>50</sup> Vandel 1949, pp. 124-125: "Les naturalistes ont fait preuve, en la circonstance, d'une curieuse inconscience. Alors qu'ils ont poursuivi sans relâche toute conception entachée d'anthropomorphisme, ils ont attribué, avec une surprenante unanimité, une qualité proprement humaine au phénomène de la variation. Depuis Darwin, l'immense majorité des biologistes a placé l'origine des variations dans des modifications individuelles ou mutations. Ils ont ainsi transposé dans l'organique une propriété essentiellement humaine, l'invention individuelle."

*Evolution*, also deeply concerned with the exhaustion of evolutionary dynamics and the potential extinction of species that it might entail.<sup>51</sup> A similar objection was constantly arising in the field of biology, and the late Stephen Jay Gould was still asking the same question, most conspicuously in his *Wonderful Life*.<sup>52</sup>

— Cuénot and Guyénot: mutations and the origin of species? —

Among the various sources upon which Rostand's *Chromosomes* strongly though tacitly relied, I will focus on the works of two important biologists, Émile Guyénot and Lucien Cuénot. Both were internationally respected and very well informed. Cuénot was well-known, his views were respected, and his papers were at times translated in *Science* or other journals.<sup>53</sup> Guyénot was much younger but the bibliography of his two volumes on *Variation and Evolution* (1930) is impressive and shows an international network of information.

Émile Guyénot started his doctoral thesis in a Lamarckian spirit, hoping to show how the conceptions of the geneticists were biased, but he ended up showing that the mutant flies he was studying did not change in an altered environment. As Gayon, Burian, and Zallen aptly remarked:

Furthermore, he had been able to verify the exactness of Mendel's laws on stable mutants given him in 1913 by T.H. Morgan. — *In other words*: — Guyénot brought genetics before a tribunal composed of Claude Bernard and Louis Pasteur. ... Having turned on his teachers, and declared his allegiance to the genetics of the Morgan school, Guyénot (with the support of Caullery) became embroiled in a prolonged and vicious polemical debate with Rabaud and Raymond Hovasse.<sup>54</sup>

Guyénot's research took a strong anti-Lamarckian stance, as is sufficiently shown in two articles published in *La Revue scientifique*, in 1921. The first paper, "Mutations and Monstrosities," criticized the Lamarckians (a general name for Rabaud and his followers), who had "according to their habit, muddled up a very simple question by trying to tie together the production of monstrosities and the action of external factors." He even referred to the happy times when "the Lamarckian virus had not poisoned biology yet."<sup>55</sup> In the following paper, "The Prejudice of Adaptation," he severely chastised the "finalism" of the Lamarckian theory and its radical focus on adaptation, which was, according to Guyénot, "a remnant (*survivance*) of the old creationist conception."<sup>56</sup> Another fault in the Lamarckian conception of evolution was that it entailed a very slow transformation process.<sup>57</sup> Finally, Lamarckians had taken the problem in the wrong way: they tried to understand how the environment had created some refined adaptations, whereas the problem should be taken the other way around: mutant organisms might be eliminated in a particular environment, but they may end up being accidentally "preadapted" to a different environment. Guyénot borrowed this concept of "preadaptation" from Cuénot, and rejected "the

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<sup>51</sup> Conn 1886, pp. 413-422.

<sup>52</sup> Gould 1989.

<sup>53</sup> See for instance Cuénot 1906; Cuénot 1909; or a review of his 1911 book, *La Genèse des espèces animales*, in *Science*, vol. 35, n°903 (19 April 1912), pp. 624-625.

<sup>54</sup> See Gayon/Burian/Zallen 1988, pp. 375-376 and the polemical articles published by Rabaud, Guyénot et Caullery, in the 1937 issue of the *Bulletin biologique de la France et de la Belgique*.

<sup>55</sup> Guyénot (Mutations) 1921, p. 614.

<sup>56</sup> Guyénot (Préjugé) 1921, p. 644.

<sup>57</sup> Guyénot (Mutations) 1921, p. 616.

easy and illegitimate irony” that assimilates preadaptation with “coarse finalism.”<sup>58</sup>

In those two papers, Guyénot stressed the “evolutionary importance of mutations,” without taking a deVriesian stance. He took up Bateson’s remarks that deVries’s *Oenothera* experiments might suffer from very important faults in the choice of the model organism. Therefore, deVries’s contribution to science might be reduced to the most general statement: the idea of discontinuity in evolution.<sup>59</sup> For Guyénot, *variations*, *anomalies*, and *monstrosities* were three synonymous terms and he did not hesitate in his two papers to describe some important taxonomic groups in terms of monstrosities: whales and sirenians were “biabdominal ectromels”; moles were animals with achondroplastic anterior limbs and suffered from variable micropsy; birds or turtles were “anodonts” (deprived of teeth). Guyénot’s systematics was a teratology, and it followed, as its leading principle, “the teratological origin of certain animal species.”<sup>60</sup> This conception of evolution entailed a conception of the organism freed with the Lamarckian obsession with adaptation. For Guyénot, “animal nature presents with a host of variations deprived of utility and functional signification. Organisms go on living, after a fashion (*tant bien que mal*), in spite of those characters, rather than thanks to them.” This conception can be traced through William Bateson’s 1913 *Principles of Genetics* to the spirit of the pre-Lamarckian French naturalist the Count de Buffon.<sup>61</sup>

Bateson’s influence is also palpable on Lucien Cuénot, whose fame comes from his successful attempt (concomitant to Bateson’s) to apply Mendelian genetics to the study of animals, especially to populations of mice. A committed evolutionist, Cuénot was also described by Rostand as an ardent but moderate mutationist.<sup>62</sup> But mutationist though he was, Cuénot stated: “I believe indeed that morphological mutations, *in themselves*, can almost never found a species.” For the sake of this presentation, I will focus on a paper published in 1929 in the *Swiss Journal for Zoology*, on “the origin of species and mutationism.”<sup>63</sup> For Cuénot, the problem of the origin of species was emblemized by a sentence of William Bateson:

it is easy to imagine how Man was evolved from an *Amoeba*, but we cannot form a plausible guess as to how *Veronica agrestis* and *Veronica polita* were evolved, either one from the other, or both from a common form.<sup>64</sup>

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<sup>58</sup> Early in his career, Cuénot developed a concept of preadaptation, which was an anti-selectionist stance. In another context, George Romanes had observed the emergence of a German school of evolutionists who considered “*self-adaptation*” as more important than both natural selection and inheritance of acquired characteristics or use-inheritance: such evolutionists were neither Darwinian nor Lamarckian (See his Romanes 1895, p. 11). And it seems that Cuénot belonged to the same school of thought. For him, only some mutants were apt to survive: those that were lucky enough to encounter some environments (*milieux*) to which they were, by means of their mutations, relatively *pre-adapted*. See Guyénot (Préjugé) 1921, p. 649 and 650: “Ce n’est pas parce que la taupe vit sous terre qu’elle a des yeux réduits, mais parce que la micropsie n’avait chance de persister que chez les animaux dont le genre de vie rend la vue à peu près inutile. Ce n’est pas parce qu’ils nagent qu’un grand nombre d’animaux aquatiques ont les pattes palmées, c’est parce que la syndactylie membraneuse, rendant la marche difficile, n’avait guère de chance de persister que chez les organismes aquatiques.”

<sup>59</sup> Guyénot (Mutations) 1921, p. 611.

<sup>60</sup> Guyénot (Mutations) 1921, p. 614; Guyénot (Préjugé) 1921, p. 649.

<sup>61</sup> Bateson 1913; Guyénot (Préjugé) 1921, p. 648.

<sup>62</sup> See Rostand 1928, p. 265: “l’éminent zoologiste Cuénot qui soutient la thèse mutationniste avec une éloquence aussi nourrie que subtile, reconnaît loyalement qu’elle laisse irrésolus la plupart des grands problèmes.”

<sup>63</sup> Cuénot 1929.

<sup>64</sup> Bateson 1913, p. 97. The sentence is often quoted: for instance, by Cuénot 1929, pp. 163-164; or Thompson 1925, p. 99.

To meet the challenging question of the origin of species, Cuénot first contested the validity of the traditional definition of the species as “a collection of individuals, similar enough to be considered, with good reasons, descended from a couple or a common progenitor, mutually fecund and producing fecund offspring, and infertile with close species.”<sup>65</sup> For him, the true definition of a species was Mendelian: an homozygote individual (or a group of such individuals), whose descent was perfectly homogeneous: such “pure-breeds” or “unit-species” were embodied in nature by the “jordanons,” or elementary, stable, recognizable, and self-fertilizing forms.<sup>66</sup>

For Cuénot, mutations were unlikely to give birth to new species. His objections took up some of the traditional objections raised against Darwinian variations, most forcibly by Fleeming Jenkin, St. J. Mivart, or G. Romanes: that mutants inevitably cross with the unvaried type, which become heterozygote; that two mutant forms rarely conjoin; and that their offspring can hardly be isolated from the original stem.

Cuénot stated that the key to the origin of species was elsewhere: in self-fertilization; in the complete substitution of the mutant form for the old form; in some invisible mutations, for instance when two forms are made as if they were inter-sterile by a little lapse in their periods of reproduction; or by accidental geological isolation. Those various factors were always invisible and this was why one would never “attend” the formation of a new species. The essential part of the process of speciation, dealing with the production of an isolated group, remained, most of the time, unseen. In other words, Cuénot put an end to the hopes of “experimental transformism,” stating:

Man, during the short duration of his life, has no chance to attend the beginning and the end of the phenomenon of edification of a specific type; but all the various steps are currently abundantly under his eyes, and there remains no doubt on the order of their succession.<sup>67</sup>

Under such circumstances, the hope that the *Castorrex* mutants could be an incipient species were mere hypothetical fancies. In this 1929 paper, Cuénot rephrased Darwin’s question of the origin of species in mutationist terms. He appears to have been a devoted Mendelian for whom the question of the origin of species should not only be plainly answered, but needed to be completely re-conceptualized.

In later years, Cuénot would evolve all the way from his early Neo-Darwinism of the 1890s to a form of finalism in the 1940s.<sup>68</sup> In a book published in 1941, *Invention et finalité en biologie*, he claimed that some structures could not be understood without a teleological finalistic principle. As Richard Goldschmidt wrote in the obituary he dedicated to Cuénot in *Science*, in March 1951:

It is remarkable that a great zoologist, with unusual command of all aspects of the facts, simultaneously a pioneer of genetics and great contributor to recent evolutionary thought, felt himself constrained in the end to become a defeatist by advocating mystical powers. [...] It will be good to realize that his attitude was the result of a clear realization that the Neo-Darwinian

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<sup>65</sup> For a similar move, see Morgan 1923, which states that Mendelism is concerned with the origin of “new types”: “How far these new types furnish the variations that make new species may depend on what we call ‘species’.” (p. 237)

<sup>66</sup> “Jordanon” comes from Alexis Jordan (1814-1897), a botanist from Lyon. Jordan’s method for taxonomy tended to describe more and more forms as species, while they were previously considered as mere varieties; Jordan always verified experimentally that those forms do not interbreed. By dividing a taxon into multiple, often new, taxa, Jordan can be considered a “splitter.”

<sup>67</sup> Cuénot 1929, p. 167.

<sup>68</sup> Limoges 1976.

doctrine does not lead beyond the confines of micro-evolution and that the best rebuttal of mysticism in this field will be the elaboration of new ideas that will bridge the gap left by Neo-Darwinism, without recourse to defeatist philosophies.<sup>69</sup>

Most certainly, Goldschmidt is taking the opportunity of the *post mortem* eulogy to preach to his own choir. But it is interesting to see how various evolutionary thinkers were resisting the Neo-Darwinian synthesis and looking for accounts of evolution that would avoid the mutation and/or selection model.

— Elements for a Conclusion —

Mutations and their effects — the mutants — are at the crossroads of various fields of inquiries: evolution, heredity, pathology, variation, breeding.

The role of mutations in the origin of species has been highly debated among evolutionists. Heavy doubts were bearing on the creative power of natural selection, often considered as barely an eliminating process, but also on the undemonstrated status of the inheritance of the acquired characteristics and equally on the creative power of mutations, often regarded as mere monstrosities. As Guyénot clearly stated in 1930: “We have to acknowledge that transformism is a reality, but there’s not much left of the classical theories of evolution.”<sup>70</sup> Mutations are certainly the “only evolutionary possibilities that biologists have witnessed,” but the mutations that they observed seemed incapable of accounting for evolution. If mutations are/were the key to evolution, then they have/had to be of a nature and scope different from what we have actually seen. Most of the mutations we observe today seem deprived of any creative power and merely concern hereditary defects: this is clearly evinced by the case of the *Castorrex* rabbit, and many others such as the Ancon sheep. The connection between teratology and genetics and especially the connection with *Erbpathologie* is particularly relevant here. Bateson in his 1909 *Mendel’s Principles of Heredity* gave a complete inventory of anomalies that obey Mendel’s rules: hemophilia, cataract, brachydactyly, alcaptonuria (all recessive conditions) and his French followers such as Rostand and Guyénot would do the same.

But are these mutations in the first place? Many biologists, but also breeders, asked the question of the nature of mutations. How can a variation be identified as a mutation especially when the nature of a gene is still unknown? In other terms, if every individual is singular, can every “variant” be identified or interpreted as a mutant? What kinds of variations are the mutations and how are they to be distinguished from other types of variations (such as mere ‘*somations*’)?

Very representative of this type of questions is an article by Mr Cotte, “bacteriologist and poultry breeder in Die” (Department of the Drôme), “Le *castorrex* est-il une mutation?”, published in *La revue avicole*, in December 1928. For Cotte, the case of the *Castorrex* is “a typical example of the simplistic way that was adopted to explain any unexpected character, as a *mutation* or a sudden sport in heredity (*saut brusque de l’hérédité*).” Cotte simply denied that mutations or discontinuous variations could produce a new type “all of a sudden (*d’emblée*)”:

Each time I had to examine cases of so-called mutations, I could observe that the scientists who had studied them, had totally neglected to look for what had been, from a biological and

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<sup>69</sup> Goldschmidt 1951.

<sup>70</sup> Guyénot 1930, p. 363: “Il faut bien reconnaître que si le Transformisme est une réalité, il ne reste plus grand’chose des théories classiques de l’évolution.”

physiological standpoint, the generations preceding the mutation. As for me, I noticed that those new characters, seemingly appeared ‘all of a sudden,’ or so did the bad observers claim, were indeed the logical follow-up either of an infection, or of a mutilation occurring during the youth, and already present for three or four generations.<sup>71</sup>

The question of the laws of inheritance (esp. of acquired characters) underlines the alternative between mutation and somation. Is the observed variation only accidental and due to the action of the environment, or is it a genetic mutation? Lack of knowledge about the laws of heredity probably accounts for part of the French resistance to mutations, but not all.

The case against *mutagenesis* as an impossible mechanism of evolution was strongly taken up through the 20<sup>th</sup> century, for instance again in the 1970s by the very influential master of French zoology and paleontology, Pierre-Paul Grassé (1895-1985). If Rostand’s, Cuénot’s, or Guyénot’s critics of evolution through mutations were mostly targeting the deVriesian account of the origin of species, Grassé’s critics were aiming at the basic tenets of the Neo-Darwinian “evolutionary synthesis.” Grassé developed a whole battery of arguments against mutations.<sup>72</sup> Central to his argument is the emergence in the scientific literature of the “neutral mutations” of Motoo Kimura. Grassé argued that, if the micro-mutations were neutral, they would not constitute the material upon which natural selection can act. The case of the peppered moth was also considered by Grassé as a mere theoretical case whose mutational nature had been simply affirmed but never established. One assumed that the *Biston betularia f. carbonaria* was a mutation, but this claim still needed to be proven; the change of color could be a matter of mere *somations* (nonhereditary modifications).

As the case of Grassé makes perfectly clear, the discovery of the structure of the DNA and the perfection of the scientific understanding of the mechanism of heredity did not suppress all resistance to evolutionary mutants.

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<sup>71</sup> Cotte 1928.

<sup>72</sup> Grassé 1973.

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## *Organisms*



# *Tracing the Totsuzen in Tanaka's Silkworms: An Exploration of the Establishment of Bombyx Mori Mutant Stocks*

Lisa A. Onaga

## *Introduction*

On October 2nd, 1965, members of the Genetics Society of Japan, Japan Society of Breeding, and Japan Society of Human Genetics gathered in Tokyo to commemorate the centennial anniversary of Mendel's Law. There, the silkworm geneticist Tanaka Yoshimaro (1884-1972) delivered a talk entitled "Mendel's Law and Today's Genetics."<sup>1</sup> The speech walked listeners through a seven-decade historical progression of the stages of genetics beginning with 1) morphogenetics or phenogenetics in 1900, followed by 2) cytogenetics, 3) physiological genetics, 4) induced mutation, 5) biochemical genetics, 6) population genetics, and 7) microbial genetics of the 1960s. Such an overview had little to do with silkworms explicitly. Tanaka, who taught the first known Japanese college genetics course in 1913, had authored a number of textbooks on sericultural science, silkworm genetics, and genetics in general. By the time of the centennial event, Tanaka was an emeritus professor at the University of Kyushu, had enjoyed years of fruitful research at the National Institute of Genetics, and his authority was further stamped with approval by election to the Japan Academy. His string of accomplishments beg the question of why and how a silkworm geneticist managed a significant role in the institutionalization of genetics in Japan and further to that, where silkworm studies fit into this neatly packaged seven-decade history of genetics. Tanaka's review of the field centered mostly on European and American geneticists and did not recognize much work from Japan or the heritage of Japanese silkworm production, but his references to two Japanese scientists (including himself) point to some ruptures in an otherwise "western" timeline that present opportunities to understand how Tanaka envisioned a "place" for silkworms. This paper initiates a probe of the development of research on silkworms conducted by Tanaka that strives to understand what would count as a mutation and its significance for articulating meanings of heritability.

### *I. The Place of Japanese Research in "History of Genetics"*

Tanaka's first stage of genetic history (形質遺伝, or morphogenetics or phenogenetics) described tests regarding the universality of Mendel's law. His first reference to a Japanese scientist arose here when he referred to the late Toyama Kametaro.<sup>2</sup> In the last sentence of this section, he wrote, "In Japan around the middle of this period, Toyama Kametaro (1906) produced splendid results without delay." The next Japanese scientist Tanaka mentioned was himself in a description of stage

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<sup>1</sup> メンデル遺伝法則100年記念出版委員会 (Committee on the Centennial of Mendel's Law) 1967. All Japanese names follow the convention of last name preceding first name.

<sup>2</sup> For analysis of Toyama's work on the Mendelian inheritance of silkworms, see Onaga 2007. The full paper based on this presentation, "Toyama Kametaro and Vernon Kellogg: Silkworm Inheritance Experiments in Japan, Siam, and California, 1900-1912," is in press at the Journal of the History of Biology.

4, induced mutation, “Again with the silkworm, Tanaka (1928) also used x-rays, high and low temperatures, centrifugal force, etc., to humanly induce sudden variation.”<sup>3</sup> Indeed, in *The Genetics of the Silkworm*, Tanaka’s student, the venerable Tazima Yataro (\*1913) discusses how Tanaka started to conduct experiments along this vein in the wake of Muller’s 1927 publication on induced mutations.<sup>4</sup>

The gap between these two references, Toyama’s seminal 1906 paper, “On the hybridology of the silkworm”<sup>5</sup> and Tanaka’s 1928 review paper on “The Future of Genetics”<sup>6</sup> raises questions about what took place between those years. While a full of genealogy of “variation” (*henyi*) and “mutation” (*jinyi totsuzen henyi*) in Japan is beyond the scope of this paper, any attempt to do so would, I am convinced, require an examination of the history of the silkworm in twentieth century Japan.

Silkworms, bred millennia for their silk cocoons, gave rise to a somewhat tractable degree of diversity that functioned as toolkits for further improving qualities of export-bound silk skeins during the early 20th century.<sup>7</sup> By the 1910s, not only were economically valuable organisms being maintained, but silkworm varieties that would otherwise be discarded by industrialists were separately preserved for their scientific value. Tanaka did not merely appreciate silkworm diversity, but he had amassed a toolkit for his Japanese genetic research and also created the foundation for what now serves as the world’s largest biobank of mutant silkworms. This paper analyzes Tanaka’s notebooks containing silkworm breeding records in order to trace and understand how he ended up using the strains that were used in his experiments on mutation.<sup>8</sup>

## II. Tracing to Tanaka, 1928

Tanaka’s speech at the 1965 meeting structurally reflected a historical staging he introduced in a 1928 paper, which reviewed progress in genetics at the time. His discussion of stage 4 (induced mutation) covered the state of the field leading up to de Vries’ mutation theory (突然変異説, *totsuzenhenyi setsu*) and subsequent work by Muller on X-ray mutagenesis. The emphasis he puts on the work and words of de Vries and Muller raises the question of when Tanaka began to use this shared language of mutation theory himself.

In his 1928 paper, Tanaka provided some initial clues when he introduced an experiment he conducted in 1916 at the Fukushima Sericulture Experiment Station. In this experiment, Tanaka worked with a bivoltine hime (姫, princess) variety of silkworm, specifically a kind called *chiyozuru* (千代鶴, thousand generation crane) which was actually a breed developed by Tanaka’s father,

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<sup>3</sup> Tanaka 1965. This publication appears in Japanese. Any and all translation errors are mine.

<sup>4</sup> Tazijma 1964, p. 127.

<sup>5</sup> Toyama 1906.

<sup>6</sup> Tanaka 1928.

<sup>7</sup> I use “somewhat” here because there was an over-production of silkworm cocoon diversity during the Meiji period in the mid-19th century that allowed silkworm egg producers to create new “brands” (new varieties). This flood of diversity was a major dilemma necessary to overcome through a process ambiguously called *touitsu* (統一), to industrialists in America as well as within Japan who sought uniformity in their products. This issue *touitsu*, which roughly is synonymous with “unification,” is discussed in Onaga. 2008.

<sup>8</sup> Tanaka’s original laboratory notebooks migrated from Sapporo in Hokkaido, to Fukushima, to Kyushu Island, to Mishima, and finally to Ibaraki, where they have rested since scientist Tazima Yataro, who inherited these, retired. The Tanaka notebook for 1911 and an additional experiment notebook entitled “Die Kreuzungsexperimente: 1911, 1912” are of noteworthy interest.

Yuichi, in Meiji 25 (1892), a professional silkworm egg producer in Nagano Prefecture.<sup>9</sup> This variety is white and grows quite plump, and has grey eyespots near the larva's head.<sup>10</sup> Before allowing the raw eggs to hatch after being laid, he took two moths and placed them in a freezer for one hour and then spun them in a centrifuge-like machine.

Upon examination of the resulting larvae that hatched from those parent moths, he found one that was a "mosaic." The right side of the body of one of them had "oily" features (oiliness is a known characteristic of larvae, which means they are slightly translucent-skinned), and the left side was normal-skinned (not-transparent). This was remarkable to Tanaka because *chiyozuru* had been bred for an very long time, and it had never once produced larvae with oily features before.

In 1927, Tanaka worked with a colleague to conduct a second test to see what kind of conditions would generate the appearance of a mosaic or other unusual silkworms. They tested the duration of exposure to X-rays that silkworm eggs could withstand without getting killed. In addition to mosaics and abnormal (畸形) silkworms, Tanaka was also able to produce gynandromorphs and exceptional instances of sex-linked inheritance. He could determine that exposing female silkworm moths to high temperatures and centrifugation prior to egg-laying could yield a small number of mosaics.<sup>11</sup>

Tanaka elaborated upon the excitement over the prospect of using mutations in biology. Within his concluding remarks is a reference linking these advances with practical application in improvement, or *kairyô* (改良):

Up until that time, it has been thought that sudden variations occur for some internal reason, but now it has become somewhat possible to artificially use this left and right. The results of incurring change in chromosomes (*senshokutai*, 染色体) or genes (*inshi*, 因子), be it through physical or chemical means, are the same.

According to academic theory of today, outside of hybridization (*kôzatsu*, 交雑) or sudden variation (*totsuzenhenyi*, 突然変異), there is no other method for evolution. Moreover, evolution by way of hybridization is limited; it cannot be infinite. *On top of that, in order to improve* (*kairyô*, 改良), *it is necessary to approach sudden variation*. If it is the case that humans can freely induce sudden variation, it can be interpreted that the scope and application of genetics should broaden extremely.

As of the certainty of the coming fourth stage, we should rather sooner than later expand the heaven and earth of this field. Whom from what country will have to perform as the actor of this future's stage? The audience greatly anticipates one person, America's Muller.<sup>12</sup>

<sup>9</sup> Japanese years are traditionally numbered after the reign of the emperor. The first year of the Meiji Emperor's reign began on 08 September 1868. Greater credence is attributed to dates recorded under this system unless a Western calendar date is clearly specified by the source.

<sup>10</sup> The *hime* type of silkworm is a general name used to describe a phenotype whereby the silkworm has no larval markings. This is a common feature of silkworms derived from China. *Chiyozuru* was developed during the Meiji period, but it was largely used during the Taisho period (1911-1924) and was mass-produced as part of the breed unification movement. In 1911, a production rate of 13,000 eggs increased by 1916 to 78,000. <http://www.nises.affrc.go.jp/nisesDB/bombygen/raireki/R132.html> [accessed 11/10/08].

<sup>11</sup> A question that undoubtedly arises is what kind of interactions, if any, Tanaka had with Richard B. Goldschmidt, who conducted work in Japan in 1914 and from 1922-1923. This is currently under investigation.

<sup>12</sup> Emphasis added. Kanji characters from original text are included for reference purposes. I opted to use a more literal descriptive style of translating in order to reflect the different ways expressions of the concept of mutation can be described in Japanese by virtue of different combinations of Chinese characters. Tanaka 1928.

The word *kairyô* evokes a layered meaning suggestive of both silkworm breed improvement and progress in sericulture itself. Tanaka's genetic research easily and jarringly folds at once into this mindset as silk production continued to play an important role in drawing foreign capital to Japan through global silk trade. Silkworm improvement already held the attention of sericulture scientists, many of whom were government servants or employed by within the imperial university system. Tanaka's work, however, also produced new occasions for *kairyô* that related to improvement of genetics itself. This did not necessarily lend to the production of "better" silkworms in the eyes of a textile manufacturer, but the creation of unique mutants with which to understand genetic principles. While they could one day foreseeably be used directly or indirectly to "improve" silkworms and their silk, as alluded to by Tanaka, we must keep in mind that deliberately produced mutants and monsters may have seemed at odds with the expected goals of silkworm breeding. The normalization of the codification of phenomena that reflect certain kinds of hereditary effects now known as "mutation" in the sericultural world may become apparent through further articulation of the initial moments the phrase and notion of *totsuzenhenyi* stabilized prior to Tanaka's encounter with his (presumably) induced 1916 mosaic.

### III. Tanaka and the Mosaics, 1916

Tanaka's 1916 report discussed experiments he conducted on silkworms reared at the Tohoku Imperial University College of Agriculture until 1913 and silkworms reared in the summer of 1913 and spring of 1914 at the Sericultural Institute of Hokkaido. The experiments also included those based on silkworms reared in 1915 at the Imperial Institute of Sericulture at Fukushima. It was during this most transient period of Tanaka's career that his system for cataloguing silkworm traits took shape.

In 1916, Tanaka described five mosaics that resulted from the spring and summer cultures of 1914, as well as six more from 1915. These occurrences were not induced cases, but seemed to have spontaneously appeared amongst silkworms of varying larval patterns, body color (as in the fore-mentioned normal and oily), sex, and even size. The cause of the mosaic specimens or gynandromorphism "must, I believe, be explained by mutations taking place in the course of ontogeny," Tanaka surmised.<sup>13</sup> This is one of the earlier, if not earliest instances of Tanaka's use of the English word, "mutation." Taking into account existing scholarship on possible causes of gynandromorphism, he continued,

By the term "mutation" I do not mean a sudden elimination or addition of certain factor or factors, but some reorganization or disturbance taking place among somatic cells or chromosomes, by which certain factor or factors are suppressed, or suppressed factors called into activity.<sup>14</sup>

Tanaka qualified his concept of mutation as that which 1) affects non-sexual characters only, giving rise to a simple mosaic, or 2) gynandromorphs, in which sexual characteristics only are affected, or 3) instances in which both are affected, giving rise to a mosaic gynandromorph.<sup>15</sup> In his concluding remarks, he further qualified,

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<sup>13</sup> Tanaka 1916.

<sup>14</sup> Tanaka cites Boveri 1915, Lang 1912, Goldschmidt 1912, Morgan 1913, 1914, 1916.

<sup>15</sup> Tanaka 1916, p. 239.

I believe mosaics are produced by mutations, either major or minor, occurring in the segmenting cells in different stages of embryonal development. By “mutation” I mean assumed sudden check of physiological functions of a gene or genes, or a sudden revival of them in the egg cells.<sup>16</sup>

Tanaka did find that while mosaics appeared in hybrids and pure breed crosses, hybrid crosses tended to generate more mosaics.

What exactly was the basis for astonishment? That is, in order to detect what “counts” as a mutant, monster, or abnormality versus a character change that may be mundane to a silkworm breeder, it is necessary to understand the basis for surprise that constituted the collection of “pure breeds” that Tanaka cultivated and studied. Indeed, other silkworm researchers such as Toyama had shown the occurrence of gynandromorphs in the past,<sup>17</sup> and today, 428 “mutant” strains of silkworms, unfit for commercial use, are maintained in the Japan National BioResource Project.<sup>18</sup> Insofar as understanding the concept of “mutation” or *totuzenhenyi* is concerned, I believe it is necessary to compare mutant-creation with the practice of *akeawase*, or hybridizing, which once was a common activity among egg producers until the practice came under regulation in 1911 and again in 1930.

Remarkably, stability in the record-keeping format of Tanaka’s silkworms has roots starting in 1910-1911, which temporally parallels the development of national policies regulating the hybridization and creation of new commercial silkworms. The Sericulture Industry Law of 1911 responded to opinions that argued for establishment of a central sericulture experiment station and regional branches that would produce the parental pure breeds for the whole country of Japan. The resulting pure breeds would then be distributed to all prefectures. As a basis, the government would make and distribute pure breeds, but superior local varieties (*zairaishu*, 在来種) were also useable in various regions of Japan so long as the cocoon characteristics exhibited a certain standard in appearance, volume, and texture.<sup>19</sup>

The shift in Tanaka’s own research agenda seems suggestive of a temporal relationship with this rise in regulation. He recognized fairly early in his career while in Fukushima of the necessity to have a genetic toolkit or stocks of silkworms. To what extent was this linked to commercial concerns as well as those of genetics? More simply, what would this toolkit make, maintain, or fix? My project continues to examine the development of the mutant silkworm collection in light of Tanaka’s post-1913 work which overlaps in a timely fashion with scientific inquiries of the cross hybridizing practice of *akeawase* (reported initially by Toyama in 1906 using Mendelian terms) that contrasted to conventional inbred lines of familial silkworms.<sup>20</sup>

#### IV. Tanaka and larval markings

Tanaka was the son of a silkworm farmer yet did everything he could to avoid following this line of work, such as joining the army after failing his first attempt at college entrance exams. He returned to school to study zoology but realized that he disliked dissections, so by 1908, bending under the

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<sup>16</sup> Tanaka 1916, p. 244

<sup>17</sup> Toyama, Kametaro. “On the Hybridology of the Silkworm.” 1906.

<sup>18</sup> See <http://www.nbrp.jp/report/reportProject.jsp?project=silkworm>.

<sup>19</sup> Kitamura and Nozaki 2004.

<sup>20</sup> Tanaka 1913.

shadow of his father and escaping from mammalian blood, Tanaka reverted to the study of silkworms. In 1909, he became an assistant professor at Tohoku Imperial University, and until 1911, Tanaka's earliest papers focused predominantly on silkworm physiology, especially on silk glands.<sup>21</sup>

After 1913, nearly everything Tanaka published concerned genetics. His two papers, "A Study of Mendelian Factors in the Silkworm, *Bombyx Mori*" and "Gametic Coupling and Repulsion in the Silkworm, *Bombyx Mori*," both part of his doctoral thesis, provide important insight to understanding the circumstances that bore upon the stabilization of the nomenclature system used to organize silkworms and their distinct traits.<sup>22</sup>

The Mendelian study reviewed Toyama's work, affirming that "his system of analysis seems to have been based on the original view of Mendel..." Yet, Tanaka also critiqued that it did not apply easily to more complicated cases of Mendelian inheritance.<sup>23</sup> Using his "own" factors, Tanaka conducted a set of experiments. For his gametic coupling and repulsion paper Tanaka deliberately worked from an amalgamation of silkworms of different, unknown pedigrees. Female silkworm moths usually lay their eggs on cardboard sheets prepared by their human handlers, and a single sheet contains information that indicates that these moths are from the same cohort, and if they are from different cohorts, each moth can be contained in a space on the sheet in which she lays her eggs. However, the batch of eggs Tanaka received in 1910 from a Chinese friend in Shan-tung was an amalgamation of different silkworm eggs. "The population reared from this material proved to be a mixture of various strains, not only as to the larval markings but also in respect of the cocoon colours and moulting-frequency..."<sup>24</sup> He isolated five unique strains from this mixed group, each of which was sib-crossed and cultivated or hybridized with Japanese silkworms.

Tanaka's decision to work from a mixed "cohort" is intriguing, especially because the basis for Tanaka's silkworm overall collection appears to have derived in large part from crosses between the newly isolated Chinese silkworms and conventional Japanese varieties. In spring of 1913, Tanaka recorded a pedigree chart that crossed the Chinese trivoltine (支那三眠, *Sina sanmin*) silkworm with a "normal" white speckled (飛白, *kasuri*) moricaud type.<sup>25</sup> This yielded three general kinds of silkworms: normal yellow, striped, and plain yellow. Tanaka maintained these lines and made further hybrid crosses between the lightest and darkest silkworms of the normal form to generate a new line for experimental purposes.<sup>26</sup>

The difficulty of pinpointing an explanatory logic behind an individual's method of variety-creation is pertinent to the question of what "counts" at any point in time as a mutant. The inner cover of one of Tanaka's notebooks on crossing experiments (Die Kreuzungsexperimente) shows a list of the ten grades of silkworm cocoon colors ranging from golden yellow to white. According to discussions with Professor Banno Yutaka, who maintains the current mutant silkworm biobank at the University of Kyushu, these fine differences in color are something that probably only Tanaka would be able to figure. At the University today, for example, they only differentiate the cocoon colors into three groups, and even so, it is mostly Banno who can tell the differences apart with

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<sup>21</sup> Tanaka 1956. For example of this early work, see Tanaka 1911.

<sup>22</sup> Tanaka 1913a; Tanaka 1913b.

<sup>23</sup> Ibid.

<sup>24</sup> Tanaka 1913.

<sup>25</sup> "Normal" silkworms have some distinctive markings on their dorsal side, as opposed to "plain" silkworms, which have no dorsal markings. Moricaud is another kind of marking, which in this case occurred in combination with the normal markings.

<sup>26</sup> Ibid.

certitude.<sup>27</sup> It then may not surprise that the distinctive requirements that facilitated the recognition of a new variety, let alone “mutant,” could have changed over time, not only as breeding work proceeded, but as individual scientists in charge of the silkworms assumed their respective authority and exercised personal preferences.<sup>28</sup>

## V. The Elongates

How did Tanaka distinguish between mutants and the new strains he made based on cross hybridization? A look at his detection of the “elongate” mutant in the spring of 1918 provides some clues. This mutation gave rise to markedly long abdominal segments of the larvae and moth, and the larval body is doughy compared to normal larvae. Similarly, the pupae are unusually formed. Cocoons were deformed and tended to be flimsy. Tanaka determined, “The mentioned characteristics of the mutant are, as a rule, distinct and easily distinguishable from the normal type.”<sup>29</sup>

This group of abnormal larvae resulted from a hybrid cross between a “plain, smooth, white blooded” female parent and a “plain knobbed, white-blooded” male parent.<sup>30</sup> Tanaka found that this family (labeled 18am6) consisted of 241 normal and 77 elongate silkworms. He suspected that the 77 were all female because 23 surviving adult moths were female.<sup>31</sup>

Tanaka continued breeding the elongates. He also bred them with conventional commercial varieties, such as *chiyozuru*. In the summer of 1921, he crossed elongate males and females to produce a pedigree of “pure” elongate strains in spring 1922, which he fixed in 1923.<sup>32</sup> Through experimentation, he came to understand that the characteristic is actually sex-linked. While the first case of sex-linkage determined by Tanaka in 1917 involved a characteristic for translucent (oily) larval skin, this was a common trait mundane to silkworm diversity.<sup>33</sup> Tanaka reported that the elongate mutation, which he designated as a recessive gene (e), and its normal allelomorph (E) are carried on the Z sex chromosome (In Tanaka’s literature, *Bombyx mori* sex chromosomes are ZZ ZW, in which the W determines femaleness.)

Tanaka worked through the pedigree and determined that the first appearance of “elongate” had to have occurred from an Ee (female) x Ee (male) cross, which gave rise to normal males, normal females, and elongate females in a 2:1:1 ratio. Tanaka deduced that the mutation itself must have arisen some time no earlier than in the spring of 1917 or 1916 and manage to pass without

<sup>27</sup> Personal communication, May 2008.

<sup>28</sup> By personal preference, I refer to the individual judgment that is exercised by the investigator in charge of yearly maintenance of the silkworm strains, in which choices are made about which individual silkworms to keep and remove over the course of determining what larval characteristics ought to be kept.

<sup>29</sup> Tanaka 1924, p. 136.

<sup>30</sup> Toyama (1906) discusses silkworm “blood color” as an indicator of silkworm cocoon color, seen through the skin of the inside of the larvae’s abdominal legs. This helped him collect data on cocoons even if the worm never spins a cocoon.

<sup>31</sup> The female parent came from a line that had been previously bred for about four generations without generating any “elongates.” Interestingly, this line resulted not from conventional Japanese varieties, but from crossing a Chinese tri-moulting race from Shantung (likely from the 1910 silkworm eggs) in 1911, 1913, and 1915, using conventional Japanese varieties, Aojuku, Kojikisan, and Seihaku. The male parent was a distinct line of “multilunar” silkworms of Chinese origin (Multilunar is a common larval marking of half-moons, on the dorsal side) (1918).

<sup>32</sup> The pedigree was labeled 22am6.

<sup>33</sup> Tanaka 1922.

being detected until 1918. We can regard this as one of the first instances a mutant silkworm strain became inscribed in Tanaka's lab notebooks. The elongate strain, consequently, has continued to be maintained to this day and is part of the National Bioresource Project maintained at Kyushu University's Silkworm Genetic Resource Database.<sup>34</sup>

## VI. Summary

An examination of Tanaka's notebooks has shown that the number of strains in Tanaka's notebooks markedly increased in 1913, partly because of the use of Chinese silkworms imported from Shandong Province. But, it is also important to think about other possible origins of the silkworm stocks. There is a possibility that Tanaka had at some point interacted with Toyama around 1912 to maintain silkworm lines for him while he toured Europe. This was also shortly after the installation of the silkworm breed protection regulations which catalogued and organized breeds available for commercial use, so it could have been possible that lines were collected as cataloguing was completed elsewhere.

Since Tanaka "officially" began his work on induced mutations, one might expect that his record-keeping method underwent significant changes after 1928, but my examination of the records for Tanaka's silkworm strains show no marked changes subsequent to this year. Rather, examination of Tanaka's laboratory notebooks detailing silkworm hybridization experiments shows fluidity in record-keeping style prior to the routinization of his data entry format in 1924, evidenced by the use of a rubber stamp. Examining the pre-1924 experiments have made it possible to understand how Tanaka had gradually devised a way to systematically recognize, account for and study the phenomenon of "mutation" prior to 1928. In fact, the very occurrences of "mutants" or *totsuzenhenyi* seem to have been instrumental for working out a functional recording system.

In Tanaka's reflections of the historical development of genetics and his own silkworm experiments, distinctions were gradually made between heritable mutations on one hand and non-heritable instances of "monsters."<sup>35</sup> Continued efforts to understand Tanaka's arrival at making distinctions between heritability and non-heritability should shed further light on the mediation of his conception of mutation, as suggested by his work with the "elongates." This first analysis of Tanaka's data-entry process in a historical context reveals insights about the tensions between the silkworm's material offerings and theoretical interests of scientists, namely Tanaka, who underwrote the production of mutant silkworms. The creation of these new silkworm stocks and their increased diversity stemming from the production of mutants helped gear research intended for enhancing commercial breeding to allow space for the development of genetic research in Japan such that the silkworm, could for a moment, enjoy a place as an emblematic research organism of the twentieth century.

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<sup>34</sup> See <http://kaiko.kyushu-u.ac.jp/>

<sup>35</sup> See Tanaka 1953, p. 280.

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# *Supporting the Balance View: Dobzhansky's Construction of *Drosophila pseudoobscura**

*Matt Dunn*

## *Introduction*

A dominant thread that ran through Theodosius Dobzhansky's long scientific career was his concern with what John Beatty has called "the paradox of mutation," the fact that mutations are almost always deleterious, yet they must somehow be preserved in populations in order to have an available store of genetic variation necessary to adapt to changing environments.<sup>1</sup> Much of Dobzhansky's work was undertaken to provide support for his "balance view" of evolution. Dobzhansky believed that natural selection preserved genetic variation in populations, that selection for high levels of variability "balanced" the deleterious effects of mutations.

In this paper I offer an account of the development of one of Dobzhansky's most powerful tools for providing evidence for the balance view: experimental evolution. Experimental evolution is the maintenance of populations in the laboratory under controlled conditions for many generations. My account explores the way in which Dobzhansky conceptualized and constructed mutants in the lab for use as experimental tools.

This paper challenges much of the received view of Dobzhansky's work. Most significantly, it brings to light a long, productive, and influential unified experimental method that has been widely unappreciated by historians of biology. I highlight several specific ways in which my account is at odds with Kohler (1994) and Gannet and Griesemer (2004), two important treatments of Dobzhansky's work. I argue that *Drosophila pseudoobscura* was an artificial tool whose construction was guided by Dobzhansky's specific epistemological and theoretical aims as opposed to a material entity that shaped his epistemological and theoretical views through its own particular biological agency. I contend that it is only after we recognize this direction of influence that his research program in experimental evolution as a unified program will come into clear view, thus permitting the delineation of one of the most influential experimental legacies of 20<sup>th</sup> century evolutionary genetics.

## *The paradox of mutation and the received view*

In 1937, in his landmark text *Genetics and the Origin of Species*, Dobzhansky puts the paradox this way:

Judged superficially, a progressive saturation of the germ plasm of a species with mutant genes a majority of which are deleterious in their effects is a destructive process, a sort of deterioration of the genotype which threatens the very existence of the species and can finally lead only to its extinction...Looked at from another angle, the accumulation of germinal changes in the population genotypes is, in the long run, a necessity if the species is to preserve its evolutionary plasticity. The process of adaptation can be understood only as a continuous

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<sup>1</sup> Beatty 1994, pp. 202-203.

series of conflicts between the organism and its environment. The environment is in a state of constant flux, and its changes, whether slow or catastrophic, make the genotypes of the past generations no longer fit for survival. The ensuing contradiction can be resolved either through the extinction of the species, or through a genotypical reorganization...But nature has not been kind enough to endow the organism with the ability to react purposefully to the needs of the changing environment by producing only beneficial mutations where and when needed ... Hence the necessity for the species to possess at all times a store of concealed, potential, variability.<sup>2</sup>

I quote this passage in full because I think it conveys the paradox, and Dobzhansky's adherence to the balance view, very clearly. As stated at the outset, much of Dobzhansky's work was aimed at supporting the "other angle" on mutations given above. Dobzhansky was interested in showing that natural populations contained large amounts of variation and that this variation was maintained by natural selection.

One way in which Dobzhansky attempted to show this was by surveying natural populations of *Drosophila pseudoobscura*. *D. pseudoobscura* was found in many different environments in the American West. Dobzhansky made frequent trips to a variety of locales to collect flies. He found that there was a large diversity of third chromosome inversion variants both within and between different populations. An inversion occurs when a portion of a chromosome becomes inverted, thus causing homologous chromosome pairs to warp and loop in the heterozygous state to pair properly during meiosis, thus making them conveniently identifiable under the microscope. The effect of the inversion itself can be significant, but Dobzhansky also showed that the gene content in different inversions, and in the same inversions between different populations, can also have a large effect.

Dobzhansky mapped these inversions both geographically and temporally and discovered a number of interesting patterns. For example, in "Genetics of Natural Populations IX," published in 1943, Dobzhansky showed that five different inversion variants persisted in a single population in California, yet their frequencies varied cyclically with the seasons. He hypothesized that this was because the different inversions had different fitnesses at different temperatures; thus they came to dominate the population at different times of the year. Here we have Dobzhansky offering support for the balance view both by providing evidence for a large store of variation in a natural population and for the putative role of selection in maintaining that variation.

This kind of work, the mapping of variation in natural populations, has been widely dealt with by historians of biology and is part of what I am calling the "received view." For example, Gannet and Griesemer (2004) argue that Dobzhansky inferred the causes of evolution from these kinds of maps. They write, "Dobzhansky uses geographical distribution maps as qualitative representations of causal mechanisms of evolution in natural populations."<sup>3</sup>

Kohler (1994) argues for a set of explicit claims regarding Dobzhansky's methodologies and broader research strategies, comparing them to the Morgan group's in order to explicate the break the two made in the 1930s. In describing the Morgan group's work with *D. melanogaster*, particularly their use of artificial, constructed "reagent flies," Kohler writes that, "standard" drosophilas were constructed from stocks that produced recombination data conforming most closely to Mendelian theory. Their chromosomes were a bricolage, artfully put together from useful pieces of chromosomes of various mutant stocks and cleaned by selective inbreeding of the genetic

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<sup>2</sup> Dobzhansky 1937, pp. 126-127.

<sup>3</sup> Dobzhansky 1937, pp. 77.

noise that messed up genetic mapping.”<sup>4</sup> On the other hand, regarding *D. pseudoobscura*, Kohler writes, “*Pseudoobscura* was so full of new tricks because it was an undomesticated, wild organism that had not yet been stripped of its natural genetic diversity, as *melanogaster* had long since been,”<sup>5</sup> and “before, when drosophilists brought wild flies indoors they handled them as they did *melanogaster*, working with a few specimens that were stripped of their natural diversity and made into standard laboratory flies. Dobzhansky, in contrast, brought indoors thousands of wild flies from scores of local sites. He carefully preserved their natural diversity — it was the object of his study.”<sup>6</sup>

### *Dobzhansky’s experimental evolution*

At least 11 papers published by the Dobzhansky group are exemplars of his program of experimental evolution. Five of these papers were published in the “Genetics of Natural Populations” (GNP) series in the journal *Genetics*, numbers XII, XIV, XVIII, XIX, and XXXVII. Four of the remaining six papers were published in *Evolution*, and one each in *Proceedings of the National Academy of Sciences* and *American Naturalist*. The first to be published was GNP XII, in 1946 (though the experiments were begun in 1942), the last was GNP XXXVII, published in 1966.<sup>7</sup>

The experimental evolution program can be divided into two separate series of experiments. The first series is concerned primarily with natural selection and is the larger of the two; eight of the eleven total papers deal with selection. It begins with Wright and Dobzhansky’s 1946 paper on the effects of temperature on the fitnesses of different third chromosome inversion variants in laboratory populations. Dobzhansky (1947) determines at which stage of development selection acts in the system described in Wright and Dobzhansky (1946). Dobzhansky (1948) determines whether it is the inversion type or the gene content of the inversion that determines adaptive value in the original experiment. Dobzhansky (1950) shows that the heterozygote superiority observed in the original experiment was likely due to coadaptation between different chromosomes in the same population. Dobzhansky and Levene (1951) show that heterozygote superiority can evolve in experimental populations thus lending support to the results of Dobzhansky (1950). Levene, Pavlovsky, and Dobzhansky (1954) explore the relationship between fitnesses of certain inversion variants and the presence of other variants in experimental populations (i.e. frequency dependent selection). Levene, Pavlovsky, and Dobzhansky (1958) explore the relationship between the fitness of certain inversion variants and the general composition of the gene pool. Finally, Pavlovsky and Dobzhansky (1966) explore the degree and role of coadaptation between several different inversion variants. These studies are concerned with demonstrating and characterizing the ability of natural selection to maintain variation.

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<sup>4</sup> Kohler 1994, p. 53.

<sup>5</sup> Kohler 1994, p. 260.

<sup>6</sup> Kohler 1994, p. 276.

<sup>7</sup> There are many more studies that could be connected to Dobzhansky that fit his program of experimental evolution, but the difficulty here is determining how closely associated Dobzhansky has to be with a study to consider it part of *his* program. In the 1950s and 1960s there was an explosion of experimental evolution and Dobzhansky’s influence was pervasive. In fact, *Genetics* has published several other series of articles on experimental evolution since, including Richard Lenski’s groundbreaking work with *E. coli* in the 1990s. One series of papers I do not discuss here that Dobzhansky could be tied directly to is the “Release of Genetic Variability Through Recombination” series published in *Genetics* beginning in the late 1950s. There are seven papers in this series, three of which Dobzhansky is co-author on.

The second series of studies deals with genetic drift and is composed of three published papers. Dobzhansky and Pavlovsky (1953) show that variation in the genetic composition of replicate populations can lead to divergence of those replicates over time in terms of equilibrium values of inversion variants. Dobzhansky and Pavlovsky (1957) explore the relationship between founder size and the divergence of equilibrium frequencies across replicates. Finally, Dobzhansky and Spassky (1962) address the interaction of founder size and degree of genetic variation in causing divergence across replicates. These studies are concerned with drift's effect on variation and their relation to the balance view is discussed below.

I maintain that these studies represent a focused, sustained, long-term commitment to a distinctive set of aims and experimental methodologies generally unappreciated to date. The Dobzhansky group explored the influence of selection and drift on genetic variation by constructing artificial, controllable systems in the lab that allowed for the isolation and manipulation of the central elements of evolutionary mechanisms so that their basic operation could be understood. These experiments proved to be a valuable epistemological tool for Dobzhansky. They went beyond the descriptive mapping projects by providing direct tests of hypotheses about the causes of the geographic and temporal patterns found therein. I now turn to a more detailed look at two of these studies.

In GNP XII, "Experimental Reproduction of Some of the Changes Caused by Natural Selection in Certain Populations of *Drosophila pseudoobscura*", published in 1946, Sewall Wright and Dobzhansky set out to test a hypothesis derived from the results of the study mentioned above on the seasonal variation in genetic composition of populations of *D. pseudoobscura* in the vicinity of Mount San Jacinto, California. Dobzhansky (1943) showed that there were five third chromosome inversion variants persisting in the population at any one time, but that their relative frequencies "are cyclic and connected with the succession of the year's seasons... Analysis of the data has led to the working hypothesis according to which the changes in the relative frequencies of the gene arrangements are induced by natural selection in response to the seasonal alterations in the environment."<sup>8</sup>

To test this hypothesis, Dobzhansky constructed populations of flies in population cages containing the various third chromosome inversion variants in known initial frequencies and maintained them at one of three temperatures, 16.5°C, 21°C, or 25.5°C, for 60, 45, and 30 days respectively (to account for differences in developmental rates). After repeating these experiments several times, it was found that the equilibrium frequencies of inversion variants were strongly correlated with temperature and that furthermore, the same equilibrium frequencies were obtained across a temperature treatment regardless of initial frequency.

Wright conducted a lengthy statistical analysis of the data, including calculating the mean selective values of different variants at different temperatures and the predicted equilibrium frequencies based on these fitnesses. From this analysis the authors concluded that selection due to temperature was operating in the population cages. In addition, because the statistical apparatus allowed for the accurate prediction of equilibrium frequencies based on fitnesses, the results were taken to be a confirmation of Wright's population genetics theory as well. The authors conclude that "in a general way, this makes the observation that there are marked seasonal changes in the frequencies of the chromosome types in natural populations understandable."<sup>9</sup>

There are two important aspects of this study that should be highlighted. First, the

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<sup>8</sup> Wright and Dobzhansky 1946, pp. 125.

<sup>9</sup> Wright and Dobzhansky 1946, pp. 151.

descriptive project of charting frequencies of variants in the natural population over time was not sufficient to infer that selection due to temperature was a cause of the changes in frequencies, contra Gannet and Griesemer (2004). For Dobzhansky, the patterns observed in the natural populations were just that, patterns. The patterns allowed Dobzhansky to formulate a hypothesis about their cause which could then be tested in the lab. In order to determine that selection was the cause of the patterns, Dobzhansky had to demonstrate that the fitnesses of the different inversions varied with temperature in the appropriate way such that they could produce the patterns. He writes, “The selective advantages and disadvantages that must be postulated are, indeed, high enough to justify an attempt to detect them in laboratory experiments.”<sup>10</sup> Dobzhansky could improve his epistemic situation with regard to the causal claim by conducting these experiments.

Second, the reasons why Dobzhansky felt such a study was necessary illustrate why the received view is at least incomplete in another aspect of its account. In the study detailed above, the benefits of the laboratory experiment stem from greater control of the system. The relationships between specific variables, e.g. initial frequency, temperature, and equilibrium frequency, could be directly observed and manipulated. This was only possible through the construction of artificial populations of *D. pseudoobscura* in the lab.

These benefits stand in contradiction with Kohler’s (1994) claims about Dobzhansky’s general strategy. For Kohler, the Morgan group’s strategy was to build controllable artificial tools that took advantage of this peculiar nature thus making the discovery of new mutations and the elucidation of chromosomal mechanics possible. On the other hand, Kohler claims that Dobzhansky’s strategy for studying evolution, the only available strategy really, was to keep the system as “natural” as possible, to preserve the natural variation and analyze the patterns therein. According to Kohler, lab work for Dobzhansky, though laborious, involved simply “working up” samples from the field.<sup>11</sup> I hope to have shown that Dobzhansky was employing strategies of control and manipulation that had much in common with the Morgan lab’s own practices and went far beyond simply “working up” samples collected in the field and thus letting the inherent natural variation of *D. pseudoobscura* “drive” the research program.

The second study that exemplifies Dobzhansky’s program of experimental evolution is reported in the paper titled “Genetic Drift and Natural Selection in Experimental Populations of *Drosophila pseudoobscura*,” written by Dobzhansky and N.P. Spassky, published in the *Proceedings of the National Academy of Sciences* in 1962. This study is concerned with the role of genetic drift in determining evolutionary outcomes. If drift is strong in a single population, variation will likely be lost. On the other hand, drift could act to increase variation among subpopulations formed from a single parent population thus increasing the store of mutations available for adaptation to changing environments. Thus understanding how drift worked was important to Dobzhansky’s balance view as well.

An earlier study, Dobzhansky and Pavlovsky (1957), showed that replicate experimental populations of flies over many generations, though trending toward the same equilibrium frequencies, diverged significantly in actual equilibrium frequencies. Furthermore, it was shown that the degree to which populations diverged was determined by the number of flies used to found the populations. This was a demonstration of drift’s ability, in the form of the so-called “founder effect,” to cause increased variation among subpopulations.

Dobzhansky and Spassky (1962) set out to further explore the relationship between founder

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<sup>10</sup> Wright and Dobzhansky 1946, p. 125.

<sup>11</sup> Kohler 1994, pp. 282-286.

size and indeterminacy of evolutionary outcomes. The explanation of the results from the previous studies was as follows. If several small populations are founded from a single, large, highly variable population, each small population will likely contain a different, unique sample of the genetic variation in the large population, thus each small population will behave differently over the course of evolution and arrive at a unique equilibrium frequency. In Dobzhansky and Pavlovsky (1957), the large population was constructed with flies from 22 different geographic populations so that genetic variation was very high.

To test this explanation, Dobzhansky and Spassky constructed their large populations with flies from only two geographic populations, thus greatly reducing the pool of variation from which the small populations were founded. What they observed is that across small populations founded from the single large, homogenous population the equilibrium frequencies of third chromosome inversions were far more uniform than in the previous studies employing the highly variable large population. They thus concluded that, “the degree of the variability [among subpopulations] depends on the number and the genetic constitution of the “founders” of the experimental populations.”<sup>12</sup>

What is important to note about this study is that the populations used in the experiments are artificial and that they had to be in order to elucidate the mechanism of genetic drift. In the first two studies flies are pooled from 22 different geographic regions in order to artificially maximize genetic diversity and thus to more clearly see the effects of sampling that diversity on evolutionary trajectories. In the second study diversity is greatly reduced for the same reason. As we saw in the selection study in GNP XII, the variables and their relationships in the drift experiments were subject to a high degree of control, one not attainable by merely observing natural populations. Dobzhansky’s goal in the studies of drift was to manipulate the mechanism of genetic drift and to investigate its properties by building an artificial, controllable system in which the basic components of the mechanism, in this case degree of genetic variability and founder size, could be directly manipulated.

The drift case tells even more strongly against Kohler’s account than does the selection case. In the drift case, the experimental populations were not intended to mirror real natural populations; they were artificial populations whose only relevance was to a general and broadly theoretical understanding of genetic drift and how it affects genetic variation. Here we have Dobzhansky asking questions about evolutionary mechanisms that were very similar to those Morgan was asking about chromosomal mechanics, questions that were broad in scope and answerable only by employing highly artificial experimental organisms that were purpose built for the task.

## *Conclusion*

I have sketched a picture of Dobzhansky’s program of experimental evolution, a program designed most basically to provide support for his balance view of evolution. Experimental evolution allowed for the direct testing of causal evolutionary hypotheses and thus greatly improved Dobzhansky’s epistemological footing. I have also noted how previous historians have failed to recognize this aspect of Dobzhansky’s work and how that has led their accounts to be incomplete.

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<sup>12</sup> Dobzhansky and Spassky 1962, p. 156.

But as I asserted in the introduction, theoretical issues were also important in shaping his experimental program. Through an examination of their correspondence, Provine's analysis of Wright and Dobzhansky's collaboration on GNP XII provides an exemplary account of how the theoretical concerns contributed to the design and deployment of this powerful new experimental practice. Provine shows that Wright's calculations of the likely selection coefficients from the data collected on the cyclic variation of inversion frequencies in nature was an important impetus for the first population cage experiments; only after Dobzhansky received Wright's theoretical calculations that indicated the appropriate selection coefficients did he begin to design the experiments. Provine also writes that Dobzhansky's "data had far greater meaning by being imbedded in a larger theoretical construct."<sup>13</sup> Thus recognizing the theoretician's role as providing justification for the experiments through both calculation of the relevant parameters and a connection to the explanatory structure of evolutionary biology is important for understanding the development of Dobzhansky's program of experimental evolution.

I claim that Kohler's attention to the material aspects of Dobzhansky's work led him to overlook the development of Dobzhansky's program in experimental evolution. Kohler argues that *D. pseudoobscura* was "another breeder reactor"<sup>14</sup> with a productive agency similar to that of Morgan's *D. melanogaster*. While I acknowledge that *D. pseudoobscura* and the material culture surrounding it may have been important to Dobzhansky's work,<sup>15</sup> I have argued that decisions informed by epistemological and theoretical concerns also played a large, if not larger, role in shaping Dobzhansky's decisions about how to manage his experimental practice and led to the development of one of the most powerful and influential experimental tools of 20<sup>th</sup> century evolutionary genetics.<sup>16</sup>

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<sup>13</sup> Provine 1986, p. 398.

<sup>14</sup> Kohler 1994, p. 269.

<sup>15</sup> I hedge here because in France, at least ten years before Dobzhansky began his work with *D. pseudoobscura*, L'Heritier and Tessier began a similar program in experimental evolution using standard *D. melanogaster* stocks from the Morgan lab. In fact, Dobzhansky based the construction and maintenance of his population cages on L'Heritier's design. Comparing the two programs could shed some light on Dobzhansky's commitment to the balance view, vis a vis the need for a more variable organism. See Burian and Gayon (1999) for a brief discussion of L'Heritier and Tessier's program.

<sup>16</sup> My account thus shares something with Creager's (2002) analysis of Wendell Stanley's tobacco mosaic virus research program. She writes that "The point of my emphasis on the activity of modeling in experimentation is not to deny the agency of materials, but rather to argue that it is intertwined with human choices in the management of experimental systems." (p. 327)

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## *The First Bacteriophage Mutants: Changing “Genespeak” in the 1930s*

*Neeraja Sankaran*

### *Abstract*

In 1936, Macfarlane Burnet published a paper entitled “Induced lysogenicity and the mutation of bacteriophage within lysogenic bacteria,” in which he demonstrated that the introduction of a specific bacteriophage into a bacterial strain consistently and repeatedly imparted a specific property — namely the resistance to a different phage — to the bacterial strain, which was originally susceptible to lysis by that second phage. Burnet’s theory to explain this change was that the first phage was causing a mutation in a gene of the bacterium that rendered it and its successive generations of offspring, resistant to lysogenicity.

While Burnet’s theory may not seem revolutionary in the context of what we know today about genes and mutations, it was quite a novel idea that needed compelling evidence to be accepted at the time when the paper was published. During that period mutation was not the only available explanation for the acquisition of phage-resistance by bacteria. Indeed, Burnet went to special efforts in his paper to explain why he thought that the high frequency as well as rapidity with which resistant strains developed in response to the first phage, was evidence of an active mutation, rather than simple selection of pre-existing resistant individuals in a population of bacteria containing both resistant and susceptible forms.

Today we cannot conceive of mutations and genes outside the paradigm of DNA as the physico-chemical basis of genes. But in the mid 1930s, when this paper was published, DNA was yet to make its appearance as a player in the chemistry of life, and genes and mutations were yet to acquire physical and chemical forms. So, while the word gene still represents a carrier of hereditary traits, and a mutation is still a change in the gene that manifests itself as a change in a visible trait, the physical basis of both genes and mutations has changed considerably since Burnet published his paper. Also, during that time genes were really considered to exist only in organisms capable of sexual modes of replication and the status of bacteria and viruses as organisms capable of containing genes and manifesting mutations was still in question. Burnet’s paper counts among those pieces of data helped dispel the notion that genes, inheritance and mutations were tied to an organism’s sexual status. In my paper, I propose to analyze the implications of Burnet’s paper for the understanding of various concepts — such as “mutation,” “gene,” and bacterial “variation” — at the time it was published, and how those understandings shaped the development of the meanings of these terms and our modern conceptions of them.

## *Introduction*

In 1936, Frank Macfarlane Burnet, together with a colleague Dora Lush, published a paper entitled “Induced lysogenicity and the mutation of bacteriophage within lysogenic bacteria,”<sup>1</sup> describing what the bacterial geneticist Joshua Lederberg later identified as “one of the earliest and clearest cases of mutation in a bacteriophage.”<sup>2</sup> At first glance, there may seem to be no reason to single out the isolation of this particular mutant as a significant event in the history of genetics and mutations. After all, in genetics as in many fields of inquiry, it is the study of the aberrant “other” — in this case mutants and mutations — that provides the basis for understanding the normal. And considering that the first few decades of the 20<sup>th</sup> century represents a particularly fertile period of growth in the history of classical genetics, the first mutant bacteriophage could be considered as just another example in a roll call of mutant organisms that were studied in this time, a roster that includes among others, peas, fruit flies, guinea pigs and maize.

But the discovery of the mutant phage had a special significance among the new mutant discoveries of the early twentieth century because of the way in which mutations and the nature of heredity were understood at the time the paper was published. Whereas most the other discoveries of mutants mentioned were made in the context of plants and animals — organisms that were clearly multi-cellular and sexually differentiated — Burnet’s paper spoke of mutations in viruses and bacteria, entities that were neither cellular nor sexual. In many ways then, his claims that bacteriophages (which are viruses) could mutate and furthermore induce mutations in bacteria opened up a new context for the discussion of the concepts of mutation and heredity. In this paper I will discuss implications of Burnet’s paper for the understanding of various concepts such as genes and mutations at the time, and how those understandings shaped the development of the meanings of these terms and our current conceptions thereof.

## *The Paper*

### — Background and Antecedents —

Burnet’s 1936 paper was actually just one of a series of papers on bacteriophages to emerge from a line of investigation that he had embarked on as part of his Ph.D. research in the mid-1920s. Specifically, it was a follow-up to an investigation on staphylococcal phages that Burnet had begun in order to expand his studies on the nature of bacteriophages. At the time, the bacteriophages were rather newly discovered entities<sup>3</sup> whose biological identity and nature — as a virus infecting bacteria from without vs. as an enzyme or other lytic agent produced within the bacteria — were

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<sup>1</sup> Burnet and Lush. 1936. Although this paper is a co-authored one, I will, for the most part, be using only Burnet’s name in my discussions, because Burnet was the primary author while Lush (and other co-authors in earlier papers such as Margot McKie) were research assistants in his laboratory. Although they undoubtedly contributed to the design and execution of the experiments, Burnet was the only author whose name appears consistently in all 28 papers on the bacteriophage to emerge from his laboratory and therefore, it is fair to assume that he was responsible for the arguments and reasoning that developed through these papers.

<sup>2</sup> Lederberg 1952, p. xviii.

<sup>3</sup> The phenomenon of bacteriophagy was discovered and reported independently by Frederick Twort in 1915 and Felix d’Herelle in 1917.

matters of contentious debates within a small but vigorous community of researchers, primarily in Europe and the U.S.<sup>4</sup> Between 1927 and 1936, the young Burnet, working mostly in Australia but also intermittently in Great Britain, played a small but key role in resolving the debate, or at least in facilitating a tacit acceptance of the idea that phages were bacterial viruses.<sup>5</sup>

Although his studies on phage had begun with those isolated from intestinal bacteria — in which the phenomenon of bacteriophagy was first described<sup>6</sup> — Burnet had sought to extend his investigations to phages from other sources. This project was born of his belief that phages, rather than being a single type of entity as suggested by Felix d’Herelle (the co-discoverer of bacteriophagy, who was also responsible for giving the phenomenon and its agent their names) constituted a mixed population and that studies on their natural history were important.<sup>7</sup> The specific choice of *Staphylococcus* as an alternate source of the phages was, in large part, an opportunistic choice, having arisen from an unrelated medical emergency that he had been assigned to investigate in 1928. Burnet published his first paper on staphylococcal phages — entitled, “Type differences among staphylococcal bacteriophages,” — the following year.<sup>8</sup>

As the title of this first paper indicates, Burnet, at this stage of his investigation, was mainly interested in characterizing the differences among the phages that he was able to isolate. Like his earlier papers on the phages of intestinal phages,<sup>9</sup> this paper also focused on the properties of the phages that related to the antigenic structure of the bacteria and to the ability of the phages to induce resistance in the host bacteria. Mainly these studies served the purpose of consolidating the ideas that Burnet had formed about the nature of the bacteriophages as bacterial viruses, namely as obligate intracellular parasites of bacteria. In his words, the results confirmed, “*for another group of bacteria [i.e. the staphylococci] the persistent and genetically transmitted individuality of bacteriophage types [...] that has never been adequately interpreted by any opponent of the theory that bacteriophage is an autonomous living unit.*”<sup>10</sup> Burnet followed up on this initial investigation with a more thorough and systematic investigation of the staphylococcal phages, the results of which he published in 1935,<sup>11</sup> using the data to generalize the connections between the intestinal and staphylococcal phages, which were the groups of phages that he studied most closely. In the 1936 paper, Burnet went from the general to the specific, and focusing on an investigation of a single pair of phages whose isolation he had reported in his 1929 paper.

There is a second line of bacteriophage investigation — on the phenomenon of lysogeny — that foreshadowed Burnet’s work on his 1936 paper and must also be explained before we can discuss the latter meaningfully. First described in 1920/21 by Jules Bordet’s group at L’Institut Pasteur in Belgium,<sup>12</sup> lysogeny was the seemingly spontaneous ability of certain bacteria growing in phage-free cultures to undergo lysis and subsequently produce bacteriophage, which could then cause lysis in later generations of bacteria. Ever since its discovery, this phenomenon had posed a major hurdle to the theory that the bacteriophage was an exogenous virus that infected bacteria

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<sup>4</sup> Van Helvoort 1992a, 1994b; Varley 1986.

<sup>5</sup> Sankaran 2006.

<sup>6</sup> Twort 1915; d’Herelle 1917.

<sup>7</sup> Burnet 1968, p. 54. The mentality of a biologist and evolutionary thinker was one of the hallmarks of Burnet’s scientific style. His studies on phages exemplify this approach, and represent the testing grounds on which he developed and honed this style.

<sup>8</sup> Burnet and McKie 1929a.

<sup>9</sup> Burnet 1925; 1927a; 1928.

<sup>10</sup> Burnet and McKie 1929a, p. 28.

<sup>11</sup> Burnet and Lush 1935.

<sup>12</sup> Bordet and Ciuca 1921.

and induced lysis (most vigorously defended by phage discoverer d’Herelle). It was impossible, argued Bordet and others of his camp, that bacteria could harbor viruses for generations without any outward manifestation of an infection, and suddenly spontaneously undergo lysis due to the action of those selfsame viruses.<sup>13</sup> Rather, these scientists suggested, the lytic principle in bacteriophagy and lysogeny was some sort of enzyme or ferment produced by the bacteria themselves, which was triggered to induce bacterial lysis by certain (admittedly unknown) environmental or internal factors. D’Herelle countered these arguments with the contention that the ferment theory was unable account for the fact that the lytic agent (bacteriophage) was able to maintain a high level of activity through several generations of exponentially growing bacteria, which would not have been possible with an enzyme or other bacterial product, which would have been diluted greatly through these generations.<sup>14</sup>

Entering phage research in 1924/25, Burnet stepped directly into the crossfire of this debate over the matter of the nature of the lytic principle of the bacteriophages. His findings and theories over the next decade exerted enough influence so that by mid-1930s the issue of lysogeny, while not completely resolved, no longer held center stage in the controversy over bacteriophage identity. In 1929 he published a paper in which he demonstrated, at least to his own satisfaction, that classical bacteriophagy (as described by d’Herelle) and lysogeny were distinct phenomena, in which two completely different mechanisms produced a common effect — namely bacterial lysis followed by a release of bacteriophage particles outside the bacterial cell.<sup>15</sup> While agreeing with d’Herelle that a virus induced lysis in classical bacteriophagy — earlier that same year Burnet had published the results of his experiments on phage growth demonstrating the virus-like behavior of phage<sup>16</sup> — he proposed an alternate mechanism for lysogeny. As he explained in his paper, “The permanence of the lysogenic character makes it necessary to assume the presence of bacteriophage or its *anlage* in every cell of the culture, i.e. it is part of the *hereditary constitution* of the strain.”<sup>17</sup> In other words, he proposed that in lysogenic bacteria, the virus (phage) was somehow becoming a part of the bacterial gene,<sup>18</sup> which was then passed down through the generations of bacteria without any manifestation of its viral properties, and which conferred a resistance to lysis by that phage on the lysogenic bacteria. The spontaneous lysis that could be observed in later generations occurred due to the action of some unknown trigger, which induced the phage to leave the bacterial gene and reproduce itself as a virus again.

Burnet’s paper, with its simple and elegant solution to the problem of lysogeny, did not garner as much attention as it perhaps should have from his contemporaries. I will elaborate on the possible reasons in the next section, but it’s worth noting here that in his own phage research thereafter, Burnet would either reiterate or treat as given, his idea that lysogeny and bacteriophagy were distinct phenomena and that underlying mechanism for lysogeny was the incorporation of the phage into the genetic material of the bacteria.

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<sup>13</sup> Bordet 1922.

<sup>14</sup> Sankaran 2008, p. 93.

<sup>15</sup> Burnet and McKie 1929b, p. 280.

<sup>16</sup> Burnet 1929.

<sup>17</sup> Burnet and McKie 1929b, p. 282; emphasis added.

<sup>18</sup> Although absent in this first paper, the actual word “gene” appears explicitly in this context in subsequent papers by Burnet.

## — Content: Claims and Conclusions —

The specific bacteriophages that were the subject of the 1936 paper on bacteriophage mutations, included a phage (designated as phage C) that Burnet had isolated from rodent feces based on its ability to lyse staphylococci (SF) obtained from the same source, and a second phage, designated as C', which was “apparently a mutant derivative of the other.”<sup>19</sup> Phage C was characterized, Burnet observed, by its ability to “produce resistant cultures with extraordinary facility.”<sup>20</sup> That is, when staphylococci were cultured in the presence of phage C, the bacterial cultures would at first produce clear plaques (as in the case of classical bacteriophagy) but when incubated for longer times, they would develop new bacterial growth at the center of the plaques. These new bacteria were consistently resistant to any further lysis by phage. The fact that these newly “resistant” bacteria could give rise to phage C at sporadic intervals when cultured over several generations, led Burnet to the conclusion that the phage had somehow been incorporated into the gene of its host — in other words, the bacteria had become lysogenic with phage C.

When incubated for longer periods, the same lysogens gave rise to new plaques, which differed from those producing the C phages by the absence of central growth. The phages isolated from these aged lysogens (designated as C' phages) were identical to the C phages in all respects but one: they appeared to have lost their power to lysogenize bacteria. In other words the C' phages rarely, if ever, induced lysogenicity in fresh cultures of non-lysogenic bacteria with the consistency and frequency of phage C. The few colonies of resistant bacteria whose formation the C' phages did induce were distinct from both the parent strain as well as the C-induced lysogens.<sup>21</sup>

The nature of the difference between the C and C' phages, and the differing susceptibilities of the different parent and lysogenic bacterial strains to these phages, provided Burnet with the tools necessary to conduct a detailed investigation of the influence of phage C in converting the parent bacteria to the resistant lysogens, using the C' phages as a control.<sup>22</sup> Details of the actual experiments and their results are somewhat beyond the scope of this paper, but Burnet's comments in the discussion of the paper indicate that he was evidently pleased with the results. Not only did his experiments reinforce his ideas on the nature of bacteriophagy and lysogeny, and but they also provided new insights into what phages were capable of.<sup>23</sup>

First, as Burnet argued, “the extraordinary ease with which phage C produced resistant variants suggested strongly that if any phages were capable of multiplication without lysis of the sensitive bacterium this should be one of them.”<sup>24</sup> Experimental results demonstrated that phage C multiplied “explosively” in culture<sup>25</sup> and thereby provided “fresh confirmation of the correctness of d'Herelle's original view of the nature of phage multiplication.”<sup>26</sup>

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<sup>19</sup> Burnet and Lush 1936, p. 27.

<sup>20</sup> *Ibid.*

<sup>21</sup> *Ibid.*, p. 28, Table 1. The difference between the bacterial strains was demonstrated by their differential susceptibility to a battery of phages different from and unrelated to C and C' phages.

<sup>22</sup> *Ibid.*, p. 29.

<sup>23</sup> *Ibid.*, p. 36.

<sup>24</sup> *Ibid.*

<sup>25</sup> *Ibid.*, p. 34, Table 4a.

<sup>26</sup> *Ibid.*, p. 36.

The second argument developed in the discussion concerned the issue of whether the production of lysogenic phage-resistant bacteria was directly caused by the phages, or whether the phages simply acted as a factor in selecting the resistant variants from a mixed population of bacteria. Burnet's journals and letters from this period indicate that the issue of causality vs. selection had been a matter of considerable preoccupation to him,<sup>27</sup> but the experimental data reported in this paper appeared to clinch the evidence in favor of causality. Namely, the bacteriophage induced a change (mutation) in the host bacterium, which was then passed on to successive generations. Furthermore, the data gave further weight to his earlier model of lysogenicity as an incorporation of bacteriophage into the bacterial gene. In Burnet's words:

The production of the resistant lysogenic strain provides a clear-cut example of the direct positive induction of change in bacterial character by the action of a bacteriophage. In this instance the alternative of selection by phage from pre-existent variants in the population submitted to lysis is definitely excluded. The rapidity with which the change [from phage sensitivity to phage resistance] is induced is noteworthy. Within an hour of contact with phage C the surface of the bacterium has changed so that it no longer adsorbs either phage C or C' and becomes insusceptible to their action. This changed character is then transmitted indefinitely to its descendants. It is not possible to say whether this surface change results from an altered genetic constitution of the bacterium or is directly induced by the associated phage at each generation. According to Wollman's hypothesis the distinction between the two alternatives would disappear, the phage being regarded as a gene re-introduced into the genetic makeup of the organism.<sup>28</sup>

The third and final point in the paper's discussion is the claim that the experimental data demonstrated a "definite mutation of a bacteriophage in the course of lysogenesis."<sup>29</sup> Whereas earlier reports of phage mutations were "open to the same objections as can be raised against the claims to have produced phage from normal bacterial cultures," Burnet argued, "in the present instance the mutation appears to affect only one aspect of phage," while leaving its other recognizable properties intact.<sup>30</sup>

### *The Intellectual Context for Burnet's Paper*

Burnet's propositions about bacteriophage mutations and before that, lysogeny appear to provide perfectly reasonable explanations for the phenomena, and to date, have stood the test of time. For example, his claim that lysogeny represented an instance of bacteriophage (a virus) becoming a bacterial gene, was in its essence, the same notion that was presented as the prophage hypotheses in 1950 by the French scientist, André Lwoff.<sup>31</sup> But the reception and acceptance of the two men's ideas at the times of their respective publication was markedly different. Whereas Lwoff's theory caused a big splash and was heralded with high acclaim and eventually rewarded with a Nobel Prize,<sup>32</sup> Burnet's work was noted by only a few. As the immunologist Melvin Cohn recounted in a

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<sup>27</sup> Sankaran 2006.

<sup>28</sup> Burnet and Lush 1936, p. 37.

<sup>29</sup> *Ibid.*

<sup>30</sup> *Ibid.*

<sup>31</sup> Lwoff et al. 1950.

<sup>32</sup> Lwoff won his third of the 1975 Nobel Prize in Physiology or Medicine for "discoveries concerning the genetic regulation of enzyme and virus synthesis," which in his case referred specifically to his work on

tribute to Burnet on the occasion of his 80<sup>th</sup> birthday, Burnet’s “insight into lysogeny slept for twenty years ... to be awakened after World War II by André Lwoff...”<sup>33</sup> One of the reasons for the difference between the reactions to the two papers was the difference between the environments in which they were published. Certainly, phage research in the mid-1930s was a subject of interest to only a small community of researchers, whereas by Lwoff’s time it was a well-known entity having drawn the attention of the famed American Phage Group. Furthermore, as Burnet himself observed in his memoirs many years later:

I think that even a layman can see that basically the interpretation did not change much in thirty-five years. What did change was the precision of experimental technique and the development of biochemical genetics to provide a framework for the interpretation.<sup>34</sup>

In fact, the very attributes that render Burnet’s paper reasonable today may have contributed to its lackluster reception in the 1930s. The ideas make sense to us today because we consider it from within a biological paradigm in which DNA is the material basis of genes and heredity. Regardless of the limitations in our understanding of genetics today and the inarguable fluidity of the gene concept,<sup>35</sup> it is difficult for biologists and historians of biology to think of genes, heredity and related concepts without a tacit understanding that DNA gives them their physical form. This assumption gives us a concrete way to visualize Burnet’s ideas, for example the way in which a virus might become part of a bacterial gene. But this paradigm was only established after the 1944 discovery that DNA played any role at all in the transmission of genetic information.<sup>36</sup> Prior to 1944, the word “gene” was largely an abstract concept representing a carrier of a hereditary trait, but had little basis in a physical or chemical reality beyond acknowledging that genes were contained in the chromosomes. Still another confounding issue at the time was that any talk of genes and mutations in bacteria and viruses would have been problematic because heredity then was understood strictly within the context of sexually reproducing organisms (this issue is discussed in detail below). All of Burnet’s phage research was conducted and published within the context of the gene as an abstraction, whereas the DNA paradigm had already taken hold by the time Lwoff forwarded his theory. As such, while Lwoff in the 1950s provided a mechanistic explanation for lysogeny, Burnet in 1929 had to provide a *justification* for the very existence of the phenomenon.

The gene was not the only undefined, uncertain element that Burnet was dealing with in his theorizing about phages and lysogeny. Indeed, I would argue that many of his claims regarding the nature of viruses and phages were problematic because they implied or assumed an underlying consensus within the scientific community on the meanings of terms where in fact, none existed.

The concept of virus for instance, had remained in a state of flux throughout the period he worked on phages,<sup>37</sup> and in fact, did not crystallize into the version we accept today until the 1950s.<sup>38</sup> It is possible for us to tell from Burnet’s papers and later writings how *he* visualized them, but we cannot assume that his readers conceived of them the same way. Consequently, any claims that a bacteriophage — about whose chemical constitution little or nothing was known — was a

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lysogeny.

<sup>33</sup> Cohn 1979.

<sup>34</sup> Burnet 1960, p. 56.

<sup>35</sup> Portin 1993, p. 172.

<sup>36</sup> Avery et al. 1944.

<sup>37</sup> Sankaran 2006, pp. 41-50.

<sup>38</sup> van Helvoort 1994a.

virus — itself an imprecise concept at the time — would have stood on shaky grounds at best, and, in addition, would have meant different things to different investigators. This state is well exemplified in d’Herelle’s remarks during his Harvey lecture about the opposition that he faced to his proposal that bacteriophage was a virus:

Those who have endeavored to prove that the bacteriophage is a principle elaborated by the bacterium, are but a repetition of those which have been raised against the living nature of each ultra-filterable virus.<sup>39</sup>

Bringing genes into the picture, as Burnet did in the matter of lysogeny — another disputed phenomenon — would have likely complicated matters for most people rather than simplified or resolved debates over it, as Burnet hoped.

But fluid as the concepts were, Burnet’s ideas obviously held some value for some scientists, because he never encountered the outright hostility about his claims that d’Herelle had consistently faced just a few years earlier. Part of the reasons for this reaction might well be the personalities of the two men involved, as well as geography — Burnet in Australia may be considered to have been at the periphery rather than the center of activity, while d’Herelle in France was certainly in the thick of the action. But the main reason that I think most people ignored Burnet’s similar claims was the changing nature of their conceptual environment. Over the course of the first decade when Burnet worked on phage research, the meanings of different words and concepts had morphed sufficiently so as to accommodate ideas that earlier paradigms were unable to fit.

— What was a virus? —

Various historians of science have written extensively about the development of the modern concept of virus and there is no need to revisit this well-trodden ground in depth. Instead I have highlighted only those ideas about the nature of viruses that were afloat in the early decades of the 20<sup>th</sup> century and attempt to situate Burnet’s particular views within this picture.

As Waterson and Wilkinson have noted in their account of the history of virology, a survey of the literature from the early 20<sup>th</sup> century reveals that during this period scientists tended to distinguish viruses from other entities — such as bacteria — by certain negative criteria. That is, viruses were so small that they were *neither* retained by bacteriological filters *nor* visible under an ordinary microscope; and they could *not* be cultured in the laboratory outside of living hosts.<sup>40</sup> Or as Burnet succinctly put it in an interview, “nothing was known about them [viruses] — except that they were invisible, caused nasty diseases and one couldn’t grow them in medium.”<sup>41</sup>

One of the main points of contention over the nature of viruses was the issue of whether or not they were living organisms. Those against the notion argued that the small size of the viruses and their failure to propagate without living cells were good reasons to consider them to be ferments rather than living organisms.<sup>42</sup> The noted biochemist John Northrop (Nobel Prize in Chemistry, 1943) also maintained similar views and in fact, considered the debate on the viral identity of bacteriophages uninteresting, if not irrelevant, on the grounds that both were enzymes.<sup>43</sup> Arguments that favored the view of viruses as organisms cited their infectivity, “Possibly best

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<sup>39</sup> D’Herelle 1928.

<sup>40</sup> Waterson and Wilkinson 1978, p. 78.

<sup>41</sup> Burnet made these remarks in an interview with his biographer Christopher Sexton.

<sup>42</sup> Rutherford et al. 1929, pp. 537-540.

argument in favor of living nature is their transmissibility in series, a phenomenon which one feels forced to associate with a progressive multiplication of the virus particles,” wrote one reviewer in 1930.<sup>44</sup>

As a young medical scientist at the beginning of his career during this period, Burnet would have needed to weigh the different arguments and evidence regarding viral nature even as he conducted his own research. For him then, much more so than for any of his predecessors (such as d’Herelle and Bordet) working on bacteriophagy, the formulation of the concepts of virus and phage were intricately intertwined and mutually influential. Eventually, Burnet came to regard viruses as living organisms of some sort, exemplified in the title of a lecture (later published as a book) that he delivered at Harvard University in 1944 — *Virus as Organism*.<sup>45</sup> An excerpt from one of his letters to his fiancée at the time he was working on his Ph.D. provides an excellent snapshot of his conception of the phenomena of phages and viruses:

Bacteriophage is either living or not living — a perfectly simple question that nobody has been able to answer conclusively or to propound an alternative formulation to. There are experiments, which to my mind almost prove that it is not an independent living organism. There are others equally valid that go as far as to prove that it can’t be anything else. ... You see we are dealing with what may very well be a single molecule of protein endowed with most of the properties of life something at the very beginning of life — something that doesn’t fit into any of the present biological categories but has amazing possibilities of helping a way toward understanding many things. ... Phage phenomena in rather a vague way at present seem to suggest a handle that may help to an understanding.<sup>46</sup>

— What was a gene? —

Although the concept of virus was vague and fluid during the period under consideration, it has since solidified into a concrete definable entity for which we have a precise definition today. Getting an handle on the gene concept is rather more complicated, for the term continues to evolve in meaning into the present day; indeed as the biologist Portin has remarked, even as our “comprehension of the structure and organization of the genetic material has greatly increased, we are left with a rather abstract, open and general concept of the gene.”<sup>47</sup> According to Portin, the history of the gene concept may be considered to have undergone three major paradigm shifts in the 20<sup>th</sup> century: from the idea of an “indivisible unit of genetic transmission, recombination, mutation and function,” in the first three or so decades, through an twenty year period immediately following the discovery of DNA, to the modern day when the concept is considerably more abstract.<sup>48</sup> Since Burnet’s phage work was situated completely within the first of these paradigms — in the so-called “classical era” — this discussion will focus on this period.

A survey of the literature reveals that during the early decades of the 20<sup>th</sup> century, the gene was largely an “epistemic thing,” something whose name was introduced into language as a target of research rather than to designate an object or entity that was already known about.<sup>49</sup> The scientist Wilhelm Johannsen had coined the word gene in 1909 to explicitly denote a unit of heredity (defined in Mendelian terms of the transmission and assortment of traits), which he

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<sup>43</sup> Northrop 1937, p. 480.

<sup>44</sup> Schulz 1930, p. 430.

<sup>45</sup> Burnet 1945.

<sup>46</sup> Burnet 1927b.

<sup>47</sup> Portin 2002.

<sup>48</sup> Portin 1993, p. 173.

<sup>49</sup> Griffiths 2002, p. 274.

wanted, “to be free of any hypotheses regarding its physical or chemical nature.”<sup>50</sup> Now, the term was not used consistently in the exclusively functional way Johannsen intended, because as we know, soon thereafter Thomas Hunt Morgan’s famous “fly room” in New York developed the chromosome theory of inheritance, whereby they gave “genes” a physical form as beads residing on the string — the chromosome, which was undeniably a physical entity. Even so, the nature of these beads, i.e. their chemical basis, remained unknown until 1944, when Rockefeller microbiologist Oswald Avery showed that genes were made of DNA.<sup>51</sup>

A paper published by a pair of geneticists Hermann Muller and Daniel Raffel in 1940 provides the following snapshot of the way in which genes and heredity had come to be viewed by the mainstream scientific community at the time.

Although there is nowadays little practical disagreement among geneticists as to what constitute the criteria for distinguishing the gene material, or genetic material, from the other material of the cell (the definition involving the concept of self-determination of its own characteristics of the mother material in the reproduction of the daughter material, together with a mutability that does not interfere with this property), no such understanding has been arrived at concerning the question of how the limits of *a* gene, as distinguished from its neighboring genes may be defined.<sup>52</sup>

Muller and Raffel’s definition underscores the idea that the genetic community at the time recognized the gene in conceptual and functional terms, while still uncertain of its physical-chemical nature. This conception is further reinforced by the continuation of the above description, wherein the authors speculated on the nature of a single gene, again, on the basis of its functions rather than its form:

In genetic theory, genes have been considered as (1) crossover units — hypothetical segments within which crossing over does not occur; (2) breakage units — again hypothetical segments within which chromosome breakage and reattachment do not occur (at any rate, not without destruction of one or both fragments); (3) mutational and functional units — those minute regions of the chromosomes, changes within one part of which may be so connected with changes in the functioning of the rest of that region as to give rise to the phenomenon of (multiple) allelism; or (4) reproductive units — the smallest blocks into which, theoretically, the gene-string could be divided without loss of the power of self-reproduction of any part.<sup>53</sup>

Embedded in Muller and Raffel’s description genetic function above, are such terms and concepts that provide clues to the intellectual framework within which most scientists envisioned the gene. For instance, the fact that they sought to define genetic material in terms of how it differed from the rest of the material within a cell, reveals their assumption that genes (and consequently inheritance) did not exist outside the context of eukaryotic organisms — namely organisms made up of cells with clearly differentiated nuclei, where the genes resided. Similarly, their reference to such concepts as crossovers and allelism, underlines a conception of genetic function and heredity as inseparable from sexually reproducing organisms wherein genes for traits existed in pairs, each half derived from one parent. While a mutation was, in and of itself, a straightforward enough concept — other authors had explicitly defined it as a “heritable modification which had been

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<sup>50</sup> Portin 1993, p. 176; Johannsen 1909.

<sup>51</sup> Avery MacLeod and McCarty 1944.

<sup>52</sup> Raffel and Muller 1940, pp. 569-570.

<sup>53</sup> *Ibid.*, p. 570.

induced,<sup>54</sup> in an organism, which is certainly the sense in which Muller used it — it too was understood within the context of genes and inheritance as characteristics of organisms that were eukaryotic and sexually reproducing.

### *Analysis & Discussion: The Significance & Impact of Burnet's Paper*

The problem with the Burnet and Lush's claims in 1936 was that they talked about mutations in bacteria and bacteriophages (viruses) at a time when such beings were simply not accommodated within the genetic paradigm of the time. Viruses, as discussed previously, were not even considered as true living beings, while bacteria, though decidedly living, were still outside the paradigm because they were prokaryotic organisms that exhibited no sexual differentiation. As Angela Creager has pointed out in her analysis of the debates over the nature of microbial drug resistance in the 1940s and 1950s,

Bacteria had not previously been regarded as “genetic” organisms — they did not possess chromosomes, nor could they exhibit Mendelian patterns of inheritance, since they lacked the morphological apparatus associated with the genetics of sexual reproduction.<sup>55</sup>

This distinction of bacteria from other living beings in the view of geneticists of the time is reflected in the range of subject matters covered in the disciplinary journals during that period. A perusal of the titles of papers published during the first thirty years (1910-1940) of *Journal of Genetics* for example, revealed only two papers that even dealt with micro-organisms,<sup>56</sup> and even of these (both contributed by the same author), the first dealt with mutations in trypanosomes, which were eukaryotic, and only the second dealt with bacteria. As late as 1945, the famed plant and yeast geneticist George Beadle, maintained that

The genetic definition of a gene implies sexual reproduction. ... In bacteria, for example, in which cell reproduction is vegetative, there are presumably units functionally homologous with the genes of higher organisms, but there is no means by which these can be identified by the techniques of classical genetics.<sup>57</sup>

This view was by no means confined to the geneticists of multi-cellular organisms; most bacteriologists bought into the view with equal ease. For example, J. A. Arkwright, a prominent bacteriologist at the Lister Institute during that period, wrote that terms such as “chromosome” and “mutant” were inappropriate for bacteria.<sup>58</sup>

As is evident from Beadle's statement, however, the fact that bacteria were considered to be somehow “different” did not mean that genes and mutations — meaning heritable induced changes — were not discussed in the context of microbes during this period. In fact, the first half of the twentieth century represented an extremely active period of research into matters of changes or variation in bacteria. Arkwright was actually one of the leading experts in this field (and coincidentally also, one of the two advisors oversaw Burnet's Ph.D. research), and despite his

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<sup>54</sup> Dobell 1913a, p. 201.

<sup>55</sup> Creager 2007, p. 160.

<sup>56</sup> Dobell 1913a and 1913b.

<sup>57</sup> Beadle 1945, p. 18.

<sup>58</sup> Arkwright 1930, p. 356.

quarrels with the terminology of classical genetics being used in bacteriology, he agreed that bacteria were subject to “true hereditary variation,” and not just adaptive changes in response to their environment.<sup>59</sup> Researchers who published work on the subject during this period often prefaced their writing with some acknowledgment of the fact that bacterial mutations or variations were a special case. So while Dobell, for example, began his 1913 paper on bacterial mutations, with a definition of the latter term as “a permanent change, which takes place in a bacterium and is then transmitted to subsequent generations,” he immediately added the caveat that, “I am well aware of the difficulties involved in applying the word — generally applied to certain changes in multicellular organisms — to the Protista.”<sup>60</sup>

By the time Burnet published his papers in the twenties and thirties, however, the use of words such as “mutation” and “genes” seemed to have become more widespread among microbiologists, though yet not so commonplace as to have their meaning be taken for granted. In the conclusions and discussion of his 1936 paper for instance, Burnet explicitly spelt out the way in which he conceptualized genes, heredity and mutation at the time. His claims that the results of the experiments showed “direct positive *induction of change in bacterial character* by the action of a bacteriophage,” and further, that this “changed character is then *transmitted indefinitely to its descendants*,”<sup>61</sup> clearly demonstrate his understanding of mutations (which word he also used) in basically the same terms as Dobell had defined some decades earlier, albeit minus the caveats about micro-organisms representing a special case. Even more significantly perhaps, Burnet’s conclusions regarding the induction of mutation by phages tell us that he saw genes as discrete units that prescribed different functions in an organism,<sup>62</sup> and that a mutation in one of these units did not require all functions to change.<sup>63</sup> This idea was certainly a departure from the views of bacteriologists such as Arkwright, who had tempered their claims about hereditary variations in bacteria with the idea that in these organisms, “the hereditary apparatus is so changed that the new characters appear continuously in the offspring.”<sup>64</sup>

The immediate impact of Burnet and Lush’s paper on the genetics community is a little difficult to assess, in part due to the relative obscurity of the journal on the international scene — Burnet had published most of his findings in journals in Australia, whereas the majority of researchers in the field published in American and European journals — and also because of the phenomenon under investigation, which was as the authors noted, “almost unique as far as can be judged by the literature.”<sup>65</sup> As Burnet recounted years later in his memoirs,

The investigation gave Dora Lush and me a lot of pleasure but I remember feeling worried as to whether we should publish it. ... I was still naïve enough then to think that what I was doing should have some direct or indirect bearing on human disease. To study viruses acting on dysentery bacilli or staphylococci seemed obviously legitimate ... But the reactions of a harmless white coccus seemed almost too trivial for publication.<sup>66</sup>

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<sup>59</sup> Ibid.

<sup>60</sup> Dobell 1913b, p. 326.

<sup>61</sup> Burnet and Lush 1936, p. 37; emphasis added.

<sup>62</sup> Burnet’s writings make it clear that from a practical standpoint he regarded viruses as functioning organisms within the context of other living cells, and following his lead, I too use the word in its inclusive sense.

<sup>63</sup> Burnet and Lush 1936, p. 37. See note 29 for the entire quote.

<sup>64</sup> Arkwright 1930, p. 356.

<sup>65</sup> Burnet and Lush 1936, p. 36.

<sup>66</sup> Burnet 1968, p. 59.

Regardless, he realized the potential implications of his investigations for he not only published his findings, but also commented in the discussion of the paper, that their investigation had, “led us considerably further than we had anticipated.”<sup>67</sup> And, “Ten years later that paper was reprinted by Lederberg as one of the classical papers in the development of bacterial genetics.”<sup>68</sup>

One of the main reasons Lederberg offered for the inclusion of this paper in his compendium was its demonstration that “the phage-bacterium complex may be profitably regarded as a unit for comparison with other cellular systems which carry extranuclear hereditary component.”<sup>69</sup> In other words, Lederberg was claiming that Burnet’s paper offered the bacteriophage-bacterium system as a possible simple model for studying genes and mutation, which was precisely the goal of the American phage group as proposed by Salvador Luria in 1946:

If a case could be made ... for similarity of the processes of mutation in bacteria and in higher organisms ... then these organisms might prove to be invaluable material ... for an attack on the problems of gene structure and mutability.<sup>70</sup>

If we accept Lederberg’s assessment of Burnet’s importance, however, — and nobody rose to challenge his inclusion of Burnet’s paper in his book along with papers by Luria and Delbrück — we must be also willing to consider his implied charge that the case that Luria sought for the similarity of mutations in bacteria, had already been made, in the guise of Burnet’s paper nearly a decade before Luria sounded his call.

While I will not belabor the issue of the Phage Group’s attitudes towards their forerunners in phage research here it is worth noting as a curiosity if nothing else that this instance was not the first example of an oversight of Burnet’s work on their part. Elsewhere, I discussed the implications of their having overlooked Burnet’s work on bacteriophage growth in some detail, and here I would just like to point out the similarities in the way they treated his work.<sup>71</sup> In both cases, the scientists — Emory Ellis and Max Delbrück on the issue of growth and Luria on the matter of phage genetics — cited the relevant Burnet papers but seem to have overlooked the larger theoretical implications of his ideas.

Meanwhile, what of the impact of this 1936 paper on Burnet himself? Paradoxically enough, the very reasons that made this paper important in Lederberg’s estimation — namely its seminal role in microbial genetics — appear to have played a role in steering Burnet *away* from phage research once and for all. Publication records show that this paper was his penultimate publication on the subject of bacteriophages, and that soon thereafter his focus had shifted entirely to studying various animal viruses.<sup>72</sup> While institutional and professional demands certainly played a major part in Burnet’s decision to change the direction of his research, I argue that the projected trajectory of bacteriophage research indicated by his own work (and most compelling so by the 1936 paper) played an equally significant role. As he confessed later, “I am positively schizophrenic about molecular biology,”<sup>73</sup> which was the evident direction in which phage research was going.

Returning to the issue of the broader impact of Burnet’s paper, in addition to his claims for

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<sup>67</sup> Burnet and Lush 1936, p. 36.

<sup>68</sup> Burnet 1968, p. 59.

<sup>69</sup> Lederberg 1952, p. xviii.

<sup>70</sup> Luria 1946, p. 130.

<sup>71</sup> Sankaran 2008, pp. 90-93; Burnet 1929.

<sup>72</sup> Burnet 1968, pp. 4-5. Burnet provided an outline of the main topics of experimental work during his career, including an estimate of the primary papers he published on each subject.

<sup>73</sup> Burnet 1968, p. 175.

the value of Burnet's paper in suggesting a model of studying mutations, Lederberg had elsewhere, also identified Burnet's ideas, and particularly his model for the mechanism of lysogeny — whereby the phage became gene re-introduced into the genetic makeup of its host bacterium organism<sup>74</sup> — as ideas that “had a profound effect on my own thinking about virus-gene relationships and the concept of the plasmid.”<sup>75</sup> Recently, Creager argued that bacterial genetics, or at least, the genetic view of antibiotic resistance was “accompanied by a recasting of the ‘gene’ to include extrachromosomal hereditary units carried on viruses and plasmids.”<sup>76</sup> Burnet's arguments in combination with their reported impact on scientists such as Lederberg, leads me to extend her argument farther back in time and suggest that the foundations for the broader recasting of the gene were laid down in the 1930s when Burnet solidified his views on lysogeny and the induction of the property in bacteria by the phages.

Evidence for an earlier recasting the gene concept is also to be found in the change in the language used by various authors in their discussion of microbial heredity during this period. Burnet's paper with its evidence that viruses could induce heritable changes in bacteria marks the beginning of the acceptance of the idea that sexual dimorphism (*i.e.* the existence of two sexual forms) was not inextricably linked to the passage of traits from one generation to the next, but he not the only investigator to do so. In the same year that he published his classic paper, for example, André Gratia, an investigator in Bordet's laboratory had published a report on a mutation in a phage from *Bacillus megatherium*.<sup>77</sup> And even as they went about looking for a model organism to study gene mutations, the members of the Phage Group spoke readily enough of genes and mutations in viruses and bacteria with no reference to their special status.<sup>78</sup> In the final analysis then, Burnet's paper is assured its place in the annals of microbial genetics, not just because of Lederberg, but because in making a mutation, it functioned as one of many pieces of the complicated machinery that married classical genetics with microbiology, and drove the discipline from a position of debatable legitimacy to one of the active arenas of research in the twentieth century.

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<sup>74</sup> Burnet and McKie 1929b; Burnet and Lush 1936, p. 37.

<sup>75</sup> Lederberg 1992, p. 263.

<sup>76</sup> Creager 2007, p. 159.

<sup>77</sup> Gratia 1936.

<sup>78</sup> Luria and Delbrück 1943; Luria 1946.

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## Commentary on “Organisms”

Karen Rader

Richard Goldschmidt observed succinctly in 1951 that mutations provided the primary evidence for the existence of genes, “All our knowledge of the genetic material,” he wrote, “...is derived from the study of mutation. In classical genetics the gene is an extrapolation from the mutant locus.”<sup>1</sup> But as Susan Lindee noted in her 1992 *JHB* article, “‘mutation’ [like gene] has been a remarkably plastic concept, interpreted differently depending on the problem being investigated, the organism of interest, or the consequences of the interpretation.”<sup>2</sup>

The question today’s session encourages us to ponder is straightforward: Why and how does the organism matter to the process of making and understanding “mutation”? These three papers provide three different answers from three different organisms — so clearly it matters! My goal in my brief commentary, then, will be to draw out thematic commonalities as well as differences in their answers, in order to encourage us to think about how model organisms (as Staffan Mueller-Wille put it yesterday) “have a life of their own” but also (as a way of providing a bridge to tomorrow’s sessions) how they also connect ideas about mutation to larger social and cultural contexts of twentieth century biology.

### Lisa Onaga

Lisa presents us with a case study of the scientific practice of silkworm breeding from roughly the 1910s through the 1930s. Her analysis is sensitive to linguistic turns, as well as to changing conceptual definitions of mutations in both laboratory and commercial contexts. In this way, her case of silkworm genetics explores *the relations between the scientific and practical (or if you’d rather “pure and applied”) understandings of mutation — and their consequences.*

Tanaka, she tells us, positioned his own work in ways that minimized contributions of the Japanese geneticists. But she argues that such absence belies significance: understanding the relation between “variation” (*henyi*) and “mutation” (*jinyi totsuzen henyi*) requires precisely understanding Tanaka’s positionality in broader historical context than the one he himself provides. Tanaka was a scientist who “appreciated silkworm diversity” as a “toolkit for Japanese genetic work”; at the same time, the system for cataloging silkworm traits that his work generated provided a practical foundation (*kairyô* or “application”) for silkworm improvement. She shows how a period of rapid hybridizing or *kakeawase*, designed to deliberately generate silkworm mutants in the laboratory, maps onto the development of national policies regulating hybridization and the creation of new varieties in the silkworm industry. Something that was once a common activity among silkworm breeders thus became disciplined as a consequence (even if this was not the full intention) of Tanaka’s science.

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<sup>1</sup> RG, “Chromosomes and Genes,” *Cold Spring Harbor Symposium on Quantitative Biology* 16, 1951, pp. 1-11.

<sup>2</sup> M. Susan Lindee, “What is a mutation? Identifying heritable change in the offspring of survivors at Hiroshima and Nagasaki,” *Journal for the History of Biology*, 25, 1992, pp. 231-255, p. 231.

Turning attention to Tanaka's notebooks yields Lisa still more insights about the importance of the laboratory for shaping ideas of mutation. She argues that to understand "what 'counts' as a mutant — a monster abnormality versus a character change" for a silkworm breeder we must also understand "what constituted the amalgamation of pure breeds" of silkworm with which Tanaka worked: namely he was mixing Japanese and Chinese strains. Such an understanding, she says, must be located simultaneously in the organism, in historical time, and (in her words) in "the respective authority and personal preferences" of the scientist. Tanaka's requirements for what constituted distinctiveness changed over the course of his own work; also, how he was able to recognize fine-grained differences between strains that one contemporary Japanese scientist Banno could recognize but few other Japanese scientists would. This raises the question of *not just experimental but experiential expertise and its role in shaping understandings of mutation*. We have heard from other papers how such a "feeling for the organism" may have been important, but I would like to hear Lisa reflect more on this — especially in light of the scientific relationships Tanaka may or may not have had with breeders and the silkworm industry and in light of her own interest in the "how silkworm geneticists gained authority to vocalize their views on humanity" in the eugenic discourse of the time.

### *Matthew Dunn*

Matt turns our historical attention to the practice of experimental evolution in Dobzhansky's work with *Drosophila pseudoobscura*. His analysis is sensitive to the relationship between theoretical and experimental concerns of biologists, and the so-called "agency of the experimental organism." Challenging Rob Kohler's interpretation, Matt shows how Dobzhansky's populations of *Drosophila pseudoobscura* were a deliberately artificial and constructed population — necessarily so, as in order to understand the phenomenon of genetic drift and its impact on the balance view of evolution experimentally, he needed a "high degree of control" in the laboratory. Matt thus elevates simultaneously *the role of the laboratory and the role of epistemology in shaping our scientific understanding of mutation*. His focus on the theoretical issues involved in Dobzhansky's work sheds light on the development of Dobzhansky's experimental practices (as others have pointed out, this is a kind of material culture) and their role in shaping understandings of both the organism — *Drosophila pseudoobscura* — and ideas of mutation. Mutation, to Dobzhansky, was a tool for understanding variation.

What I am left wondering about here, however, is how the larger context may have shaped Dobzhansky's practices and ideas as well. Theory clearly shaped Dobzhansky's experimental work and his commitment to the balance view of evolution. But the balance view, with its emphasis on the positive role of maintaining increased variation, was (as time went on, especially in the context of the Cold War) sometimes interpreted as scientific support for the acceptability of increased exposure of human populations to radiation. The geneticist James Crow once said of Dobzhansky that "in contrast to Muller, he was not a deep thinker. His contribution was of a different sort: he was an incredibly active and productive worker, and his personality and enthusiasm were such that he, more than anyone else, popularized the field of experimental population genetics." But Dobzhansky did, for example, speak out against Lysenkoism — so he himself clearly recognized the broader implications of genetic work, and I would like to hear if it was also the case with his work on evolution and mutation in *Drosophila pseudoobscura*.

## Neeraja Sankaran

Lastly, Neeraja gives us a study of the bacteria-bacteriophage system as a model for studying mutation. She argues that the first bacteriophage mutants — found by Burnet, in his work on resistance to lysogenicity in the 1930s — recast the meaning of “genes” and the requirements for sexual dimorphism in their reproduction. Here, then, mutation is viewed not as a *practical goal* (as it was for Tanaka and the silkworm breeders) or as an *experimental tool* for studying evolution (as it was for Dobzhansky) but as an *explanation* for the acquisition of phage resistance and thus an *object of study* in its own right. The use of mutation, then, linked bacteriological workers to a new understanding of genes that legitimated bacterial genetics as a field and contributed its increased prestige. What most interests me here, though, is that Burnet himself responded to this whole state of affairs by turning away from bacterial genetics and phage research. So I would like to hear her say more about what larger contexts may have framed this choice, since (by her own explanation) it seems paradoxical for Burnet to abandon this work just as research with bacterial mutation was gaining the experimental steam and disciplinary respect that might have “spilled over” to problems in animal biology which consistently interested him.

By way of a final comment, I wanted to observe that we have discussed already in this session some various domains that ideas about mutation traversed — *pure/applied* and *lab/field* being the two main ones — but bringing Neeraja’s case into the dialog with these other ones on different organisms suggests another domain being crossed: from *microscopic, invisible organisms* to *macroscopic, visible organisms* — so I am wondering if this is a significant one as well, particularly in light of concerns about *visualizing mutation* raised by Lisa’s paper as well as some of the papers tomorrow.

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## *Populations*



## *Hermann J. Muller and the Biopolitics of Mutations and Heredity*

*William deJong-Lambert*

Though the mutant may be called “abnormal” in the given respect, if we carefully define our term abnormal as meaning merely the less usual in that respect considered alone, nevertheless the phenomenon of mutation itself, that is, the occurrence of changes which become reproduced in subsequent generations, is in a sense the most normal thing about all living matter, being the property that most basically distinguishes living matter from non-living and that has allowed living matter to develop, in its evolution, all the further peculiarities of its marvelous organization.<sup>1</sup>

— Hermann J. Muller 1948

### *Introduction*

Hermann J. Muller is not only among the central contributors to the modern synthesis of genetics and Natural Selection, but was also at the center of two of the most important scientific controversies in the history of the Cold War — the Lysenko affair, and the debate over the genetic impact of radiation. Muller’s success using X-rays to produce genetic mutations in 1926 stimulated belief that scientists would soon be able to direct the process of evolution — a perception Muller himself did initially seem to have resisted. The notion of directed evolution — albeit by completely different means — was also at the center of the Lysenko dispute, and constituted the essence of his appeal to supporters such as Stalin. Meanwhile, Lysenko’s critics — such as Muller — decried Lysenko’s used political influence to impose his theories and suppress genetics in the communist bloc. Ironically during this same period Muller found himself at the center of science politics in the U.S., as the government attempted to censor his views on the mutagenic power of radiation. A consideration of Muller’s role in these issues, demonstrates the extent to which the dichotomies which structured perceptions of scientific developments during the Cold War, actually obscured the extent to which both societies shared much in common.

A comparison between Muller’s activities vis-à-vis Lysenko, and the radiation controversy, shows how biologists increasingly came to appreciate the importance of popular perceptions of their work. Lysenko and his followers based their appeal on the idea that, whereas they labored in collaboration with the workers on collective farms to increase agricultural production, “bourgeois” geneticists were unconcerned with achieving practical results. Though members of the American Genetics Society resisted giving the perception that only advances which seemed immediately useful were worth celebrating, they did concede that Lysenko’s success showed how much they had failed to demonstrate the value of genetics to a popular audience. This “public relations” issue was central to Muller’s experience both opposing Lysenko, and speaking out on the dangers of exposure to radiation. In both cases Muller was surprised to find that the public often did not trust his opinion. Even worse, some of those who criticized Muller’s interpretation of Lysenko, were motivated to do so because they resented his position on radiation.

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<sup>1</sup> H. J. Muller, “Mutational Prophylaxis,” *Bulletin of the New York Academy of Medicine* 24/7 July 24, (1948): p. 467.

## Muller, Eugenics, X-rays, and Mutation

Hermann J. Muller's early fascination with socialism and the Soviet Union, his bitterness over his relationship with T.H. Morgan and Alfred Sturtevant in the "fly room" at Columbia, have been well-documented. The evolution of his views on eugenics has not been as closely outlined, and is important for analyzing his views on Lysenko and radiation. From the beginning of his career, Muller was attracted to the belief that biologists had the ability and obligation to improve human evolution. His ideas on eugenics can be traced to his years as an undergraduate, when he began formulating the ideas that would later appear in his "manifesto" — *Out of the Night*. In 1910 Muller gave a speech before the members of the Peithologian Society, a discussion group at Columbia University where he was a student. In his talk "Revelations of Biology and Their Significance," Muller presented his developing views on mutations and heredity, noting that if mutations were the raw material of natural selection, then most of them were probably negative.<sup>2</sup> Muller declared:

I reach the conclusion that we should not only check degeneration — negatively — but further evolution. ... Those will become supreme who not only care for those now living, but include, as it were, in the social organization, the remotest future, by applying the principles of heredity and variation. ... Only tradition is opposed to the plan, and our own stupidity and defective social nature. ... With knowledge of the laws of nature comes power to manipulate them, and knowledge of life thus means the perfection of man.<sup>3</sup>

This address is not only the earliest record of Muller's ideas on eugenics, but it demonstrates beliefs which he stuck to for the rest of his life.<sup>4</sup> He recognized that mutation was the key to controlling evolution and was impatient with anything, be it "tradition" or "defective social nature," which impeded the advance of science. During this period Muller became an atheist, replacing belief in God with a faith in technocracy.

Muller joined T.H. Morgan's "fly room" at Columbia two years later, where he developed a well-documented rivalry with Morgan's protégé, Alfred Sturtevant.<sup>5</sup> That same year British biologist Julian Huxley visited Morgan's lab on his way to Texas where he was to take a position as founding-chair of the biology department at the William Marsh Rice Institute in Houston. Two years later Huxley invited Muller to join his staff at Rice, beginning a relationship that would also prove a continual influence on Muller's ideas and career.

In 1916 the Institute's president, Edgar Lovett, invited Muller to give a series of public

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<sup>2</sup> Elof Axel Carlson, *Genes, Radiation and Society: The Life and Work of H.J. Muller* (Ithaca: Cornell University Press, 1981), p. 33.; "Revelations of biology and their significance." An address read to the Peithologian Society of Columbia University, March 24, 1910. Series: Writings, Box 1. Muller MSS, Lilly Library, Indiana University.

<sup>3</sup> *Ibid.*, p. 41.

<sup>4</sup> In the preface to *Out of the Night*, Muller's eugenics manifesto published 26 years later, he wrote that the "main biological views" presented in the book dated back to his address before the Peithologian Society. H.J. Muller, *Out of the Night* (London: Victor Gollancz Ltd, 1936), p. 5.

<sup>5</sup> A recently-published account is James Schwartz, *In Pursuit of the Gene: From Darwin to DNA* (Cambridge, MA: Harvard University Press, 2008). See particularly chapter 10.; For an account of Muller's relationships with Morgan and Sturtevant from one of Muller's former students, and authorized biographer, see Elof Axel Carlson, "The Drosophila Group: The Transition from the Mendelian Unit to the Individual Gene," *Journal of the History of Biology* 7 (Spring 1974): pp. 31-48.

lectures. In his second, “Applications and Prospects,” Muller once again expressed his belief in science for science’s sake by stating that “the attainment of such fundamental knowledge is usually of the utmost immeasurable practical importance in the end.” He also talked about the importance of mutations, noting that attempts to induce them with “radium, ultraviolet light, alcohol, ether, low air pressure, crossing races from opposite ends of the earth, and even shaking the flies up and down for days at a time” had so far been unsuccessful. He referred to mutations, along with examples of the transmutation of elements in physics such as radium, as “rainbow bridges to power!”<sup>6</sup>

Muller also touched on what had become another dominant theme in his thinking — the necessity to control human reproduction. The fact that “the more shiftless, less intelligent, and less progressive members of our communities are actually reproducing at a higher rate,” he argued, was a “crumbling process” whose impact upon heredity would not be evident for thousands of years.<sup>7</sup> Cautionary references to the future our ancestors would see were also to become a staple of Muller’s warnings on radiation — albeit for entirely different reasons. It is interesting that despite Muller’s dire warnings about degeneration, the complaints Lovett’s office received concerned Muller’s endorsement of evolution.<sup>8</sup>

Huxley left Rice after the outbreak of the First World War and in 1918 Muller eagerly returned to Columbia as an instructor where he immersed himself in experiments to directly measure the frequency of mutations. Muller focused his attention on lethal mutations because they occurred the most often and were the easiest to spot. Theodosius Dobzhansky later described the logic behind Muller’s approach.

Mutations are frequently described as spontaneous — of course, the word “spontaneous” used with respect to any natural phenomenon is simply a delicate way of saying that you don’t know about what causes it. Experiments attempting to make mutations, induce mutations by environmental agencies, were made for many years, even in 19th century, when the word mutation did not exist. Such attempts were made before Muller in 20th century. They were made, among others, by Morgan himself, and in fact among the various agencies used in these attempts were X-rays. But it was Muller who first succeeded at present, it’s perfectly clear why he was the first to succeed.

Before he started his x-ray experiments, he had evolved a technique for quantitative estimation of the frequency of mutation. That is to say, instead of just looking at flies and hoping to goodness you will find some mutation, you study the frequency of mutations quantitatively, and compare the frequency of mutations in the untreated flies with the frequency in the progeny of treated flies. The type of mutation which Muller and his successors found convenient for this purpose were lethal mutations, mutations which kill the organism. That is not because geneticists have particularly gruesome tastes, but for the reason that a lethal mutation eliminates what sometimes is called the personal equation. With mutations which change the eye colors or body colors or bristle shapes, it is very important to be able to see that the fly has actually altered one of its organs. And for slight mutations, there is a great difference between different people in their ability to see such changes.<sup>9</sup>

After two years Muller’s contract at Columbia was not renewed, and he reluctantly accepted an offer from the University of Texas at Austin.<sup>10</sup>

<sup>6</sup> “Applications and prospects. Discussion of eugenic views and human evolution,” 1916 (unpublished lecture). Series: Writings, Box 1. Muller MSS, Lilly Library, Indiana University.

<sup>7</sup> Ibid.

<sup>8</sup> Carlson, *Genes, Radiation and Society*, p. 105.

<sup>9</sup> B: D65 Dobzhansky, Theodosius. *Reminiscences*, Part I, 280. The American Philosophical Society.

<sup>10</sup> Correspondence, Hermann J. Muller to Julian Huxley, June 28, 1920. Series: Correspondence 1910-1972, Box 1. Muller MSS, Lilly Library, Indiana University.

Muller's first year back in Texas was disappointing. He found only one mutant "the whole winter" and confessed in a letter to Huxley that it wouldn't be "profitable" to talk about his results "at present because I can't interpret them."<sup>11</sup> He made fruitless attempts to increase the rate of mutation by exposing the flies to ether. In September, 1921, Muller attended the Second International Congress of Eugenics at the Museum of Natural History in New York City — a gathering which typified the close association between genetics and eugenics circles during the time period. Muller gave a fourteen point account of the major features of mutation, and biologists such as H.S. Jennings, Calvin Bridges, and R.A. Fisher presented on similarly important topics. Other presenters, however, covered subjects such as the Tribe of Ishmael — a group which could supposedly be used to prove the inheritance of degenerate behavior — and the Mayflower pilgrims.<sup>12</sup> Leslie Clarence Dunn — a biologist who later replaced Morgan at Columbia and joined Muller as a vocal critic of Lysenko after World War II — was also present. Dunn later remembered that among the conference participants, "there were queer ducks of a variety of kinds...people who wanted to change the world."<sup>13</sup> The close association between genetics and eugenics would later prove very useful to Lysenko's characterization of the former as "fascist" science.

In 1922 Muller brought the first samples of *Drosophila melanogaster* to the Soviet Union. Upon returning to the United States Muller published an article describing his visit in *The Scientific Monthly*, as well as a partial list of biological research institutes and the work they conducted in *Science*.<sup>14</sup> Muller's motivation for visiting the Soviet Union and writing an article chronicling his experience was to reestablish communication between U.S. and Soviet biologists. The purpose of the list of institutes and research was to persuade American scientists to send reprints and back numbers of periodicals, to help their Russian colleagues gain knowledge of the work being done in the West.<sup>15</sup>

In the *Scientific Monthly* Muller began by dispelling the notion that the typical Soviet biologist was a "starving creature in rags, hiding in some attic, where perhaps he may be clinging despairingly to his microscope and to some few remaining books."<sup>16</sup> In fact, Muller wrote, what he found was an active scientific community whose greatest obstacle was keeping up with research being conducted beyond their own borders. This resulted in wasteful duplication — a situation which slowed progress in Western genetics as well, "How can they build with us, bricks on our bricks, as they ought to?" Muller asked.<sup>17</sup>

Muller wrote it was important to let Soviet biologists know that they were welcome to publish in American journals, and also to issue official invitations to enable them to visit. Muller cited a recent trip by renowned Soviet geneticist Nikolai Vavilov, at the invitation of the American Society of Phytopathologists, as an example of the impact such exchanges could have:

Professor Vavilov ... on returning to his country, had made a special tour throughout the land, giving numerous illustrated addresses to interested audiences of thousands of persons on

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<sup>11</sup> Correspondence, Hermann J. Muller to Julian Huxley, May 12, 1921. Series: Correspondence 1910-1972, Box 1. Muller MSS, Lilly Library, Indiana University.

<sup>12</sup> Carlson, *Genes, Radiation and Society*, p. 125.

<sup>13</sup> The Reminiscences of L.C. Dunn, pp. 165-166, Oral History Research Office. Columbia University, 1961.

<sup>14</sup> H.J. Muller, "Observations of Biological Science in Russia," *The Scientific Monthly*, 16/5, 1923, pp. 539-552; H.J. Muller, "Partial List of Biological Institutes and Biologists Doing Experimental Work in Russia at the Present Time," *Science*, LVII/1477, 1923, pp. 472-473.

<sup>15</sup> Muller, "Partial List of Biological Institutes," p. 472.

<sup>16</sup> Muller, "Observations of Biological Science in Russia," p. 539.

<sup>17</sup> *Ibid.*, p. 551.

scientific work in America. And, on account of this, wherever I went, I found certain general viewpoints and salient features of our American research already familiar, even though the investigators might not have had a chance to read a single American paper.<sup>18</sup>

Muller's account of his trip also included an exchange he had with one of Vavilov's colleagues, L.S. Berg, which illustrated what he felt was an important difference in official attitudes towards science in the United States and the Soviet Union. When Muller mentioned that some state legislatures in the U.S. were considering bills to outlaw the teaching of evolution, Berg countered that he was having problems getting his book cleared for publication by the Soviet government because they suspected that its content contradicted Darwin.<sup>19</sup> The following year a bill came up in the Texas Legislature to outlaw the teaching of evolution. Muller and his colleagues in the zoology department at Austin organized against it, recognizing that if the bill passed their jobs might be threatened.<sup>20</sup> The initiative was narrowly defeated but the Scopes Trial which followed two years later in Dayton, Tennessee was to become a frequent point of reference for Muller. It came up often in his analyses of the Lysenko affair. Moreover, the campaign against Darwinism in the U.S. made Muller skeptical of the public's ability to appreciate the complex relationship between genetics and evolution, much less how they might be affected by atomic radiation.

The same year Texas nearly banned evolution Muller began using radium and X-rays in a number of projects at Austin. At the time he doubted that radiation had a mutagenic effect so he didn't bother testing the flies for mutations.<sup>21</sup> However by the spring of 1926 he had begun to change his mind. Morgan and a few others had already tried without success to use X-rays to produce mutations, however Muller's review of the early literature on radiation effects convinced him to give it a try. On November 3, 1926 he began the experiment and by the time it was over, less than two months later, he had found over one-hundred mutations. This was about half as many had been found in the previous sixteen years of *Drosophila* research.<sup>22</sup>

Muller's demonstration of the mutagenic effect of X-rays was confirmed within the year and elicited awards, recognition, and the acclaim of his colleagues. However Muller immediately warned of the dangers radiation could pose. In an article in *Science* he acknowledged the desire of biologists to overcome the "sluggish" rate at which mutations occurred naturally. But he warned that the "time is not ripe" to discuss the practical use of X-rays on humans and criticized their application as a means of birth control in males.<sup>23</sup>

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<sup>18</sup> Ibid., p. 552.

<sup>19</sup> Ibid. A description of the controversy surrounding Berg's theory of nomogenesis can be found in David Joravsky, "Soviet Marxism and Biology Before Lysenko," *Journal of the History of Ideas*, 20/1 (1959): pp. 85-104.

<sup>20</sup> Carlson, *Genes, Radiation and Society*, pp. 131-132.

<sup>21</sup> Ibid., pp. 137-138.

<sup>22</sup> Ibid., pp. 141-145. Carlson writes that studies conducted by Oscar and Paula Hertwig proved most convincing for Muller. See Oscar Hertwig, "Die Radiumstrahlung in ihrer Wirkung auf die Entwicklung tierische Eier," *Sitzungsberichte der Preussischen Akademie der Wissenschaften* 30 (1910): pp. 221-233.; and Paula Hertwig, "Durch Radiumbestrahlung hervorgerufene Veränderungen in den Kernteilungsfiguren der Eier von *Ascaris megalocephala*," *Archiv für Mikroskopische Anatomie* 77 Abt. II (1911): pp. 301-311.

<sup>23</sup> Hermann J. Muller, "Artificial Transmutation of the Gene," *Science* 66 (1927): pp. 84-87.; Telling evidence of the hopes and fears underlying public ignorance of X-rays was a scandal that was publicized in August, 1927, less than a year after Muller's discovery. A couple in New Jersey were arrested for swindling domestic servants out of their savings by convincing them to invest in an "X-ray camera" which, they claimed, would not only cure "all human ills" but was also capable of destroying "cities a hundred miles away." See "Maid Loses \$16,000, 20 Years' Savings," *New York Times*, August 3, 1927, p. 48; and "Held as Swindlers of Maid's Savings," *New York Times*, August 4, 1927, p. 3. For some reason they specialized in conning German immigrants, one of whom, ironically, also had the surname Muller.

Muller's public pronouncements on X-rays continued along the lines of his article in *Science*. The next year he was invited to give a talk at Baylor University. By this time Muller was becoming well-known for his work and the audience expected him to offer an optimistic account of the promise of radiation for medicine and agriculture. Instead he warned physicians of the dangers of exposure, advocating that X-ray machines be regularly inspected, encouraging that radiation only be used when necessary, and that the lowest dose possible be administered. Muller also voiced skepticism that radiation could be used to improve humanity. While clearly, given his support for eugenics, Muller was not opposed to scientific interference in reproduction, he did not view artificial inducement of mutations as a promising approach. The crowd reacted angrily and several listeners stalked out of the room.<sup>24</sup>

The next years in Muller's life were tumultuous. Muller became involved with a socialist youth organization — the National Student League — his marriage began to dissolve, and he attempted suicide.<sup>25</sup> Fortunately he also received a Guggenheim fellowship to work at the Kaiser Wilhelm Institute for Brain Research in Berlin, where he would have the opportunity to collaborate with Russian geneticist Nikolai Timoféeff-Ressovsky. Before he left Muller made two dramatic appearances in New York — the first at the Third International Congress of Eugenics at the Museum of Natural History, and the second at the Sixth International Congress of Genetics in Ithaca. The former proved to be the last international eugenics conference for reasons related to the issues Muller raised in his presentation.<sup>26</sup> Muller decried the misery inflicted on individuals by the unplanned economy in the U.S. It was this, not genetics, which kept Americans from progressing. In the *New York Times* Muller was quoted saying that, “slums in our cities constitute veritable factories for the production of criminality among those who happen to be born in them, whether their parents were of the criminal class or not ... Under these circumstances it is society, not the individual, which is the real criminal, and which stands to be judged.” “The ‘respectable’ captain of industry, the military leader, or politician, and the successful gangster,” Muller added, “are psychologically not so far apart.”<sup>27</sup>

The scandal Muller provoked followed him to Cornell. Muller's talk at Ithaca was also covered by *The Times* in a story entitled — “Evolution Process is Aided by X-rays.”<sup>28</sup> This time Muller was quoted saying, “If it is true that we can produce various qualitative changes inside the gene artificially by X-rays, then eventually we should be able to produce desirable changes in species.”<sup>29</sup> It is ironic that Muller's presentations delivered just days apart in Manhattan and Ithaca, outlined his beliefs on eugenics as they continued to develop throughout his career. However it would not be until his faith in socialist eugenics was shattered by his experiences in the USSR, that he would turn his focus to the debilitating impact of radiation upon human evolution.

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<sup>24</sup> Carlson, *Genes, Radiation and Society*, p. 160.

<sup>25</sup> Carlson, *Genes, Radiation and Society*, pp. 173-174.; Schwartz, *In Pursuit of the Gene*, p. 249.; A memo in Muller's FBI file contains testimony from a source whose identity is not revealed, saying “that about 1930 or 1932, Dr. Muller became insane, he believed temporarily so from an overdose of some drug.” Federal Bureau of Investigation. Form No. 1. File no. 61-219. 8/19/41. Subject: Muller, Hermann J. Freedom of Information/Privacy Acts No. 1024867-000. Federal Bureau of Investigation. U.S. Department of Justice. Washington, D.C. 20535.

<sup>26</sup> Many historians who cover the eugenics movement in the U.S. attribute the decline in popularity of eugenics during the 1930s to the Great Depression. The economic collapse seems to have soured people on the idea that success or failure was purely a product of one's innate abilities.

<sup>27</sup> “Holds Capitalism Bars Eugenic Goal,” *New York Times*, Aug 24, 1932: 8. Muller published the talk later in *The Scientific Monthly*, 37/1 (1933): pp. 40-47.

<sup>28</sup> “Evolution Process is Aided by X-rays,” *New York Times*, Aug. 27, 1932.

<sup>29</sup> *Ibid.*

The Sixth International Genetics Congress is a significant point in the history of the Lysenko affair because it was the last time that a number of individuals, who would become most actively involved in the debate on Lysenkoism after 1948, saw Nikolai Vavilov. Though accounts differ in certain details, Vavilov was the only Soviet geneticist allowed to attend. He was accompanied by the director of Amtorg, the Soviet trade agency in the U.S. Prior to this meeting Vavilov had tried to convince Theodosius Dobzhansky, who had come to the U.S. in 1927, to return to the Soviet Union and help build genetics. Now, however, Vavilov told Dobzhansky, “Dobzhansky, do what you want. If you want to return, do so. If you do not want to return, don't. Stay here.”<sup>30</sup>

Dobzhansky's future colleague at Columbia, Leslie Clarence Dunn, maneuvered a way to bring Vavilov up to dinner at his house in Riverdale, New York City, where future Lysenko-defender J.B.S. Haldane was also present. Though Dunn and the others suspected something was wrong they decided not to press Vavilov. Dunn met Vavilov one last time on his way back to the Soviet Union from a research trip to Peru after the conference. Vavilov was nervous for being late back from collecting and told Dunn, “The real reason why I'm late is because I collected — and don't let anybody else tell you any differently.”<sup>31</sup> Vavilov's apparent paranoia and sense of the precariousness of Soviet genetics would prove prescient.

### *Muller and Lysenkoism*

From Berlin Muller — at Vavilov's invitation — moved to Moscow.<sup>32</sup> What Muller experienced in the Soviet Union during the next four years completely changed his attitudes towards socialism and state of support science. By the 1950s his attitude had become “better dead than red.” When Muller published articles denouncing Lysenko in popular press sources like the *Saturday Review of Literature*, he focused on the issue of interference in scientific research.<sup>33</sup> Just as Muller had disappointed Texas doctors who wanted him to say optimistic things about radiation, he was also to provoke the ire of the American public by comparing the VASKhNIL session to the Scopes Trial. He also refused to bother to explain, in scientific terms, why Lysenko was wrong. Instead Muller lashed out at Stalin and summarized Lysenko's beliefs using bitter sarcasm.

At first things had gone well for Muller in the Soviet Union. However by the end of the 1930s — as documented in numerous accounts of the Lysenko affair — the situation in Soviet genetics became so precarious that Muller was forced to leave.<sup>34</sup> During this time Muller continued

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<sup>30</sup> B: D65 Dobzhansky, Theodosius. *Reminiscences, Part I*: 166-167. The American Philosophical Society. In his oral history Dobzhansky describes Vavilov as having been accompanied by two men from Amtorg, the agricultural trade agency in the U.S. — “who were officially his helpers, helping him to put up charts and that kind of thing. But these two individuals never left Vavilov alone. It was perfectly clear that they were far more than they were officially calling themselves.” Nikolai Kremontsov, however, informed me that Vavilov was actually accompanied only by a man named Saenko, the head of Amtorg, who was supposed to assess the exhibition, which was part of the genetics congress, for new varieties of crops etc., with the view of purchasing some of them for use in Soviet agriculture. Personal communication. Nikolai Kremontsov. March, 2006. For further details on the congress see Kremontsov, *International Science Between the Wars*, pp. 36-42.

<sup>31</sup> *The Reminiscences of L.C. Dunn*, pp. 694-695.

<sup>32</sup> Carlson, *Genes, Radiation and Society*, pp. 184-192.

<sup>33</sup> Elof Axel Carlson. Lecture. New York, NY. June 10, 2005.; Muller's FBI files contain numerous documents emphasizing that by the 1950s he believed the Soviet Union was even a greater threat “civilization” than atomic warfare.

<sup>34</sup> A comprehensive account of Lysenko's rise to power in Soviet biology during these years in Nikolai

work on his eugenics manifesto — *Out of the Night*. In the preface he wrote:

I realise that I am bound to meet the opposition of most professional eugenicists of the stereotyped school that at present (as an outgrowth of modern social conditions) is in the ascendancy in this as yet semi-scientific subject. In fact, it may be admitted that “Eugenics,” in the sense in which most of us are now accustomed to thinking of it, has become a hopelessly perverted movement. Beyond imposing some slight limitation on the numbers of the most grossly defective, it would be, with its present methods and outlook, powerless to work any positive change for the good. On the other hand, it does incalculable harm by lending a false appearance of scientific basis to advocates of race and class prejudice, defenders of vested interests of church and state, Fascists, Hitlerites and reactionaries generally. Even the least unreasonable of the professional spokesmen of this modern “Eugenics” have taken no clear stand against the atrocities recently proposed and carried out in its name.<sup>35</sup>

In May 1936, Muller sent Stalin a copy of *Out of the Night*. Stalin’s negative reaction — compiled by Lysenko’s increased influence, would become the primary reasons Muller left the Soviet Union. After his departure Julian Huxley arranged a position for Muller with Francis Crew at the Institute of Animal Genetics in Edinburgh, Scotland.<sup>36</sup> Muller remained in Great Britain until after the outbreak of the Second World War and then returned to the U.S. Though initially none of the inquiries Julian Huxley and Francis Crew had made for Muller panned out, he finally received an offer for a temporary appointment at Amherst College.<sup>37</sup> An obvious complication to Muller’s job search was his reputation as a “Red.” The impact of Muller’s dissipating communist sympathy upon his career must have been maddening. As a result he became more cautious. In 1944 Leslie Clarence Dunn at Columbia invited Muller to join the American-Soviet Science Society but Muller declined fearing what effect, “the continuance of a pro-Soviet attitude ... so openly expressed,” could have upon his career.<sup>38</sup> Muller’s appointment at Amherst ended in June, 1945 and was not renewed. Once again, at age fifty-four, he found himself looking for a position. Fortunately by the fall he had received an offer from Indiana University where he would remain for the rest of his career.

The failures and successes of Muller’s career prior to the Second World War set the course of his progress afterwards. Just over a year after the bombs were dropped on Hiroshima and Nagasaki, Muller received the Nobel Prize for being the first to discover that X-rays produce mutations in fruit flies. Muller’s position as an authority on genes and radiation, along with his belief that scientists should educate the public on the significance of their work, put him at the center of controversy as the U.S. continued to test atomic weapons. Eleven months after Muller received the Noble Prize, Trofim D. Lysenko banned genetics in the Soviet Union. Once again Muller’s experience, combined with animosity for someone whose ideas he considered a — “dangerous superstition,” comparable to the “belief that the earth is flat,” and intended to “degrade rather than advance humanity” — placed him on the front lines of a passionate debate among scientists, conducted before a public audience.<sup>39</sup> It is this last factor — that both atomic radiation and Lysenkoism were issues of tremendous interest and concern to non-scientists — that made

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Kremontsov’s *Stalinist Science* (Princeton, N.J.: Princeton University Press, 1996).

<sup>35</sup> Muller, *Out of the Night*, 10-11.

<sup>36</sup> Carlson, *Genes, Radiation and Society*, pp. 242-243.

<sup>37</sup> Correspondence, Hermann J. Muller to L.C. Dunn, June 6, 1946. Series: Correspondence 1910-1972, Box 1. Muller MSS, Lilly Library, Indiana University.

<sup>38</sup> Melina Gormley. *Geneticist L.C. Dunn: Politics, Activism and Community* (Ph.D. Dissertation. Oregon State, 2006), p. 341.

<sup>39</sup> H.J. Muller, “The Destruction of Science in the USSR,” *The Saturday Review of Literature*, December 4, 1948, 65.

them treacherous subjects for scientific discussion. Public opinion was often swayed by factors completely unrelated to the details of the topic being considered, most of which often only vaguely understood. This was an environment which could favor the charismatic or politically astute, rather than the professionally competent.

Muller was one of many biologists in the U.S. and Great Britain concerned with the situation in Soviet genetics after the war. Recognizing that the period of good-will between the U.S. and Soviet Union as allies against Nazi Germany was going to be brief, Muller and others began translating and publishing the manuscripts of Russian geneticists to promote their work.<sup>40</sup> Leslie Clarence Dunn and Theodosius Dobzhansky at Columbia arranged for Kings Crown Press (a now-defunct division of Columbia University Press) to publish one of Lysenko's major works, *Heredity and Its Variability*. Julian Huxley orchestrated reviews in England, while Muller and Dunn wrote letters to colleagues that said negative reviews of Lysenko's work would weaken him. Reviews of *Heredity and Its Variability* appeared in all the major biology journals, including *American Naturalist*, *Physiological Zoology* and *Discovery*.<sup>41</sup> When J.B.S. Haldane refused to write a critical review of Lysenko's work Muller's suspicions were confirmed. He was outraged, but not surprised.<sup>42</sup>

Haldane's reasons for supporting Lysenko — even endorsing him in an obituary he taped for the BBC in 1964 — are not easy to discern. Like Muller, Haldane seemed to prefer the unpopular side of any argument. Also, he lacked Muller's first-hand experience of what had taken place in Soviet genetics in the 1930s. Most of those who spoke out on Lysenkoism in the U.S. and Great Britain had not been to the Soviet Union since the late 1920s or very early 30s. Even Theodosius Dobzhansky — who of course was from the Soviet Union — had not returned since he'd left in 1927. Of them all Muller was the one with the most recent — and when it came to Lysenko — most personal experience. For this reason he maybe had more at stake than anyone in proving Lysenko wrong. Despite an initial optimism that Lysenko's "star" was "in decline," the situation soon appeared troubling.

In the summer of 1945 Soviet geneticist Anton Zhebrak had come to the United States as part of a UN delegation. Zhebrak attempted to meet with Dunn and Muller, however due to last-minute changes he was forced to return to Moscow immediately via Alaska. During his short stay, however, Zhebrak was confident enough to predict to Western geneticists that it would not be long before Lysenko had enough rope to "hang himself."<sup>43</sup> Zhebrak followed up with an article in the October issue of *Science* downplaying Lysenko's influence in Soviet biology.<sup>44</sup> However by the fall of 1947 Zhebrak was criticized in *Pravda* for his article. He was charged with humiliating and defaming Lysenko, while failing to mention other great figures in Soviet science such as Michurin. Zhebrak was forced to defend himself in a court of honor and relinquish his position with the

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<sup>40</sup> Kremontsov, *Stalinist Science*, p. 121. The other geneticists who participated were Isadore Michael Lerner, Ernest Babcock, G. Ledyard Stebbins, Walter Landauer and Jack Shultz.

<sup>41</sup> Kremontsov, *Stalinist Science*, p. 122. See *The American Naturalist*, (80) 790, 1946, pp. 241-243.; *Physiological Zoology*, XV 1946, pp. 332-334.; *Discovery*, February, 1947, pp. 40-43.

<sup>42</sup> Kremontsov, *Stalinist Science*, p. 123.

<sup>43</sup> Correspondence, Th. Dobzhansky to L.C. Dunn, July 4, 1945. B: D917 L.C. Dunn Papers. Dobzhansky, Theodosius, 1943-5. The American Philosophical Society.; Correspondence, I.M. Lerner to H.J. Muller, June 25, 1945. Correspondence, I.M. Lerner to L.C. Dunn, June 27, 1945. Correspondence, I.M. Lerner to H.J. Muller, June 29, 1945. B: L563 Isadore Michael Lerner Papers. Newspaper – Z. The American Philosophical Society.

<sup>44</sup> Anton Zhebrak, "Soviet Biology," *Science*, 102/2649 1945.

Belorussian Academy.<sup>45</sup> Muller served as president at the international genetics congress in Stockholm in July 1948 and not a single Soviet geneticist attended. At the end of the month a week-long session of the Lenin All-Union Academy of Agricultural Sciences (VASKhNIL) was held, presided over by Lysenko, and on the last day he made his notorious declaration, “The Central Committee of the Party examined my report and approved it.”<sup>46</sup>

Less than two months later Muller drafted a letter of resignation from the Russian Academy of Sciences.<sup>47</sup> It is clear from Muller’s letter, as well as his criticism of Lysenko which followed, that he did not consider “Lysenkoism” a problem limited to the Soviet Union. Muller’s rebuke was published widely in the American press, and the Russian Academy’s reply, which appeared in *Pravda* a few months later, was equally heated.<sup>48</sup> The battle lines between Muller and the Lysenkoists were now drawn. The way in which Muller and his work were portrayed is demonstrated by an excerpt from *Land in Bloom*, a socialist-realist account of Lysenko and Michurinism which was awarded the Stalin Prize in literature in 1949:

“Professor Muller’s Flies”

Muller was a pupil of Morgan.

He laboured in the laboratory with tireless zeal. From the test tubes teeming with *Drosophila* he expected an answer to the riddle of heredity, to the riddle of variability, the riddle of what controls forms, and many other riddles. ...

So Muller invented the queerest means of changing the hereditary nature of the winged captives in his test tubes. One day he put them under X-rays, and the flies which had been in the green spotlight of these rays brought forth unusual offspring. ...

Indeed, when turning his green spotlight upon his test tubes, Muller himself had no idea what would come of it. And when he obtained variations in his flies, he could not say why they changed in this way and not in another. It was like in the old fairy tale, “Go — I don’t know where; bring — I don’t know what.”

And the idea began to creep into many minds that it may have been a mistake to repose these joyous hopes in the American flies that had been treated to X-ray shower baths.<sup>49</sup>

As nasty as the image of Muller as an irresponsible, X-ray fanatic, with no idea what he was doing may sound, Muller’s characterizations of Lysenko were not dissimilar. One of the most interesting thing about the way in which U.S. biologists like Muller responded to Lysenko was the degree to which they traversed the boundaries of scholarly discourse.<sup>50</sup> In doing so they aroused the suspicion and resentment of their colleagues who, while they agreed Lysenko was almost certainly incorrect, did not believe arranging negative reviews of his work or criticizing him with words like “charlatan” was professional, or even ethical.

Four months after the VASKhNIL conference Muller published two articles in the *Saturday Review of Literature* — “The Destruction of Science in the USSR” and “Back to Barbarism Scientifically.”<sup>51</sup> *Saturday Review of Literature* was a popular publication for an educated audience that

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<sup>45</sup> Kremontsov, *International Science Between the Wars*, pp. 141-142; Kremontsov, *Stalinist Science*, pp. 120-124, pp. 146-148.

<sup>46</sup> *The Situation in Biological Science: Proceedings of the Lenin Academy of Agricultural Sciences of the U.S.S.R., Session: July 31-August 7, 1948, Verbatim Report* (Moscow: Foreign Languages Publishing House, 1949), p. 605; Kremontsov, *Stalinist Science*, p. 173.

<sup>47</sup> *Ibid.*, pp. 307-309.

<sup>48</sup> *Ibid.*, pp. 309-312.

<sup>49</sup> V. Safonov, *Land in Bloom*, trans. J. Feinberg. (Moscow: Foreign Languages Publishing House, 1951).

<sup>50</sup> An excellent example is the full issue of *Journal of Heredity* devoted to the controversy in 1949. See *The Journal of Heredity*, 40/7, 1949.

<sup>51</sup> H.J. Muller, “The Destruction of Science in the USSR,” *The Saturday Review of Literature*, December 4, 1948, pp. 13-15, pp. 63-65.; H.J. Muller, “Back to Barbarism Scientifically,” *The Saturday Review of*

featured the work of writers ranging from E.M. Forester to Ring Lardner. By using it as a forum for his opinions of Lysenko, Muller was addressing a wide audience of middle-class American readers who he expected to trust his education and authority. Muller discovered, however, that he did not know his audience as well as he thought.

In “The Destruction of Science in the USSR” Muller wrote that as far as Soviet genetics was concerned, “all that we can now hope to do is to conduct an autopsy.”<sup>52</sup> He described the “success” of Lysenko’s work as “dubious,” and said it gave “him no more claim to being a geneticist than does the treatment of dogs for worms.” “Lysenko’s writings along theoretical lines,” he added, “are the merest drivel.”<sup>53</sup>

Muller’s second article, “Back to Barbarism Scientifically,” was more of a cautionary piece in which he described the elements of Lysenkoism he saw present in American society. The article included a photograph of William Jennings Bryan and Clarence Darrow, captioned, “When we criticize the Soviet attack on science, let us not forget...the assault on the teaching of evolution during the Scopes trial in Tennessee, led by the politician William Jennings Bryan.” Muller said that the Scopes trial was “only the most publicized” of many similar “scandals.”<sup>54</sup>

In addition to the threat to science posed by religious fundamentalism, Muller also pointed out the “danger” created by the dependence on private foundations to fund scientific research. “Why,” he asked, “should the scientist have less prestige than the businessman and be considered less qualified for handling funds in his own field?” The “gravest present danger,” however, Muller said, stemmed from the “activities of super-patriots,” such as the House Un-American Activities Committee (HUAC), “who, on the plea that they are battling totalitarianism and defending democratic freedoms, are themselves attempting to fasten the very evils they warn against upon our own country.” According to Muller, when criticizing the “shocking treatment accorded scientists in Nazi Germany, and which is now being given them in the USSR, we must also exert ourselves to prevent the same thing from happening in our own midst.”<sup>55</sup>

It is clear from the letters to the editor that followed Muller’s articles, most readers were suspicious. On the one hand, they seemed to think Muller should have spent more time discussing why genetics was right than why Lysenko was wrong. On the other hand, readers of the *Saturday Review of Literature* did not see why they should care about Soviet biology. They understood that the USSR was a totalitarian society and hoped that any by-products — such as the censorship of scientific theories — would work to the advantage of the United States. Of the six respondents, only one agreed with Muller. He was accused of being “unscientific” and “emotional.” One respondent referred to Muller’s “vehemence,” and accused him of not offering any conclusive evidence for why he disagreed with Lysenko. Another reader said what Muller had written was a “political diatribe,” while another argued that rather than criticize Lysenko we should “welcome anything that decreases” the “ability” of the Soviet Union “to conquer us.”<sup>56</sup>

Among the ironies of the response Muller received, is that two of the letters were written by doctors who were upset by his statements on radiation. As Muller wrote to Robert Low, an editor at the *Saturday Review*:

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*Literature*, December 11, 1948, pp. 8-10.

<sup>52</sup> Muller, “The Destruction of Science in the USSR,” p. 13.

<sup>53</sup> *Ibid.*

<sup>54</sup> Muller, “Back to Barbarism Scientifically,” p. 9.

<sup>55</sup> *Ibid.*, p. 10.

<sup>56</sup> *Saturday Review of Literature*, January 8, 1948, pp. 23-24.

In a previous letter I called attention to the fact that the Dr. Thomas Who adversely criticized my articles in your issue of January eighth had special animus against me owing to my having criticized practices prevalent in his profession of radiology. I now find that the other medical man who had a letter in the same issue, M. Friedman, has the same name, and therefore is probably the same man, as one whose practices in radiology I took especial exception to in my lectures ... Neither Thomas nor Friedman mention this.<sup>57</sup>

Thomas and Friedman aside, the response to Muller's articles should have indicated that he was better off criticizing Lysenko on scientific grounds and leaving other issues — such as fundamentalist hostility to Darwinian evolution and red-baiting — out of it. A debate with Irish playwright/Fabian socialist George Bernard Shaw, published five months later in the same publication, showed Muller recognized the latter problem much sooner than he did the former. Since Shaw was not a scientist, his support for Lysenko was grounded more in sociological issues, such as whether the state had an obligation to monitor scientific research, and philosophical questions, such as the potential consequences of believing in inherent biological superiority. Muller, unfortunately, responded in similar terms, and once again made the mistake of not restricting himself to the topic of heredity.

Shaw and Muller's articles appeared in the April, 1949 issue of *The Saturday Review of Literature*.<sup>58</sup> Shaw began his article by saying that to "anyone who knows the ropes," of the Lysenko controversy, "the rumpus is laughable." He contrasted Lysenko's theories with the determinism of August Weissman and said that clearly a socialist state could not "tolerate" such fatalism. Shaw also claimed Lysenko was a "vitalist" but had to pretend he was materialist for the same reasons Anglican bishops had to swear they literally believed everything that was written in the Bible.<sup>59</sup>

Muller's response to Shaw was polite, but it's clear he was annoyed. Muller wrote that debate over Lysenko's theories would not be settled by "philosophical argument." However, he also stated that "the public has not the patience to be bothered with the intricacies" of genetics.<sup>60</sup> He seemed to expect readers of *Saturday Review of Literature* to trust his credentials, something he should have known by now they were not going to do. Muller called on "humanists" and "modern man" in general to cease their hostility towards science, and "give up the escapism of believing that caprice is in itself a virtue."<sup>61</sup> Muller also questioned why Shaw, "a non-scientist," thought he was "competent to condemn the hard-won conclusions of geneticists."<sup>62</sup>

A few weeks later the editors of the *Saturday Review of Literature* wrote that the debate had provoked "considerable comment" from readers — most of the commentary was against Muller.<sup>63</sup> Respondents criticized him for writing that the public was not patient enough to "be bothered with" an explanation of genetics. One reader pointed out that if scientists were capable of producing atomic bombs and biological weapons then everyone had an interest in their work. Moreover, for Muller to claim that Shaw presumed too much, as a non-scientist, in discussing scientific topics, then what right had Muller, as a non-politician, to question governmental oversight of the

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<sup>57</sup> Correspondence, Hermann J. Muller to Robert Low, February 5, 1949. *Saturday Review* 1948-1951. Muller MSS. Series I Box 24, Lilly Library, Indiana University.

<sup>58</sup> George Bernard Shaw, "Behind the Lysenko Controversy," and H.J. Muller, "It Still Isn't a Science: A Reply to George Bernard Shaw," *The Saturday Review of Literature*, April 16, 1949, pp. 10-11, pp. 11-12, p. 61.

<sup>59</sup> Shaw, "Behind the Lysenko Controversy," p. 10.

<sup>60</sup> *Ibid.*, p. 12.

<sup>61</sup> *Ibid.*

<sup>62</sup> *Ibid.*, p. 12, p. 61.

<sup>63</sup> *The Saturday Review of Literature*, May 7, 1949, p. 26.

sciences? Did the simple fact that Lysenko's influence was granted to him by Soviet authorities mean that he was wrong?

Other readers agreed: Why had Muller, by not discussing genetics, "become the fanatical advocate rather than the objective scientist"? Why not be "dispassionate"?<sup>64</sup> Why did Muller expect readers to accept their own ignorance along with his authority, "Is their curiosity about genetic research never to be even partially satisfied unless the sacred text of the geneticists' actual words is perused reverentially?"<sup>65</sup> Muller would have been better off, they argued, by countering Shaw and Lysenko with facts, rather than "his own dogma."<sup>66</sup> If in fact the *Saturday Review of Literature* was not, according to Muller, the proper place for discussing the complexities of genetics, then why bother using it as a forum to discuss Lysenkoism at all?<sup>67</sup>

Muller was caught in a bind. On the one hand, he wanted to criticize Lysenko in a publication that would reach a wide audience. When doing so he was forced, he felt, to address the issue in terms non-scientists could understand. The reaction of readers against Muller indicates a tremendous public mistrust of scientists, particularly when they tried to limit who had the right to debate scientific issues. Clearly government interference with scientific practice was not regarded by the general public with the same hostility as it was by scientists.

One of the readers criticized Muller in the *Saturday Review of Literature* referred to Ralph Spitzer, a chemistry professor at Oregon State, who that same year had been dismissed for publicly supporting Lysenko. Spitzer's troubles began when he wrote a letter to a professional journal, *Chemical and Engineering News*, in response to a column by the editor, Walter J. Murphy, titled "State Science." In his editorial Murphy referred readers to Muller's initial articles in the *Saturday Review of Literature*, and said that Muller spoke with authority not only as a scientist, but also as someone who was "personally acquainted" with many of those involved in the "recent purge of Russian scientists."<sup>68</sup> Murphy focused on Muller's contention that the issue was neither limited to Eastern Bloc countries, nor to scientists and science. Though "the fate of the anti-Lysenkos may seem to have little direct bearing on what goes on outside the Iron Curtain," Murphy argued, "both liberalism and conservatism are fields where the enemies of freedom roam seeking to accomplish their ends undetected."<sup>69</sup>

Spitzer was one of three readers who responded to Murphy's editorial. One agreed and one disagreed. Spitzer's letter was the longest, and he went the furthest in directly refuting Muller to defend Lysenko on scientific grounds.

Contrary to Dr. Muller's assertion that, "despite the pretenses of Communist officials and their followers, this matter is not a controversy between scientists or a dispute over the relative merits of two scientific theories. It is a brutal attack on human knowledge," a perusal of Lysenko's report shows that the issue is largely over matters of biological and technological fact and theory. Are vegetative hybrids possible? Mr. Lysenko has samples. Can the heredity of organisms be changed by changing the environment at an appropriate time and in an appropriate way? The Michurinists have changed 28 chromosome spring wheats to 42 chromosome winter wheats by suitable temperature treatment during several generations.

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<sup>64</sup> Ibid., p. 27.

<sup>65</sup> Ibid., p. 28.

<sup>66</sup> Ibid., p. 27.

<sup>67</sup> Ibid., p. 28.

<sup>68</sup> Walter J. Murphy, "State Science," *Chemical and Engineering News* 26 (52) 1948, p. 3815. See references to Muller's articles above: Muller, "The Destruction of Science in the USSR," and Muller, "Back to Barbarism Scientifically."

<sup>69</sup> Ibid.

Finally, it is asserted that the Lysenko theory and techniques are far more productive of economic results than the classical theory which is also assailed as being “idealist,” a term which in the Soviet Union has roughly the connotations of supernaturalist or unscientific.<sup>70</sup>

Spitzer also said the organization of science in the Soviet Union was superior to “our method of allowing boards of directors, Congress, or the military to decide (often on a smaller scale) which branches of science and which projects to encourage.”<sup>71</sup>

Spitzer had been promoted to associate professor but had not received tenure. After his letter was published the president of Oregon State, Dr. August L. Strand, dismissed him. Spitzer did not go quietly. He brought his case to the campus chapter of the American Association of University Professors and the college faculty council. Both refused to help. In desperation Spitzer turned to the press. The story soon made its way from the campus newspaper, *The Daily Barometer*, to the front page of the *Oregonian*. The *New York Times* covered the story as well. In “Oregon Teacher Out as Lysenko Backer,” Strand was quoted describing Lysenko as a “charlatan” whose views were opposed by the world’s “leading geneticists”, “Any scientist who has such poor power of discrimination so as to choose to support Lysenko’s genetics against all the weight of evidence against it is not much of a scientist or has lost the freedom that an instructor or investigator should possess.”<sup>72</sup>

The scandal ultimately made its way back to the pages of *Chemical and Engineering News*.<sup>73</sup> At this point noted-chemist Linus Pauling and Muller’s old rival, Alfred H. Sturtevant, weighed in to defend Spitzer. Though Sturtevant did not agree with Lysenko, he questioned the wisdom of “an American university adopting the very policy, of making academic tenure dependent on conformity that we so strongly object to in Russia.”<sup>74</sup> Sturtevant didn’t mention Muller directly, but he portrayed Spitzer as a martyr to academic freedom. Even if the data Spitzer referred to in support of Lysenko would later come under question — Spitzer was redeemed in the scientific community for not resorting to language echoing either Lysenkoists, or the polemics of anti-communist “red-baiters.” By remaining dispassionate and citing evidence Spitzer was able to gain support from those who might otherwise be disturbed by his belief that Lysenko was credible.

Muller agreed with Spitzer’s dismissal. If Spitzer supported Lysenko because Spitzer was a communist then he should be fired.<sup>75</sup> With reference to communist sympathizers Muller said, “These people have blood on their hands; they stink; and there is no use in letting them get away with their pretense that they are representatives of science and culture.”<sup>76</sup> Muller formed the Committee on Public Education and Scientific Freedom in the Genetics Society of America to educate the public about Lysenkoism, and keep his followers from infiltrating genetics in the U.S.

Muller’s attitude towards Spitzer was representative of his broader views on communism and academic freedom. Muller declined to support faculty at the University of California who had refused to sign a loyalty oath stating that they were not members of the Communist Party or any other subversive organization. Muller commented that forcing people to sign oaths was a stupid way to spot communists because we take oaths all the time — in church, school, and when we want

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<sup>70</sup> Ibid.

<sup>71</sup> Ibid., p. 307.

<sup>72</sup> “Oregon Teacher Out as Lysenko Backer,” *New York Times*, February 24, 1949: p. 1.

<sup>73</sup> “Strand and Spitzer Issue Statements on Spitzer’s Dismissal,” *Chemical and Engineering News* 27 (13) 1949, pp. 906-909.

<sup>74</sup> Ibid., p. 936.

<sup>75</sup> Carlson, *Genes, Radiation, and Society*, p. 331.

<sup>76</sup> Ibid., p. 375.

to get married. The more important issue for Muller was that communists — just like Nazis or members of the Ku Klux Klan — should not be allowed to teach.<sup>77</sup>

Just as Muller was attacked by readers of mainstream publications like the *Saturday Review of Literature*, he also came under fire in the leftist press. *The Worker* published an article “Soviet Science is Changing Heredity,” which labeled Muller as the primary activist in a “cold war against the USSR.”<sup>78</sup> In *Masses and Mainstream* an instructor from the Jefferson School of Social Science in New York City wrote that there was no disagreement between Lysenko’s views and genetics, just a disagreement between Lysenko and certain geneticists like Muller.<sup>79</sup>

Muller’s friend and former-colleague, Julian Huxley, finally came to his defense in his expose on the Lysenko affair *Heredity East and West: Lysenko and World Science*.<sup>80</sup> In the book Huxley juxtaposed criticism of Lysenko’s theories and Soviet interference in biological science with an argument for something he called “evolutionary humanism.” Evolutionary humanism was Huxley’s idea that capitalist democracies should provide the same sort of official support for genetics that the Soviets provided for Michurinism. Though there seems to be an obvious contradiction in simultaneously arguing for and against state interference in science, Huxley was actually saying that biology should underpin every aspect of state policy. He used the Lysenko affair as an opportunity to pitch his vision for technocracy because he feared that the inevitable alternative was obstruction of science by political actors and an ignorant public.

Huxley cited Muller repeatedly in the text, relying on his account of the cancellation of the International Genetics Congress in Moscow in 1936 and Vavilov’s final confrontation with Lysenko in 1939.<sup>81</sup> He also used Muller’s work to explain how scientific research is normally conducted — precautions, repeated experiments, and the publication of results in a format that they can be replicated.<sup>82</sup> Huxley also covered Muller’s debate with Shaw in the *Saturday Review of Literature* and refuted readers who’d insisted Muller should explain why genetics is correct rather than why Lysenko was wrong: a magazine article did not allow sufficient space to explain the intricacies of genetics.<sup>83</sup> Also Lysenko didn’t deserve to be debated in scientific terms, according to Huxley, because he “doesn’t observe the rules of the scientific game.”<sup>84</sup>

### *Muller and Radiation*

Muller’s struggles in the realm of public opinion over the Lysenko conflict took place simultaneous to his involvement in the postwar controversy over the dangers of radiation, and the challenges he faced were similar. Public concern focused on atomic warfare. While understandable, this diverted attention from what Muller believed to be more relevant dangers such as the use of X-rays in medicine. Common practices included the use of X-rays to photograph fetuses to spot potential

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<sup>77</sup> *Ibid.*, pp. 331-332.

<sup>78</sup> Peter Stone, “Soviet Science is Changing Heredity,” *The Worker* XIII (51), 1948, pp. 5-6, 12.

<sup>79</sup> Bernard Friedman, “Revolution in Genetics,” *Masses and Mainstream* 2 (3), 1949. The Jefferson School was a Marxist adult education school in New York City that operated from 1943 to 1956. Friedman taught courses on Marxism in biology. The archives of the Jefferson School are housed at the Tamiment Library at New York University.

<sup>80</sup> Julian Huxley, *Heredity East and West: Lysenko and World Science* (New York: Henry Shuman, 1949).

<sup>81</sup> *Ibid.*, pp. 27-29.

<sup>82</sup> *Ibid.*, p. 64.

<sup>83</sup> *Ibid.*, pp. 211-212.

<sup>84</sup> *Ibid.*, p. 213.

problems for delivery, radiation to slow bone growth in bow-legged children, eliminate warts, and stimulate ovulation in females.<sup>85</sup> Up until the early 1940s most of what scientists knew about the effects of radiation was the result of fruit fly research.<sup>86</sup> The bombs dropped on Japan which ended World War II offered biologists a “natural” experiment for examining the impact of radiation on humans.

In 1947 Muller became part of a study initiated by the Atomic Bomb Casualty Commission to research the genetic impact of the blasts at Hiroshima and Nagasaki upon survivors. A report in the *New York Times* quoted Dr. Lewis H. Weed of the National Research Council.

Dr. Lewis H. Weed, chairman of the council’s division of medical research, said there was not yet any evidence to support reports of abnormalities in children born of survivors of the blast. But he added that “widespread interest” had been aroused concerning the effect of radiation on heredity, and he said a major study would be made in that field.<sup>87</sup>

The story added that U.S. President Truman had “authorized the committee to ‘undertake a continuing study of the medical and biological effects of the atomic bomb on man’.”<sup>88</sup>

The Atomic Bomb Casualty Commission study was led by James Neel of the University of Michigan. Muller drew upon Neel’s work in a 1949 presidential address he gave to the American Society of Human Genetics, “Our Load of Mutations,” later published in the *American Journal of Human Genetics*.<sup>89</sup> Muller presented his fears concerning the role of medicine and atomic testing in increasing the “genetic load” of mutations in the human population. Echoing once-popular eugenic arguments that progress had undermined the mechanism of natural selection, increasing the number of unfit individuals, Muller warned that the benefits of modernity preserved those who previously would have been eliminated from the population by genetic causes. Moreover, as atomic testing continued we would be increasingly exposed to radiation, speeding the reproduction of deleterious and lethal mutations. As a result, human beings of the future would form a population “devoted chiefly to the effort to live carefully, to spare and to prop up their own feeblenesses, to soothe their inner disharmonies, and, in general, to doctor themselves as effectively as possible. ... everyone would be an invalid, with his own special familial twists.”<sup>90</sup>

Muller’s vision of dysgenic dystopia inclined him towards the eugenics implied by Huxley’s evolutionary humanism. According to Muller, the tainted reputation of eugenics should not impede the establishment of policies to reduce the genetic load anymore than the failure of Greek democracy could be used as an argument against “democracy in general.”<sup>91</sup> Muller’s knowledge of the dangers of radiation became the new framework for his belief in controlling human reproduction. As with his efforts against Lysenkoism, however, Muller was forced to struggle with rejection from the scientific community, as well as how his views were interpreted by the public at large.

A major problem in both cases was something Muller described as the “erroneousness of the

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<sup>85</sup> Carlson, *Genes, Radiation and Society*, pp. 336-337.

<sup>86</sup> Daniel Kevles, Daniel Kevles, *In the Name of Eugenics: Genetics and the Uses of Human Heredity* (Berkeley and Los Angeles, CA: University of California Press, 1985), pp. 223-224.

<sup>87</sup> “Experts to Study A-Bomb Survivors,” *New York Times*, September 1, 1947, p. 21.

<sup>88</sup> *Ibid.*

<sup>89</sup> Hermann J. Muller, “Our Load of Mutations,” *American Journal of Human Genetics* 2 (June, 1950).

<sup>90</sup> *Ibid.*, 145-156. Hermann J. Muller, “The Guidance of Human Evolution,” *Perspectives in Biology and Medicine*, 3 (autumn, 1959), p. 9.

<sup>91</sup> Correspondence, Hermann J. Muller to R.L. Schulz, October 7, 1954. Series: Correspondence 1910-1972, Box 1. Muller MSS, Lilly Library, Indiana University.

popular notion that mutants are ordinarily monstrosities or freaks.”<sup>92</sup> Muller’s experiences in the Soviet Union inclined him to believe that a certain amount of atomic testing was an acceptable price to pay for national security, and that the incautious use of X-rays in the medical community remained the primary issue.<sup>93</sup> The treatment of genetic disorders, which had the unintended effect of increasing their frequency, presented further problems. Muller made this point directly in an address to The New York Academy of Medicine in 1947.

Some medical men may think that it is going far afield into dubious and exotic biological theorizations to consider the phenomenon of mutation in connection with the subject of public health. Perhaps the word “mutation” will convey to their minds the picture of rare and bizarre monstrosities, such as the armless-legless man, the microcephalic idiot, the lion-faced boy, and other circus wonders. Although most such curiosities have, in fact, arisen as a result of mutation, this is an entirely one-sided and far too narrow view of the phenomenon. . . . the phenomenon of mutation itself, that is, the occurrence of changes which become reproduced in subsequent generations, is in a sense the most normal thing about all living matter, being the property that most basically distinguishes living matter from non-living and that has allowed living matter to develop, in its evolution, all the further peculiarities of its marvelous organization.<sup>94</sup>

The fact that mutations were in one sense so quotidian kept people from appreciating their dangers. Meanwhile, Muller believed the amelioration of human suffering, in the case of genetic disorders, increased misery.

We must recognize then that hereditary ills are unlike diseases of other kinds, in that in “curing” one of them today we are creating another case of the same kind tomorrow. The more success we have, and with the more ailments, the more does mutation take advantage of this to encumber the population with these ailments, for which more and more individuals have to be treated anew in each generation. . . . Mutation, consolidating her victory, then goes on to take the next line of our defense. For we have won no permanent respite, as, pressing the attack on the already weakened biological basis, further mutations in the same and other genes now arise to plague it, and these, too, accumulate just in so far as we seem to be successful in parrying them. Offering a finger, we eventually find our hand taken; yielding up the hand, we find the whole arm drawn in, and so on and on.<sup>95</sup>

Darwinism owed its revival to the discovery that mutations were the building blocks of evolution. Yet this knowledge was leading Muller, a vital contributor to what Huxley had termed the “Modern Synthesis,” to conclude that human foundations were inherently unstable. Human progress led to human extinction — “genetic death.”

Ironically the medical community defended itself against Muller’s warnings about radiation by accusing him of perpetuating the myth of “monstrosities.” In a letter to fellow-geneticist C.C. Little, Muller complained:

When referring to my warnings, they usually made it appear that I had indulged in the same kind of sensational presentation of them as that of the alarmists, because, of course, that is the kind of claim that can more readily be disproved and dismissed. In other words, they raised a strawman and then knocked him down and merely distracted attention from the real issue.<sup>96</sup>

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<sup>92</sup> H.J. Muller, “Mutational Prophylaxis,” *Bulletin of the New York Academy of Medicine* 24/7 July 24, (1948): p. 467.

<sup>93</sup> Carlson, *Genes, Radiation and Society*, p. 354.

<sup>94</sup> *Ibid.*, p. 447.

<sup>95</sup> Muller, “Mutational Prophylaxis,” pp. 448-449.

<sup>96</sup> Correspondence, Hermann J. Muller to C.C. Little, March 31, 1953. Series: Correspondence 1910-1972,

Muller also correctly predicted in his address at The New York Academy of Medicine that the genetic damage done by the atomic bombs dropped on Hiroshima and Nagasaki would not be immediately apparent.<sup>97</sup> When James Neel and his colleague at Michigan, William J. Schull, published *The Effects of Exposure to the Atomic Bombs on Pregnancy Termination in Hiroshima and Nagasaki* in 1954 they wrote that no statistically significant genetic damage had been found. Neel and Schull added that, given what was known about radiation, no one had expected “major findings.” They also cautioned that their results should not be “interpreted to mean that there were no mutations induced in the survivors of the atomic blasts.”<sup>98</sup>

That the public would misinterpret Neel and Schull’s findings was exactly what Muller feared. He expressed his concerns directly to Neel at a meeting at the National Academy of Sciences in Washington D.C. in the summer of 1947. Nevertheless, Muller agreed the project should proceed due to the important information about radiation it would surely reveal.<sup>99</sup> The “widespread interest” mentioned in the *New York Times* report meant their work would promote popular ignorance. But this was a cost which must be accepted.

It was not just the lay community, however, that presented a problem. Muller found his views on radiation challenged by the scientific community as well. In a letter to Robley Evans of the Massachusetts Institute of Technology Muller combined blunt criticism of Evan’s research with the accusation that certain scientists working for the Navy and the Atomic Energy Commission actively misled the public on the harmful effects of radiation.<sup>100</sup> Evans, as Muller knew, was funded by the Navy.

On February 25, 1951 *New York Times* science writer Waldemar Kaempffert published a brief article claiming that Muller did not believe radiation from atomic bombs was harmful, yet still warned against the use of X-rays to treat female sterility.<sup>101</sup> Kaempffert then cited the work of British biologist Ira Kaplan as evidence that the procedure was harmless. Muller fired off a letter to Kaempffert in which he called Kaplan’s views “asinine” and strongly criticized Kaempffert for giving “aid and comfort” to those who wished to “give the public an opiate on the subject of radiation dangers.”<sup>102</sup> Kaempffert not only defended himself to Muller by denying there was any active opposition to his views on genes and radiation, but he also forwarded Muller’s letter to Kaplan.<sup>103</sup> The latter, unsurprisingly, was incensed, and accused Muller of “angry sniping” and “envy” of Kaplan’s “success.”<sup>104</sup>

Muller was also convinced the U.S. government was deliberately hiding the dangers of fallout. On December 3, 1954, an article appeared in the *New York Times*, “President Alerts Mayors on Attack.” The reporter quoted Federal Civil Administrator, Val Peterson, advising anyone who lived within seven or eight miles from Washington, D.C. to build a bomb shelter in their backyard.

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Box 1. Muller MSS, Lilly Library, Indiana University.

<sup>97</sup> Muller, “Mutational Prophylaxis,” p. 462.

<sup>98</sup> Kevles, *In the Name of Eugenics*, p. 227.

<sup>99</sup> *Ibid.*, 362, ft. p. 10.

<sup>100</sup> Correspondence, Hermann J. Muller to R.D. Evans, February 5, 1949. Series: Correspondence 1910-1972, Box 1. Muller MSS, Lilly Library, Indiana University.

<sup>101</sup> “Science in Review: Effects of X-Rays, No Inherited Abnormalities Found as a Result of Treatments,” *New York Times*, February 25, 1951.

<sup>102</sup> Correspondence, Hermann J. Muller to Waldemar Kaempffert, March 14, 1951. Series: Correspondence 1910-1972, Box 1. Muller MSS, Lilly Library, Indiana University.

<sup>103</sup> Correspondence, Waldemar Kaempffert to H.J. Muller, March 26, 1951. Series: Correspondence 1910-1972, Box 1. Muller MSS, Lilly Library, Indiana University.

<sup>104</sup> Correspondence, I.I. Kaplan to H.J. Muller, March 22, 1951. Series: Correspondence 1910-1972, Box 1. Muller MSS, Lilly Library, Indiana University.

On the other hand, Dr. Willard F. Libby of the Atomic Energy Commission said that danger of fallout “could be minimized by fairly simple methods,” such as “staying indoors” or “taking cover behind a few feet of earth.”<sup>105</sup> The article caused Muller to wonder why the government would bother keeping the information classified, since the Russians must already know it anyway.<sup>106</sup> Clearly Muller didn’t recognize the possibility that the government might wish to downplay the dangers of radiation as part of an effort to persuade the American people that atomic weapons should be considered for conventional use. Whether the issue was radiation, fall-out, or Lysenkoism, Muller seems to have assumed that the public would understand things the way he did. He was continually hobbled by his inability to foresee that they might not.

Muller’s belief that the U.S. Atomic Energy Commission was not only deliberately misinforming the public, but actively opposed to his views on radiation, was confirmed in the summer of 1955. In March he received an invitation from the AEC to prepare a paper for the United Nations International Conference on the Peaceful Uses of Atomic Energy, scheduled for Geneva in August. Things proceeded smoothly until July when the AEC informed him that the paper had not been accepted by the UN selection committee for oral delivery. Muller was stunned. By this time he was already in Europe, having decided to use the trip as an opportunity to also visit his wife’s family in England and Germany. Muller was told he could do a five minute talk, but then that offer too was withdrawn. Muller decided to attend the conference anyway as an observer. After several speakers favorably cited his research on radiation genetics, the vice-chair of the panel he was to have presented on suggested that the audience stand in tribute to Muller. They did, and then followed up with an extended ovation.

On September 17 *The Washington Post* published a story, “AEC Accused of Blocking A-Report,” wherein the UN denied the AEC account.<sup>107</sup> Referring to the AEC’s claim that the UN had been the ones to reject Muller’s paper, the executive assistant to the Secretary General of the conference said:

The implication is totally false. Dr. George L. Weil (AEC technical director for the conference) wrote us June 30 that Dr. Muller would not be a member of the United States delegation and they did not want his paper (“How Radiation Changes the Genetic Constitution”) presented. As far as we’re concerned, the paper was naturally of great interest. But if a country says the person who has written the paper should not be on the program, we have to do but agree.<sup>108</sup>

The AEC defended its position by saying that Muller’s intention to discuss the use of atomic weapons on Hiroshima and Nagasaki could lead to discussion of non-peaceful uses of atomic energy. This, according to the AEC, amounted to a violation of the “rules” since the conference was organized to discuss only peaceful uses of atomic energy.<sup>109</sup>

In an editorial, “Muzzling Dissent,” published two days later, the *Post* compared the AEC’s actions to science policy in the Soviet Union:

This double dealing involved much more than a discourtesy or injustice to a distinguished scientist. It involves a grievous blow to the prestige of the United States abroad, representing

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<sup>105</sup> “President Alerts Mayors on Attack,” *New York Times*, December 3, 1954, p. 1.

<sup>106</sup> Correspondence, H.J. Muller to M. Hersnat, December 11, 1954. Series: Correspondence 1910-1972, Box 1. Muller MSS, Lilly Library, Indiana University.

<sup>107</sup> “AEC Accused of Blocking A-Report,” *The Washington Post and Times Herald*, September 17, 1955.

<sup>108</sup> *Ibid.*

<sup>109</sup> “AEC Explains Blocking of Muller’s A-Report,” *The Washington Post and Times Herald*, September 18, 1955.

this country as one, like the Soviet Union, where scientific opinions are suppressed if they are at variance with official prejudices and policies. And, most serious of all, it involves the right of a self-governing society to learn what it needs to learn if it is to remain self-governing.<sup>110</sup>

Former AEC consultant Walter Lapp made the point more directly a few days later in an address urging President Eisenhower to be more candid about the size of the U.S. stockpile of atomic weapons. Lapp said the AEC's censorship of Muller in Geneva, "smacked of 'Lysenkoism — the weird Soviet policy of thought control in genetics'."<sup>111</sup> Eugene Rabinowitch, a former research associate on the Manhattan Project, rose to defend Muller, and also found a way to invoke Lysenko. Rabinowitch explained that the AEC's defensiveness on the issue of radiation was due to the fact that "Communist and Communist-influenced opinion in Europe and Asia had seized upon" the warnings of biologists like Muller, even though "the official Soviet 'line' — as proclaimed by Lysenko but dismissed by all serious geneticists — denies the very existence of genes and maintains that hereditary properties can be changed by such means as diet."<sup>112</sup>

Years later Muller's biographer, Elof Axel Carlson, interviewed Willard F. Libby, who was commissioner of the AEC when Muller was snubbed. This was of course the same Libby, quoted above, who claimed that the dangers of fallout could be easily avoided by simply not going outside or hiding behind a small mound of dirt. Libby told Carlson that his review of Muller's FBI file convinced him that Muller could not be trusted.<sup>113</sup> Muller's resignation from the Russian Academy of Sciences and his vocal rebuke of Soviet science over Lysenkoism were still not enough to allay suspicion in the mind of ardent anti-communists like Libby. Muller's early enthusiasm for Soviet socialism, complemented by his later rejection of these beliefs, made him uniquely suited for suspicion and resentment by both sides.

Once again Muller seems to have been relatively oblivious to these concerns, as well as the lingering antipathy some of his colleagues felt towards him. The most obvious case, once again, was Sturtevant. Just as his old rival from the fly room had sided with Ralph Spitzer over Lysenkoism, he also publicly disagreed with Muller's view of radiation. In 1954 Sturtevant gave a presentation at a health conference in Houston, Texas on radiation danger that was later reprinted in the journal *Engineering and Science*.<sup>114</sup> Stewart Alsop published an account of Sturtevant's talk in the *New York Herald Tribune* claiming that Sturtevant expressed a "fear of monsters." Muller wrote an angry letter to the *Tribune*, claiming this was not what Sturtevant had meant, which Alsop forwarded to Sturtevant. Sturtevant confirmed Alsop's account for reasons which Muller could only believe had to do with a dislike for him personally. Muller didn't think Sturtevant could be "so stupid" as to really think the problem with radiation was the production of gross deformities. As he wrote to a colleague, "I have reason to believe that he has long had a personal resentment against me since the early days of the *Drosophila* work."<sup>115</sup>

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<sup>110</sup> "Muzzling Dissent," *The Washington Post and Times Herald*, September 20, 1955.

<sup>111</sup> "U.S. Bomb Pile Set at Several Tons of T.N.T. for Every Person on Earth," *The Washington Post and Times Herald*, September 21, 1955.

<sup>112</sup> "Banned Atomic Paper is Opposite of 'Alarmist'," *The Washington Post and Times Herald*, November 6, 1955.

<sup>113</sup> Carlson, *Genes, Radiation and Society*, pp. 364-367.

<sup>114</sup> A.H. Sturtevant, "The Genetic Effects of High-Energy Irradiation of human Populations," *Engineering and Science* 4/18 (1955): pp. 9-12.

<sup>115</sup> Correspondence, H.J. Muller to Benjamin Sonnenblick, November 5, 1954. Series: Correspondence 1910-1972, Box 1. Muller MSS, Lilly Library, Indiana University.

## *Conclusion*

By considering Hermann J. Muller's struggles to educate the public and his fellow scientists on the dangers of radiation in context with his simultaneous involvement in the Lysenko affair, we gain a broad understanding of the challenges facing U.S. biologists during the Cold War. Muller's renown was based upon aiding scientists to study how mutations functioned as the building blocks of evolution. His unique insight into mutations made him aware of their dangers — an understanding rejected by an audience that seemed to prefer an optimistic view of scientific progress. Had Muller been advertising his concerns in the Soviet Union he would have found a better reception. The political climate for postwar Soviet biology was engineered towards suspicion of genetics as a path pursued for its own sake, rather than the contributions it could offer. Lysenkoists also exploited public fears of X-rays and mutation to portray genetics as perverse and un-natural. But Muller's efforts in the U.S. to explain Soviet prejudice towards genetics as the product of state interference in science, along with his warnings on radiation, met with rejection.

Muller's career constitutes an important case study in the history of mutation and genetics for both these reasons. He tried to have it all — a society which appreciated the opportunities and dangers genetics offered, which would also be willing to trust scientists to manage the outcome. Muller clearly over-estimated what was possible. It would be easy to pin blame on non-specialists who presumed more than they knew. As Muller's biographer pointed out, biology is different from a science like physics in that people are less inclined to accept that they don't really understand it. Evolution and human development too-frequently overlap into social issues like racism and class-prejudice to be left to the judgment of experts. Nevertheless, many of Muller's colleagues also rejected his ideas on radiation, as well as his approach to "debunking" Lysenko. A history of genes and mutation absent this understanding cannot account for the treacherous landscape biologists covered as they moved genetics forward in the second half of the twentieth century.

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## *Tools*



## *Mutations in the Nuclear Age*

*Soraya de Chadarevian*

As the organizers of this workshop remind us, the search, identification and uses of mutants and the production and explanation of mutations have been at the heart of the new science of genetics in the 20th century and had an impact far beyond it. It could perhaps even be claimed that the production of mutants, next to the production of pure lines, stood at the beginning of the new science of genetics. We will surely analyze these claims — as well as the different political contexts in which mutations came to matter in the first half of the century — during the workshop.

My talk will deal with the changing meaning of mutations in the atomic age. That radiation could produce disease and mutations was known at least since the tragic case of the radium dial painters (even before then by the victims of X-ray applications) and Hermann Muller's work on the mutational effects of X-rays in *Drosophila* in the 1920s. Yet that the mutational effects of radiation would become a dominant political, societal and scientific concern of the mid-20th century could hardly have been predicted. With the proliferation of the uses of ionizing radiation and the invention of new tools to track its mutational effects also the meaning of mutation changed.

I will suggest that one tool played a particularly important role in changing the understanding of mutations: this is human chromosome analysis or karyotyping. Human cytogenetics, I will argue, crystallized as a new field at the intersection of deep political, military, medical and scientific concerns variously connected to the widespread use of radiation in the battlefield, the industrial setting, the test ground and the clinic. The global reach of these effects became increasingly clear in the 1950s and 1960s. The broad use of cytogenetic techniques propelled the expansion of genetic approaches into new areas such as cancer research, pediatrics, toxicology and criminology — changing the understanding of mutations and where they mattered. Following the use of cytogenetic techniques can thus help us locating the place and meaning of mutations in the atomic age.

Cytogenetics was not the only tool for tracking mutations in the 1950s and 1960s. Traditional crossing experiments — although not applicable to humans — were performed on a large scale to assess the effects of radiation in other organisms (see below). Also, just around the time when human karyotyping techniques started to become feasible, molecular biologists linked changes in amino acid sequences of proteins to mutations on the DNA level.<sup>1</sup> From the 1960s, electrophoresis, protein finger printing and, eventually, protein sequencing were widely used for identifying protein variants, for diagnostic purposes (e.g. for identifying sickle cell hemoglobin), for genetic studies of populations and for building evolutionary trees. DNA sequencing itself, of course, was still unattainable.

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<sup>1</sup> I am referring here to Vernon Ingram's work in 1956 and 1957 that indicated that the hemoglobin of patients with sickle cell anemia, an inherited disease, differed in one single amino acid from normal hemoglobin (Ingram 1956). Mutations played a central role both as object and tool of research in the early history of molecular genetics. Not by chance Crick and Watson stressed the fact that their model offered a molecular explanation for mutational events (Watson and Crick 1953, p. 966). Mutants, mutations and mutagens played a crucial role in establishing protein-DNA relationships and the basic features as well as the universal character of the genetic code. An important example is Crick and Brenner's experiments with acridine mutants that established the triplet structure of the genetic code.

Yet all these studies — besides being an indirect proof of mutations on the DNA level — used few markers to track mutations or looked at mutations in one particular protein while chromosome analysis, at least in principle, offered a glimpse of the complete genetic make up of an individual. It thus promised to offer a much more comprehensive and powerful method to track mutations. Concerns about the effects of radiation in the nuclear age focused on humans with far-reaching political and social implications. Human karyotyping provided the tool to track the effects of radiation (and chemical mutagens) in every single cell — often before the potentially damaging effect became apparent. It thus contributed to a new disseminated meaning of mutation to which humans were constantly and otherwise invisibly exposed.

In the following I will flesh out this argument by, firstly, briefly highlighting the concerns about the mutational effects of radiation in the post-Hiroshima era. I will then discuss the efforts invested into visualizing mutations, including the development of human karyotyping, and follow the ever-expanding use of the new technology for tracking mutations, in cancer research, in the clinic and in the population as a whole. I will conclude with some remarks on the connection of radiation, mutation and karyotyping.

### *Hiroshima and the Study of Mutations*

The mutational effect of radiation literally exploded as an issue with the dropping of the two atomic bombs on the populated cities of Hiroshima and Nagasaki that marked the end of WW II. As several historians have now argued, the atomic bomb was conceived as a super-explosive rather than an atomic weapon, yet the radiation effects of the two bombs dropped on Japan on the surviving population quickly became a medical, diplomatic and political problem of vast dimensions — further complicated by the postwar development and testing of atomic weapons and the expanding civil uses of atomic energy.<sup>2</sup>

Susan Lindee has described how the genetic or mutational effects of the bomb moved center stage in the work of the Atomic Bomb Casualty Commission (ABCC). Apparently this was due to a large extent because of the interest of the leading scientist on the American team, James Neel. The ABCC based its first assessment of the genetic effects of the atomic bombings on such indicators as the rates of stillbirths, sex ratio, congenital anomalies, infant mortality, bodily dimensions and life span in the children of the survivors. All these factors were seen as related to the mutational effects of radiation. Lindee has discussed the problems with these indicators and the way in which the choice reflected political and social concerns. Mutation, she argued, was defined as a “dangerous, threatening, or socially disturbing trait with implications for future human survival” (Lindee 1994, 192). The studies based on these parameters were declared as “inconclusive,” opening up the way for further investigations into the mutational effects of radiation (Neel and Schull 1956, p. 204). The survivors of the atomic attacks in Japan would remain a test population for a long series of new studies and approaches. Meanwhile the publication of reassuring reports on the health of Japanese children served to pacify alarms on the deleterious effects of atomic radiation in the population that had suffered an atomic attack as well as among Americans back home.

Also a concern from the beginning and intensively studied were the somatic, cancer inducing effects of the bomb. Little was known about the actual mechanisms by which radiation

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<sup>2</sup> On the bomb’s conception as a super-explosive rather than a radioactive weapon see Gordin (2007); on the diplomatic and political effects of the bomb see Beatty (1991).

acted on organisms, but somatic effects (showing up during the life time of people exposed to radiation) and genetic effects (due to mutations in the reproductive cells and showing up in the next generation) were treated as separate effects. This separation would eventually break down, contributing to a vastly expanded meaning of mutation and its connected risks.

### *Visualizing Mutations: Crossing Experiments and Human Chromosome Research*

The decision by the American, British, French and Russian governments to pursue the development of atomic energy for military and civilian uses was accompanied by vast new programs for radiobiological research. Radiobiological research centers were established in close proximity to nuclear energy research and development sites such as the Atomic Energy Research Establishment at Harwell in the UK and Oak Ridge, the uranium enrichment site of the Manhattan Project. At Harwell the brief of the radiobiological unit was, “to investigate the toxic actions of radioactive substances and to develop methods of protecting workers against them.” (This was before the fallout debate that raised concerns about the effects of radiation not just on the workers handling radioactive materials but on the population at large.)<sup>3</sup>

An important program, pursued both at Harwell and Oak Ridge, was the long-term low-dose irradiation of vast populations of mice to establish safe limits for radiation exposure.<sup>4</sup> The method used for these experiments consisted in classic crossing experiments using the multiple recessive method or single locus test. The first step consisted in developing a stock of mice that was homozygous for several recessive mutations that could be easily identified and thus allowed for quick scanning. Seven mutations were chosen, including characteristics such as brown coat, short ears and pink eyes. In the experiments sperm from irradiated wild-type male mice was used to fertilize females carrying two doses of a recessive mutant gene. If irradiation had produced mutation in the male, the offspring would show the mutation. If no mutation occurred, the offspring would appear as the wild type.

Despite large investments in the question of the long-term effects of low-dose radiation the answer remained elusive, but the question persisted. Irradiation experiments at Harwell — using increasingly sophisticated irradiation regimes — continued well into the 1990s. Yet concerns about the genetic effects of radiation stimulated parallel efforts to visualize mutations on the chromosomal level. At Harwell this aim was pursued in the cytogenetics division under Charles E. Ford.

Chromosomes had long been an active area of genetic research. In the 1920s Theophilus S. Painter, working in the same department as Hermann Muller in Texas, had established that humans have 48 chromosomes; the count was confirmed by other researchers. However, human chromosomes, as chromosomes from animal cells more generally, were difficult to work with. The giant salivary gland chromosomes of *Drosophila* represented an exception. For the rest, most research on chromosomes was performed on plant cells — because of the ease to work with that material but possibly also in view of its potential use for plant breeding (see for instance the use of colchicine in karyotyping and for achieving polyploidy in plants<sup>5</sup>).

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<sup>3</sup> E. Mellanby to A. Barlow, 27 September 1946, FDI 468, National Archives, Kew (UK).

<sup>4</sup> On the mice experiments at Harwell and Oak Ridge see de Chadarevian (2006) and Rader (2004) respectively.

<sup>5</sup> See Helen Anne Curry, “Making Marigolds: Colchicine, Mutation Breeding, and Ornamental

After WWII, widespread efforts to establish the effects of radiation in humans provided new incentives to develop methods to study human chromosomes. The career of Ford who became one of the key players in the establishment of human cytogenetics is paradigmatic here and serves to illustrate the changed opportunities. A trained botanist, Ford moved to the Radiobiological Research Unit at Harwell in 1949 after having spent three years at the Department of Atomic Energy at Chalk River in Canada, where he had studied the biological hazards of radiation using plant material for his experiments. Once at Harwell, Ford and his collaborators set out to develop the technologies to study radiation-damaged chromosomes in mammalian cells.

Advances in chromosome preparation at the time depended on a combination of new techniques. These included: development of tissue culture; the use of colchicine to arrest cell division in the metaphase; the use of hypotonic medium; and squash techniques to spread the chromosomes. Ford's contribution consisted in further developing the squash technique and in adapting the whole set of techniques to work with the most difficult of tissues such as the testis and bone marrow that were crucial for genetic research. His technical skills allowed Ford in 1956 to be the first to confirm new observations published in the same year by Joe-Hin Tijo and Albert Levan from the University of Lund that indicated that the number of human chromosomes was 46 and not 48. The Swedish group had made their observation on cultured cells of lung tissue of aborted foetuses which were available to the Swedish researchers following the new abortion law in their country. Ford's use of fresh tissue of human testis, supplied to him by an Oxford surgeon, eliminated any speculation regarding the general applicability of the new chromosome count (Tijo and Levan 1956; Ford and Hamerton 1956).

### *Mutation and Cancer*

Levan's and Tijo's interest lay in establishing the chromosomal changes in cancer cells rather than studying radiation damage. That cancer cells showed abnormal chromosome pictures had been known since the time of Theodor Boveri at the turn of the century, but accurate description had been difficult and it remained unclear if the observed chromosome abnormalities, including increased numbers of chromosomes, breakages and re-arrangements, were the cause or rather the effect of cancer and therefore an epiphenomenon. Improved techniques in human karyotyping, especially the use of hypotonic medium by Hsu in 1952, provided new incentives to take up the question. The accurate description of the chromosome complement in healthy tissues undertaken by Levan and Tijo was meant to serve as a standard against which to compare and study cancer cells.

The study of carcinogenesis remained an important area of chromosome research, yet by the mid-1950s radiobiological and cancer research had become deeply intertwined. This was especially true in respect to leukemia research. Many researchers working in the cancer field came from radiation research and many radiobiologists became engaged in cancer research. Similarly, much of the funding in cancer chromosome research came from sources funding radiation research at a time when the induction of cancer through the ever expanding clinical use of radiation and through the effects of radioactive fallout became a growing concern of the nuclear age.<sup>6</sup> Also many

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Horticulture, 1937–1950," this volume.

<sup>6</sup> Note here the chronology of events: in 1954 the Bikini test raised concerns over the biological effects of world-wide fallout from atomic testing; in 1956 the US and UK governments issued reports which raised the alarm on the rising cases of cancer through the clinical use of radiation; in 1956 the number of

of the techniques developed for human karyotyping were originally devised to study the chromosomes of patients or experimental animals with radiation-induced leukemia. This is true for both the bone marrow method developed by Ford and Patricia Jacobs at Harwell and for the peripheral blood method developed by David A. Hungerford and his colleagues in the USA, that became the standard approach to karyotyping. By offering a less intrusive method to gain human tissue for karyotyping, the peripheral blood method opened the way for chromosome analysis to be performed on a much larger scale, in the clinic and on the population level.

Significantly, among the first observations that linked particular karyotypes to known clinical syndromes in the mid-to late 1950s, was the discovery of an unusually small chromosome in the marrow cells of patients with a specific form of leukemia known as chronic myeloid leukemia. The chromosome became known as the “Philadelphia chromosome.” This observation, that linked a specific cancer to a specific chromosome abnormality, gave support to the thesis that cancer originated from one mutated cell that proliferated. Peter Nowell who, together with Hungerford, made the observation, came to the Philadelphia School of Medicine after a stint in the Navy where he had studied radiation carcinogenesis and bone marrow transplantation. Nowell and Hungerford’s work opened the way for the use of karyotyping in the study of other carcinogenic substances besides radiation and, more generally, for the field of cancer genetics. Cancer development and congenital diseases could all be studied with the same karyotyping techniques.

### *Karyotyping and the Clinic*

Next to the Philadelphia chromosome other unusual chromosome pictures were found to be associated with specific congenital syndromes in fast succession in the late 1950s. These findings concerned especially sex-chromosome linked anomalies like in the case of patients with Turner and Klinefelter Syndrome that were identified as having an XO and XXY karyotype respectively, and the association of “mongolism” with an extra chromosome 21 (later to be identified as chromosome 22). All these studies were initiated by clinicians who had become interested in human genetics. They provided the relevant tissues from patients in their clinics as well as their clinical knowledge of the cases.<sup>7</sup> In turn, karyotyping found direct application in the clinic.

The possibility to trace complex clinical syndromes to a change in shape or number of chromosomes that was detectable under the microscope much impressed clinicians at the time. The British human geneticist Lionel Penrose famously found “the photograph of the cell from the man with two extra chromosomes from which the intelligence level, the behaviour and sexual character can be confidently predicted, just about as astonishing as a photograph of the back of the moon.”<sup>8</sup> Theodore Puck, one of the pioneers of cytogenetics in the US with an active interest in

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human chromosomes was revised and improved protocols for human karyotyping became available.

<sup>7</sup> Ford was approached by Paul Polani, a physician at Guy’s hospital, who had for a while been studying women patients with Turner syndrome and had come to believe that they might only have one X chromosome - as was confirmed by Ford. Polani as well as Lazlo G. Lajtha, a haematologist at Churchill Hospital in Oxford, also supplied Ford with tissue from Klinefelter patients. Jacobs who bet Ford at establishing the Klinefelter case, collaborated with a local physician, John A. Strong. Following the results of the Klinefelter case, Penrose provided Ford with the bone-marrow cells of a Klinefelter’s Down patient. Yet before either Jacobs or Ford concluded their investigation, it became known that Jérôme Lejeune in Paris had observed an additional chromosome in Down patients.

<sup>8</sup> Penrose in 1959 as quoted in Kevles 1985, p. 248. Penrose most likely referred to a Klinefelter-Down Syndrome patient in his care.

radiobiological questions, also highlighted the novelty of the findings and the corresponding notions of mutation and disease, while at the same time making a strong link to the radiation context. He wrote:

The current value of the maximum allowable dose was adopted in 1959. Since then we have become aware of a whole new group of human diseases which appear to be capable of being induced by radiation but whose importance and indeed very existence was unknown at the time the currently employed standards were adopted. These diseases constitute the genetic diseases due to chromosomal aberrations ... This set of diseases is so costly to man and to society that a re-examination of the permissible dose of radiation for large populations must be carried out as soon as possible.<sup>9</sup>

The initial euphoria of some of the early practitioners about the diagnostic power of the new tool was tempered by contradictory observations as for instance the case of a Down patient with 46 chromosomes.<sup>10</sup> The more precise characterization and standardization of the human karyotype achieved in the early 1960s, helped resolving some but not all disputes. Nonetheless, with the establishment of amniocentesis and the passing of abortion laws — in the UK legislation was passed in 1967 — karyotyping became routine practice in pre-natal screening. In the late 1960s new chromosome banding technologies significantly increased the resolving power of cytogenetics and with it the scope of the technique in clinical diagnosis and modern reproductive medicine.

The new connections between mutations on the chromosomal level and complex disease patterns in the late 1950s were won through the study of single cases. Large-scale population studies undertaken with the new technology further extended the scope of karyotyping and with it the meaning of chromosomal mutations.

### *Population Studies*

Karyotyping was not only used in clinical diagnosis but also for large-scale epidemiological studies, especially after the development of the new technique that made it possible to analyze chromosomes in blood. In Britain this project was most enthusiastically embraced by Edinburgh medical researcher William M. Court Brown.

Court Brown's career is of interest here as it once more marks the connection between radiation research, cancer research and karyotyping. Court Brown started off as a radiologist with an interest in the acute effects of radiation. He then embarked on a gigantic study aimed at establishing the cases of leukemia among patients treated with radiation for ankylosing spondylitis, an arthritic condition. The study included follow-up studies of 14,000 patients that had been treated for the condition between 1935-1954 at 82 radiotherapy centers throughout the UK. 73 radiotherapists and 45 other colleagues helped extracting and analyzing the data and the whole task required "military-like planning" (Smith 2007, p. B6). A preliminary report appeared in the 1956 White paper (Court Brown and Doll 1956). It was followed up by a more rigorous statistical analysis of the data with the London statistician Richard Doll (Court Brown and Doll 1957). The

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<sup>9</sup> T. Puck, Why low-level human radiation damage is difficult to assess, but dangerous to ignore [undated]; uncatalogued file box, Theodore T. Puck Collection, University of Denver Penrose Library Special Collections, Denver, CO. I thank Daniella Perry for pointing me to this document.

<sup>10</sup> See Maria Jesus Santesmases, "Size and the Centromere: Translocations and Visual Cultures in Early Human Genetics," this volume.

data showed a dramatic rise in leukemia cases following radiation treatment. Together with the survivor studies in Japan this was the most important study to establish the carcinogenic effect of low doses of ionizing radiation.

Following his leukemia study Court Brown very quickly picked up the new cytogenetic techniques that were just being developed. His primary aim was to study the mechanism of the cancer-inducing effects of radiation. Court Brown also traveled to Japan to study the incidence of leukemia in the survivors and tried to convince the ABCC to engage in a large-scale cytogenetic study. By that time Court Brown was heading the MRC Unit for Research on the Clinical Effects of Radiation at the Western General Hospital in Edinburgh. The unit later changed its name to MRC Clinical and Population Cytogenetics Unit to better reflect the work the group was engaged in.

From the study of leukemia patients Court Brown initiated an expanding series of studies aimed at investigating the chromosomal constitution of the general population, at correlating specific karyotypes with particular clinical and phenotypical characteristics and at investigating the chromosome damaging effects of various agents, including ionizing radiation that represented the original point of departure and remained a constant thread of his work.

In this context the new born screening programme performed at the Western General Hospital in Edinburgh was of special importance as it served to establish the frequency of abnormalities in the general population and as point of comparison for “normal population.” The long-term aim was to correlate the abnormalities with parental age, social class, and ethnicity and thus to study the causes of the anomalies. In addition, the new born screening was aimed at identifying the individuals that might need special attention and to provide data for genetic counseling.

The screening revealed an unexpected large number of chromosomal abnormalities or — as was now more carefully stated — genetic variance. Findings indicated that about 1% of children showed a chromosome anomaly in their mitotic cells. One quarter of these regarded a sex chromosome anomaly; one quarter showed other kinds of trisomies, with the majority being “mongols”; the rest showed detectable structural rearrangements. This quite certainly represented an underestimate of the chromosomal anomalies present in the general population because of the various difficulties connected to visualizing chromosomal mutations.<sup>11</sup>

Other populations that the unit studied included inmates of institutions for the mentally retarded; infertile males; subjects exposed to ionising radiation such as cancer patients, industrial workers, people involved in the refueling of depleted uranium, people exposed at the Windscale accident; and people exposed to other toxic substances like aromatic hydrocarbons, herbicides and pesticides. The latter studies dovetailed with the equally new field of chemical mutagenesis and with incipient ecological concerns.

Furor was caused in 1966 by the finding of an increased frequency of XYY males in two English State hospitals for patients who required special security because of persistently violent or aggressive behavior. However, further investigations quickly revealed that XYY males that did not show any particular behavior were also found in the general population. More generally, the population surveys revealed that in addition to the few gross chromosomal differences that were associated with specific congenital characteristics a whole range of variation existed in human chromosomes that did not show any visible effect on the phenotypic level.

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<sup>11</sup> W. M. Court Brown, Contributions of human cytogenetics to clinical medicine, MRC 67/357 - CR 67/26, 16 March 1967, p. 2; FD 9/1281, National Archives, Kew, UK.

To deal with the ever increasing scope of karyotyping Court Brown early on saw the need to harness computers to help with the task. The hope was that computers would not only help with speeding up the work and alleviate some of its tediousness, but also that computerized micro-densitometric method could be applied to find aberrations that could not be observed with the light microscope (the method would quasi “weigh” chromosomes rather than measure them). Work on the automation project was started in the Pattern Recognition Group under Dennis Rutovitz in London in 1966 (that is when it got going seriously) and eventually moved up to Edinburgh. Rutovitz’s group built on the work of Robert Ledley of the National Biomedical Research Foundation in Bethesda who pioneered the use of electronic computers in biomedical research and, among many other things, had developed a “Film Input to Digital Automatic Computer” (FIDAC), which automated the analysis of chromosomes. Yet Rutovitz group quickly decided that film scanner was not practical and that it was necessary to work directly down the microscope rather than from photographs. Although the computerization project always lagged behind the needs of the expansive karyotyping projects, eventually Rutovitz’s group built its own self-contained interactive system with a screen-based editor that it commercialized successfully.<sup>12</sup>

Court Brown’s unit was not the only one involved in population karyotyping. From the late 1950s, the WHO supported large-scale genetic surveys of newborn babies across various continents as well as genetic studies of “primitive” or “vanishing populations.” Initially, most of these studies were based on the analysis of developmental malformation and on the study of variants and frequencies of hemoglobins or other serum proteins. They also included pedigree analysis and consanguinity studies. Yet from the 1960s karyotyping found increasingly its place among the tools deployed in these surveys that linked anthropological approaches with genetic and public health issues. The interest of the WHO in human genetics and in karyotyping stemmed from the same public health concerns on the mutational effects of radiation to which patients and the population at large were exposed in the atomic age, and expanded from there. Recognizing the usefulness of karyotyping techniques for tracking mutations, the WHO organized regular widely attended cytogenetic courses from the late 1950s.

### *Radiation, Mutation and Karyotyping — Concluding Remarks*

Human cytogenetics came to the fore in the context of, and itself fueled, raising concerns on the effects of radiation on humans after Hiroshima. The new techniques of karyotyping helped to track mutations as well as to study the mechanism by which radiation acted on the genetic material. Chromosome banding techniques provided a wealth of new information on mutations at the chromosomal level. Although karyotyping could not provide a molecular explanation of the mechanism of mutation, it made mutations visible and opened them up to direct inspection and statistical analysis. Population surveys revealed common patterns but also much more variation than expected. The fallout debate in the mid-1950s moved attention from genetic to somatic risks of radiation exposure, but karyotyping techniques — developed at exactly that time — revealed a biological connection between the two effects, blurring the boundaries between what, until then, seemed two neatly separated phenomena.

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<sup>12</sup> For more details on the computing project see de Chadarevian (forthcoming).

Karyotyping mapped the mutational effects of radiation. Following the shadow of radiation and other damaging factors it revealed an ubiquitous and dispersed presence of mutations, inscribing itself into the fabric of the nuclear world while at the same time fuelling the expansion of postwar human and medical genetics. Five decades on, genome sequencing seems to follow many of the same trails as karyotyping yet the concerns in the post-Cold War era lie with ancestry testing, history, medicine and commercial products rather than with radiation politics and nuclear strategies.

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*Size and the Centromere:  
Translocations and Visual Cultures in Early Human Genetics*

*María Jesús Santesmas*

Visual reports were both basic input and output in early human cytogenetics. By the early 1960s, a given person could be described in the clinic on the basis of her or his set of chromosomes and the narrative, which correlated her or his body features with those chromosomes. Those images of chromosomes and of the physical, anatomical description of a person made visual reports the main source of knowledge production for early human genetics. Images of chromosomes combined with that of the person they belonged to and this combination claimed an epistemological status; that is, images carried knowledge as such and articulated a whole narrative of visual evidences that became the bases upon which human genetics was constructed in the clinic.

This paper is about the origins of a term: translocation. This term was introduced in the early stages of clinical genetics to explain a lack of correlation between a physical feature — that of a Down syndrome girl — and the number of chromosomes: 46 instead of the expected 47 already assigned to this anomaly. Translocation referred to a chromosome rearrangement during cell division, exchanges between chromosome arms, as if one chromosome breaks up and each piece moves to other chromosomes and becomes part of them, or as if two chromosomes interchange pieces. The term spread rapidly and was used at early stages of genetics in the clinic.

In order to understand what kind of practices brought about this idea of chromosome rearrangements that might take place during cell division, I present earlier uses of the term and its images so as to show an early biography of the concept of translocation in genetics and cytology.<sup>1</sup>

Rearrangements or movements of chromosome pieces have their own genealogy. It can be traced back to early works on genetics and cytogenetics. I would like to present here a history of early genetics, from plants to humans, which is a history of images involved in the early biography of the term “translocation.” It is a history of chromosome diagrams, either drawn or photomicrographed. This means that genetics, a way of thinking about heredity, expectations in hereditary patterns and their deviations or mutations, has a history of images whose visualisation is at the very core of the origins of human cytology and cytogenetics. This reconstruction shows cytology’s genealogy itself, as well.

The term “translocation” is used here as a guideline to articulate a historical account of the ancestries of human genetics, of the knowledge held and the connections made between what was observed by the naked eye and what the microscope revealed to a trained eye. In the first part I will deal with the first uses of the concept of translocation in human cytology in 1960. In the second part, the previous uses of this concept in *Drosophila* and in maize are described to account for the origins and genealogy of the term. In both human cytology and *Drosophila* and maize genetics, images were basic supports for and main objects of knowledge; they carried practices and cultures. This led me to suggest that genetics at that time was articulated around visual cultures; around images as objects of knowledge.

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<sup>1</sup> On distinctions between genetics and cytology from the geneticist’s point of view in the 1920s, when both fields seemed somehow separated, genetics related to population calculations and physical, anatomical characterisation, see Carlson 1981, pp. 151-155.

## *Human Cytogenetics at Early Stages*

In 1959, Paul Polani, from the Paediatric Research Unit at Guy's Hospital in London, and Charles Ford, from the Medical Research Council Radiobiology Unit at Harwell, were involved in cytogenetic studies on Down syndrome. Polani was born in Trieste when it was part of the Austro-Hungarian empire. He studied medicine in Siena and Pisa and went to Britain in 1939. After his studies on the aetiology of congenital heart disease in the 1950s, in 1960 he was appointed director of a new paediatric research unit at Guy's Hospital, which became one of the first medical genetics centres in Britain<sup>2</sup>. Charles Ford had obtained his PhD for work on the cytogenetics of the flowering plant, *Oenothera*, and after studying the biological hazard of radiation on the roots of the broad bean, *Vicia faba*, during WWII at the Department of Atomic Energy at Chalk River (Canada) for the British Ministry of Supply, in 1949 he was appointed head of the cytogenetics section of the British Atomic Energy Research Establishment (AERE) in Harwell.<sup>3</sup> By the mid-1950s, they had started to work together on cases of infertility found by Polani in the clinic, which were cytologically characterised jointly with Ford.

In 1956, the number of human somatic chromosomes was established as 46, after Joe Hin Tjio and Albert Levan published a paper in which they suggested that, from their experience, the previous number, 48, was not accurate (Tjio and Levan 1956). The number was soon confirmed by Ford and Hamerton (Ford and Hamerton 1956). Once the technique of making the chromosomes visible and, by showing the separated chromosomes on the slide, countable, had been described,, studies on human chromosomes developed.<sup>4</sup>

In March 1959, Jerome Lejeune, Marthe Gauthier and Raymond Turpin from Paris reported that Down syndrome children under their study had one chromosome too many, when counted on samples of their bone marrow, compared with the number of human chromosomes given by Joe Hin Tjio and Albert Levan in 1956. The “neuf enfants mongoliens”, whose karyotypes — the set of images of chromosomes identified by their size, shape and the distance from the end of the arms to the centromere — were reported by Lejeune, Gauthier and Turpin, had 47 chromosomes instead of 46 (Lejeune, Turpin and Gauthier 1960). From then on, and after this was confirmed by the French group and others, human geneticists accepted 47 as the chromosome number in Down syndrome.<sup>5</sup>

In 1960, Polani and Briggs from Guy's Hospital, Ford and Clarke from Harwell and Berg from London, not only jointly confirmed the case of Down syndrome with an extra chromosome but, with three collaborators, identified a “mongol girl with 46 chromosomes”, that is, with the same number of chromosomes as if she was not a “mongol” person. This so thought unusual number for Down syndrome was carefully analysed by the team (Polani et al. 1960).

This girl, born in December 1949, was diagnosed neonatally as “a mongol.” The pregnancy was characterised as uneventful and the family had no history of mental defects. The clinical research team that studied the case worked with samples of bone-marrow suspensions from three “mongol” patients. The samples were sent to Harwell for investigation and, among them, one offered results of the unusual case of 46. Radiation and its effects, which had been studied since the report published by Herman Muller (1927) on the artificial changes in *Drosophila* genes produced

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<sup>2</sup> On Polani, see Harper 2007 and also Kevles 1985, pp. 242-246.

<sup>3</sup> On Ford, see Lyon 2001. On Harwell and genetics, see de Chadarevian 2006 and Gowing 1974.

<sup>4</sup> On human chromosome counting until late 1956, see Kottler 1974; Martin 2004.

<sup>5</sup> See Gaudillière 2000 and 2001.

by X-rays, were a concern: the mother was described as having been repeatedly X-rayed during pregnancy (Polani et al. 1960: 721). Ford himself had experience on the subject (Lyon 2001).

Identification of each chromosome pair was “difficult” but the clinical diagnosis in this case was “undoubted.” The extra chromosome, they suggested, was hidden; divided into two parts. Each was attached to other chromosomes. As the size of two of them was unusual, they suggested that the extra chromosome was made up of a large portion of chromosome 15 (as one of them was unusually large) and the expected additional chromosome 22 (also, in this case, larger than expected). The “most likely interpretation” was that an unequal reciprocal translocation had taken place. The long arm of the expected Down syndrome chromosome was in chromosome 15 and the short arm was in chromosome 22, which also appears to be larger than normal<sup>6</sup>. This explanation provided a correlation between the accepted extra chromosome of Lejeune, Thurpin and Gauthier and the Down syndrome anatomy of the girl. The extra chromosome was considered by Polani et al. (1960, p. 723) to be “the chromosome material necessary for the expression of mongolism.” All this led them to suggest a hereditary factor in Down syndrome occurrence.<sup>7</sup>

For them, the reference was what they call “neonatal diagnosis”: she had been diagnosed as a mongol child. The photograph of the girl showed that she had the usual Down syndrome appearance: a flat face, roundish cheeks, small nose and some other signs which were described by J. Langdon Down (1866). In this particular case, the photograph of the girl and the diagrams showing the number and shapes of her chromosomes established a dialogue; they talked to each other. By doing so, the face was reinforced by the karyotype and led to the possibility of one talking for the other. The face and the chromosome diagrams were representations of Down syndrome that carried comparable epistemic status. Both were images of the same life and of the same genetic diagnosis.

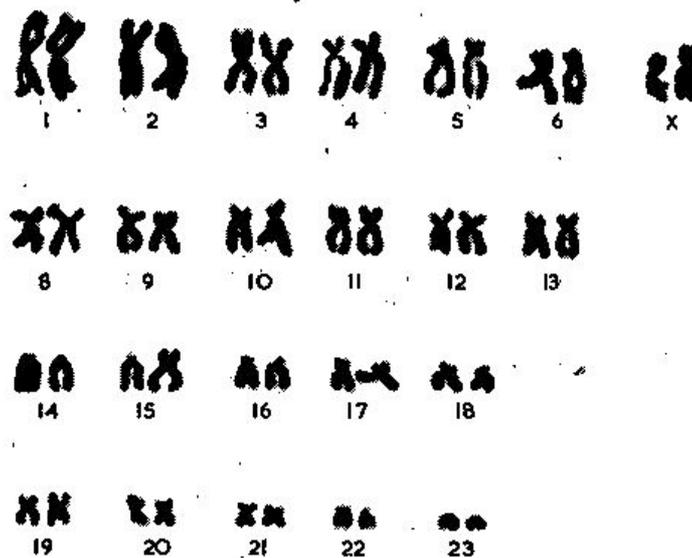


Fig. 1: Polani et al. 1960, p. 722.

<sup>6</sup> Harper’s (2007) obituary of Polani suggests that this contributed to generate interest in chromosome analysis for genetic counselling, despite the small number of cases observed.

<sup>7</sup> Kevles 1985, p. 248, Harper 2007; Polani et al. 1960.

The ideogram shown in Figure 1 was constructed from the photomicrography of the slide in which chromosomes were identified. Each chromosome was cut out and stuck back together, arranged by size. This practice became a standard way of making so-called ideograms. It was the ideogram of chromosomes, their images, their shape and their number, which should correlate to the photography and to the anatomy of the child. The counting led to 46, as if she were a normal girl, and the case was undoubted, and so the idea of translocation was introduced and became a reasoning path towards a correlation with the anatomical diagnosis.

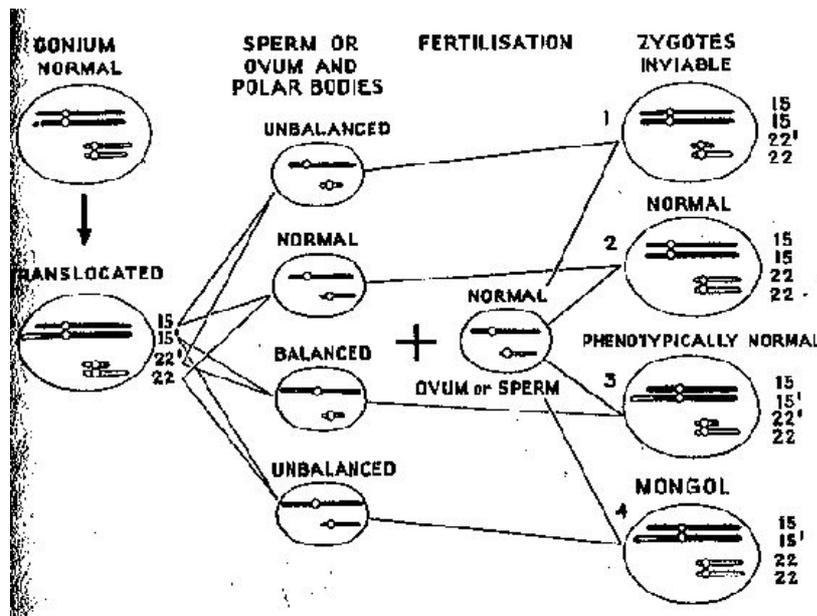


Fig. 2: Polani et al. 1960, p. 723.

In figure 2 Polani et al. explained the process figured out by the authors through which the translocation might have led in this case to a Down syndrome anomaly. The proposed translocation carried the possibility that it might have been inherited: an individual might have had it and be phenotypically normal but in his or her progeny the extra chromosome associated with Down syndrome might be “translocated” or rearranged, i.e. broken up, divided in two parts, one of which will be attached to two different chromosomes.

### *In Search of Genealogy*

Some months later the same year, a group led by Cedric Oswald Carter from the Clinical Genetics Unit at the Institute of Child Health in London, in which Polani and Hamerton were also included, reported a case of translocation in Down syndrome, this time characterised by the authors as “familial mongolism” (Carter et al. 1960). They studied the chromosomes of a Down syndrome child born in 1949 who was a patient at the Hospital for Sick Children in London, and those of some of her relatives, to find out who from among them carried the translocation. With the results, the authors traced a genealogy of the case. The samples came from peripheral blood, whereas in the

previous case it came from a bone marrow sample. Being much easier to take and less painful, blood samples contributed to this wider exploration of the case, and so cytological evidence provided the basis for the construction of the family pedigree. The pedigree, shown in figure 3, allowed them to advise parents of the risk that they might have a second mongol child and detect relatives who themselves had a high risk of being carriers.

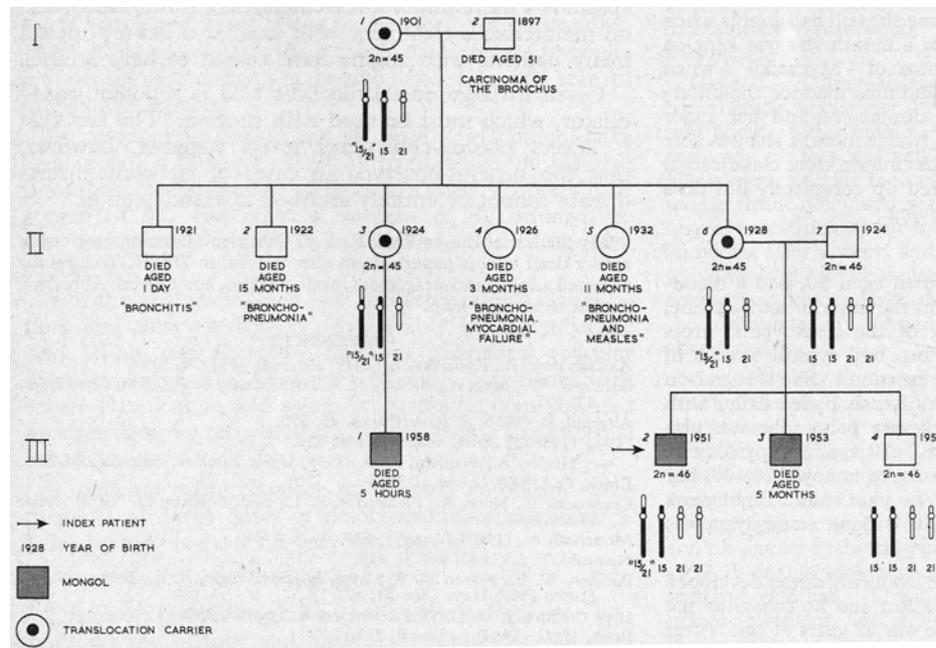


Fig. 3: Carter et al. 1960, p. 678.

The paper shows the karyotype of the patient and that of the persons who were identified as translocation carriers: the mother, the maternal aunt and the grandmother. It reported that two Down syndrome babies had also been born in the same family and had died shortly after birth. According to the authors, the translocation, which came from the grandmother, was “responsible for the mongolism in three of her grandchildren, and possibly one or more of her children.” For constructing the karyotypes, the Denver diagram, in use from April 1960 onwards, was used as a reference.<sup>8</sup> As can be seen, it was very hard for an untrained eye to identify a translocated chromosome. Very slight differences were detected, so slight that they needed careful analysis that included comparing a subgroup of chromosomes, pairs number 6 to 12, and the translocated 15/21, as that showed and it is reproduced in Figure 4. Those karyotypes were so identified with the help of the anatomy and the clinical diagnosis of the anomaly. Anatomy appeared to remain a reference for further characterisation at chromosome level.

<sup>8</sup> A meeting was held in Denver and was attended by Ford, Hsu, Levan, Puck, Tjio and a few of the other 14 scientists involved in human karyotyping at that time. In that meeting, they reached an agreement on the design of a chromosome diagram on the basis of the data available (Lindee 2004).

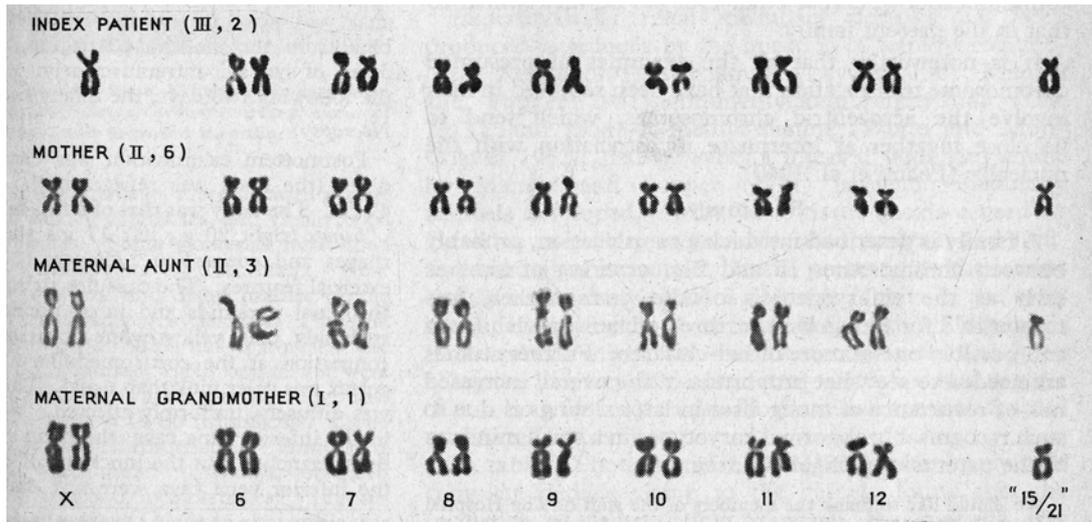


Fig. 4: Carter et al. 1960, p. 679.

This group of Down syndrome patients born to younger mothers had been observed previously by Lionel Penrose at the Galton Institute, at a time when Penrose was generally considered to have become a leader and a strong inspiration for the development of human genetics in Britain, and more specifically for Polani's research and interests (Harper 2007).

The identification of this translocation suggests that hereditary factors, and not only heredity exceptions, might play a part in the cytogenetics of babies born with Down syndrome, thus contributing to further development of genetic counselling based on the probabilities of couples who carried translocation or who already had a Down syndrome child having future children with this disorder<sup>9</sup>.

As Polani et al. (1960, p. 723) stated, reciprocal translocations were well known in other species. Plant and *Drosophila* geneticists had detected such rearrangements. Translocation was a concept borrowed from *Drosophila* and plant geneticists. They had shown translocated chromosomes and had correlated those rearranged chromosomes with gene maps in *Drosophila* and with features in maize and other plants. Practices and objects of cytology and genetics were condensed in images, in photomicrographs and in camera lucida drawings, setting the basis for ways of thinking in genetics and of manufacturing knowledge by constructing visual cultures.

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<sup>9</sup> This identification of the lack of an extra chromosome in a person diagnosed with Down syndrome led to a more complex cytology of Down syndrome diagnosis. It may well be considered to be one of the bases upon which cytology came to be regarded as a more accurate method for diagnosing Down syndrome than clinical observation by expert physicians, even if dermatoglyphics was considered accurate, too. See also Kevles 1985.

## From *Drosophila* and Maize

Translocation is a concept found in studies on *Drosophila* genetics and on plants, among others, maize, from the late 1910s onwards. Maize, or Indian corn, has been the subject of research in agronomy stations in the US and the biography of maize as an experimental system in cytology practices is associated with Barbara McClintock (Fox Keller 1984, Barahona 1996, Comfort 2001, Kass and Boneuil 2004). *Drosophila* geneticists from the research group at Columbia University (New York) also contributed to the development of this concept. This means that the idea of translocation came from early cytology in plants and the fruit fly as a way of reasoning that established a correlation between what was observed in the plant crops or in the fly and what was observed in chromosomes.<sup>10</sup>

The chromosomes of *Drosophila* (early on called *ampelophila* and from some point on called *melanogaster*) were first described and drawn by Nettie Stevens (1908), as drosophilists used to mention. In a paper in which this woman cytogeneticist identified the chromosomes of a wide set of flies and midges of the genus *Diptera*, among the four plates of chromosome drawings, twenty seven figures showed *Drosophila* chromosomes at different stages of cell division. Four of them are reproduced in figure 5. Following a detailed procedure for preparing the slide, images of chromosomes were “camera drawings”, and since then, unless otherwise said, chromosome images of *Drosophila*, as well as of other species, were taken using this method.

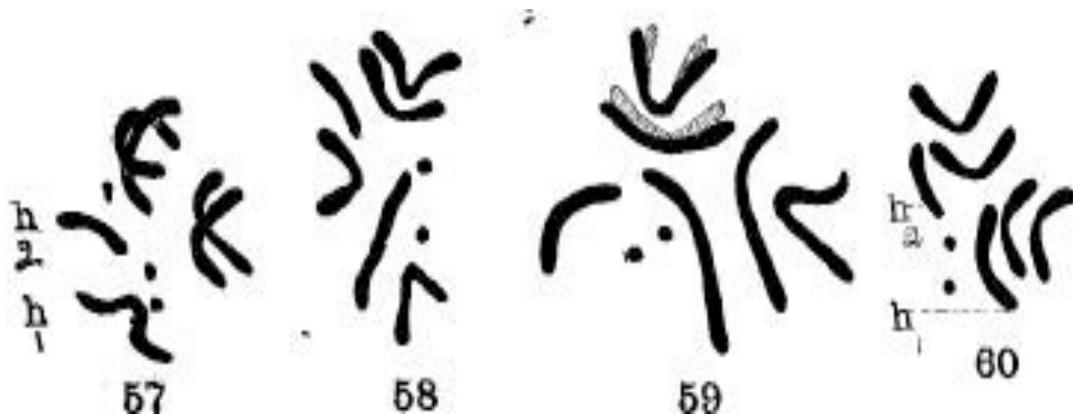


Fig. 5: Stevens 1908, from Plate III.

Later on, in 1916, Calvin Bridges from Columbia University gave a nice schematic version that was also included in *The Mechanism of Medelian Heredity* (1972, p. 7) reproduced in figure 6. This paper, followed by a second one published the same year, was presented at Columbia University as his doctoral thesis (Morgan 1940).

<sup>10</sup> On *Drosophila* and its role in history of genetics and biology, see Allen and Kohler.

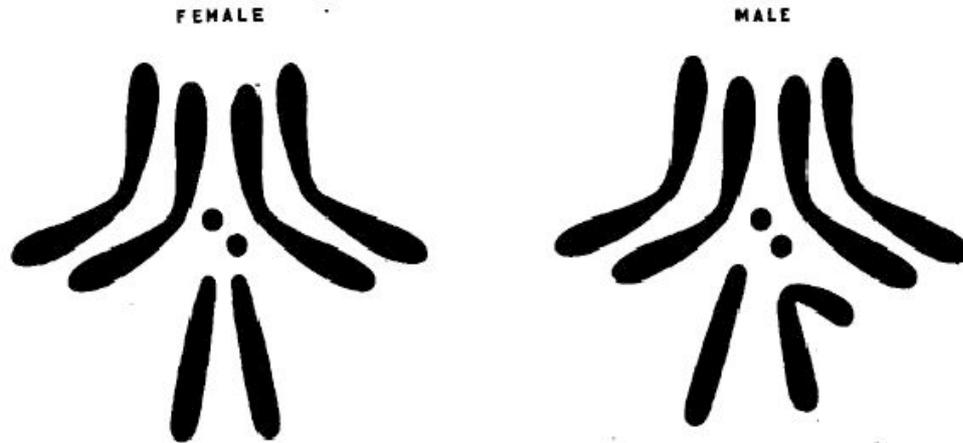


Fig. 6: Bridges 1916, p. 7.

From then on, many *Drosophila* chromosomes were drawn so as to show particularities of a fly or a given line. The images of chromosomes, like other materials from *Drosophila* cultures and practices, kept Morgan, Sturtevant, Muller and Bridges as references. When Lilian Morgan (1922) drew chromosomes, the references of those drawn by Bridges (1916) allowed her to correlate her images with her analysis of the genetic “behaviour” of this line. From their early stages, both cytological practices and images of chromosomes created references and standards. Those standards were put into dialogue with new images and new mutated exemplars. Figure 7 shows three of Lilian Morgan’s drawings in which her double-yellow females g and h are presented next to i, the wild type drawn “after Bridges” (Morgan 1922, p. 273), so as to show the thicker shape of the double X chromosome she was studying, whose two parts were inseparable.



Fig. 7: Morgan 1922, p. 273.

On the basis of Nettie Stevens’ chromosomes, the fly group at Columbia drew *Drosophila* chromosomes, although they are better known for their earlier success in making genetic maps. In order to develop further skills in correlating chromosomes and genes, a few cytologists began to collaborate or even compete (according to Kohler 1994), with cytologists such as T. S. Painter and Theodosius Dobzhanski (Carlson 1981, p. 155). Obtaining good chromosome preparations provided evidence

of what Sturtevant and Muller had inferred regarding translocations. The order of genes in the map represented the order of sequences of those genes in the chromosomes.

This history of images shows that “chromosome” was a biological term associated with images. And it was by means of images that translocation was defined, characterised and researched. “Translocation” as a term appeared to have been suggested for the first time by Calvin B. Bridges in a paper published early in the 1920s, where he gave the “interpretation that [chromosome] PII is a broken-off end of the second chromosome and PIII is the second chromosome from which this end has been broken” to explain the behaviour of a *Drosophila* eye-colour mutant, Pale (Bridges 1923).<sup>11</sup> Later reconstruction by drosophilists included that of Sturtevant in 1921, in which he detected that three identical loci were not in the same sequences in two different species. This led him to suggest that a change of sequence had taken place in the same chromosome and this explained the “accident” of the occurrence of a “deficiency” because of the move to another part of the chromosome, different from that already known (Sturtevant 1921). Translocations were unusual and at that point they were described in genetic maps.

During the 1920s, X-rays were used to induce mutations in plants and the fly to check for Mendelian behaviour and chromosomal features. Muller’s evidences of the artificial transmutation of the gene by X-rays in *Drosophila* (Muller 1927) included studies of rearrangements in the linear order of the genes and of pieces of chromosomes. By means of this method of irradiating the fly, translocations came to be extensively studied. X-rays became a source of mutations and contributed to promote research on *Drosophila* genetics and mutations.<sup>12</sup>

In 1929, Dobzhansky reviewed “chromosomal aberrations” in *Drosophila*. He qualified translocations as aberrations which involved parts of chromosomes instead of the whole chromosome. To study these cases, the production of them by action of X-ray radiation became the research tool (Carlson 1981). Dobzhansky regarded translocation as “specially valuable” for their study because it produced changes in the “genetical behaviour” of some characters and visible alterations in the chromosomes. These radiated products provided information on the role of chromosomes in the transmission of characters in *Drosophila* (Dobzhansky 1929, 347).

The frequency of spontaneous translocations was low, but increased “considerably” when flies were treated with X-rays, so he followed the method suggested by Muller and looked for artificial translocations. In his many drawings, such as the ones reproduced in figure 8, Dobzhansky showed cases in which some chromosomes were absent, like the small absent dot pair represented in 34 and 35, apparently substituted by a larger-sized pair.

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<sup>11</sup> This was part of the mapping project of Sturtevant and Bridges (see Kohler 1994).

<sup>12</sup> Albert Blakeslee showed in 1927 the chromosomes of a jimsonweed mutant he called Nubbin, which was produced by “radium emanation” and had an extra chromosome (Blakeslee 1927). I thank Luis Campos for calling my attention to Blakeslee’s contribution to chromosome images and mutated chromosomes produced by radiation. On Blakeslee and the concepts of mutation, see Campos 2008.

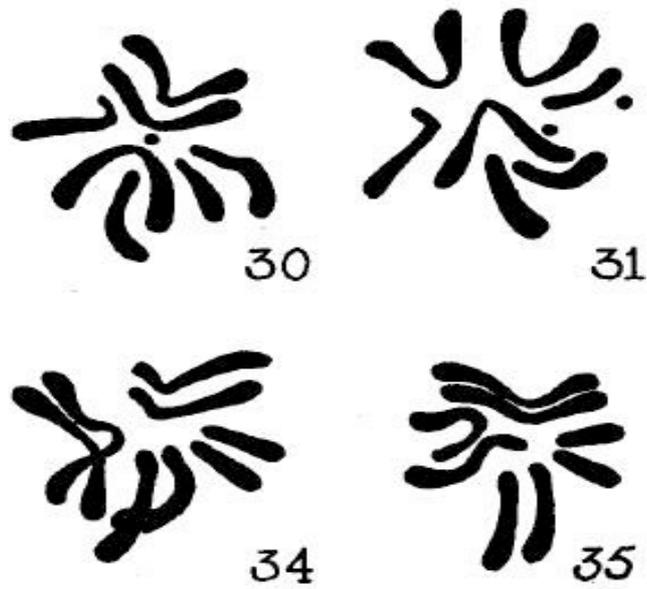


Fig. 8: Dobzhansky 1930, p. 362 Plate I.

In practices which at that time were also becoming stabilised, Dobzhansky included a diagram to show the concept of translocation.

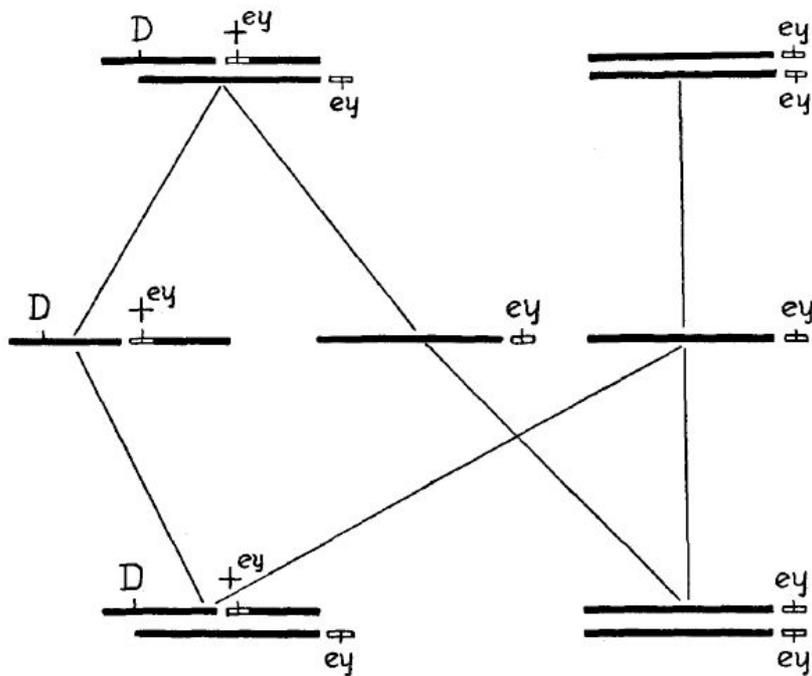


Fig. 9: Dobzhansky 1930, p. 355.

The collaboration between Muller and University of Texas cytologist T. S. Painter resulted in reports of their joint work from 1929 onwards, in which maps stood side by side with chromosomes. Painter's cytological skills provided a detailed figure of the X chromosome and their joint practices became conclusive evidence of the chromosome theory of heredity (Carlson 1981; Satzinger 2005 and 2008).

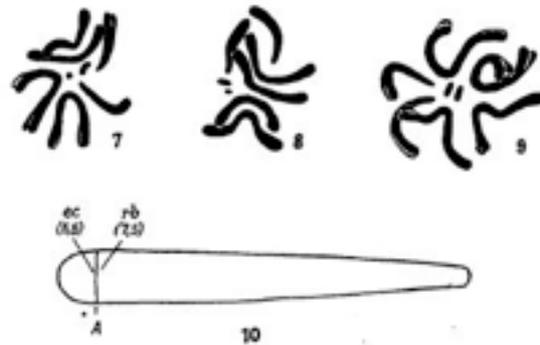


Fig. 10: Muller/ Painter 1932, p. 326.

As Morgan (1940, p. 39) stated, Muller and Painter laid the basis for correlating certain genetic translocations with images of chromosomes like the ones shown in figure 10, in which the smaller pair could be seen to have one chromosome larger than the other (7 and 8). Below these translocated sets of chromosomes, the X chromosome was drawn in a shape that was, by then, becoming recognised as standard, thus suggesting that visual cultures in *Drosophila* genetics and chromosome images were stabilised as genetic objects.<sup>13</sup>

Diagrams combined with chromosome drawings with the aid of the camera lucida. The same year, Muller and Altenburg also addressed the issue of X-ray induced translocation. The evidence was that Muller's X-ray experiments produced numerous changes in gene alignment, as well as translocations. This prompted them to conduct experiments with *Drosophila* to determine translocation frequencies as a "result of exposure to short wave-length radiation." They showed a diagram of combinations produced by normal and translocated chromosomes, one of them is reproduced in figure 11.

<sup>13</sup> Morgan (1940, p. 39) put it very much in this way although he did not mention *images* of chromosomes, but only chromosomes.

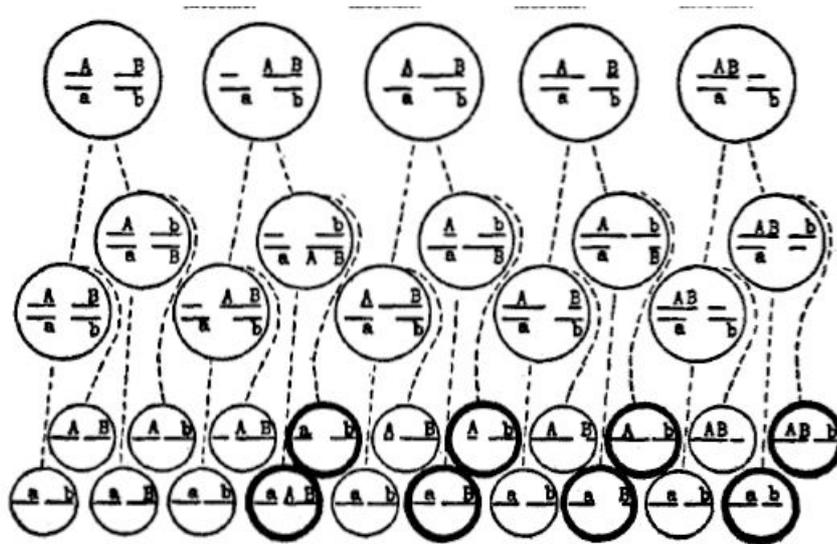


Fig. 11: Muller/Altenburg 1930, p. 285.

In the meantime, a first diagram of maize chromosomes was reported by McClintock (1929) (also Comfort 2001, p. 51; Kass and Bonneuil 2004, p. 105). It was a “representation of the haploid set” composed of ten chromosomes, as she saw them in the “first division in the microspore where only the haploid complement is present.”

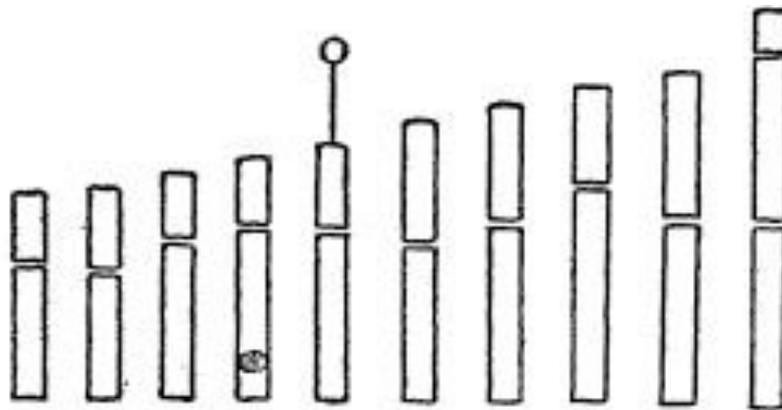


Fig. 12: McClintock 1929, p. 629.

Later on, McClintock (1930) posed and answered the question regarding whether semisterility in maize was related to the occurrence of a simple translocation or a reciprocal one. She showed an unequal interchange, both by drawing the case with the aid of the camera lucida and as a diagram. This combination, based on images, that is to say, the visual evidence, was the result of her research. The image of the interchange shown in figure 13 exhibits clear portions of each chromosome sharing some pieces in a particular shape.

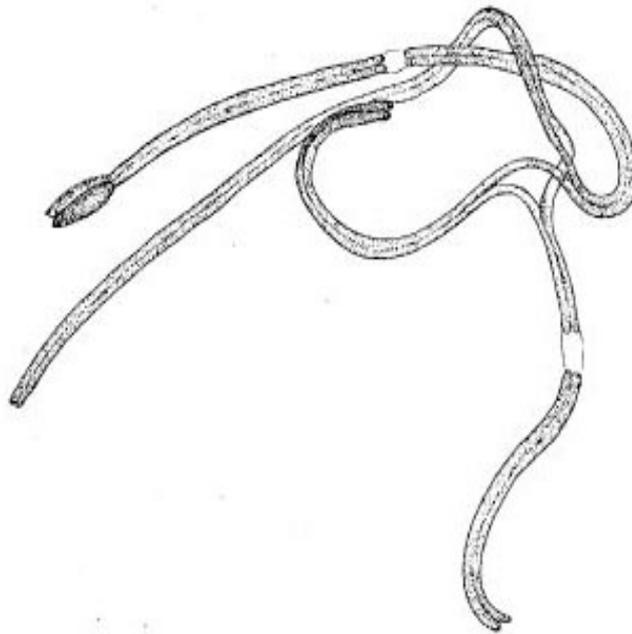


Fig. 13: McClintock 1930, p. 792.

On the next page she made a diagram to make her vision of the phenomenon even clearer: normal components appear ready to interchange segments of the chromosomes with a pair which was already an interchange. Note the straight lines and right angles of figure 14 compared with the circular shape of the camera lucida drawing in figure 13, as if straight idealisation may make knowledge of such images far more evident.

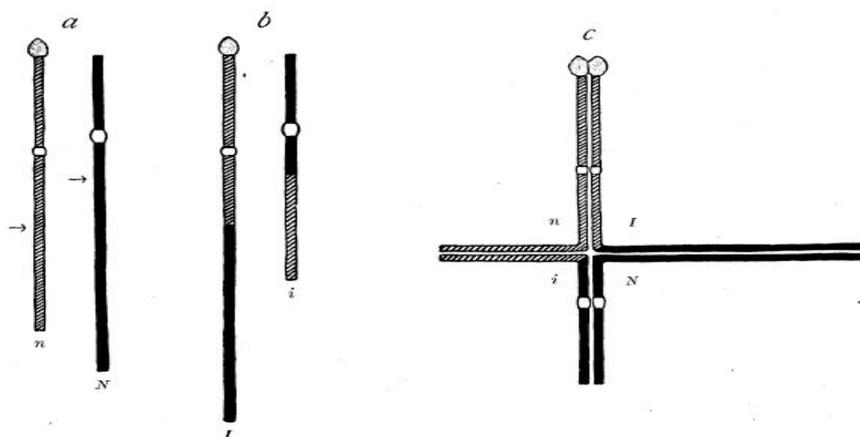


Fig. 14: McClintock 1930, p. 793.

In 1931, she showed segmental interchanges in a diagram from two normal chromosomes. The diagram suggests the way in which these rearrangements took place. Her trained eye (as Nathan Comfort put it) led her to “present evidence indicating the serial order” of some given genes (McClintock 1931). Her diagrammatic and visual culture was part of her way of working, producing images once and again that alluded to each other, as she did for one of her next papers, one of which is reproduce in figure 15.

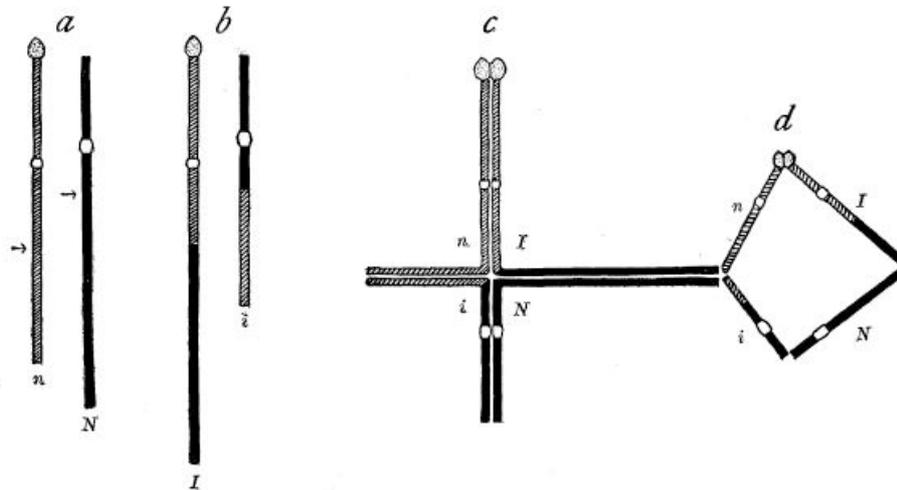


Fig. 15: McClintock 1931, p. 486.

The powers of microscopy had been at the core of natural knowledge and natural history for centuries. McClintock appeared to have relied on them and on her trained eye to see maize chromosomes and draw them, so as to offer correlations between the crop’s colours, shapes, and fertility features, on the one hand, and chromosome sizes and shapes, on the other. The reference was not only a known point in the chromosome which may serve as a reference, but the forms and colours she observed herself in the field or greenhouse. Her skills as a cytologist, very often celebrated, were related to her powerful sensibility for new forms and shapes and her ability to correlate images which crossed and rearranged themselves in unknown ways.

It can be seen that McClintock’s and Dobzhansky’s diagrams fitted early diagrams of human chromosomes, on one hand, and human translocation diagrams, on the other. They would also fit later proposals regarding translocation in the case of the “mongol girl” with 46 chromosomes made by Polani, Ford et al.<sup>14</sup>

Deficiencies in the fly had a correlation with chromosomes: Bridges correlated “diminished” individuals with the loss of an entire chromosome, one chromosome instead of a pair (Bridges 1921). For drosophilists, a gene meant a piece of chromosome to which a character was assigned by observing a correlation, once the chromosome theory of heredity was accepted in the practice of drawing them beside gene maps.

<sup>14</sup> In 1961, human cytogeneticists called on their colleagues to recognise misleading connotations in the term ‘mongol’ and suggested Down anomaly or Down syndrome instead (Allen et al. 1961).

The succession of images shows the extent to which plant and *Drosophila* genetics inspired early human genetics. Colchicines as a mitosis promoter and the plant cytology practices used when searching to see human chromosomes became a useful task; as did image-making. Image trajectories suggest cultures, visual cultures, or even cultures of making visual, of making images in order to make genetics reliable to an audience-in-progress.

As Morgan said when praising Bridges' work:

As early as 1919 Bridges described "duplication" as a chromosomal aberration, and here, as in his other work, his conclusions rested not on vague hypotheses but on experimental proof. Much later he also reported the occurrence of "repeats" in the normal chromosome which will have to be seriously considered in future interpretations of certain types of genetic behaviour.

In the first edition of her popular book *Genetics in the Atomic Age*, Charlotte Auerbach (1956) from the Institute of Animal Genetics in Edinburgh, UK, where Muller himself worked by the late 1930s (Carlson 1981, pp. 244-257) also mentioned translocation as "an exchange of pieces between broken chromosomes", that "may involve any two chromosomes, whether there are partners or not, and the exchanged pieces may be of different lengths." She went on to explain how these accidents affect the cell and the developing embryo. She was dealing, as Muller and Dobzhansky were in the publications mentioned above, with radiation-induced mutations (Auerbach 1956, pp. 78-79).

These ways of reasoning, involving translocation induced by radiation, suggest the close connection between genetics practices and radiation practices, and led Soraya de Chadarevian (2006) to suggest that the increasing role of genetics in contemporary research and practices, and the biological knowledge associated with it, has developed due to the support given after WWII to research into radiation and how it affected cells and animals.

This was precisely the subject of Charles Ford's research in Harwell, at the radiobiology unit that the MRC had set up there. While working on *Oenothera*, Ford himself identified several chromosome translocations that resulted in ring structures, called catenations (Ford and Gates 1938). He had begun his career as a plant cytogeneticist and his experience in both plant cytogenetics and radiation biology formed part of the knowledge which contributed to the interpretation of the cytology of the Down syndrome case with 46 chromosomes, by giving translocation as an explanation for the lack of the extra chromosome that Lejeune, Thurpin and Gauthier had assigned to Down syndrome.

The ideograms remained a reference. The length of each chromosome in the human set and its centromere position were significant data to make them correlate to anatomy (remember the photograph of the girl). There was a lineage of images of chromosomes in this suggested correlation by Polani, Ford and their collaborators at Guy's Hospital and at Harwell.

Images not only rested on drawings, diagrams and photographs. Descriptions of shapes, sizes and locus also constructed images and correlations of images, i.e. in *Drosophila* the "Peach eye" type and the chromosome mapping. It is significant, however, how the production and reproduction of images offer a lineage of visual knowledge, in the case of human cytogenetics associated with photographs of the faces of the people to whom the chromosomes belonged, and how this type of correlations come from earlier ones made for flies and plants.

This close association of images became so useful that in 1962 Hamerton and Polani recommended “that patients with Down’s syndrome found to have normal chromosome complement should be fully and extensively documented from the clinical and cytological viewpoints, so as to enable readers to assess their significance and implications” (Hamerton and Polani 1962) That significance and those implications embedded genetic knowledge in images, in visual representations that themselves might provide evidences. This image-making carried some of the most influential practices in human genetics, shown by following the term “translocation” from *Drosophila* and maize to inherited Down syndrome.

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## *Tracing Mutations: Biodosimetry Tools in Post-Cold War Radiation Epidemiology*

Susanne Bauer

In February 2002, mutation effects of fallout due to Soviet nuclear weapons testing featured prominently in scientific journals: the news section in *Science* covered the story “DNA Mutations Linked to Soviet bomb tests” (Stone 2002). This was related to a research article “Nuclear Weapons Tests and Human Germline Mutation” (Dubrova et al. 2002) that reported the detection of mutations as evidence of past and possibly on-going exposure and effects. Local radiation effects in exposed populations were surveyed in terms of alterations of the chromosome structure — for instance minisatellite mutations, increased rates of somatic mutations, and chromosome aberrations (Dubrova et al. 1996, 2002; Alipov et al. 1999). In much of cytogenetic monitoring and population studies, “mutation” has been broadly conceived in terms of “any heritable change in the structure of the genetic material” (Hook 1978, 485). In some areas exposed to radiation in the former Soviet Union, radiation biology developed into a burgeoning research field; this became possible with changes in the political conditions, the availability of genomics tools and with specific funding slots<sup>1</sup> for scientific collaborations on assessing the legacies of the Soviet nuclear program.

With respect to the implementation of broader scientific and compensation programs, preliminary studies on mutations conducted in 1989 were instrumental (Sevankaev 1995; Balmukhanov 2002). Mutations were a key argument when local scientists called for more international attention to Semipalatinsk — both in terms of humanitarian aid and further radiobiological investigation of the relationship between radiation and cancer, for example. For western radiation biologists, the situation of past — and largely unstudied — exposures in the former Soviet Union brought about the “unique opportunity” to derive direct risk estimates from data for a human population exposed to multiple radiation doses due to fallout; this was of interest since these new empirical data could add to current radiation risk knowledge (Burkart 1996). Such regulations on radiation protection and occupational threshold values had been based on extrapolations from the high external dose studies in the atomic bomb survivors of Hiroshima and Nagasaki. In the US context, it was argued that “findings are relevant to the current debate over how to protect people from chronic low-dose radiation near some of the DOE sites that represent the U.S.’s nuclear legacy” (Stone 2002, 946).

Hence, mutations detected at increased frequencies among exposed populations in the vicinity of Soviet nuclear facilities were able to mobilize international resources, concern and specific funding slots for radiobiological and epidemiological studies. In epidemiological risk assessment, mutation frequencies were used as validation tools for dose estimates calculated with other methods. In the course of some projects, the research focus shifted from the investigation and management of effects toward scrutinizing the evidence of radiation exposure, using mutations as *in-vivo* tools for biodosimetry.

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<sup>1</sup> Funding was provided for instance from the European Commission in specific programs for collaborations with New Independent States. In Southern Urals, major funds came also from the US Department of Energy (DOE) and National Cancer Institute (NCI).

In what follows I will explore the role of mutation research for risk assessment in post-Cold War radiation biology, in particular for research on areas adjacent to the Semipalatinsk test site. The Semipalatinsk nuclear test site was officially closed in 1991, the year of the independence of Kazakhstan.<sup>2</sup> My material includes published research papers on fallout exposure, dosimetry and radiation epidemiology as well as documents and observations related to projects funded by the European Commission. This paper describes how mutations developed into tools to measure cumulative radiation doses in post-Cold War radiation epidemiology.

### *Cytogenetic Monitoring: Radiation-induced Mutations in Human Cells*

In the Soviet Union, classic human cytogenetics was established in the 1960s as a research field and developed throughout the 1970s and 1980s. Experimental studies of radiation effects were conducted in the laboratory, where human lymphocyte cultures were irradiated in vitro.

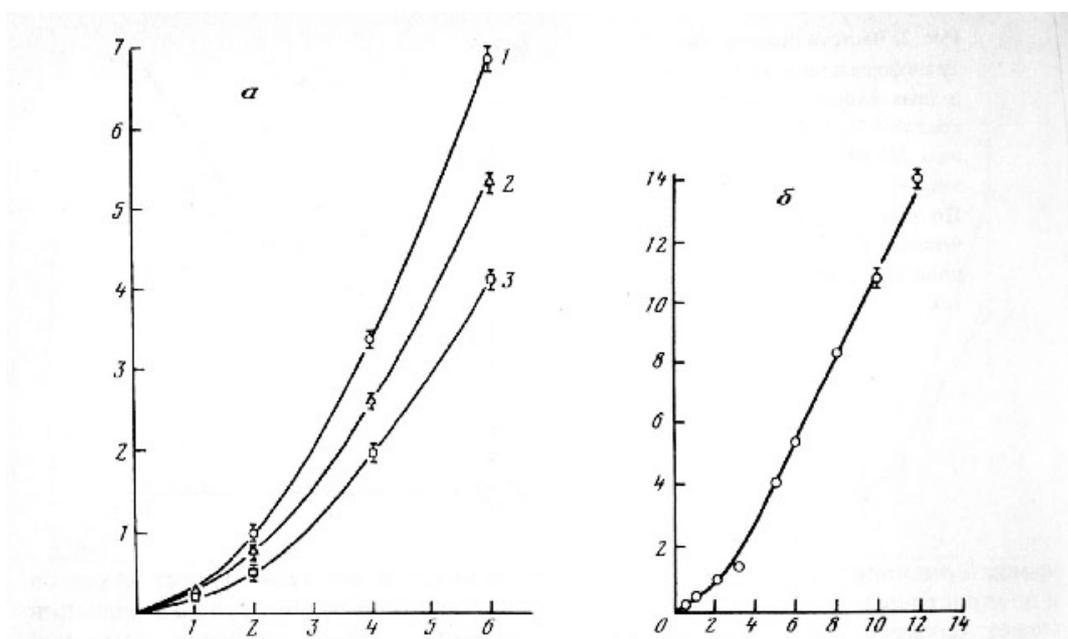


Fig. 1: Studies of radiation effects in the laboratory: chromosome aberration in human lymphocytes after in-vitro irradiation at different doses and dose rates, Sevankaev 1991, p. 609.

<sup>2</sup> At the test site near Semipalatinsk, more than 110 atmospheric nuclear weapons tests and hundreds of underground tests had been carried out between 1949 and 1989. An end to nuclear testing has been one of the issues around which the movements for independence were formed in the late 1980s.

In these laboratory experiments with human cell cultures, increases of chromosomal aberrations after irradiation at defined doses and different dose rates were observed and quantified. Dose-effect curves were visualized and regularities for dose-response relationships identified (Luchnik & Sevankaev 1976; Sevan'kaev 1991).

Studying human mutation rates in relation to environmental agents in human populations had not only been discussed in Soviet biology since the 1970s, but broadly discussed in western science as well; this holds also for various concepts of cytogenetic monitoring of the population:

At a first glance the surveillance of populations for individuals with chromosome aberrations may seem a somewhat crude method for detecting of an environmental agent capable of producing genetic damage. However, further consideration shows that chromosomes are not quite the blunt instrument they first appear (Jacobs 1978, p. 463).

With respect to mutations, a distinction was made between germinal cell mutations (understood as changing the entire organism with a direct contribution to morbidity and mortality), and somatic mutations (in malignancies, and with aging). Both were of interest to cytogenetic studies. In the radiation biology of the 1970s, there was a discussion about whether there should be a comprehensive “mutagen monitoring system” at the population level to examine spontaneous abortions. Envisioned applications of mutation analysis ranged from plans to monitor germline mutation rates for environmental effects as well as for congenital conditions and Down's syndrome and to examine somatic mutations as a means of monitoring the effects of environmental agents. Germline mutation rates were also put in evolutionary perspectives; it was discussed, for instance, whether it was desirable to halt mutation entirely or whether there was a degree of mutation necessary for the benefits of human variation. In general it was assumed that zero was the optimal mutation rate; “should it be discovered that a small positive mutation rate is preferable, society can quickly make the adjustments with agents readily available” (Hook 1978, 484). While many of these remained speculative propositions, some fields of occupational health, *e.g.* for nuclear workers, conducted surveys of chromosomal changes for cases of occupational exposure.

Scoring chromosome aberrations in peripheral blood lymphocytes became routine in monitoring nuclear workers and radiotherapy patients in the Soviet Union (Bochkow 1993). Cytogenetic monitoring played a role in medical monitoring of radiation workers of the plutonium production site Mayak in Southern Urals as well. Cytogenetic techniques were also used when examining “liquidators” (clean-up workers) after the Chernobyl accident.

With the end of the Cold War, the legacies of the nuclear program — including nuclear weapons testing near Semipalatinsk — were gradually made accessible to local and international assessments. In 1989 the Soviet Ministry of Health issued a study that included cytogenetic methods when evaluating effects of nuclear tests: 98 persons were recruited locally for the study, including students of the Medical University departments who had moved to Semipalatinsk recently, students and faculty born and living in Semipalatinsk, employees of an institute for radiation effects, and inhabitants of four different rural settlements close to the test site (Sevan'kaev et al. 1995). Cytogenetic analyses of blood samples were performed at the research centre in Obninsk near Moscow; analyses included chromosomal aberrations — dicentrics and monocentric rings, anomalous monocentrics, pair fragments, dots in acentric rings- [and] chromatid aberrations (deletions, iso-deletions and exchanges) (Sevan'kaev et al. 1995). The highest frequencies of chromosome aberrations were reported for people living in villages near the test site; increases in

mortality rates in exposed villages and the presence of alpha-emitting radionuclides in soil samples were also described (Sevan'kaev et al. 1995; Balmukhanov et al. 2002).

These results were drawn upon by the government of Kazakhstan when asking for international assistance in the assessment and management of the nuclear legacy. The call for assistance to the UN led to a debate over Semipalatinsk in the UN General Assembly and, in 1998, to a resolution which enabled allocation of funds for research and mitigation activities in the Semipalatinsk area. Subsequently, international agencies such as the World Health Organization (WHO) launched further missions and research projects. Thus, radiation-induced chromosomal change played a key role, when it came to the issue of dose estimation and evidence for the actual exposure. For epidemiological assessments common for institutions such as WHO, reliable dose estimates were crucial to estimate effects and the issue of dosimetry moved to centre stage in on-going collaborative projects.

### *Mutations as Markers Between Effect and Dose*

While international research was initiated in the early 1990s,<sup>3</sup> local scientists in Kazakhstan and the Russian Federation had also established their own investigations into the health effects of nuclear testing, as more data had become accessible. Local exposure assessments included measurement of radionuclide concentrations in soil samples and fallout deposition modeling. Based on first dose reconstructions, different “zones of radiation risk”, as they were termed for the Semipalatinsk region, were assigned. These provided an orientation in the sampling of study groups for cytogenetic assessments. A review of local epidemiological studies listed chromosome alterations as radiation-induced health outcomes — together with data for cancer, congenital conditions and Down's syndrome (Rozenon et al. 1996; Gusev 1998). In the context of early local studies, chromosome aberrations were understood as clinical outcomes in terms of health effects — along with paragraphs on cancer incidence and mortality, endocrine, circulatory, respiratory, digestive, genitourinary, nervous systems disease (summarized as “non-cancer disease”), infant mortality and congenital anomalies, blood pressure, and effects on hemopoiesis. In the review, the results on chromosome aberrations were reported as part of the section “Epidemiological and clinical studies” (Rozenon et al. 1996, p. 132).

In residents exposed to 80cSv chromosomal aberrations were encountered in 73.7 % of the investigated persons. The percentage of aberrant cells per individual ranged from 2 to 7%. In this exposed group, too, the frequency of chromosomal aberration, percentage of aberrant cells per individual, number of pair fragments and dicentrics were significantly higher as compared to the control (Rozenon et al. 1996, pp. 139-140).

Thus, the phenomenon of chromosome aberrations was worked with as a clinical measure of a health effect. When investigating cytogenetic alterations as a biological effect on tissue, the radiation dose was assumed to be known, while the health consequences — chromosome aberrations —

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<sup>3</sup> Beyond local studies, the effects of exposure due to nuclear accidents and nuclear testing were investigated by first international collaborations in the 1990s. US-NIH, in particular NCI, provided funding for studies in the southern Urals region, the plutonium workers at the Mayak nuclear facilities and exposed populations in adjacent villages. Bilateral research programs from the Japanese government were initiated in Kazakhstan in the early 1990s.

were the outcomes to be investigated. This was the case for many early studies conducted in the 1990s in Kazakhstan and in the Altai region, where cytogenetic studies were initiated to corroborate somatic differences between exposed and unexposed groups of the population (Shevchenko et al. 1995). Likewise, the National Centre for Reproductive Health based in Almaty performed cytogenetic studies among the population living in areas exposed to fallout from nuclear testing since the early 1990s:

A cytogenetic study was conducted for the first time on human populations neighboring the Semipalatinsk nuclear test site and exposed to radiation for a long period of time. The spectrum of chromosomal aberrations and the frequencies of the aberrations of different types in persons living in the areas with the highest radionuclide contamination confirmed the mutagenic effect of radiation on chromosomes in the human populations studied (Sviatova et al. 2002, p. 376).

The research goal formulated here was whether the given radiation exposure had caused, among other clinical effects, detectable mutations. In contrast, the goals of some first EU projects included above all “to verify the hypothesis of existing contamination” (Testa et al. 2000, p. 126). Core aims of some of the joint projects showed a slight but significant shift: cytogenetic analyses were conducted to investigate whether or not the true radiation exposure exceeded certain threshold levels. This research used classic cytogenetics for a first appraisal of the presence of an exposure; it was established that the applied classic cytogenetics would not necessarily be sensitive to exposures of the past: in the case of the Goiania accident in Brazil — where a cesium-137 source left behind in an abandoned hospital had caused heavy exposure to 250 people in 1987 — these types of reversible aberrations had not been detectable even after less than 6 months. Still, the analysis of dicentric chromosomes was considered suitable to detect “hallmarks of exposure to ionizing radiation” (Testa et al. 2000, p. 128) — despite the uncertainty with respect to their persistence over time. While some elevated rates among examined individuals from exposed areas were found, no clear dose-response was detected that would be seen as evidence for an exposure effect.

While in the radiation biology of the 1970s, population monitoring had been discussed in terms of evolutionary population genetics, the methods of cytogenetics in this case became part of applied investigations into health effects in the population. For radiation risk research, the use of mutations, however, also took on a different direction. Much collaborative research moved from a focus on clinical effects toward assessing doses and began investigating whether exposures of the populations were “real” as a first step. Here, chromosome aberrations and mutations came to function as measurement tools for biodosimetry.

### *Candidates for Exposure Assessment: Mutations as Biodosimetry Tools*

For the non-uniform multiple exposures due to nuclear test fallout in Semipalatinsk, dose estimations were subject to sustained controversy: the exposure assessment by official authorities in the Russian Federation boards were lower than those given by their counterparts in Kazakhstan. The research situation was difficult: When the test site was closed down in 1991, most archive materials and technical documents were taken to the Russian Federation, where many remained classified. Additionally, the fact that the results obtained by different methods of dose reconstruction differed substantially gave rise to further uncertainty: mathematical modeling of fallout deposition led to

much higher dose estimations than dose reconstructions with other methods, e.g. thermoluminescence techniques (which measure the radiation-induced signal change upon heating of this material using bricks or ceramics to reconstruct external dose). Therefore, Semipalatinsk was often viewed as a test case for biological dosimetry; i.e. as a site where validation using biodosimetric methods was expected to narrow down uncertain dose estimates. The development of biodosimetric tools can be followed along a chronology of radiation exposures and accidents in Goiania, Chernobyl, the Mayak production site and Techa river in Southern Urals, Totsk and Semipalatinsk. To radiation biologists, each of these sites provided specific kinds of research opportunities, i.e. to study the effects of acute or chronic exposures, of different radiation qualities and internal and external irradiation directly in human populations. During the 1990s with the availability of genomics techniques, new methods and markers were introduced into the field of mutation research and cytogenetics. A key requirement for test systems for biodosimetry was the presence of a dose-effect curve that allowed relating the measured signal to a dose value. In what follows, three examples of mutation assays and biodosimeter tools and their respective applications in the context of radiation biology are described.

### *Glycophorine A (GPA) Somatic Mutation Assay*

The glycophorine A mutation assay is a test based on counting variant frequencies in cell types. The assay measures the variant frequencies in erythrocytes at the GPA locus as a quantitative indicator; exposure to radiation or chemical mutagens causes a dose-dependent increase in frequency of variants (Grant & Bigbee 1993).<sup>4</sup> It was therefore viewed as particularly promising among the techniques explored for biodosimetry. As a biomarker in the validation of dose estimates, the method was successful in that it correlated well with dose estimates for the acute, high dose, whole body exposure of the A-bomb survivors (Langlois et al. 1987). The quantification of somatic mutations at the glycophorine A locus in erythrocytes was widely applied, for instance after the Goiania accident as well as for Chernobyl clean-up workers (Bigbee et al. 1996) and nuclear worker at Sellafield (Tucker et al. 1997). Whereas the assay worked well for the acute exposure of the Goiania accident, the test showed no correlation with doses for Sellafield workers who were exposed to low doses over a long period of time. For the population exposed in the vicinity of the Semipalatinsk test site, a study by Lindholm et al. (2004) found only minor effects in this assay. However, it was pointed out that it was unknown whether the effect to be measured was indeed persistent over decades after exposure. Still, the fact that this assay showed no or only slight effects for the Semipalatinsk context contributed to the increasing skepticism and doubts about the actual exposure in the areas adjacent to the test site, in particular since this was in line with other biodosimetry findings in the same population.

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<sup>4</sup> The assay was applicable with samples from individuals heterozygous for GPA, which is about 50% of the general population.

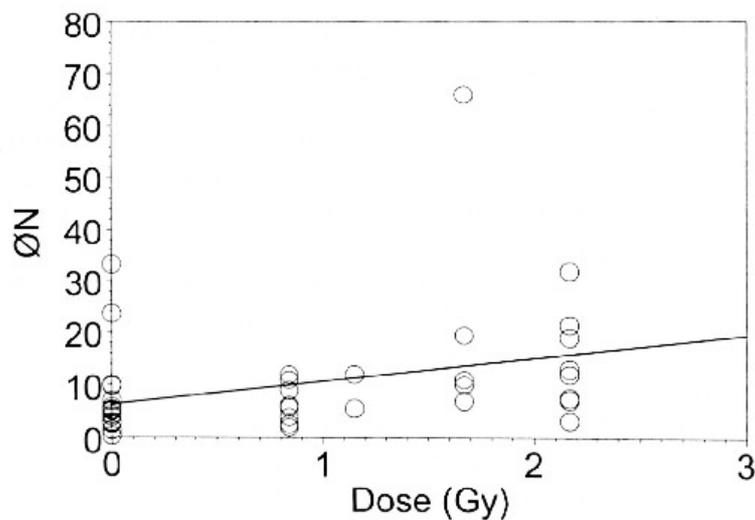
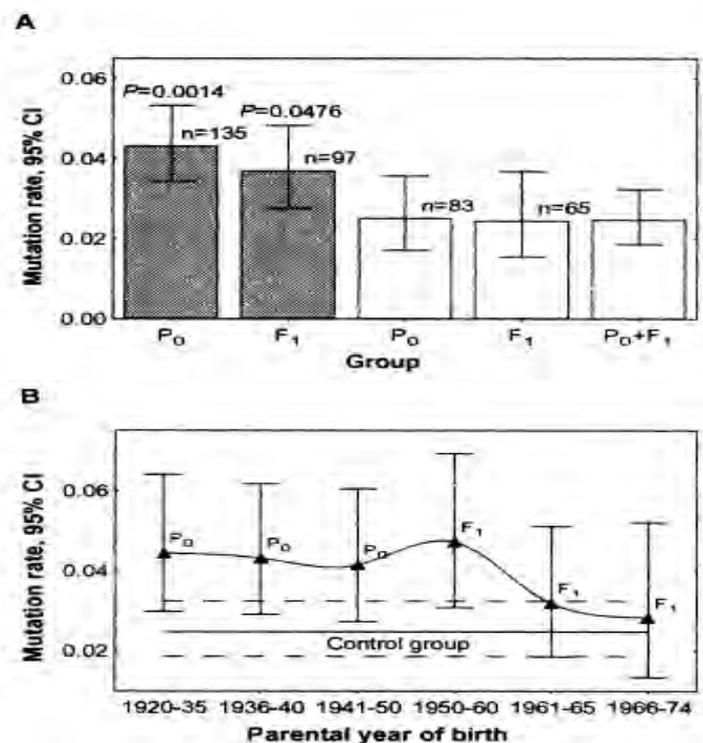


Fig. 2: Results of the glycophorine A assay: variant frequencies in relation to external dose due to fallout in the Semipalatinskaya oblast' (Lindholm 2004, p. 168).

### *Minisatellites as a New Technique: "Just a Biomarker or More?"*

So-called "minisatellite mutations" — tandem repeats in non-coding DNA (sometimes referred to as "junk DNA") — were also studied as a potential system to detect radiation-induced germline mutations by comparing parents and children. Due to their generally high spontaneous mutation rates, even small overall samples would be sufficient to statistically detect differences. Unlike somatic mutations, germline mutations could be transmitted to offspring; they were therefore viewed as potential tools to measure inheritable effects of radiation. However, no increases in minisatellite mutations and no correlations with dose were found for the A-bomb survivors in Japan (Kodaira et al. 1995). Against this backdrop, a paper by Britain-based radiation biologist Yuri Dubrova (et al. 1996), suggesting that radiation leads to mutations in the germline and therefore to effects in the next generation, received much international attention. Dubrova's study was based on examinations of families living in highly exposed areas in Belarus after the Chernobyl accident and compared mutation frequencies to a non-exposed control group from the UK for targeted high mutation rate loci, using multilocus minisatellite probes. Germline mutation rates in the exposed areas were found twice as high.

Several years later, Dubrova's team applied the same technique in the Semipalatinsk area. This time they compared their findings with local unexposed controls. In the Semipalatinsk area, they found increased mutation rates among individuals born in the early 1950s and declining rates among people born over the following decades. Rates decreased substantially in particular among those born in the mid 1960s and later, i.e. after the moratorium for atmospheric nuclear tests (Dubrova et al. 2002).



**Fig. 1. (A)** Germline mutation rates [ $\pm 95\%$  confidence intervals (CI)] in the control (open boxes) and exposed (hatched boxes) groups. Probabilities of difference from the whole control group and the number of offspring in each cohort are given. **(B)** Germline mutation rate in the exposed parents grouped according to year of birth. The solid line represents mutation rate ( $\pm 95\%$  CI) for the whole control group.

Fig. 3: Graphical presentation of minisatellite mutation rates for two generations of exposed and non-exposed people (Dubrova et al. 2002, p. 1037).

While no longer dismissed as “junk DNA” the potential significance of minisatellite mutations and their association to disease risk remained unclear. Yet it was assumed that the presence of minisatellites close to relevant genes affected transcription and may dispose to heritable forms of cancer (Bouffler et al. 2006). Although unknown whether this was “just a biomarker or more” (Stone 2002), it was hoped that minisatellites could become a useful monitoring system for biodosimetry.

The goal of first minisatellite studies near Semipalatinsk was to determine the rate of heritable mutations in their germline, by including several generations and to establish a biosample database in order to assess novel molecular biological methods in the future. As a rule, expectations were formulated with caution — described in terms of gaining “information on the utility of this innovative mutational technique” and “information on the inheritability of mutations” (Blanc & Dechamps 1998, pp. 2-41). However, it proved difficult to translate minisatellites mutations into a biodosimetry tool and mostly since no consistent dose-response effect was found. Later consensus documents on biodosimetry did not even mention minisatellite methods because there was no dose-response relationship that would allow derivation of dose estimates from a calibration curve. In short, findings for minisatellite mutations could not be transformed into a dosimetry tool and yet with the Semipalatinsk minisatellite study, discussions on transgenerational effects and inheritable effects of radiation took place.

## Chromosome Aberrations: from Dicentrics to FISH

Since the 1970s the most widely used method of cytogenetics for biodosimetry has been the microscopic analysis of chromosome aberrations, with staining and karyotyping.

With the emergence of primer technologies in the 1990s, the FISH (fluorescence in situ hybridization) method became available as a new tool for cytogenetic assessments. This technique made it possible to visualize and automatically count chromosome rearrangements, in particular stable translocations.

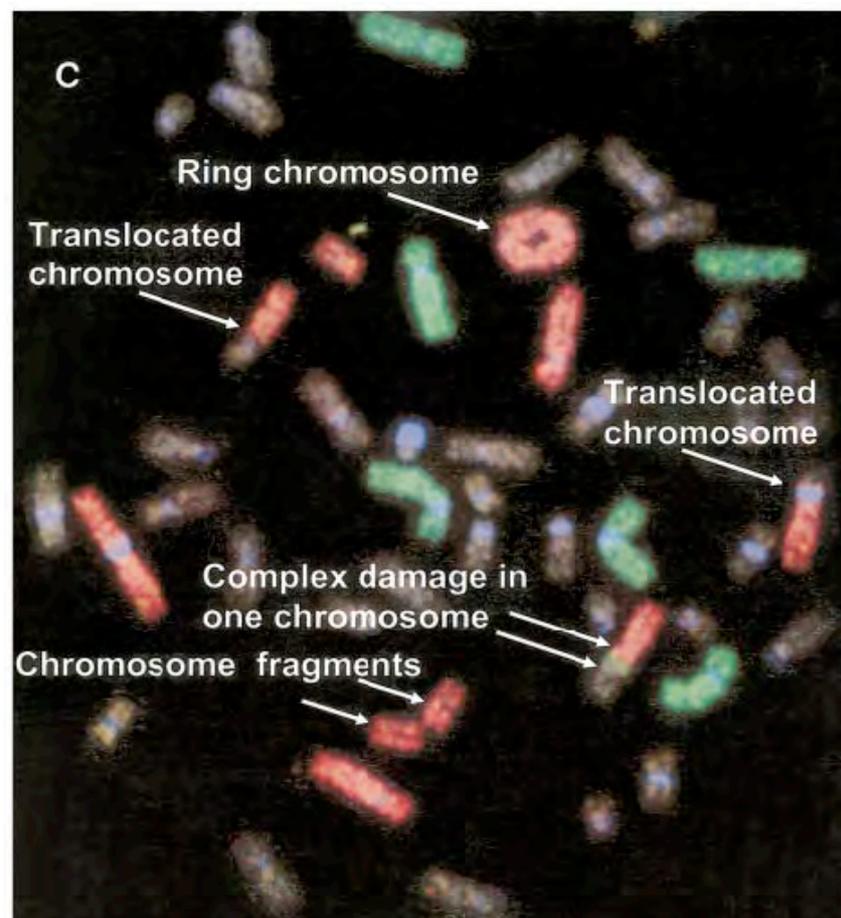


Fig. 4: “Chromosome painting” with the FISH method: visualization of chromosome aberrations following radiation exposure (Kleiner mann et al. 2006, p. 290).

Based on an empirical calibration curve, data on persistent translocations could be used as a basis to calculate quantitative dose estimates. The FISH method was often combined with conventional cytogenetic analyses or with the GPA mutation assay. While classic analyses of dicentrics decreased within several months after exposure, the FISH technique was hoped to allow quantification of persistent translocations due to exposures that occurred in the past. However since the FISH reagents were expensive, its application in large-scale population studies was not affordable.

Rather, the technique served as a validation tool for dose estimates calculated with other methods. The FISH method was applied to samples from the Semipalatinsk region together with classic cytogenetics (Stephan et al. 2000, Salomaa et al. 2002, Bersimbaev et al. 2002). Together, the biodosimetric studies indicated lower doses than physical modeling of fallout distribution; however, some uncertainty remained on whether the translocations had really been persistent over 50 years.

Problems for cytogenetics using FISH that were unresolved at the time included considerable inter-laboratory differences in procedures: the method was sensitive to small variations in chemicals and procedures, and the findings were hardly comparable between different labs. Since calibration curves were developed locally, the lack of standardization (of chemicals, procedures and counting) in assessing mutations posed problems in particular in the early years when the FISH technique had just been introduced. Despite automation of counting and much of the analyses, qualitative assessments remained also important for the study of chromosome aberrations. For instance there were always singular particularly damaged cells (so-called “rogue cells”); standardization protocols deal in particular with the issue of which cells should be included in the counting and how cells with multiple aberrations should be dealt with.

### *Mutations and Risk Management*

Preliminary exposure assessments in terms of effective doses to the population had been published only in few internal reports. In the open scientific literature, local dose estimates were published in 1990 (Tsyb et al. 1990; Stepanov et al. 2002), which estimated maximal effective doses of 1.6 Gy in the settlement of Dolon and much lower doses for other villages. Some researchers based in Semipalatinsk estimated the exposure at doses well above those given by the Russian dosimetry groups (Gusev et al. 1997).

It was in the context of managing Cold War legacies of the nuclear programs that mutation studies became used for purposes of “biodosimetry.” Conceived of as proving or disproving exposure, mutation studies gained some influence in mitigation policy, e.g. with respect to the allocation of resources to scientific and social compensation programs.

The scientific investigation and the compensation policies that were implemented in the early 1990s in the Russian Federation and to some extent in Kazakhstan worked with different concepts of dose assessment. For compensation purposes, mostly area-based dose estimates were developed and assigned to all inhabitants in exposed areas according to place of residence — this was the documentation that entitled to benefits. In addition to these “legal” estimates, “scientific” dose estimates were developed for epidemiology — these were more specific and intended to be continually updated with new results.

Results of biodosimetry influenced decision-making on further research strategies: based on the first small-scale biodosimetric studies then available, the WHO report of 1997 estimated cumulative doses at the order of 0.1 Gy or less.<sup>5</sup> However, there had been many practical problems for instance in sampling: samples needed to get to the laboratory from remote areas within 24 hours to start preparation for chromosome analyses. In particular in the early 1990s, samples were often shipped to laboratories elsewhere — to Moscow or to Western Europe, Japan, or the US.

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<sup>5</sup> See Chaizhunusova et al. 2006.

Collecting blood samples in winter was cumbersome due to the road conditions — and during the summer months, heat turned out a problem and samples sometimes arrived at the bench in unusable state.

Following the recommendations by the WHO, many studies focused on dosimetry, methods and laboratory comparison and standardization; these dose validation activities concentrated on the village of Dolon, located within the fallout trajectories of the most dose-contributing nuclear test to this settlement, i.e. the first Soviet nuclear detonation of 28 Aug 1949. This settlement was chosen as a site for validation studies also for practical reasons: it was hardly more than an hour's drive from Semipalatinsk city and bricks from an abandoned community building could be analyzed with thermoluminescence dosimetry for comparison.

In a second WHO report in 2002, it was concluded that the doses were most likely to be below 0.5 Gy (Salomaa et al. 2002; Simon & Bouville 2002); further, the need of inter-calibrations between laboratories and standardization of procedures in order to produce comparable results was stressed. It remained uncertain whether biodosimetric techniques were suitable for the exposure situation in the Semipalatinsk area; international projects focused first and foremost on methodological problems and technologies rather than on the documentation of effects. Local scientists criticized the lack of research results that were of relevance to the communities under study. From the sites of radiation exposure in the former Soviet Union, blood samples travelled to laboratories not only in Moscow but also to Italy, Germany and to the Cold War nuclear laboratories in Rockville, and Oak Ridge in the US. Yet, these transnational journeys of samples were not without potential repercussions to local struggles for compensation and mitigation. The largely negative results obtained with the FISH method could mean to lose some economic support provided by governments as compensation in the areas affected by fallout.

In a review of the state of the art in biodosimetry with cytogenetic methods, Léonard et al. concluded that

biological dosimetry has serious limitations exactly for situations where the need for information is most urgent. It renders its most useful results when an individual has been exposed to a rather homogeneous high-level radiation over a short time interval, i.e. accidents at high-intensity radiation devices (2005, p. 448).

For the case of fallout exposures near the Semipalatinsk test site, however, exposures were in part decades ago, multiple, both acute and chronic, with external and internal dose fractions and at different dose rates and radiation qualities.

More generally and with respect to the common practice of extrapolating from high radiation doses to low doses, radiation epidemiologists viewed the study of molecular markers as promising because this could help open the epidemiological black box between exposure and disease. “It is anticipated that the addition of the molecular parameters to the population-based studies will allow determination of real rather than calculated risks” (Neta 2000, p. 44). Moreover, the results of a direct individual cytogenetic test were seen as a powerful proof at the individual level, as opposed to the assessment of a statistical risk that relied on area-based collective dose estimates. In this context, biodosimetry also has a significant impact on risk management at yet another level:

It should be noted that the study of mechanisms and biomarkers of radiation-induced alterations allows to form a notion of an exposed versus an affected individual. The latter issue is of immense social and economic significance for the Urals region with its dozens of thousands of exposed residents (Akleyev 2000, p. 80).

Issues of insurance, liability and compensation generate new meanings to dose-response relations — not only as to the question whether “radiation signatures” can be traced along pathways. In turn, these were used for the assessment of a causal influence, i.e. of whether radiation can be substantiated as a causal factor which entitled to compensation.

This discussion reflects two models of compensation — of which the first was applied in the Russian Federation for a short period and is oriented toward compensations based on the conditions experienced, while the second one was more rooted in the logic of insurance, only giving benefits for proven harm combined with evidence for the cause. For the latter, molecular markers and mutation assays constituted the methods with which this individualized evidence was to be generated.

## *Conclusions*

This paper has described how mutations came to be used in the assessments of nuclear test legacies. As ambiguous intermediary markers between radiation exposure and carcinogenesis, mutations often occupied a boundary position. They could be used in multiple ways, for instance as proxies for radiation dose or as early stage markers of cancer. Radiation biologists made use of sites of radiation exposures in terms of opportunities to study mutations as markers of radiation effects and along molecular pathways of radiation carcinogenesis. By comparing exposure situations, radiation quality and linear energy transfer, acute versus protracted exposure, knowledge about the mutagenic effects of radiation has been developed by taking advantage of population exposures for research: the atomic bomb survivors of Hiroshima and Nagasaki, people exposed in Southern Urals, Sellafield, Goiania, Chernobyl, Nevada, Semipalatinsk and many more. The given local population exposures provided large-scale research systems for radiation epidemiology, in which there was variation in radiation type, minimum detectable dose, time limitations, modifiers and interindividual susceptibility in response.

While epidemiologists required validated dose estimates in order to derive risk estimates in population studies, the biodosimetric tools to assess individual exposure were still at the stage of development toward standardized methodologies. Therefore, the testing of new tools for biodosimetry kept open questions that epidemiologists needed to see closed. In this situation inter-comparisons and validation of biodosimetric techniques were given priority. This has prompted dynamic research activities that centered on radiation-induced mutations as a marker of exposure — in this way, the investigation of effects was combined with methodological development and validation. Uncertainty both in effects and in the test systems themselves set off a particular research dynamics; most projects followed methodologically driven research agendas.

Some local officials of the formerly closed city of Kurchatov saw the future of the Semipalatinsk nuclear test site as a “radiobioecological laboratory.” With the “uniqueness in radionuclide composition,” there would be opportunities to study long-term radiobiological processes, including assessment of the genetic detriment the population, but also genetic monitoring of flora and fauna. During the 1990s, opening these areas to an international research community was envisioned as a source of income to the entire region — one of the responses to the vast economic and institutional changes after the end of the Cold War.

While mutations initially drew attention to the effects of nuclear fallout, they proved unstable and difficult to transform into tools for radiation biodosimetry, when applied to validate the complex radiological situation. Rather the other way around, the exposure situation turned into the testing ground for new molecular biology tools. Here, it was an alteration in the exposed human body at the molecular level that became the signal to be monitored when assessing environmental exposure. When it came to applied biodosimetry, it seemed that mutations created more questions than they could help answer. In the first decade of research, there were few conclusions about local radiation effects. Instead research had moved on to explore mutations as tools for biodosimetry.

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## *Commentary on “Tools”: Radiation, Health, and Heredity*

*Angela N. H. Creager*

The three papers in this session on “Tools” deal with how mutations were generated, detected, and visualized, particularly after World War II. Radiation had been a tool in genetics since the third decade of the century, but the new level of radiation exposure generated by nuclear weaponry — as well as the “peaceful” developments of atomic energy — gave new urgency to measuring and understanding the biological effects of radiation. As Soraya de Chadarevian suggests (and I also make this point in my own contribution), the old distinction between somatoplasm and germplasm shaped the basic understanding of radiation damage — mutations were largely conceptualized as genetic effects, i.e., in the germline, whereas somatic effects (including the increased incidence of cancers such as leukemia) were not usually viewed as genetic but somatic. This bifurcation, evident in the fallout debates, meant that genetic effects were often viewed in terms of long-term evolutionary fitness rather than immediate health effects. The genetic and health-related effects of radiation, previously distinct, converged in the 1950s and through the 1960s, with the emergence of the somatic mutation theory of cancer causation. The somatic effects of radiation exposure were now imagined as (at least partly) mediated by genetic damage in somatic cells. This gave mutations a new medical salience: the induction of mutations could be responsible for disease in an individual, not only deleterious effects in the offspring.

Medical researchers used the practices of cytogenetics to search out disease-related mutations by looking for damaged chromosomes in patients. The growing interest in cytogenetics in the clinic, however, generated its own paradox, as de Chadarevian indicates. Karyotyping of patients with congenital diseases made Turner and Klinefelter Syndromes into chromosome diseases — Turner syndrome being associated with XO individuals and Klinefelter with XXY. Further screening showed other correlations, such as the high percentage of XYY individuals among institutionalized patients. But population screening revealed plenty of XYY males who did not show behavioral pathologies. Could the mutations associated with certain diseases be used as diagnostic markers in the general population? This question has bedeviled the Human Genome Project and its applications as well. When are polymorphisms indicative of pathologies, and when are they simply biological variation?<sup>1</sup>

Another theme that comes through in all three papers, but which is especially well-developed by María Jesús Santemas, is the importance of technologies of visualization in working with genetic variants. We think now of mutations as changes in nucleotide sequence of the DNA, but sequencing was a latecomer among technologies for making mutations visible. Cytogenetic methods, protein electrophoresis, and CoT curves of nucleic acid hybridization were all ways of detecting mutations, and each highlighted a different kind of mutation. Electrophoresis picked out changes in protein (and thus DNA) sequence, whereas cytogenetics made chromosome abnormalities visible. (To say that these methods represented different stages of development of genetics would be too simple — as Susanne Bauer shows, cytogenetic screening was still being used in the 1990s, alongside genomic and genetic marker methods.) Theories could move between these techniques — the somatic theory of cancer causation was advocated by John Gofman in the early 1960s based on chromosomal abnormalities, but then became a theory about radiation-induced

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<sup>1</sup> For more on these debates, see Reardon 2005.

(or chemical mutagen-induced) nucleotide substitution.<sup>2</sup> Also, scientists adapted these techniques from organism to organism. Santesmases points out how cytogenetic techniques migrated from maize genetics, to fly genetics, to human genetics — and thus, more broadly, from the realm of agricultural to medical research.

Susanne Bauer's paper adds another more contemporary dimension to the theme of technologies and visualization. In the post-Soviet screening programs she discusses, human bodies, as assayed through their chromosomes and genetic markers, became instruments of dosimetry. Rather than testing the effects of radiation on human genetic material, humans were used to test the mutagenic hazards of the environment. She analyzes the remarkable use of people as "biodosimeters," even for the recovery of retrospective information, the hidden histories of exposure. As Bauer shows, scientists had to face the issue of co-calibration between humans as instruments and physical instruments; which had priority in establishing radiation levels? The human body is an especially dynamic detector; not all mutations are permanent, nor is radiation exposure the sole source of mutations.

In this set of papers, one cannot miss the everpresence of radiation in shaping these themes of somatoplasm vs. germplasm, techniques of visualization, and the use of organisms as instruments to measure mutagens. Radiation itself was a critical tool, but it was more than a tool. As Staffan Müller-Wille suggested, perhaps it should be regarded as a *medium* of genetics, penetrating everywhere. In part this was an effect of novel technologies: radiation was produced in ever-increasing amounts by the new instruments of nuclear physics, from cyclotrons in the 1930s to reactors and nuclear weapons in the 1940s and 1950s. The development of atomic energy for the bomb project intensified and reshaped the social motivations for making and understanding mutations, yet it is important to bear in mind that the instruments and clinical uses of radiation (along with protective measures) characterize the entire twentieth century and played a non-incidental role in Muller's own understanding of mutation. The era of nuclear weaponry, particularly once peacetime tests result in substantial radioactive fallout, certainly raised the stakes for the consequences of radiation-generated mutations (Beatty 1987). Yet in the 1960s, even as atmospheric atomic weapons testing ceased, geneticists begin to reckon with the idea that many mutations are neutral rather than deleterious.<sup>3</sup> A fuller history of mutations in the postwar period would also include the re-envisioning of mutations as often evolutionary neutral, and of genetic variation as more pervasive than the eye can see.

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<sup>2</sup> On John Gofman's contributions, see Semendeferi 2008.

<sup>3</sup> On the controversies surrounding the "neutral theory" of Motoo Kimura, see Dietrich 1994.

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## *Chemicals*



*Medical Physicists, Biology, and the Physiology of the Cell  
(1920–1940)*

*Alexander von Schwerin*

*Introduction: Mutations and Target Theory in Germany*

It seems nearly impossible to speak about German genetics and mutation research in the 1930s without mentioning the genetic target theory — an early theoretical account of the material nature of genes. Historians have described how, in 1935, three men invented the genetic target theory when they published the article “Nature of Gene Mutations and the Structure of Genes.” The three scientists were the geneticist Nicolai Timoféeff-Ressovsky and the physicists Karl Günther Zimmer and Max Delbrück; all three lived in Berlin at the time. The genetic target theory was path-breaking because the authors tried to use the genetic effects of radiation to draw a conclusion about the molecular make-up of genes.

A loose circle of geneticists and physicists was quite strongly interested in this new approach since it claimed to provide new insights into the nature of the gene. Looking into Hermann Muller’s papers at Indiana University, Bloomington, one finds evidence of the lively discussion that went on all through the 1930s. The topic was so exciting — but also controversial — that several informal meetings were held throughout the 1930s. For instance, in 1936 geneticists and biophysicists met in Copenhagen to discuss the problem of mutations.<sup>1</sup> The next meeting took place one year later in the Belgian resort of Spa — Timoféeff-Ressovsky had begun referring to the “members” of the “Gene Group.”<sup>2</sup> Another “gene meeting” was planned following the International Congress of Genetics in Edinburgh in September 1939.<sup>3</sup> Central topics of the meetings were questions related to mutagenesis and X-ray-induced mutations. In particular, the participants discussed the thesis published by Timoféeff-Ressovsky and the physicists Karl G. Zimmer and Max Delbrück in 1934.

The genetic target theory was quite ambitious not only in terms of quantitative genetic experimentation and dosimetric techniques, but also the mathematical calculations related to quantum mechanics.<sup>4</sup> This juncture of genetics and physics became influential in supporting a physics-based model of mutagenesis. The proponents of the biophysical model repeated its basic assumptions like a mantra: (1) Mutations are contingent. (2) They have no clear direction. (3) They are not reversible. This doctrine became even more important in contrast to theories

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<sup>1</sup> Participants included the geneticists Hermann Muller and Nicolai Timoféeff-Ressovsky, the physicists Max Delbrück and Niels Bohr, “and others.” (Delbrück and Timoféeff-Ressovsky: Summary of discussions on mutations, Lilly Library, Indiana University Bloomington, Muller Mss., series III, box 1)

<sup>2</sup> Timoféeff-Ressovsky to Muller, 4.8.1938, Lilly Library, Indiana University Bloomington, Muller Mss., series I, box 30; Timoféeff-Ressovsky to Muller, 20.1.1939, *ibid.*

<sup>3</sup> In particular, they planned to have a subsection of the Congress consider viruses and proteins in relation to the problem of the gene. Prospective participants were Bauer, Dobzhansky, Dubinin, Dunn, Ephrussi, Haldane, Kaufmann, Linderstrøm-Lang, Metz, Mohr, Muller, Oliver, Plougn, Rhoades, Stadler, Stubbe, Timoféeff-Ressovsky, Waddington, Weinstein, White, Wrinch, and others. (Muller to Timoféeff-Ressovsky, 27.6.1939, Lilly Library, Indiana University Bloomington, Muller Mss., series I, box 30; Timoféeff-Ressovsky to Muller, 30.6.1939, *ibid.*; Muller to Timoféeff-Ressovsky, 16.1.1939, *ibid.*)

<sup>4</sup> Cf. Timoféeff-Ressovsky/Zimmer/Delbrück 1935.

addressing the effects of radiation on biological substances such as cells and tissue. As the geneticist Hans Stubbe put it:

The factors that shape all kinds of physiological reactions to radiation — restitution, change in the sensitivity to radiation, threshold value — play no role in the case of genetic effects of radiation. The induction of a gene mutation is an event that is not reversible and that leads from one stable status to another stable status.<sup>5</sup>

The quote gives evidence of the principal differences between the divergent views of the effects of radiation. In the view of most geneticists and biophysicists, there was a fundamental difference between genetic and physiological effects of radiation. They assumed that physiological effects were limited to the physiology proper and cell chemistry. In contrast, genetic mutations appeared to be just pure physical events. The physical agent — e.g., radiation — disturbed the genetic integrity in a direct way with no physiological or biological mediation involved. Thus, the energy of the agent was transformed almost directly into a genetic effect. The distinction between physiological and genetic events was quite strict in that model.<sup>6</sup> It suggested that there were two different epistemic kinds of organisms with respect to environmental effects: the physiological and the genetic organism.

The model represented by the target theory can be referred to as the *genetico-biophysical model* since this strict distinction emerged from the confluence of genetics and physics in the early 1930s and was touted — almost programmatically — by a network of physicists and geneticists who collaborated and conversed in close contact. In Germany, this network involved about a dozen researchers mainly based in Berlin. All of them were represented in leading German journals such as the *Induktive Abstammungs-und Vererbungslehre* and *Naturwissenschaften*. This community became the founding stock, in the early 1940s, of the German Biophysical Society, which started with thirteen members.<sup>7</sup> The society met twice during World War II. The first post-war meeting was held in 1947 at the Kaiser Wilhelm Institute for Physics in Göttingen under the auspices of Werner Heisenberg and Karl Bonhoeffer.<sup>8</sup> The fact that the American Biophysical Society was founded only in 1957 can be seen as evidence for the strong influence of the genetico-biophysical radiation network and the target concept in Germany.<sup>9</sup> In 1947, however, the target theory no longer played a particular role in the program of the biophysical meeting. By then, the target theory had done its job and was already losing its significance with the rise of molecular genetics.

It is not just branding to speak of a genetico-biophysical model; there is also a historical reason. We can witness in the biological discourse of the time two different camps, or better put, two poles: on the one side those defending a physical view and on the other those defending a biological view. This paper will focus on the latter since it has been totally neglected in the past. However, one must take into account that radiation genetics was not an isolated scientific field but practically and discursively interconnected with radiation biology and medical genetics.

Historians have mentioned the local network with Nicolai Timoféeff-Ressovsky as one key

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<sup>5</sup> Stubbe 1938, p. 315, cf. also pp. 316-320 (trans. AS).

<sup>6</sup> For instance, see Timoféeff-Ressovsky 1937, p. 58.

<sup>7</sup> Schwerin 2010.

<sup>8</sup> K. Wirtz: Biophysikalische Konferenz im Max Planck-Institut für Physik, Göttingen, Januar 1947, Lilly Library, Indiana University Bloomington, Muller Mss., series III, box 1.

<sup>9</sup> Correspondence with Garland Allen.

figure — although, unfortunately, there has been no thorough analysis thus far.<sup>10</sup> A detailed analysis of the discourse and collaborations would probably come up with surprising results. The discourse about the target theory was not as uniform as it has been described thus far. Quite a number of biologists and physicists usually go unmentioned, but were nevertheless present in the discussion on radiation effects, mutagenesis and, hence, the target theory, in particular the biologists Hans Langendorff, Edgar Knapp, and Hans Marquardt and the physicists Kurt Sommermeyer and Boris Rajewsky. These researchers were engaged with experimentation and in discussions, although they were — mostly — not part of the circle that met regularly in Berlin and they did not become members of the Biophysical Society. Today, these names are almost forgotten. This is probably because all of the mentioned scientists did not fit in the expected picture since they were in some way or another critical towards the target theory and the genetical-biophysical model of mutagenesis at that time.<sup>11</sup>

In this paper, I shall go beyond the standard narratives that consider only those geneticists whose interests were theoretical and focused on mutagenesis and gene theory and theoretical physicists who became interested in the very secrets of life.<sup>12</sup> Thus far historians have been fascinated by and focused on the crucial influence of the physicist Max Delbrück.<sup>13</sup> Delbrück, of course, is a big draw because he became one of the founding fathers of molecular biology. The common story misses the practical context and the origins of the genetical-biophysical conjunction with medical physics. A re-evaluation of the early history of biophysics and radiation genetics would locate it within the social context of radiology and the roots of biophysics in medical physics. This paper argues that medical physicists laid the foundation for the genetical-biophysical approach to mutagenesis and as well were interested not only in genetics but in a broader approach towards the effects of radiation.

In the following paragraphs, I will argue that the target concept originated in medical physics and that consideration of medical physics highlights additional aspects that haven't been addressed. (1) It is interesting to note that the early versions of the target theory dealt with a completely different *explanandum* from the genetical-biophysical adaptation. (2) It has not yet been considered that these early approaches did not end when the genetical-biophysical conjunction emerged. On the contrary, the tradition of this early and less focused biophysical approach continued, or to put it more concretely, there are trajectories from the medical physics of the 1920s right through to the radiation biology of the 1930s. (3) This tradition of a physiological view of mutagenesis questioned the clear-cut distinction between the physiological organism and the genetic organism. This physiological view, however, cannot be compared with physiological approaches that would emerge in the 1960s; these later approaches had in common the premise that mutagenesis was not a physical event, but a biological process proper.

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<sup>10</sup> See for example Fischer 1985 and several portraits in Pasternak 1994.

<sup>11</sup> Actually, American geneticists such as Hermann Muller were also quite negative, but most of them did not discuss the impact and legacy of this approach at all.

<sup>12</sup> For a more contextualized account see Gausemeier 2004, p. 170-174. A detailed account is presented in Sloan/Brandon 2010 that could not be considered for this paper.

<sup>13</sup> Hayes 1984; Kay 1985; Fischer 1985.

## *A Theoretical Approach Out of the Needs of Radiology*

In its original version, the target concept was not invented in the context of genetics, but in the context of advanced medical therapy.<sup>14</sup> Since the 1910s radiologists had come to rely more and more on the help of physicists able to handle X-ray apparatuses and dosimeters.<sup>15</sup> However, radiology was still a field of medical practice in its infancy. Radiologists were only roughly able to control the quantity of applied radiation. Medical physicists came to be at the intersection of clinic and industry developing and improving X-ray technology.<sup>16</sup> The improvement of the technology required exact knowledge of how radiation affected the organism, the tissue, and cells. In other words, a more efficient use of X-ray technology was only possible when the effects of certain quantities of radiation could be calculated. The program of medical physicists was to rationalize the practice of radiology. In particular, Friedrich Dessauer, who built X-ray apparatuses, became one of the first proponents of this scientific and practice-oriented program.

Still the biggest — and for the future of deep therapy, critical — problem is waiting to be solved ... In order to influence the seat of disease deep in the body, and at the same time to spare normal tissue, one needs to know quantitatively the exact distribution of the energy of X-rays in the human body.<sup>17</sup>

Dessauer ran an X-ray company before moving completely into research when he was appointed director of the first German institute for medical physics in 1920, the *Institut für physikalische Grundlagen der Medizin*, the forerunner of the Kaiser Wilhelm Institute for Biophysics in Frankfurt/Main. Dessauer was convinced that the biological effects of radiation could be handled similarly to the way the effects of radiation in physical matter were controlled by radiation physicists. In other words, Dessauer looked for a uniform mechanism — “basic laws” — that could be mathematically expressed in a formula as was the custom in physics.<sup>18</sup> To simplify the uncertainties and to reduce the variability of biological experiments, he tried different models, ending with a water cube that — according to Dessauer — represented best the essential characteristics of biological matter since cells consisted predominantly of water.

On the basis of the water model, Dessauer was able to develop a theoretical model of the biological effects of radiation. It was first published in 1922 and became known as the “point of heat hypothesis” (*Punktwärmehypothese*).<sup>19</sup> Dessauer proposed that, in general, the energy of X-rays was converted into heat. However, the production of heat did not occur continuously. The distribution of radiation in water followed certain patterns of refraction that resulted in overlapping rays. (See figure 1.) The energy of the rays was cumulative at these points, and the process resulted in critical hot spots. Although the hotspots were only microscopic points, the cascade of damaging effects of X-rays originated from there.

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<sup>14</sup> There were similar approaches developed quite independently in United Kingdom, France, and Germany. This account deals only with the German conditions.

<sup>15</sup> Dommann 2003.

<sup>16</sup> Schwerin 2009.

<sup>17</sup> Dessauer/Vierheller 1921, p. 656 (trans. AS).

<sup>18</sup> Dessauer 1921, pp. 1155-1156.

<sup>19</sup> Dessauer 1922; Dessauer 1923.

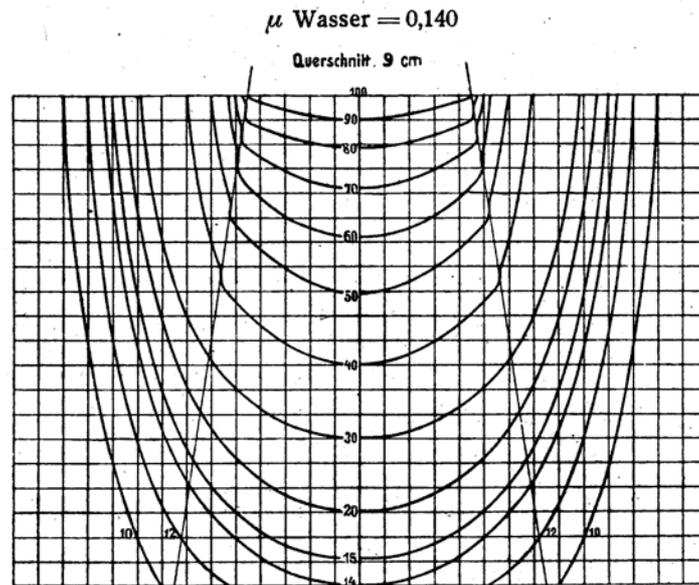


Fig. 1: The distribution of radiation within water. From: Dessauer 1923, p. 12.

Dessauer was quite aware that this simple model was not sufficient to explain fully the effects that were reported by clinicians, radiologists, and biologists. In response, he compared the dynamics of radiation effects with the dynamics of the effects of pharmacological substances.<sup>20</sup> His claim was that the heated spots were the location of the transformation of the radiation energy. The transformation could be fully explained in physical terms.

### *Target Theory Proceeds*

Dessauer's attempt stimulated other physicists and radiologists, in particular, the physicist Richard Glocker. Glocker was a pupil of Wilhelm Roentgen, and during the First World War, he was sent to support the radiological units in the field. Having become fascinated by this field, Glocker stayed interested in radiological problems when he was appointed the head of the X-ray Laboratory at the Technische Hochschule Stuttgart in 1919. Glocker was revealed to be an ingenious jack of all trades. He successfully collected money from the industry, the German Research Fund (*Notgemeinschaft der Deutschen Wissenschaften*), foundations, and from private and municipal donors. In later years he invented X-ray crystallography for use in metal research and materials testing.<sup>21</sup> He also worked together with physicians of a well-established local hospital to perform biological experiments on beans. Glocker was partly skeptical of Dessauer's approach and based his own views more on the work of the English physicist J. A. Growther. For Growther, the crucial event

<sup>20</sup> Dessauer 1922, p. 42.

<sup>21</sup> For a detailed analysis see Maier 2007, pp. 235-243.

was the ionization of a molecule in a sensitive area of the cell. Glocker, however, had ambitions to conceptualize radiation effects more on the principles of quantum physics — quite similar to the later efforts of the theoretical physicist Pascual Jordan, a pupil of Niels Bohr.<sup>22</sup>

In principle, Glocker, like Dessauer, aimed at a physical explanation of the observed phenomena in biological radiation experiments. His efforts resulted in a general “law of biological radiation effects.”<sup>23</sup> But while Dessauer’s approach was qualitative, Glocker’s strategy was based on the quantification of visual biological effects. In order to visualize the quantitative relationship, Glocker introduced the dose-effect curve: a representation of the relation between an increasing dose and the indicator effects. It was necessary to choose a striking effect that was easy to detect and to count, e.g., cessation of germination in beans, or the death of irradiated eggs or irradiated bean seedlings. This is why Glocker called the dose-effect curve a “damage curve” (*Schädigungskurve*).

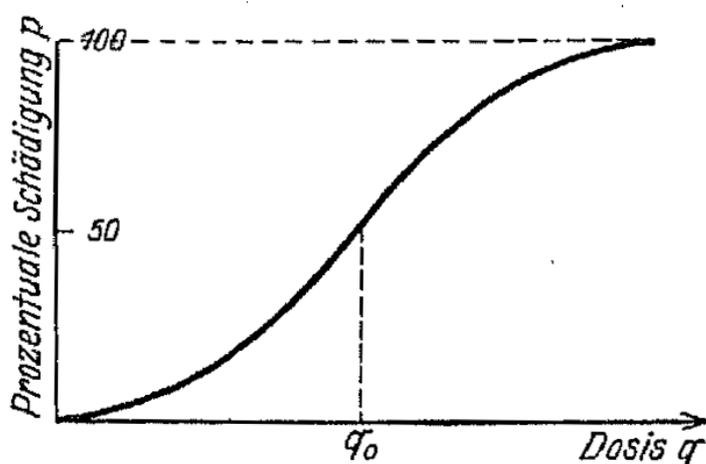


Fig. 2: The principle of the damage curve (*Schädigungskurve*): with the increase in dose (x-axis), the percentage of damaged objects (eggs, dead organisms, etc.) changes — normally in an increasing fashion. The experimenter tries to conclude something about the mechanisms from the exact form of the curve. From: Glocker 1929, p. 110.

Glocker first used the damage curve in joint medical-physical experiments on beans and described it as a path-breaking invention.<sup>24</sup> Glocker: “The starting point of all considerations of this kind [the significance of quantum physics for the effects of radiation on cells] is the damage curve.”<sup>25</sup>

To summarize, by the end of the 1920s, there were already different approaches of the target theory that tackled the basic physical effects of radiation on biological matter. There was an ongoing discussion of these basic effects and of ways to involve quantum physics in studying them. In

<sup>22</sup> Glocker 1932. For the approach of Jordan see Beyler 1996.

<sup>23</sup> Glocker/Hayer/Jüngling 1929, p. 37.

<sup>24</sup> Glocker 1929, p. 204. Similar graphs representing the “killing ratio” were used by Ralph W.G. Wyckoff from the Rockefeller Institute for Medical Research working with irradiated bacteria. E.g. Wyckoff 1930, p. 437.

<sup>25</sup> Glocker 1932, p. 653.

Germany, the biophysicists dominated this discussion, but, radiologists were also involved, in particular, Hermann Holthusen and Hans Holfelder.<sup>26</sup> An important feature of the medical physicist approaches was the translation of biological variation into physical variation. Early experiments with biological model organisms had shown that the effects of radiation differed from individual to individual. Medical physicists referred to the target concept and argued that the variation in the biological effects of radiation was due to stochastic physical events and thus was a matter for physical laws of probability.<sup>27</sup> Many physicians did not agree with this view — they claimed that there was real biological variation — however, this idea turned out to be path-breaking when geneticists adapted the target theory to explain the induction of mutation by radiation.

### *The Conjunction of Medical Physics and Genetics*

Medical physics left a two-fold legacy: the first at the conjunction of medical physics and genetics and the second at the conjunction of medical physics and radiation biology. These conjunctions changed not only the biological fields in question, they also changed medical physics. In Germany, the shift from medicine to biology was unquestionably one of the major driving forces in the establishment of biophysics, i.e., a research field (and later scientific discipline) at the border between physics and biology that was no longer dependent on the disciplinary structures of medicine. The two conjunctions were similar as they involved the exchange of concepts, methods, and techniques. I will deal in this section with the conjunction of medical physics and genetics.

The quantitative approach as it was introduced by Glocker and other medical physicists became the core of the genetical-biophysical target theory. This conjunction, which I will discuss only briefly here,<sup>28</sup> involved the transfer of the target concept and the introduction of physical instrumentation, in the form of dosimetry first. One driving force was the interest in mutation rates as a newly recognized health problem.

Mutation genetics developed rapidly after 1927 when the American geneticist Hermann Muller reported that he had succeeded in inducing mutations artificially with X-rays. Most of the geneticists who were thrilled by this report and jumped into the new field started to quantify the mutations. Quantitative mutation genetics was based on the measurement of mutation rates and repeated the principle of the dose-effect curve. However, the turn from qualitative to quantitative mutation genetics did not happen quickly. The first time Timoféeff-Ressovsky used the dose-effect curve was in 1934 in a research article on mutation rates (of *Drosophila*) and in an English review article.<sup>29</sup>

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<sup>26</sup> Glocker (1932) gives here a short historic overview of the target theory and different approaches. See also Schwerin 2010.

<sup>27</sup> Glocker 1929, p. 112.

<sup>28</sup> This analysis is the result of research on German genetics that was done by both Bernd Gausemeier and me in recent years.

<sup>29</sup> Timoféeff-Ressovsky 1934a, p. 475; Timoféeff-Ressovsky 1934b, p. 420.

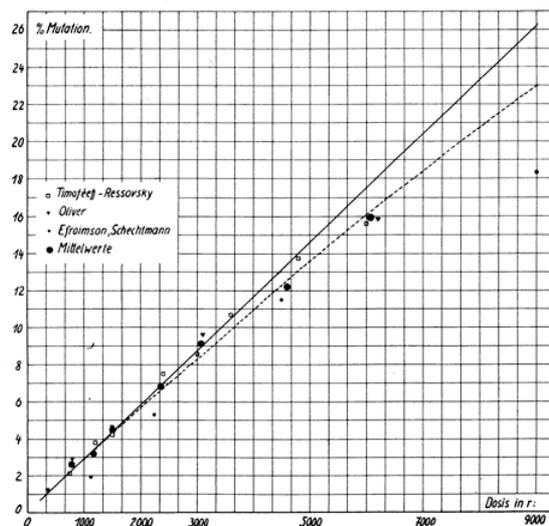


Fig. 3: This often-repeated figure shows the relation between dose and mutation rate. This version was printed in the initial paper of Timoféeff-Ressovsky, Zimmer, Delbrück (later called the “Three-Man Paper”) in 1935. It showed the linear progression of the mutation rate — a key feature of the genetical-biophysical theory of mutagenesis and of the genetic target theory. From: Timoféeff-Ressovsky/Zimmer/Delbrück 1935, p. 202.

The dose-effect curves were the perfect intersection between mutation genetics and biophysical target theories, although this was not yet mentioned in the 1934 articles. On this methodological basis, it was easy to apply and test the biophysical concepts for the purposes of mutation genetics. Thus, it is no wonder that one year later in their paper “Über die Natur der Genmutation und der Genstruktur,” Timoféeff-Ressovsky, Zimmer and Delbrück referred quite naturally and explicitly to the work of medical physicists, in particular Glocker.<sup>30</sup> In the part of the paper on the target theory authored by the physicist Zimmer, Glocker’s work was cited to provide evidence for the basic physical nature of the primary processes that occur when rays hit biological matter. Zimmer also argued that the genetic reaction was quite different from the biological reaction measured by the medical physicists.<sup>31</sup> In a later book on the target theory in biology, Timoféeff-Ressovsky and Zimmer paid tribute to the medical physicists and their achievements in developing the biophysical target theory.

It has been the special merit of F. Dessauer and of [the English physicist] J.A. Crowther and [the French physicist] F. Holweck, to have founded the ‘target principle of the biological effects of radiation’ when they realized the discontinuing nature of the transfer of energy of radiation to the irradiated matter.<sup>32</sup>

<sup>30</sup> Timoféeff-Ressovsky, Zimmer, Delbrück 1935, p. 222.

<sup>31</sup> Timoféeff-Ressovsky, Zimmer, Delbrück 1935, p. 222.

<sup>32</sup> Timoféeff-Ressovsky, Zimmer 1947, p. 2 (trans. AS).

Timoféeff-Ressovsky and Zimmer showed that the emergence of the genetic target theory was directly related to the ongoing discussion in medical physics on the principles and nature of basic effects of radiation. In fact, in the early 1930s, radiologists and biophysicists claimed to have clarified the physical-biological bases of the mathematical-formalistic target theory, and this physical-biological base was one of the crucial questions the geneticists tackled when they applied the target theory to genetics.<sup>33</sup>

But there was also a quite concrete and practical background that shows that the genetic target theory was based on the concerns and expertise of medical physicists. The biophysical target theory had developed within the context of radiology. Likewise, the work on the genetic target theory was reinforced by the medical application of X-rays. Quantitative genetics and the measurement of mutation rates were in the general interest of radiology as Timoféeff-Ressovsky pointed out in 1934.<sup>34</sup> However, he warned of dysgenic effects that had to be calculated in terms of mutation rates.

I believe slight treatments applied to many persons, performed without the control of good specialists, and without considering the danger of genetic injuries, to be most harmful in this respect. We must not forget that in *Drosophila* a general mutation rate of 1 per cent. (i.e. 1 mutation per 100 gametes) is produced by X-ray dosages of about 40-50 r. units.<sup>35</sup>

In the early 1930s, both geneticists and medical physicists became involved in urgent questions of health policies. In the early 1930s, the concern was growing that the use of X-rays in the clinic would induce mutations and increase the number of “detrimental mutations” dramatically. The German Research Fund set up a commission on “detrimental hereditary effects of X-rays” that was tasked with determining whether the society faced a eugenic crisis when relying on the radiological innovations.<sup>36</sup> The commission involved radiologists (including the radiologist Hermann Holt-husen), medical physicists (including Richard Glocker), and geneticists (including N. Timoféeff-Ressovsky). Even the compilation of the commission members indicates a new conjunction.<sup>37</sup>

As a reader of the joint publication of Timoféeff-Ressovsky, Zimmer, and Delbrück would notice: the experimental work that informed this theoretical paper was — at least in part — financed by the German Research Fund (DFG).<sup>38</sup> Actually, this money was given to Timoféeff-Ressovsky to figure out experimentally the exact number of mutations in relation to the dose. Timoféeff-Ressovsky was familiar of course with the methodological option of expressing the quantitative relation of dose and genetic effects in the dose-effect curve; but in practice, the exact quantification of the dose effects also required the help of a physicist who was able to manage the dosimetry.

Timoféeff-Ressovsky relied on the help of the Institute for Medical Radiation Research at the Charité in Berlin to perform the mutation experiments in a way that made use of advanced genetics and physics. The head of the Institute was Walter Friedrich, who had worked in medical physics since 1914 and who also joined the commission. One of Friedrich’s assistants was the young physicist Karl G. Zimmer. Timoféeff-Ressovsky began working in cooperation with Zimmer. This

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<sup>33</sup> Timoféeff-Ressovsky, Zimmer 1947, p. 5.

<sup>34</sup> Timoféeff-Ressovsky 1934a, p. 475.

<sup>35</sup> Timoféeff-Ressovsky 1934b, p. 445.

<sup>36</sup> Schwerin 2004, p. 125; Gausemeier 2005, p. 167; in more detail Schwerin 2010.

<sup>37</sup> In Germany, the radiologist Hermann Holthusen was involved in the discussion on the target theory and contributed significant result.

<sup>38</sup> Timoféeff-Ressovsky, Zimmer, Delbrück 1935, p. 222.

was probably the way that Zimmer became part of the little discussion group in Berlin that met at Delbrück's to consider various theoretical questions of genetics and biophysics.<sup>39</sup> In the end, Zimmer not only managed the dosimetry of the genetic experiments but also turned out to be the ideal co-author of the "Three Men Paper."<sup>40</sup> Timoféeff-Ressovsky contributed to the genetics part, Max Delbrück to the theoretical part on gene structure, and Zimmer to the practical part and the calculations of target theory.

To sum up, from the perspective of practical and technical constraints, the genetic target theory looks like a side effect of the efforts made by medical physicists in radiology and geneticists in radiogenetics and eugenics. Although it seems that these activities within radiology were quite distinct from the work on mutagenesis and mutation rates in genetics, there was a deep-rooted practical connection based on the dosimetric expertise of medical physicists and biophysicists. Thus, the genetical-biophysical understanding of mutagenesis was based on the practical context of radiology and its need to rationalize the use of X-rays in medical therapy.

### *A Conjunction of Medical Physics and Biology*

Even before the conjunction of medical physics and genetics, there was the integration of radiation biology with medical physics and vice versa. It was driven by the need of medical physicists to take the unique characteristics of their biological objects into account. Initially, Glocker's experiments had involved beans and tadpoles since these model organisms had been used in radiology for the previous two decades, but they were no longer appropriate, at least for the purposes of target theory. Therefore, Glocker founded a joint laboratory for biological radiation research in 1928.<sup>41</sup> The biological laboratory was situated at the Katharinenhospital but was run jointly by the radiology department of the hospital and the X-ray laboratory of the Technische Hochschule. This laboratory was the starting point for the Stuttgart School of radiation biology and continued even after Richard Glocker became absorbed with new duties. Starting in 1934, Glocker conducted his X-ray diffraction research within the growing endeavor of German arms research and as the department head of the Kaiser Wilhelm Institute for Metal Research in Stuttgart.<sup>42</sup>

Two of the biologists who started their career at Glocker's Biological Research Laboratory were Margarethe and Hanns Langendorff. The couple worked there from 1929 until 1936 when Hanns Langendorff became head of the Radiological Institute in Freiburg — a place rich in tradition since it was the birthplace of the first collaboration between radiology and physics in Germany (between the radiologist Bernhard Krönig and the physicist Walter Friedrich).<sup>43</sup> Hanns

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<sup>39</sup> Schwerin 2010. From the late 1950s on, Zimmer worked at the German Atomic Research Centre in Karlsruhe and tried to rescue something from the genetic target theory.

<sup>40</sup> Zimmer continued working in the field of radiology all through the 1930s. He made significant contributions to the organization and conceptualization of radiation protection in the clinic and in the industry. In 1938, he became an employee in Timoféeff-Ressovsky's Department of Genetics. Schwerin 2010.

<sup>41</sup> For a more thorough account, see Schwerin 2009.

<sup>42</sup> Maier 2007, pp. 387ff.

<sup>43</sup> Schwerin 2009.

Langendorff had studied at one of the most innovative places of German biology: in Jena at the Botanical Institute led by Otto Renner. Before that he had studied engineering. Thus, Langendorff was well prepared to jump into modern radiobiology and later became one of the most influential radiobiologists in the atomic energy program of West Germany.

Hanns knew that the choice of the right organism was a key question for experimentation in biology. He soon abandoned the beans and tried other specimens including *Oenothera* and *Drosophila* — both organisms that were widely used in genetics research. The experimenters in Stuttgart also tried aqueous solutions (the model introduced by medical physicists), larvae of axolotl, or spermatogonia of male mice (objects usually used by developmental biologists or in cell physiology). The Langendorffs were well aware of the developments in genetics and knew where to get the appropriate fruit flies for radiation experiments; they used breeds that Timoféeff-Ressovsky had bred for his radiation experiments.<sup>44</sup>

Thus, the biological laboratory represented an experimental arrangement that was situated at the intersection of radiology, biophysics, radiation biology, and genetics. On the one side there were the high energy and dosimetric resources of the physicists; on the other side, there were the materialized biological experiences that offered the physicists new experimental possibilities. As one biophysicist put it: the physicists needed the biological knowledge of model organisms to test their theoretical deductions.<sup>45</sup>

All efforts in Stuttgart — the material configuration and experimental rationales — were closely connected to the practical requirements of radiation therapy. The radiation of the tops of bean roots, for example, was designed to solve the internationally discussed question of whether the frequency of mitosis was the right measure to determine the optimum time and right rhythm of radiation treatment.<sup>46</sup>

For some time, the Langendorffs focused on the eggs and sperm of the sea urchin to study more thoroughly the influence of X-rays on individual cells and, especially, on cell division. For this, they referred to the “classical radiation experiments” of the Hertwig family, who had studied the biological effects of radiation on the early stages of development in the 1910s.<sup>47</sup> In the first step in a series of experiments the Langendorffs studied the sensitivity of the cell nucleus at different stages of division. The approach differed from the earlier experiments of the Hertwigs in its quantitative aspect. The Langendorffs studied the effects for a range of X-ray doses and plotted the results as a dose-effect curve. These graphs or *Schädigungskurven* — they used Glocker’s term — showed the increasing effects (“damaging effects”) on the division of the cell nucleus.<sup>48</sup> All through the 1930s the Langendorffs worked on the cellular effects, trying different experimental systems. Hanns spent the most time busy with experiments on spermatogonia of mice — an object that was used by geneticists such as Paula Hertwig, too.<sup>49</sup>

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<sup>44</sup> Langendorff/Sommermeier 1940, p. 196.

<sup>45</sup> Rajewsky, *Theorie* 1935, p. 76.

<sup>46</sup> Jüngling/Langendorff 1932; for experiments with spermatogonia of mice, see Langendorff 1936, p. 71.

<sup>47</sup> Langendorff/Langendorff 1931, p. 97; for the Hertwigs see Schwerin 2004, pp. 123.

<sup>48</sup> Langendorff/Langendorff 1931, p. 101.

<sup>49</sup> Langendorff 1936; Langendorff 1937; Langendorff 1938; For Paula Hertwig, see Schwerin 2004, pp. 122ff.

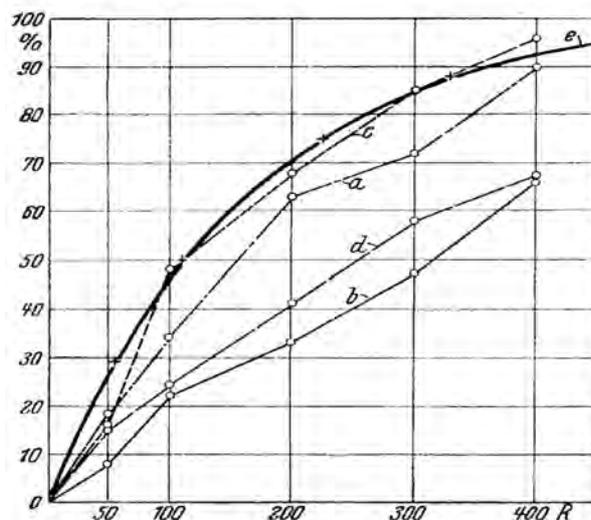


Fig. 4: The damage curve (*Schädigungskurve*) as depicted in the experiments of M. and H. Langendorff. The x-axis shows the X-ray doses; the y-axis shows the percentage of damaged objects. The single curves (a-e) show the effects on different objects (eggs and sperm of sea urchin). From: Langendorff/Langendorff 1931, p. 101.

In fact, all mentioned radiobiological experiments focused on the detrimental effects of radiation. Clear-cut detrimental effects were a subject of multiple interests: (1) These effects were used as a measure for guiding radiological practice. (2) Langendorff expected to get information on the basic biological processes underlying the radiation effects. (3) The experiments were important for radiation safety and the regulation of tolerance doses. Langendorff referred to his experimental mice system when he intervened in the ongoing discussion on the regulation of radiation protection and, especially, on tolerance doses.<sup>50</sup> This multiple meaning of “detrimental” was probably typical for the dose-effect-curve experiments.

### *Radiation Biology, the Cell, and Mutations*

After the Langendorffs moved to Freiburg in 1936 they continued the line of work they had begun in Stuttgart and stayed in close contact with the physicists there.<sup>51</sup> In addition, Hanns took care to establish a base of physical knowledge and skills at the Radiological Institute. He therefore engaged the young physicist Kurt Sommermeyer. The focus of work continued to be the effects of radiation on the *cell*. In fact, the focus on the cell was the legacy of the Glocker school of radiation biology. Hanns and Margarethe Langendorff pointed out:

The knowledge of the effects of X-rays on the cell is necessary to assess the effects on the whole organism, because only the events that happen during and after radiation give the information to conclude what the reaction of the whole cell complex is.<sup>52</sup>

<sup>50</sup> Langendorff 1942, p. 275.

<sup>51</sup> Cf. Schwerin 2010.

<sup>52</sup> Langendorff/Langendorff 1931, p. 97 (trans. AS).

It was crucial that they used the cell nucleus and the states of cell division that were visible under the microscope as parameters to assess the biological effects of radiation. The geneticists also focused on the cell nucleus when they tried to develop a theory of mutagenesis in the 1930s. In other words, this central microscopic space of the cell was the place where the transformation of radiation energy into both biological and genetic effects took place. In that respect the biological group in Stuttgart was quite near to the genetical-biophysical approach. In fact, they also shared the view of the biophysical-genetic theory that the primary effects are independent of the plasmatic physiology.

The modern view of radiation effects on biological objects assumes that the target of the effective quanta of radiation is the cell nucleus and that the primary reaction in the cell plasma has a secondary role. The locus of the primary reaction of radiation is presumably the cell nucleus both in the case of genetic and physiological (non genetic) effects. The assumption is further that the effective, primary processes that are triggered in the nucleus are independent of the state of the object ... [A]n important aim of the biological radiation research [*biologische Strahlenforschung*] is to reveal that the roots of the genetic and physiological effects are the same or to show differences in the primary effects.<sup>53</sup>

The quote shows that the Glocker school considered genetic questions, too. However, their interest was the relation of genetic and physiological effects and mechanisms. Were genetic and physiological processes similar, the same or quite different in terms of their causation? The genetical-biophysical approach ignored this question because geneticists were convinced that mutagenesis was completely independent of cellular control. Thus, the term “*biologische Strahlenforschung*” achieved a programmatic emphasis that was somewhat in opposition to the dogmatic genetical-biophysical division of physiological and genetic effects. This special emphasis resulted in a divergent idea on radiation effects.

Langendorff und Sommermeyer started experiments with *Drosophila melanogaster* in the late 1930s and irradiated some 10,000 eggs. They counted the dead eggs and drew the damage graphs of these numbers. They also compared their results with results on detrimental effects that had been published by genetical-biophysicists such as Zimmer and Timoféeff-Ressovsky.<sup>54</sup> The resulting calculation included the results of estimates of the probability of target hits, mutation rates, the different effects found with different sorts of radiation (X-rays, UV, and neutron beams) and the different absorption spectra of biological molecules.<sup>55</sup> Langendorff und Sommermeyer concluded that the nature of UV and X-rays was quite different: UV rays were likely to affect “genes,” whereas X-rays were likely to effect “morphological rearrangements of the nucleus or chromosomal changes.”<sup>56</sup> In other words, mutagenesis probably involved more than just the physical disruption of genes. The argument of Langendorff and Sommermeyer included some conflicting components

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<sup>53</sup> Langendorff/Sommermeyer 1940a, p. 196 (trans. AS).

<sup>54</sup> Langendorff/Sommermeyer 1940a, pp. 203-204.

<sup>55</sup> Relying on Glocker’s theory about the minimal space that was needed to trigger an effect they assumed that the effects of radiation affected the nucleus primarily. (Langendorff/Sommermeyer 1940a, p. 204)

<sup>56</sup> UV produced more “gene mutations” than X-rays — probably because they targeted “the superficial layers of chromosomes rich in nucleic acid” which resulted in “a disruption of essential catalysts,” i.e., “genes” as biophysical experiments of former members of the Stuttgart group and the Walter Friedrich Institute (Knapp, Reuss, Risse and Schreiber) made probable. (Langendorff/Sommermeyer 1940b, p. 116) X-rays — and the same was true for the primary effects of hard radiation such as neutron beams used in the experiments of Zimmer and Timoféeff-Ressovsky — produced rougher effects including morphological rearrangements of the nucleus or chromosomal changes. (Langendorff/Sommermeyer 1940a, pp. 203-204 and Langendorff/Sommermeyer 1940b, p. 110)

because the mentioned “morphological rearrangements” opened a space between the genetical-biophysical and physiological effects. Langendorff and Sommermeyer proceeded to test their assumption, and in the course of their experiments they came upon some irregularities. It seemed that the developmental processes influenced the radiation effects.<sup>57</sup>

Obviously, there was a non-physical factor that influenced the effects of radiation on both the biological *and* genetic side.<sup>58</sup> The results of Langendorff and Sommermeyer seemed to suggest that mutagenesis involved some cellular processes. This was in contradiction to the strict genetic-centered target theory that conceptualized mutagenesis as a physical process.<sup>59</sup>

The crucial questions — Did time effects exist? What was the critical cell volume involved? — remained relevant. The beginning of World War II and its devastating progress did not hinder the German radiation biologists, geneticists, and biophysicists from addressing this topic. The discussion on the disputed topics embraced both the genetical-biophysical group located in Berlin and the proponents that came from radiation biology and medical physics. The results were documented after the war in a volume of the FIAT review series (Biophysics, Part I) that was dedicated to the research on the target theory, gene theory, and biological effects of radiation. It featured Hans Bauer, Hans Friedrich-Freksa, Ulrich Henschke, Hanns Langendorff, Boris Rajewsky (and several of his co-workers in the Kaiser Wilhelm Institute for Biophysics), Manfred Schön, R. Schulze and Kurt Sommermeyer. The irony was that the genetical-biophysical approach was not well represented in that volume since its proponents, including Timoféeff-Ressovsky, Zimmer, and Hans Stubbe, stayed in the USSR or were in some way or another hindered because of the aftermath of the war.<sup>60</sup>

To sum up: Genetic target theory was in no way as monolithic as the historical narratives of the “Three Men” paper have suggested. The experimental field of target theory was a quite complicated configuration of biological experiments, calculations, and physical theory. The target theory built on an intellectual and experimental past (medical physics) as well as theoretic interests related to general problems of life sciences (Delbrück). The target theory was part of a lively discourse on the effects of radiation that involved geneticists and physicists who were interested mainly in genetics and radiation biologists and physicists coming from medical physics. It is worth emphasizing that this discourse was not a discourse on the genetic target theory in the first place. The medical physicists and radiation biologists were interested in the fundamental effects of radiation in an organism and, to be precise, in the cell. As in the case of the Stuttgart group, they considered genetics, but they viewed the genetic target theory as a special case of a general theory of biological effects of radiation.

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<sup>57</sup> They excluded the common assumption that the witnessed time factor was the effect of the recreation of the cells from the radiation effects. (Langendorff/Sommermeyer 1940c, p. 128)

<sup>58</sup> The clue to that result was a time effect during radiation. The longer the radiation endured the more the outcome differed. In other words, the radiation time influenced the outcome. The Langendorffs assumed that this was due to the developmental processes since the eggs were still developing while they were irradiated. Thus, the fertilized egg changed fast — faster than any gamete or somatic cell — providing the chance to observe the influence of physiology during a single experiment. This observation was striking because the genetic target theory assumed that time played no role in the effects of radiation.

<sup>59</sup> Sommermeyer suggested together with the physicist Ulrich Dehlinger — a pupil of Glocker — that the theory of Timoféeff-Ressovsky, Delbrück, and Zimmer was wrong in a crucial aspect: the mutation was not a result of a direct effect of radiation or a one-step reaction. Instead, the two physicists argued, there was a reaction chain — taking place within the structure of hereditary material — leading to a mutation. (Sommermeyer/Dehlinger 1938, p. 68)

<sup>60</sup> Rajewsky/Schön 1948.

Medical physics focused on cellular spaces as active parts in mutagenesis, whereas the genetic target theory tended to ignore the cellular milieu of the genetic material almost completely. In the view of genetical-biophysicists, the environmental influence affected the genes directly. Mutations were the immediate product of this influence. This was best represented in the linear graph that indicated a direct correlation between external physical influence and genetic effect (see above, figure 3). There was no delay — physical effect and the emergence of a mutation happened almost at the same moment. In any case, the view of a *cell-free causation of mutations* corresponded quite well with the general assumptions of Mendelian genetics: mutations happen spontaneously and there is no way to determine the heritage externally — be it by environmental or physiological influences. This was the anti-Lamarckian heritage of experimental genetics.<sup>61</sup> And that is why the idea that cell physiology played any role in the process of mutagenesis was off-limits for geneticists.

### Some Doubts

It was not only radiation biologists who questioned the genetical-biophysical dogma. In 1933, the geneticist Hans Stubbe reported that the irradiation of *Antirrhinum majus* did not directly correlate with the mutation rate. In fact, the dose-effect graph did not show a continuous curve but a line with a peak and a drop (see figure 5). Obviously, there was no direct correlation between dose and effect as the genetical-biophysical model of mutagenesis suggested. This graph was more similar to graphs of radiobiological measurements. Stubbe was only able to explain this “anomaly” by referring to biological variability. He assumed that there were loci with different sensitivities to radiation in the nucleus. This variability of the biological substance would explain the deviation from the “ideal” genetical-biophysical dose-response curve.<sup>62</sup>

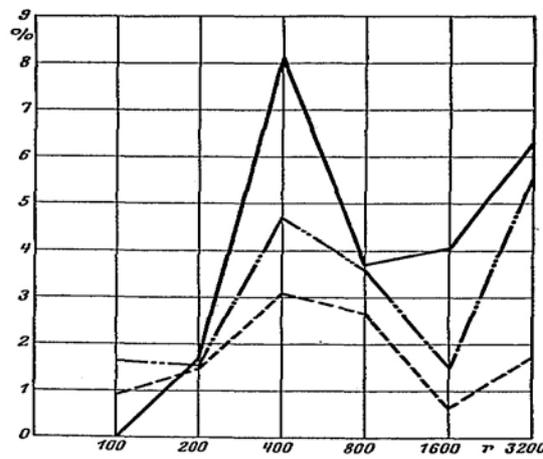


Fig. 5: The experiments of the geneticist Hans Stubbe contradicted the basic assumption of genetic mutation and target theory that mutagenesis was a physical process that showed linearity in the measured relation of external disturbance (radiation, trigger) and effects (hits, mutations). From: Stubbe 1932, p. 189.

<sup>61</sup> See, for instance, Timoféeff-Ressovsky’s historical account of mutation research (1937, pp. 8-13) and Oehlkers’s description of contradictions between Mendelian genetics and the theory of evolution (1927, p. 166).

<sup>62</sup> Stubbe 1932, p. 200; see also Stubbe 1934, p. 262.

Stubbe's results provoked a reaction from geneticists such as Timoféeff-Ressovsky who were keen to show that mutations were a direct effect of irradiation.<sup>63</sup> As long as the genetic target theory was hegemonic, there were many arguments about why these deviations should be seen as artifacts and why they did not call the genetic target theory into question. However, all these experimental results coming from radiation biology and within genetics were a challenge and kept the discussion alive through the 1930s and 1940s.

### *Chromosomes and the Physiology of Mutations*

Up to now I have shown the legacy of medical physics. One result of this legacy was that the tradition of radiobiological research strengthened a cellular view of mutagenesis. The next step is to show that this view of *physiological mutation concepts* was common in biology. This section will show that there were quite a number of different approaches to mutagenesis that were partly opposed to genetic target theory. The proponents were biologists and geneticists who had no contact with physicists.

Jonathan Harwood's book on the German genetics community, *Styles of Scientific Thought*, analyzes the field of hereditary research in Germany until 1933. But what kind of research were German geneticists pursuing in the 1930s? From the data given by Ute Deichmann, it can be concluded that quite a number of biologists undertook chromosomal research. Based on the distinction of Harwood, most of them represented a "comprehensive" research tradition: the botanist Otto Renner in Jena was busy with cytological work on chromosomes and mutations; Friedrich Oehlkers in Freiburg worked on meiosis using *Oenothera* (supplied by Renner) as did Fritz von Wettstein and his co-workers Joachim Hämmerling and Hans Bauer.<sup>64</sup> Obviously, mutations were among the most discussed genetic topics at that time in Germany.

The school of Friedrich Oehlkers was paradigmatic for the mutation research done at these places: they did not embrace biophysics and disregarded the genetical-biophysical research paradigm. In fact, Freiburg was internationally well known for the biological research done there and especially for the Black Forest School of botany.<sup>65</sup> Oehlkers, who was head of the botanical institute, had published significant work on cell division and meiosis, and his research was well situated at the boundary of developmental physiology and genetics. Oehlkers explained that he was interested in the old problem of how plasma might influence the hereditary outcome; Harwood has shown that this problem was still relevant in the view of many German biologists.<sup>66</sup> Oehlkers was interested in how physiological factors influenced the timing and course of cell division as well as the determination of sex. He studied different factors such as temperature, the amount of chlorophyll, and "very modern substances" such as biologically active agents (hormones).<sup>67</sup> Oehlkers and his school did not share their study questions or their methods with biophysics or radiation biology as the Stuttgart School did.

Nevertheless, Oehlkers and his school were a hotspot in the ongoing biophysical discussion about mutations. Cytologists including Oehlkers were far from adopting ideas on mutations such

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<sup>63</sup> In the case of Stubbe, see Timoféeff-Ressovsky 1934a, p. 463; Timoféeff-Ressovsky 1934b, pp. 420-421.

<sup>64</sup> Deichmann 1995, pp. 93-105, 98-100 and the charts with tabulated information on pp. 78 and 84; Harwood 1993, *passim*.

<sup>65</sup> Harwood 1993, pp. 79-80; Sander 1995.

<sup>66</sup> Deichmann 1995, p. 93.

<sup>67</sup> Straub 1937, p. 1149.

as the ones developed by biophysical geneticists. They criticized biophysicists and geneticists for using mutations mainly as a device in order to learn something more about the gene. Oehlkers and his assistants claimed that they were more interested in the very nature of mutations. The deep-rooted suspicion was that mutagenesis involved physiological processes and could not be understood purely in physical terms.

The boundary object between cell biologists and mutation genetics became the chromosome. Chromosomes had been a topic of mutation research since the early 1920s.<sup>68</sup> However, chromosomal genetics started to boom only in the 1930s. One reason was the discovery of polyploidy and the attempts of botanists to induce polyploidy artificially. The other reason was the discovery of the giant salivary gland chromosomes that stimulated a new morphological approach to gene research. The increased interest in chromosomes was manifested in the publication of a new journal; the first issue of *Chromosoma* appeared in 1939. Here, chromosomes were represented as cellular entities and not as abstract units of hereditary traits as in the early gene maps of experimental genetics.<sup>69</sup> Chromosome research was a matter of cell biology.

It was right in the course of the boom in studying chromosomes that cell biology met genetics. Chromosomes had been the crucial research objects for Oehlkers and other biologists for a long time. And chromosomes now directed them towards mutation research. However, for the cytologists it was quite plausible that changes in the chromosomes involved physiological mechanisms. Also, the distinction between chromosomal changes and gene mutations became a matter of heated debates — not least because this topic concerned gene theory, too. Cytologists were willing to link the physiology of chromosomes and their changes to gene mutations. In effect, chromosome research opened the space for a cellular and physiological approach towards mutagenesis as whole.

One assistant of Oehlkers, Hans Marquardt, was very much involved in this discussion. At an assembly of the German Botanical Society he pointed to the heart of the genetic target theory. At that time, he summarized, there were two approaches in experimental mutation research: the genetic and the cytological.<sup>70</sup> He claimed that the basic assumptions of the genetic approach and target theory were deceptive. His diagnosis was that the genetic target theory was at a dead end. The genetical-biophysical approach was able to describe the energetic side of the effects of X-rays and to propose a biophysical view on mutations.<sup>71</sup> However, the cost was a limited horizon because the genetical-biophysicists only considered “so-called gene mutations” within a very special experimental design.<sup>72</sup> And this approach became an obstacle when one wanted to address mutations comprehensively. Marquardt’s idea for himself was instead to be engaged at the boundary between genetics and cytogenetics with the aim to bridge the two approaches by studying a common problem: mutations.<sup>73</sup>

The crux of Marquardt’s argument was the reference to research on chromosomes. He referred to results of quite a number of researchers — including Catchside, Stadler, Sacharov, Slizynski — and to his own work on the “Röntgenpathologie der Mitose.”<sup>74</sup> Like other chromosome researchers, Marquardt distinguished phenomenologically different classes of chromosome

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<sup>68</sup> See Campos, “Mutant Sexuality: The Private Life of a Plant” in this volume.

<sup>69</sup> Falk 2004.

<sup>70</sup> Marquardt 1938a, p. 108.

<sup>71</sup> Marquardt 1938a, p. 110.

<sup>72</sup> Marquardt 1938a, pp. 110-111.

<sup>73</sup> Marquardt 1949, p. 31.

<sup>74</sup> Marquardt 1938b; Marquardt 1938c; Marquardt 1941.

changes: chromosome condensation (pyknosis), breakages, translocations, etc. Marquardt proclaimed that the proponents of the target theory wanted to reduce this diversity to only one primary event but this was not possible. This was quite provocative because Marquardt had in mind that the primary effects of radiation differed not only in quantity — as in the genetical-biophysical model — but in quality, too. From 1941 on, Marquardt argued that there were at least two kinds of targets — “Restitutionstreffer” and “Fragmentationstreffer.”<sup>75</sup> From that perspective, the linear relationship between radiation dose and effect was an artifact of the biophysical experimental system whose only purpose was to hide the underlying differences and physiological mechanisms. In 1946, Marquardt referred to the English physicist D. E. Lea as a chief witness (Kronzeuge), calling on him to testify that there were different physiological mechanisms to distinguish.<sup>76</sup> Lea had suggested that some special substances emerged after irradiation that led to variable disruptions of chromosomal function.<sup>77</sup> Marquardt’s assumption was that the disturbances of the metabolism of the nucleic acids in the cell and in the nucleus were responsible for at least some of the various phenomena (“aberrations” of chromosomes).<sup>78</sup> He saw all of these results and pieces of circumstantial evidence as contradicting the genetical-biophysical model.

The crucial advantage of this [only preliminary] interpretation is that the events that lead to the breakage [of chromosomes] are connected most tightly with the gears of the metabolism (*Stoffwechselgetriebe*) of the cell and its current physiological condition. With this, it seems that the point of departure of the biophysical interpretation — a premise that has always been suspicious in the eyes of biologists and one that features the chromosome as a completely independent object without considering the cell, constructed of molecular, formal target areas and that restricts itself to viewing the entire cell action as its projection in terms of hypothetical changes in the number, size, and energetic performance of these molecular areas — this premise has been lost by now.<sup>79</sup>

The crucial point of Marquardt’s argument — which generally represented a chromosomal mode of critique — was that “gene mutations” were in many cases not changes at the molecular level of single genes but larger rearrangements and, thus, were not really gene mutations.<sup>80</sup> In fact, there were more and more indications that chromosomal changes were predominant. This view was in harmony with the opinion that the status of genes was *per se* unclear. On the extreme end, the geneticist Richard Goldschmidt was skeptical about the existence of genes and gene mutations at all. Although Marquardt was no follower of Goldschmidt he claimed:

The separation of chromosomal and gene mutations so popular in German literature (see Timoféeff-Ressovsky and Zimmer) is out of date thanks to the new results of cytological research on *Drosophila* and corn. ... After this development, mutation research is not conceivable any more without a thorough investigation of the status of the chromosomes.<sup>81</sup>

Marquardt’s suggestion that there were different kinds of primary events met with harsh opposition. The botanist and geneticist Hans Bauer responded on behalf of the proponents of the

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<sup>75</sup> Marquardt 1941; Marquardt 1949, pp. 42-43.

<sup>76</sup> Marquardt 1949, p. 32.

<sup>77</sup> Marquardt 1949, p. 34.

<sup>78</sup> Marquardt referred to experiments of Mitchell and v. Hevesy on the changes in metabolism after irradiation. (Marquardt 1950, p. 417)

<sup>79</sup> Marquardt 1950, p. 438 (trans. AS).

<sup>80</sup> Marquardt 1938a, p. 111.

<sup>81</sup> Marquardt 1950, p. 416 (trans. AS).

genetic target theory.<sup>82</sup> When he published his objections in the *Zeitschrift für Botanik*, it was a striking exception since Bauer normally published in genetics journals (*Zeitschrift für induktive Abstammungs- und Vererbungslehre* and *Chromosoma*), whereas Marquardt published in journals for botany or cytology (*Zeitschrift für Zellforschung u. mikroskopische Anatomie*, *Zeitschrift für Botanik*, *Planta*). Bauer himself was studying mutations and was convinced that his results supported the target theory: the whole process of chromosomal mutations — the breakage and recombination — occurred in a single step.<sup>83</sup> The dispute between Marquardt and Bauer was just one of several disputes between the biophysical and the physiological camps at that time. However, in the late 1940s, Marquardt felt himself to be on the right track.

Apart from the argument that has been limited to Germany, it seems that there is some unrest developing in the judgment on the emergence of aberrations. The insight is growing that the physiological events (that take place after the absorption of the energy and before the microscopic manifestation of the effects) are not of minor importance nor must they be treated only formally as they are in the target theory approach; on contrary, they constitute the real main problem. ... Admittedly the metabolism of nucleic acids has been integrated in the experimentation, but only using morphological methods; instead it is necessary to examine the physiology and the physico-chemical condition of the chromosomes.<sup>84</sup>

### *The Physiology of Mutations*

What kind of evidence for physiological effects did the proponents of a biological view of mutations have at hand? An impression can be gained from a short glimpse at the Kaiser Wilhelm Institute for Breeding Research, which was one of the partners of Oehlkers's institute. The KWI had run a department for mutation research since the glory days of the first director Erwin Baur. After Baur's death in 1933, the institute not only became a Nazi stronghold but also changed in terms of biological thinking.<sup>85</sup> The new head of the mutation department, the botanist Edgar Knapp, did not continue the line of quantitative radiation genetics that had been established by Hans Stubbe.<sup>86</sup> Before Knapp came to the KWI, he had served as an assistant to Fritz v. Wettstein in Munich and Berlin and had worked on problems of developmental biology. He introduced the moss *Sphaerocarpus* as a model organism, and it became one of the important model organisms at Wettstein's Kaiser Wilhelm Institute for Biology.<sup>87</sup> Wettstein recognized the originality of Knapp and fostered his talent; nevertheless Knapp was one of the few who did not recognize Wettstein's politically liberal management of the institute, but openly pronounced himself for the "new state," i.e., the Nazi regime.<sup>88</sup>

Like Marquardt, Knapp aimed to bridge the gap between genetics and cytology with "cytologic-genetic studies of the genome."<sup>89</sup> He had at his disposal two assistants and technical personnel, and he was keen to investigate the significance of the physiological state of the cell in

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<sup>82</sup> Bauer 1942; Marquardt 1942.

<sup>83</sup> Bauer 1939, p. 386.

<sup>84</sup> Marquardt 1949, p. 43 (trans. AS).

<sup>85</sup> Heim 2003, pp. 33-49.

<sup>86</sup> For Stubbe see Heim 2003, pp. 200-246; for the KWI before 1933 see Harwood 1993, pp. 195-226.

<sup>87</sup> Gausemeier 2005, p. 134.

<sup>88</sup> Gau-Dozentenbundführer to Reichsministerium für Wissenschaft, Unterricht und Volksbildung, Bundsarchiv Berlin-Dahlewitz, 4.11.1936, ZB II, 1979, A.10.

<sup>89</sup> Knapp an DFG, 9.1.1942, BAK, R 73, 12199.

terms of mutability within a “bigger work programme.”<sup>90</sup> Additionally, Knapp established a good working cooperation with the biophysical institute of Walter Friedrich in Berlin.<sup>91</sup> One of his assistants was the geneticist and plant physiologist Reinhard Kaplan who later formulated a mathematically informed critique of the genetic target theory.<sup>92</sup> Knapp’s plan was to investigate a number of physiological parameters and how changes in them influenced the frequency of induced mutations. The most promising candidate was the amount of absorbed water in the cell. It was already known that the effects of radiation on proteins differed based on the amount of water. Now, the experiments of Knapp and his co-workers suggested that the water content of the cell influenced the way radiation affected the integrity of the chromosomes.<sup>93</sup> Furthermore, the experiments suggested that this physiological factor had the power to alter the cell’s susceptibility to radiation and thus the rate of mutations.

The problem that Knapp and his co-workers tackled was not completely new. The work of the geneticist Stubbe demonstrated that geneticists were aware of the problem of individual susceptibility. Generally, however, geneticists denied that the susceptibility of one individual changed over time; they believed there were only differences between *different individuals of one species*. They assumed that genetic factors were responsible for that effect.<sup>94</sup> The experiments of Knapp’s group instead highlighted physiological changes *within one individual*.

Considered rationally, the “physiological” peculiarities were more a support of the general target theory of the Glocker school. However, for Knapp they were the sought-after bridge to his physiological mutations program, which he had only just started.<sup>95</sup> The findings were a kind of precedent showing that the inconsistencies of the dose-effects curves of the genetical-biophysicists had physiological reasons. The general view of the genetic target theory was, Knapp summarized,

that the genetic effects of radiation occurred directly. However, my experiments made it likely that at least in the case of *Sphaerocarpus*, mutations are partially induced indirectly, i.e., genetic changes are the consequence of general cell physiological disruptions that were elicited by the irradiation.<sup>96</sup>

Knapp then explained why this kind of approach had thus far been hindered and pointed to the contemporary genetic dogma of the stable genotype that is only changeable by a contingent, sudden physico-chemical event called a mutation. The difficulty is

that we are used to seeing the “gene” or the “genetic substance” in the chromosomes as chemically unchangeable. But different physiological states constitute different environments that influence the “genetic substance” and might explain the differences in the mutability. If it is the case that the physiological status influences the rate of mutations inducible by radiation then it is not plausible that the “target area” belongs to the “genetic substance,” but rather extends over a wider area and comprises different substances that pass the energy on to the genetic substance. The former view always assumed that the “genetic substance” was chemically not changeable. It is more plausible to assume reversible changes in the “genetic

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<sup>90</sup> Knapp/Kaplan 1942, p. 503.

<sup>91</sup> Knapp an DFG, 9.1.1942, BAK, R 73, 12199.

<sup>92</sup> Kaplan 1950.

<sup>93</sup> Knapp/Kaplan 1942, p. 502. The PhD student and biologist Ernst Wertz did a large part of the experimental work at the Department for Mutations Research of the KWI. In 1940, his PhD was published in five parts in the *Strahlentherapie*.

<sup>94</sup> Knapp 1939, p. 839.

<sup>95</sup> Knapp carefully followed the cytological research on the structure of chromosomes and chromosomal changes. (BAK, R 73, 12199)

<sup>96</sup> Knapp an DFG, 18.12.1935, BAK, R 73, 12199 (trans. AS).

substance” that are not mutations — such as colloidal changes, changes in the connection of water to hydrophilic structures. ... Therefore my suggestion is that the differences in the frequency of mutations of the same genotypes in cells with different physiological status are partly determined by the different hydration of the genetic substance. ... These influences are reversible.<sup>97</sup>

## Conclusions

In the late 1920s and 1930s, the biological effects of radiation were epistemic objects of a transdisciplinary research field involving physicists and biologists. The genetic effects that are *mutations* became the core problem and organizing principle of the discursive and experimental exchange in the 1930s. Historic narratives that concentrated on the theoretical innovation of the *genetic target theory* have failed to grasp that interconnection. In particular, they were misleading when they concentrated on a few protagonists — mostly the later famous proponents (e.g., Max Delbrück) — and described the genetic target theory as a static attempt, albeit an early one with respect to the emergence of molecular biology.

A genealogical “reading” reveals a broader context of the emergence and development of the genetic target theory. It opens up a space of mutation research with concepts in a state of flux. The examples in this paper show that there was a quite lively discourse on the genetic target theory in Germany. The research field involved biophysicists, radiation biologists, geneticists, and cytologists. The discussion was in part driven by the anomalies of the target theory that were produced in the experiments of *quantitative mutation genetics*. Nevertheless, the discourse reflected the increasing strength of experimental genetics that was accompanied by skeptical and adaptive biological thinking on the one hand and the boom of chromosome and mutation research in the 1930s on the other.

It is not possible to differentiate clear-cut groups within that field since there were multiple overlaps among the protagonists with respect to convictions, legacies, methods, and objects. Nevertheless, I think it makes sense to differentiate loosely three groups in terms of their convictions on the nature of radiation effects: (1) *biophysicists proper and radiation biologists* and the juncture of biophysics and biology (e.g., Glocker and the Langendorffs), (2) *genetico-biophysicists* and the juncture of genetics and biophysics (e.g., Delbrück, Zimmer, Timoféeff-Ressovsky), and (3) *physiologists*, biologists who did not work in cooperation with biophysicists (mainly cytologists, e.g., Oehlkers, Marquardt, Knapp).

The difference became clear and sharpened in the discussion on the genetic target theory. The objections to the genetic target theory ranged from modest critiques to strict rejection. There were the biophysicists (group 1) who invented the target theory as a model for the biological effects of radiation. They viewed genetic mutation as a special case of a broader problem. There were biologists (1 & 3 and some from 2) who suggested that the anomalies in the dose-effect curves of the genetico-biophysicists (2) were not artifacts but hints about mechanisms beyond genetico-biophysics. The “physiology question” proposed by radiobiologists (1) and then by botanists and cell physiologists (3) resulted in a permanent irritation amidst the inner genetico-biophysical discourse and forced the genetico-biophysicists (2) into ever more rigorous experiments on mutation rates. This was one reason that quantitative genetics was so tied to mutations rates all

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<sup>97</sup> Knapp 1939, p. 839 (trans. AS).

through the 1930s and 1940s.

Also, the debate strengthened critical voices within the community of quantitative mutation geneticists who expressed skepticism about whether the biophysical approach was the best — Hermann Muller (in the U.S.) or Hans Stubbe (in Germany) are examples for that position. Actually, it would be worthwhile to explore in greater detail the dynamics and the context of this debate. The influence of the genetic target theory decreased rapidly after the war. In Germany, radiobiologists such as Hanns Langendorff, Hans Marquardt, and Reinhard Kaplan dominated the discussion on mutations and all three were heavily involved in the national atomic radiation safety program.

There are three points to be made regarding the development of biophysics in Germany.

1. *The legacy of medical physics*

Radiotherapy was the initial force behind a series of social changes and experimental re-configurations that affected physics, biology, and genetics. At the heart of this cascade was the technical problem of controlling the administered radiation dose in biological matter. The group of medical physicists that formed within that context was revealed to be technically and theoretically innovative in different fields. (The physicist Richard Glocker also became famous for his work on the structure of metals and for his invention of X-ray crystallography for use in metal research and materials testing.<sup>98</sup>) The experimental and theoretical work of medical physicists became the starting point for a more intense collaboration between physicists and biologists from the late 1920s on. *Practical questions were the major driving force in the whole cascade of these intersections: questions about radiation therapy, eugenics, and radiation safety. In the case of genetics, medical physicists assisted geneticists with dosimetric questions. In the case of radiation biology, biologists helped medical physicists with the discovery of new model organisms.*

The experimental, theoretical, and practical context reveals that the genetic target theory was not the simple and logical product of a research alliance of geneticists and theoretically interested physicists such as Max Delbrück (inspired by Niels Bohr). It was also based on the legacy of medical physics, which developed the target theory in the early 1920s in the context of radiology.<sup>99</sup> The achievement of the medical physicists' approach was the abstraction from the cell and the quantification of radiation effects. It turned out that the dose-effect curve best fitted the problems of mutation genetics because this approach was quite complementary to the formal-quantitative approach of Mendelian genetics and was appropriate to measure the dysgenic threat of the medical application of X-rays. Hence, there was a direct link between the approach of quantitative genetics and the eugenic discourse in Germany.

Thus, the genetical-biophysical understanding of mutagenesis was based on the practical context of radiology and the need to rationalize the use of X-rays in medical therapy, i.e., to find a simple and calculable description of the effects of radiation. The physicist Karl G. Zimmer represented this conjunction *in persona*. However, the radiobiological target theory was not *per se* a hindrance for a biological view on mutagenesis, as shown by the example of the Glocker school. *The genetic target theory was the double outcome of the methodological offerings of medical physics and the dogma of experimental genetics that there must be a fundamental division of cell physiology and genetics.*

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<sup>98</sup> For a detailed analysis see Maier 2007, pp. 235-243.

<sup>99</sup> One argument here was the migration of the term *Schädigungskurve* (used by Glocker and later by geneticists including Timoféeff-Ressovsky) and the use of the dose-effect curve for the purposes of radiation genetics. The dose-effect curve was an invention of medical physicists in the context of

## 2. *The role of animal models*

The three-fold connection among genetic research, practical interests, and genetic mutation theory was further reinforced by the choice of model organisms. The *Drosophila* system was revealed to be quite valuable for quantifying the fragility of genes and the hazardous effects of environmental influences such as radiation. This was no accident. It is well known that Hermann Muller designed the *Drosophila* system to give the clearest evidence that radiation induces mutations. Actually, *Drosophila* was revealed to be ideal both for generating striking events *and* establishing a clear relationship between physical stimulus and genetic effects. It was easy then to calculate mutation rates and prove the mutating effects of the environment. Thus, the *Drosophila* system functioned for some years both as an experimental system of genetic research and as a test system quantifying the genetic threat of mutations.

Due to their botanical and physiological work tradition, Oehlkers, Marquardt, and Knapp used different objects. Oehlkers developed a variety of moss (*Riccia fluitans*) for his botanical research — an object very suitable for studying the influences of the plasma that Oehlkers hypothesized. *Drosophila* was good for calculation but not for cell physiology, and cell biologists concluded that moss was much more suited to combine physiology, chromosomal, and mutation studies. Thus, the use of different organisms divided the research communities of cell physiologists and geneticists. Chromosomes and mutations functioned as boundary objects of the two different research contexts. However, this was a connection that did a connection that did not even leave ideas about mutations unmutated, but changed the conceptualizations of mutations, too.

## 3. *The legacy of cytology and chromosome research*

The zoologist Hermann Dotterweich was the author of a now-forgotten book with the title *The Biological Equilibrium*. The book was an attempt to work out a theory of physiological homeostasis that balanced the organism and environmental influences. Dotterweich called the connection of the two “biotisches Gefüge,” which included the emergence and “regulation” of mutations.<sup>100</sup> The standpoint of Dotterweich was obviously a rather esoteric one but it nevertheless points to a different conceptualization of the relation between the environment and the organism.

The biophysical geneticists were focused on external influences such as radiation and chemicals, seeing these as aspects of a *dangerous and technically shaped environment* that called for control. This attitude corresponded very well with their interest in mutations as instruments for gene theory and, hence, the interest in the physiology-free, pure genetic effects of radiation. In contrast, in the view of the physiologists, the environment of genes began in the cell; this environment was *not hostile but a biological object* of research. Likewise the mutations of the physiologists were *biological* objects, and the organism was an active part in the process of mutagenesis.

Mutagenesis in genetical-biophysical terms was an almost space-less process: the cell played no role, the transformation of radiation into a genetic effect needed almost no spatial or temporal extension. The work of radiation biologists on the edge of radiology and genetics opened a *space between the environment and the genetic material*. The impact of the experimental clashes in the 1930s was immediate. The idea that physiology influenced the emergence of mutations stimulated research in chemicals. Geneticists had suggested repeatedly that the chemicals such as tobacco might result in an increase in mutations. It was only in 1943, however, that Charlotte Auerbach

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radiology. However, this plausible connection remains to be proven.

<sup>100</sup> The term “biotisches Gefüge” refers to Woltereck. Dotterweich 1940, p. 11. For example, Dotterweich investigated the effects of hormones on mutagenesis.

showed that mustard gas induced mutations.<sup>101</sup> Less well known is that Friedrich Oehlkers achieved the same result with *Oenothera* at the same time — using inorganic substances, alkaloids, and narcotics.<sup>102</sup> In this context, the discovery of chemical mutagens was another way to think of mutagenesis in physiological and biochemical terms.

The physiological approach towards mutagenesis opened up a space of cellular mechanisms that translated the effects of external physical agents into physiological terms.<sup>103</sup> It was not until thirty years later, in 1969, that one of the most prominent proponents of genetic mutation research — Charlotte Auerbach — claimed that mutations are not quantum events, they are not physical events, they are not chemical reactions but rather they are biological and cellular processes.<sup>104</sup> It is a task of its own to draw that historic line of “physiologization” of mutations — and, hence, of the activation of the organism as an actor of its own in the process of the transformation of external stimuli into mutations.

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<sup>101</sup> The results of this research were kept secret until the end of the war. Auerbach 1949.

<sup>102</sup> Auerbach 1976, p. 346.

<sup>103</sup> The physiological approach was a quite different question than that of “Dauermodifikationen; it aimed at the nature of genetic mutations.

<sup>104</sup> Kimball in Wolstenholm 1969, p. 1; Auerbach 1976, p. 11.

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## *Making Marigolds: Colchicine, Mutation Breeding, and Ornamental Horticulture, 1937-1950*

*Helen Anne Curry*

On January 29, 1940, a representative of the W. Atlee Burpee Seed Company appeared at the Waldorf-Astoria in New York City to promote his company's latest flower innovation. In a presentation to horticulturalists and amateur gardeners, the plant breeder Burr Robinson described the Tetra Marigold, a deep orange flower with blossoms four inches across. His boss David Burpee had earlier hailed the plant as the "first new flower ever created by the use of a chemical."<sup>1</sup> For home gardeners wishing to know more, the 1940 Burpee Catalog explained the chemical process behind the marigold's production and its desirable traits, "Colchicine, the powerful chemical made from the fall crocus, was applied to Guinea Gold Marigold. It caused the doubling up of the cell contents and this new marigold is consequently big and strong growing. It is a "Tetraploid."<sup>2</sup> In its 1940 promotional activities and in the catalogs and advertisements of subsequent years, the Burpee company consistently emphasized to its customers the chemical origins of the Tetra marigold, often to an extent that overshadowed its other qualities. Nor was the Guinea Gold marigold the only plant to receive such treatment. Over the next decade, the Burpee company would introduce a range of colchicine-treated tetraploid varieties, from snapdragons to zinnias to phlox, applying colchicine in a variety of ways to produce changes in its flowers.<sup>3</sup>

The Burpee company was not alone in its interest in the use of colchicine to improve plant varieties. Two years before the Burpee company placed splashy images of giant tetraploid marigolds in its advertisements, a drier set of tetraploid marigold images accompanied an article in the *Journal of Heredity*. In that piece, the biologists Bernard Nebel and Mabel Ruttle of the New York State Agricultural Experimental Station at Geneva, New York described their initial forays into the use of colchicine. They had successfully created tetraploids of a number of common ornamental flowers as well as a tomato plant, work they called "plant breeding with non-Mendelian methods." In their estimation, these methods would generate significant economic returns through the improvement of agricultural and horticultural varieties.<sup>4</sup> The colchicine studies of Nebel and Ruttle, and similar work undertaken at nearly the same time by other researchers, produced dramatic evidence for the possibility of using colchicine to consistently generate polyploid plants in a wide range of species. These successes led to a such a flurry of investigation into colchicine-induced tetraploidy that one scientist soon referred to it as the "Colchicine Fad." It was this so-called fad that in turn led to the creation of a variety of colchicine-created ornamental plants in the 1940s and

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<sup>1</sup> "Chemical-Created Flower Put on Exhibition Here," *New York Times*, January 30, 1940.

<sup>2</sup> *Burpee Seeds for 1940* (Catalog), W. Atlee Burpee Co., Philadelphia, Penn. Collected in Trade Literature Collection, National Museum of American History (TLC-NMAH), Smithsonian Institution, Washington DC.

<sup>3</sup> Tetraploid phlox and snapdragons were introduced in the late 1940s; tetraploid zinnias were not available until the late 1950s.

<sup>4</sup> B. R. Nebel and M. L. Ruttle, "The Cytological and Genetical Significance of Colchicine," *Journal of Heredity* 29, no. 1 (1938), p. 9.

1950s.<sup>5</sup>

The apparent enthusiasm for plants “created by a chemical” could be seen not only in the commercial field and the laboratory, but also in home gardens. Buying seeds of Burpee’s tetraploid marigolds or “Tetra Snaps” (the colchicine-treated snapdragon varieties) would be in time be the simplest option for gardeners hoping to observe the growth of a colchicine creation, but they did not necessarily have to wait for the commercial releases. From the earliest public notice of the research, non-scientists asked for and received instructions on how to manipulate plants’ chromosomes with colchicine on their own. That they always achieved or understood the changes researchers described (i.e., produced polyploid plants) is doubtful; however, as this paper will show, the act of creating visibly changed or mutated plants, as opposed to “improved” varieties, and thereby participating in this scientific process seemed to satisfy the ambitions of many gardeners.

Through a history of the use of colchicine in the United States to create new plant varieties, this paper explores the role of induced mutations — which in the case of colchicine included both heritable polyploidy and other (not ploidy-related) observable, inheritable changes — in ornamental horticulture in the 1930s and 1940s.<sup>6</sup> As the circulation of both new plant varieties and the chemical colchicine indicated, geneticists and academic breeders, commercial horticulturalists, and gardeners all responded favorably to the use of colchicine to produce changes in plants. However, their interests and expectations were by no means uniform. For geneticists and breeders at governmental and academic research institutions, the inducement of heritable polyploidy was a useful tool for investigations in cytology and genetics. It also promised enhanced control over the evolution of new plant varieties: these men and women sought through the selective application of colchicine to cross varieties hitherto uncrossable and to selectively induce chromosome doubling where they believed it to be desirable. By comparison, seed sellers such as Burpee were only partly interested in colchicine as a tool for the directed evolution of new plant varieties; more often, they used it as a tool to generate novel forms, in some cases spraying fields with the chemical liberally in the hopes of disrupting their genetics and producing a new color, shape, or other characteristic that would be interesting for the market. Burpee hoped that colchicine could be used to cause what he called a “bust-up” — an event in which many individual plants in a large planting would suddenly display new and strikingly different characteristics. Home gardeners exemplified a third perspective on the use of colchicine. In addition to purchasing the new colchicine creations as either novelties or improved varieties, they sought to test the effects of the chemical themselves. These individuals wanted to experience the technology behind the manipulation of plant genes and the production of the new tetraploid varieties; to them, the means appeared to have been as interesting as the ends.

Although the mutagen and the mutant plants held a unique significance for each group, they

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<sup>5</sup> S. J. Wellensiek, “The Newest Fad, Colchicine, and Its Origins,” *Chronica Botanica* 5 (1939).

<sup>6</sup> Ornamental horticulture, whether pursued by amateurs or professionals, only rarely appears in the historiography of modern biological sciences. One exception to this is scholarship on Luther Burbank, who worked in ornamental horticulture and agricultural production, and whose place in the scientific community has been discussed at length. See for example, Katherine Pandora, “Knowledge Held in Common: Tales of Luther Burbank and Science in the American Vernacular,” *Isis* 92, no. 3 (2001); Paolo Palladino, “Wizards and Devotees: On the Mendelian Theory of Inheritance and the Professionalization of Agricultural Science in Great Britain and the United States, 1880-1930,” *History of Science* 32 (1994). Other recent exceptions to the exclusion of horticulture from the historiography of the modern biological sciences include: Philip J. Pauly, *Fruits and Plains: The Horticultural Transformation of America* (Cambridge, Mass.: Harvard University Press, 2007) and Robert C. Olby, “Horticulture: The Font for the Baptism of Genetics,” *Nature Reviews Genetics* 1, no. 1 (2000).

were united by a common interest in technological advances in breeding, in particular that of induced mutation. The use of colchicine is perhaps best understood part of a larger history of induced mutation as an agricultural breeding practice. Mutation had assumed a place in the philosophy of plant breeding in the early 1900s with the work of Hugo de Vries on mutation in the formation of new species and varieties, and attempts to induce mutation in plants by a variety of methods, most prominently via exposure to radium, followed immediately upon de Vries' work and continued without interruption for the next two decades.<sup>7</sup> Mutation breeding as a more formal enterprise did not begin in earnest until the late 1920s as different types of radiation and chemicals were found conclusively to have mutative effects on plants at the level of both chromosome and gene.<sup>8</sup> From the 1920s through the mid-1950s, individual scientists and breeders pursued the basic science of breeding plant varieties through mutation using chemical mutagens, irradiation, and other techniques.<sup>9</sup> Colchicine was understood then, as now, as part of this assemblage of breeding practices.

An analysis of the use of colchicine in the late 1930s and 1940s, especially when this use is viewed in conjunction with other mutation breeding practices, brings to light the frustrations voiced among some breeders at the slow pace of Mendelian breeding, the hopes attached to mutation as a way of circumventing this, and a widely held belief in the benefits of genetic manipulation through technological intervention.<sup>10</sup> The users of colchicine were united by a common interest in

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<sup>7</sup> For an overview of mutation breeding history and practice, see A. M. van Harten, *Mutation Breeding: Theory and Practical Application* (Cambridge: Cambridge University Press, 1998), especially chapter 2. For radium-induced mutation, see Luis Campos, "Radium and the Secret of Life," Ph.D. dissertation, Harvard University (2006), especially chapters 3 and 4.

<sup>8</sup> van Harten, *Mutation Breeding*, pp. 1-3, pp. 43-50. In 1927, Hermann Muller demonstrated conclusively that X rays could induce genetic mutations, and the geneticists Stuart Gager and Albert Blakeslee reported the inducement of chromosomal mutations in Jimson Weed exposed to radium. The following year, the plant geneticist Lewis J. Stadler published his studies of the effects of irradiation (both X rays and radium rays) on barley and maize. See Hermann Muller, "Artificial Transmutation of the Gene," *Science* Vol. 66, No. 1699 (Jul. 22, 1927), pp. 84-87; C. Stuart Gager and A. F. Blakeslee, "Chromosome and Gene Mutations in *Datura* Following Exposure to Radium Rays," *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 13, No. 2 (Feb. 15, 1927), pp. 75-79. L. J. Stadler, "Mutations in Barley Induced by X-Rays and Radium," *Science* Vol. 68, no. 1756 (August 24, 1928), pp. 186-187; see also analysis by van Harten, *Mutation Breeding*, pp. 48-49.

<sup>9</sup> A large-scale, coordinated, and application-driven mutation breeding agenda evolved in the early 1960s and was coordinated by an Advisory Group on Mutation Breeding under the auspices of the Joint Food and Agriculture Organization of the United Nations and International Atomic Energy Agency (FAO/IAEA) Division beginning in 1964; the work of the FAO/IAEA in mutation breeding continues to the present. See van Harten, *Mutation Breeding*, pp. 61-63; see also the website on "Plant Breeding and Genetics" of the Joint FAO/IAEA Programme on Nuclear Techniques in Food and Agriculture, <http://www-naweb.iaea.org/nafa/pbg/index.html>.

<sup>10</sup> Although scholars have given great attention to both the rise of Mendelian breeding practices after 1900 and the development of GM crops in the later 20<sup>th</sup> century, less attention is paid to the intervening period. For Mendelism and hybridization, see Diane B. Paul and Barbara A. Kimmelman, "Mendel in America: Theory and Practice, 1900-1919," in *The American Development of Biology*, ed. Ronald Rainger, Keith R. Benson, and Jane Mainschein (Philadelphia, Penn.: University of Pennsylvania Press, 1988); Barbara A. Kimmelman, "The American Breeders' Association: Genetics and Eugenics in an Agricultural Context, 1903-13," *Social Studies of Science* 13, no. 2 (1983); Deborah Kay Fitzgerald, *The Business of Breeding: Hybrid Corn in Illinois, 1890-1940* (Ithaca: Cornell University Press, 1990); Jack Ralph Kloppenburg, *First the Seed: The Political Economy of Plant Biotechnology, 1492-2000*, 2nd ed. (Madison, Wis.: University of Wisconsin Press, 2004), 66-90. For GM crops, see: Kloppenburg, *First the Seed*, pp. 191-241; Paul F. Lurquin, *The Green Phoenix: A History of Genetically Modified Plants* (New York: Columbia, 2001). Some attention to the period from 1930 to 1960 is given by Glenn Bugos and Dan Kevles in "Plants as Intellectual Property: American Practice, Law, and Policy in World Context." *Osiris* 7 (1992).

generating mutations; however, the divergences in their practices and expectations show that the perceived advantage of breeding by induced mutation could be either enhanced control and predictability or the generation of the unexpected, though always technological progress. The analysis also shows how the broad range of participants in ornamental horticulture and the easy accessibility of colchicine ensured the circulation of the chemical and techniques for its application beyond the laboratory, where distinct uses and meanings of both mutagen and mutant plants could develop. It suggests, therefore, that ornamental horticulture was a rare space where a diverse set of experts and amateurs could collaborate — through the material production of new plant varieties — in the generation of knowledge.<sup>11</sup>

### *Colchicine in the Laboratory*

The biologists Mabel Ruttle and Bernard Nebel began research with colchicine in 1937 while at the New York State Agricultural Experiment Station. After two years of working with the chemical, Ruttle felt confident enough in their results to announce that “colchicine from a treatment for gout has become a drug which may profoundly affect the economy of nations.”<sup>12</sup> Other scientists seemed to agree. In a 1939 presentation to plant biologists of the American Association for the Advancement of Science, Albert F. Blakeslee, another geneticist and plant biologist whose work with colchicine would become well known, spoke of his research as an exemplar of “how chemical substances may be used in the control of life processes.”<sup>13</sup> After describing the benefits of colchicine to genetic science, he emphasized “the possibilities in the way of new forms of economic value” that could now be imagined, and which “seem[ed] very great.”<sup>14</sup>

Such claims, though quickly shown to have been too bold, suggest the level of excitement felt by scientists about the newly discovered use of colchicine in producing polyploidy in plants. The exuberant pursuit of research into this effect of colchicine stretched from 1938 until the mid-1940s. A brief history of the development of this field of inquiry sheds light on how a compound known since antiquity to produce effects in living things came to be perceived as a revolutionary discovery at mid-twentieth century. Researchers saw the ability to double chromosomes as a technique both to enhance cytological and genetic investigations and to be used for the improvement of plant varieties. When combined with then-standard breeding techniques such as pure-breeding and hybridization, colchicine was thought by some to enable breeders to engineer plants to their own

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<sup>11</sup> It has been suggested that the perspective on the history of colchicine in plant breeding presented indicates that colchicine acted much like a “boundary object” according to the formulation of Star and Griesemer in their 1989 essay on that subject. Colchicine did indeed, as my paper shows, “inhabit several intersecting social worlds,” having been differently adapted within each world but still recognizable across these. Yet I understand the key importance of the boundary object in Star and Griesemer’s work to be its role in “maintaining coherence” across social worlds and allowing institutional science to develop. This is a process that I do not see as relevant to the particular case of colchicine, in which each group used the chemical for distinct purposes in most cases without need of collaborating or corroborating their knowledge (i.e., there was no central project, akin in Star and Griesemer to the development of the museum, in which all participated). See Susan Leigh Star and James R. Griesemer, “Institutional Ecology, ‘Translations’ and Boundary Objects: Amateurs and Professionals in Berkeley’s Museum of Vertebrate Zoology, 1907-39,” *Social Studies of Science* 19, iss. 3 (August 1989).

<sup>12</sup> M. L. Ruttle, “Colchicine and the Production of Polyploid Essential Oil Plants,” *Herbarist* 5 (1939), quotations 21.

<sup>13</sup> A. F. Blakeslee, “The Present and Potential Service of Chemistry to Plant Breeding,” *American Journal of Botany* 26, no. 3 (1939), p. 163.

designs.

Colchicine was not new to biological research in the 1930s.<sup>15</sup> The compound, a highly toxic alkaloid, is produced in nature by *Colchicum autumnale*, known as the autumn crocus. The crocus has a long tradition in medical practice; its use as a specific in the treatment of gout reaches back to ancient Greece.<sup>16</sup> French scientists first isolated the colchicine molecule in 1820 and European researchers in subsequent years sought to establish its toxicity on whole organisms — it was said to be able to kill sheep or cattle that grazed on it in the field — and its pharmacological uses. It was only after the turn of the century that scientists began to investigate its effects at the sub-organismal level, and not until the 1930s that research using the compound truly took off.<sup>17</sup>

Most histories of colchicine point to the work of a medical student, F. Lits, of the pathology laboratory of the biologist Albert Pierre Dustin, at the University of Brussels in 1934 as a pivotal moment in understanding the drug and its dramatic effects.<sup>18</sup> Lits first demonstrated that colchicine induced a proliferation of mitoses in 1934, a discovery that directed the interest of other members of the Dustin laboratory to studies of the chemical. Dustin himself noted the ability of colchicine to produce what would become known as “metaphasic arrest” — a slowdown or stop in cell division at the point where the chromosomes have aligned within the nucleus of the cell immediately prior to its division (the point in the cell cycle known as metaphase).<sup>19</sup> Studies produced by the lab suggested that colchicine would be a valuable tool to use in the study of nuclear and cell division, for it was effective in both plant and animal cells and enabled the researcher to exert control over a fundamental cellular process. Work with the chemical continued at Dustin’s laboratory, and from there knowledge of its effects on mitosis was conveyed to researchers at Yale whose primary interest was in its potential use in endocrinology research. News of the studies with colchicine subsequently traveled from the scientists at Yale to researchers at Cold Spring Harbor and the New York State Agricultural Experiment Station.<sup>20</sup>

As a result of the circulation of these findings, several researchers in the United States demonstrated the potential value of colchicine in the study of plant genetics and breeding at roughly the same time — Nebel and Ruttle, Albert Blakeslee and Amos Avery of Cold Spring Harbor, and O. J. Eigsti, in 1937 also at Cold Spring Harbor.<sup>21</sup> Blakeslee and Avery were the first to publish.

<sup>14</sup> Blakeslee, “The Present and Potential Service of Chemistry to Plant Breeding,” p. 170.

<sup>15</sup> That colchicine was, and is, an important compound in genetic and horticultural scientific research is well known. Goodman offers a thorough “biography” of the colchicine molecule, focused primarily on its use in laboratory science. See Jordan Goodman, “Plants, Cells, and Bodies: The Molecular Biography of Colchicine, 1930-1975,” in *Molecularizing Biology and Medicine: New Practices and Alliances, 1910s-1970s*, ed. Soraya de Chadarevian and Harnke Kamminga (Amsterdam: Harwood Academic, 1998).

<sup>16</sup> Roy Porter provides a condensed history of the use of colchicine to treat gout in Porter, “The Prince’s Poison,” *New Scientist* (2001); see also Roy Porter and George Sebastian Rousseau, *Gout: The Patrician Malady* (New Haven, Conn.: Yale University Press, 1998), pp. 17-18, pp. 131-136.

<sup>17</sup> Goodman, “Plants, Cells, and Bodies,” 18-19. Also, Ruttle, “Colchicine And The Production of Polyploid Essential Oil Plants,” p. 20.

<sup>18</sup> For example, Ruttle, “Colchicine and the Production of Polyploid Essential Oil Plants”; Haig Dermen, “Colchicine Polyploidy and Technique,” *Botanical Review* 6, No. 11 (Nov. 1940); O. J. Eigsti and Pierre Dustin, *Colchicine in Agriculture, Medicine, Biology and Chemistry* (Ames, Iowa: State College Press, 1955), 17-18; Goodman, “Plants, Cells, and Bodies,” pp. 20-21.

<sup>19</sup> Eigsti and Dustin, *Colchicine in Agriculture, Medicine, Biology and Chemistry*, pp. 24-27.

<sup>20</sup> Goodman in “Plants, Cells, and Bodies” provides a full account of the use of colchicine in twentieth century scientific investigations; this short historical sketch is drawn from that account, in conjunction with Eigsti’s 1955 text (see note 17).

<sup>21</sup> Eigsti left Cold Spring Harbor in April 1937 to work at Greenville College in Illinois; he later moved to the University of Oklahoma. The first important papers on colchicine and polyploidy include: A. F. Blakeslee, “Dédoublément Du Nombre De Chromosomes Chez Plantes Par Traitement Chimique,”

Blakeslee, a botanist and geneticist as well as the lead investigator of the pair, had arrived at Cold Spring Harbor as a resident researcher in 1915. He shortly thereafter had begun his extensive genetic and cytological investigations into chromosomal arrangements in *Datura stramonium* (Jimson Weed) and the effects of chromosome aberrations on the plants' morphology.<sup>22</sup> The colchicine research of Blakeslee and Avery was part of these ongoing experimental investigations and observations of *Datura*.

As they reported in the *Journal of Heredity* in late 1937, Blakeslee and Avery had soaked seeds of the plant in a solution of colchicine and tap water. A number of these seeds produced plants whose leaves and flowers were tetraploid (i.e., plants whose cells contained duplicate sets of homologous chromosomes) rather than diploid as the parent seed had been. The observed effect in *Datura* led the authors to pursue different methods of treatment with colchicine and to test its effects on other plant species. The article also detailed treatment by various methods, including the immersion of twigs and branches, application to the plant via agar solution and lanolin, targeted delivery of solution via capillary action along a string, the use of a single drop placed directly on a bud, and use of a fine spray generated by an atomizer. Blakeslee and Avery reported having successfully induced polyploidy in eighteen different species using these methods. The results prompted them to write enthusiastically of their achievements, "So far no limit has been found to the species which can be successfully treated with colchicine."<sup>23</sup>

On Christmas Day 1937, *Nature* published a brief notice by Bernard Nebel on the mechanism of action of colchicine based on cytological study.<sup>24</sup> Nebel, trained in Germany as a cytologist, had first arrived at the experiment station at Geneva, New York in 1927 to study horticulture and plant breeding.<sup>25</sup> He and his wife Mabel Ruttle, also a Ph.D. in plant biology, had initiated the research with colchicine in the spring of 1937 after hearing of the recent work with it at Dustin's lab in Brussels and at Yale. An extended description of their early research, co-authored, appeared in the January 1938 issue of *Journal of Heredity*. They detailed the investigations earlier presented by Nebel (and cytological investigations of other colchicine-treated plants), their observations of colchicine's effects on plant physiology, and their attempts to generate tetraploid varieties of a number of plant species and varieties. Like Blakeslee and Avery, they used a range of techniques for applying colchicine, including immersion of seedlings in solution for some number of hours and application with lanolin. More cautious in this initial document than Blakeslee and Avery, they commented that although the effect of colchicine on many genera of plants had been tested, and polyploidy obtained, "Various genera do not show the effects of polyploidy equally

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*Comptes rendus de l'Academie des Sciences de Paris* 205 (1937); A. F. Blakeslee and A. G. Avery, "Methods of Inducing Chromosome Doubling in Plants by Treatment with Colchicine (Abstract of Paper)," *Science* 86, no. 2236 (1937); A. F. Blakeslee and A. G. Avery, "Methods of Inducing Doubling of Chromosomes in Plants - by Treatment with Colchicine," *Journal of Heredity* 28, no. 12 (1937); B. R. Nebel, "Mechanism of Polyploidy through Colchicine," *Nature* 140 (1937); Nebel and Ruttle, "The Cytological and Genetical Significance of Colchicine"; O. J. Eigsti, "A Cytological Study of Colchicine Effects in the Induction of Polyploidy in Plants," *Proceedings of the National Academy of Sciences* 24 (1938).

<sup>22</sup> For a biography of Blakeslee, see Edmund W. Sinnott, "Albert Francis Blakeslee, 1874-1954," *Biographical Memoirs* (Washington, DC: National Academy of Sciences, 1959). His early career is detailed in Barbara A. Kimmelman, "Mr. Blakeslee Builds His Dream House: Agricultural Institutions, Genetics, and Careers 1900-1915," *Journal of the History of Biology* 39, no 2 (July 2006).

<sup>23</sup> *Ibid.*, p. 403.

<sup>24</sup> Nebel, "Mechanism of Polyploidy through Colchicine," p. 1101.

<sup>25</sup> Nebel initially stayed only a year; he returned in 1930 to stay until 1942. See F. Wassermann, "Obituary - Bernard Rudolf Nebel (1901-1963)," *Radiation Research* 29, no. 1 (1966).

well.”<sup>26</sup>

O. J. Eigsti was at this time also busy sorting out the mechanism of colchicine through cytological study. Eigsti had only recently received his Ph.D. in botany from the University of Illinois, for his research on plant morphology and cytology. Unable to find work as a professor upon graduation, he had taken an assignment as a research assistant at Cold Spring Harbor.<sup>27</sup> The stint at Cold Spring Harbor proved to be short, as he accepted a teaching position in Indiana in 1937 and then moved to a full-time position as a professor of botany at the University of Oklahoma in 1938. In the summer of 1937 he was still at Cold Spring Harbor, and while there he had been the one to tip off Blakeslee and Avery about the potential effects of colchicine. He was the last of this initial group of investigators to get his research into print.<sup>28</sup> In a 1938 report limited to cytological study (as opposed to effects on tissues or whole plants), Eigsti concluded that “colchicine is effective in the production of cytogenetically changed cells. The process affects the mitotic divisions.” He elaborated on this point slightly, describing how colchicine appeared to intervene very specifically in the process of cell division. It disrupted the process of spindle formation and prevented the duplicated chromosome sets from sorting into new nuclei, but did not otherwise interfere with the cell or chromosomes.<sup>29</sup>

These publications highlight the researchers’ belief in the potential of colchicine for advancing scientific research via its use as a tool of cytology and basic genetic research as well as its use in breeding. The former had been anticipated from the earlier colchicine research in Brussels, where the ability to induce metaphasic arrest had suggested that the chemical would be a valuable tool to use in the study of nuclear and cell division.<sup>30</sup> While Eigsti’s initial work pointed to these benefits for the cytologist interested in laboratory analysis, Nebel and Ruttle focused on the applied results, as in their assertion that “To induce chromosomal changes in somatic tissues of cultivated plants as obtained with colchicine may be called plant breeding with non-Mendelian methods.”<sup>31</sup> Blakeslee and Avery laid out the arguments for colchicine’s usefulness in both theoretical and practical investigations. They suggested first that control over chromosome doubling would be a useful tool for genetics research. For example, varieties with a wide range of chromosome combinations could be bred. Blakeslee and Avery explained, “The balanced polyploid types,  $3n$ ,  $4n$ ,  $5n$ ,  $6n$ ,  $7n$ , and  $8n$ , which have an equal number of chromosomes of each kind, form the basis of a considerable number of unbalanced types with individual extra chromosomes.” These “unbalanced types” where they had occurred spontaneously in nature had already been used to analyze the genetic makeup of *Datura* and other plant species and to locate genes on individual chromosomes. Therefore, as Blakeslee and Avery noted, the ability to produce different chromosomal types of the same species in the laboratory would add to the stock of types available (especially in producing

<sup>26</sup> Nebel and Ruttle, “The Cytological and Genetical Significance of Colchicine,” quotation 9.

<sup>27</sup> Many details of Eigsti’s biography can be found in John H. Woodburn, *20<sup>th</sup> Century Bioscience: Professor O. J. Eigsti and the Seedless Watermelon* (Raleigh, North Carolina: Pentland Press, 1999).

<sup>28</sup> He would make up for this in subsequent years and decades by publishing comprehensive overviews and bibliographies on colchicine, in what seems to have been an attempt to set the historical record straight. For examples, see: O. J. Eigsti and P. Dustin, *Colchicine Bibliography* (Cincinnati: Lloyd Library, 1947); O. J. Eigsti, P. Dustin, and N. Gaywinn, “On the Discovery of the Action of Colchicine on Mitosis in 1889,” *Science* 110, no. 2869 (1949); Eigsti and Dustin, *Colchicine in Agriculture, Medicine, Biology and Chemistry*.

<sup>29</sup> O. J. Eigsti, “A Cytological Study of Colchicine Effects in the Induction of Polyploidy in Plants,” *Proceedings of the National Academy of Sciences* 24 (1938), p. 63.

<sup>30</sup> Goodman, “Plants, Cells, and Bodies,” p. 20.

<sup>31</sup> Nebel and Ruttle, “The Cytological and Genetical Significance of Colchicine,” 9; Eigsti, “A Cytological

those not spontaneously generated) and therefore expand the opportunities for genetic analysis.<sup>32</sup> Although they did not elaborate on it at length, the authors noted that chromosome doubling was also of theoretical interest because it was known to have been the source of new species in nature. This was a topic that had been addressed in the previous decade by a number of researchers; it therefore made colchicine potentially of interest to those studying evolution.<sup>33</sup>

In addition, and as Blakeslee and Avery also pointed out, practical agricultural applications of the technique were many. Extrachromosomal types could be used to build up purebred stocks, or might be valuable new types in and of themselves. In addition, as a particular dramatic comparison of haploid, diploid, triploid and tetraploid *Datura* flowers demonstrated, a plant's flower (and fruit) size increased along with its chromosome number — a feature of polyploidy certainly not missed by growers and breeders. Most important, practical breeders might use it to control more precisely the development of new seeded and vegetatively propagated plant varieties by producing fertility in widely crossed hybrids (ordinarily sterile); this perceived benefit would generate the most interest among practical breeders, and is discussed in detail below.<sup>34</sup>

Given that all of these benefits to science of the ability to induce polyploidy had been imagined at the outset of the colchicine work, it should come as no surprise that the discovery of colchicine as a tool for inducing polyploidy was in part the product of the search for such a tool. As Nebel and Ruttle claimed, the ability to reliably induce polyploidy through colchicine realized “a long-cherished dream of cytologists.”<sup>35</sup> A number of techniques for doubling chromosomes were known in 1937, temperature variation being foremost among these, yet none very predictable or universally effective, and as a result scientists continued to pursue new methods.<sup>36</sup> Blakeslee himself had a history of interest in chromosomal mutations and their use in the control of heredity and experimental evolution.<sup>37</sup> In the period leading up to his colchicine publications, Blakeslee experimented with a number of mechanisms for doubling the number of chromosomes in plants, including injection of chloral hydrate, cold treatment, and heat exposure.<sup>38</sup> He and Avery reported their initial findings as part of a larger project, initiated in June 1936, specifically meant to induce polyploidy by chemical treatment.<sup>39</sup> Colchicine was the only chemical found to be effective of the several included in their trials. It is in the context of this ongoing search for a reliable means of

Study of Colchicine Effects in the Induction of Polyploidy in Plants.”

<sup>32</sup> Blakeslee and Avery, “Methods of Inducing Doubling of Chromosomes in Plants - by Treatment with Colchicine,” quotation 409.

<sup>33</sup> For example, A. Müntzing, “The Evolutionary Significance of Autopolyploidy,” *Hereditas* 21 (1936).

<sup>34</sup> Blakeslee and Avery, “Methods of Inducing Doubling of Chromosomes in Plants - by Treatment with Colchicine,” pp. 408-9.

<sup>35</sup> B. R. Nebel and M. L. Ruttle, “Colchicine and Its Place in Fruit Breeding,” *Circular of the New York State Agricultural Experimental Station*, no. 183 (1938), p. 12.

<sup>36</sup> Other options discussed in scientific literature included centrifuging, scarring or cutting of shoots, and the application of a range of chemicals. For earlier research, see: John Belling, “Production of Triploid and Tetra-Ploid Plants,” *Journal of Heredity* 16, no. 12 (1925); L. F. Randolph, “Some Effects of High Temperature on Polyploidy and Other Variations in Maize,” *Proceedings of the National Academy of Sciences* 18 (1932); E. Dorsey, “Induced Polyploidy in Wheat and Rye,” *Journal of Heredity* 27 (1936); Karl Sax, “The Experimental Production of Polyploidy,” *Journal of the Arnold Arboretum* 17 (1936). For post-1937 reviews, see: G. H. Bates, “Polyploidy Induced by Colchicine and Its Economic Possibilities,” *Nature* 144 (1939); L. F. Randolph, “An Evaluation of Induced Polyploidy as a Method of Breeding Crop Plants,” *American Naturalist* 75, no. 759 (1941); and description of techniques in Eigsti and Dustin, *Colchicine in Agriculture, Medicine, Biology and Chemistry*, pp. 274-5.

<sup>37</sup> Campos, “Radium and the Secret of Life,” pp. 265-280.

<sup>38</sup> Blakeslee and Avery, “Methods of Inducing Doubling of Chromosomes in Plants - by Treatment with Colchicine,” p. 394.

<sup>39</sup> *Ibid.*, p. 395.

producing polyploidy, for use in both theoretical and practical research, that the subsequent enthusiasm for colchicine among these scientists is best understood.

### *Polyploidy and the Practical Breeder*

As the initial colchicine publications indicated, there were a number of reasons why polyploidy interested researchers; in this discussion, I focus on those aspects that were relevant to practical breeders. Among this group, colchicine was most celebrated for its perceived potential to expand the means available for improving plants. The scientist G. H. Bates, in a discussion of the effects of colchicine, gave a bleak assessment of the tools then at hand when he wrote in 1939, “Mendelian methods have taken us as far as they can, at least in respect of our commonest crop plants. We have exhausted all possible combinations of known characters and have reached a point where... we are simply ‘ringing the changes’ on existing material.”<sup>40</sup> Hopes for experimental breeding had been bolstered around the turn of the century by the rediscovery and promotion of the late 19<sup>th</sup> century work of Gregor Mendel.<sup>41</sup> Mendel’s work had suggested to breeders that they might be able to control the transmission of characters through purebreeding and careful selection and crossing. Yet enthusiasm for scientific breeding programs was tempered in subsequent years by the slow speed at which plants and animals were improved via these methods.<sup>42</sup> Not all breeders would have agreed with Bates, yet the accuracy of his assessment is perhaps not as important as its implications for why there was such interest in colchicine. In Bates’ view, as with those of other researchers, the production of polyploidy offered a convenient route around some perceived limitations of Mendelian methods.

Nebel and Ruttle explained that colchicine would enable breeders to do a number of novel things: to easily and consistently test the direct effect of polyploidy, to create meritorious triploids, to cross species previously uncrossable, and possibly to induce fertility in sterile hybrids.<sup>43</sup> Others were in agreement with this basic assessment of the value of induced polyploidy, and had been before colchicine was discovered.<sup>44</sup> What did these proposed uses mean? What Nebel and Ruttle termed “the direct effect of polyploidy” is exemplified in the case of the Tetra Marigold; this was a case in which a polyploid represented a new variety, hopefully one with more other desirable traits than the parent plant. The creation of “meritorious triploids” referred to the potential for crossing the diploid of a species with its colchicine-induced tetraploid relative, thereby creating a (likely sterile) triploid variety that might have desirable characteristics of its own.<sup>45</sup> One example of this was the development of the seedless watermelon, a cross of a colchicine-created tetraploid with a

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<sup>40</sup> G. H. Bates, “Colchicine-Induced Polyploidy in Nature,” *Nature* 143 (1939), quotation 315; Randolph, “An Evaluation of Induced Polyploidy as a Method of Breeding Crop Plants,” p. 362.

<sup>41</sup> Paul and Kimmelman, “Mendel in America”; Fitzgerald, *The Business of Breeding*, chap. 1.

<sup>42</sup> Results from Mendelian breeding programs were long in coming. Hybrid corn is generally understood to have been the first success story. See Fitzgerald, *The Business of Breeding*, chap. 1 and 2; Kloppenburg, *First the Seed*, chap. 4.

<sup>43</sup> Nebel and Ruttle, “Colchicine and Its Place in Fruit Breeding,” p. 12.

<sup>44</sup> For example, in his studies using temperature change to induce polyploidy in maize in 1932, the Cornell geneticist L. F. Randolph offered a nearly identical list. See L. F. Randolph, “Some Effects of High Temperature on Polyploidy and Other Variations in Maize,” pp. 222-223, p. 229.

<sup>45</sup> Meritorious triploids and larger tetraploids were the focus of Belling’s 1925 study of induced triploidy and tetraploidy, one of the earliest such works. See John Belling, “Production of Triploid and Tetra-Ploid Plants.”

diploid to create a sterile (i.e., seedless) triploid.<sup>46</sup> Crosses between “hitherto uncrossable species” referred to situations such as that encountered in attempting to hybridize French marigolds and African marigolds. Because the former are tetraploid, and the later are diploid, plant breeders were long unable to cross these species easily. Once a tetraploid African marigold was created however, it was possible to cross more readily the new tetraploid African variety with a French marigold variety and produce fertile offspring.<sup>47</sup>

The final and most dramatic benefit of induced polyploidy noted by Nebel and Ruttle was the ability to make sterile hybrids fertile. Breeders knew that crossing two species might produce more vigorous plants, but these plants often displayed hybrid sterility. Blakeslee explained that plant hybrids are sometimes analogous to the sterile mule, “in that they cannot form gametes since the chromosomes of one parent are too unlike those of the other parent to mate and form pairs; and pairing of chromosomes is necessary for sexual reproduction.”<sup>48</sup> Geneticists knew that hybrid sterility could be overcome through polyploidy. Doubling the chromosomes of a hybrid would in some cases solve the problem of incompatibility of the parent chromosomes as described by Blakeslee: with two sets of chromosomes from each parent, the (polyploid) hybrid daughter plant has the two chromosomes of each kind required for pairing of chromosomes during sexual reproduction.<sup>49</sup> Scientists believed that this process of interspecific hybridization followed by chromosome doubling occurred spontaneously in nature.<sup>50</sup> It was also understood to have been the source of numerous valuable domesticated species.<sup>51</sup> Blakeslee spelled out the consequences of using colchicine to induce polyploidy in interspecific hybrids, “We now no longer have to wait ages for the chance hybridization between species and the later rare spontaneous doubling of their chromosomes in order to secure such superior varieties. We can now make them up to order.”<sup>52</sup>

Enhanced control — the ability to direct the evolution of varieties through these many potential applications of colchicine — lay at the heart of these breeders’ enthusiasm. Language that described how plants could be engineered or “made up to order” can be found scattered throughout the scientific literature on colchicine in this early moment. Blakeslee spoke of “the control of life processes” and he and Avery’s initial assessment of colchicine’s potential involved the application, by a “genetics engineer,” of the new knowledge of chromosomes and their alteration “to building up to specifications forms of plants adapted to the surroundings in which they are to grow and suited to specific economic needs.”<sup>53</sup> Other researchers agreed. Nebel implied that

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<sup>46</sup> As described in Eigsti and Dustin, *Colchicine in Agriculture, Medicine, Biology and Chemistry*, p. 327. The seedless watermelon, considered an improvement because eaters would not have to spit out the seeds, had the further advantage of being impossible to propagate in subsequent seasons without returning to the seed seller.

<sup>47</sup> Nebel and Ruttle, “Colchicine and Its Place in Fruit Breeding,” 12; William H. Eyster, “The Production of Polyploid *Tagetes*,” *Proceedings of the Pennsylvania Academy of Sciences* 15 (1941); other examples are discussed in Eigsti and Dustin, *Colchicine in Agriculture, Medicine, Biology and Chemistry*, pp. 310-1.

<sup>48</sup> Blakeslee, “The Present and Potential Service of Chemistry to Plant Breeding,” p. 168.

<sup>49</sup> For explanation, see R. W. Allard, *Principles of Plant Breeding* (New York: Wiley, 1960), pp. 14-18. Accounts of this process contemporary to the colchicine experiments include, in addition to Blakeslee, “The Present and Potential Service of Chemistry to Plant Breeding”: L. F. Randolph, “Some Effects of High Temperature on Polyploidy and Other Variations in Maize,” pp. 222-223.

<sup>50</sup> Müntzing, “The Evolutionary Significance of Autopolyploidy”; Sax, “The Experimental Production of Polyploidy.”

<sup>51</sup> Blakeslee, “The Present and Potential Service of Chemistry to Plant Breeding,” p. 170; Haig Dermen, “A Cytological Analysis of Polyploidy,” *Journal of Heredity* 29 (June 1938), p. 211.

<sup>52</sup> Blakeslee, “The Present and Potential Service of Chemistry to Plant Breeding,” p. 170.

<sup>53</sup> Blakeslee, “The Present and Potential Service of Chemistry to Plant Breeding,” p. 163; Blakeslee and Avery, “Methods of Inducing Doubling of Chromosomes in Plants,” p. 410.

colchicine enabled the plant breeder to make more controlled changes in chromosomes than other techniques then in use such as X rays and radium, which produced mostly “unbalanced” chromosomal changes resulting in plants “valueless even as breeding material,” a contrast to the valuable plants he had already produced through colchicine.<sup>54</sup> Bates suggested that colchicine would allow breeders to produce “mutations” — the basic material with which the breeder works — at will. To his mind, the methods of selective breeders, “such as Luther Burbank, were certainly spectacular, but they were laborious, expensive, and haphazard,” and Mendelian breeding was better and more controlled, but had advanced so far that “the hybridizer can only wait for some new mutation to turn up.”<sup>55</sup> Colchicine, if it proved as reliable as early results indicated, might well enable the breeder to escape such a wait.

Some researchers took a more sober view of the possibilities afforded by colchicine. L. F. Randolph, who had been working on polyploidy (induced by temperature change) since the early 1930s, was far less sanguine than many of his peers. Furthermore, and perhaps because of his own earlier researches, he did not see colchicine as distinctive from other methods of crop improvement. As Randolph wrote in 1941, “The claim is being made that the much-publicized colchicine technic constitutes a new method of plant breeding capable of producing at will next species and new giant varieties of horticultural and crop plants ... Fortunately, induced polyploidy is not a new field of investigation, and it certainly does not constitute a new method of plant breeding.”<sup>56</sup> Yet at the end of his extensive literature review of the use of induced polyploidy in plant breeding, he nonetheless agreed with Bates’ assessment of the potential for producing new plants. “It is clearly apparent from the evidence at hand,” Randolph concluded, “that the new strains of cultivated plants that are being produced by chromosome doubling furnish the plant breeder with a wealth of new material differing significantly in many important respects from the varieties at hand.”<sup>57</sup> Even though he would not have used the same grandiose terms as some of his peers, Randolph agreed in essence with the assessments of some of his peers, that colchicine had put an important new tool in the hands of breeders.

### *Colchicine in Flower Breeding*

The excitement of these academic and government researchers over colchicine was easily matched, if not exceeded, by the excitement of plant breeders in the commercial sector. This was in part because the latter shared the belief that plant breeding needed to supplement the known techniques of hybridization and selection, and looked to science to produce better methods for breeding new varieties. It also gained momentum from the specific constraints of the market for seeded plants. A look into the science and business of commercial ornamental horticulture in the United States through the career of David Burpee, one of best-known American horticulturalists, shows how and why colchicine came to represent the bright future of plant breeding — and not solely for its conferral of greater control over plant chromosomes.

In September of 1931, five years after the death of the famed American horticulturalist Luther Burbank, the W. Atlee Burpee Company with David Burpee at its helm, purchased the seed

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<sup>54</sup> B. R. Nebel, “Inducing Changes in Plants with Colchicine Shows Progress,” *Farm Research* VI, no. 1 (1940).

<sup>55</sup> Bates, “Polyploidy Induced by Colchicine and Its Economic Possibilities,” p. 315

<sup>56</sup> Randolph, “An Evaluation of Induced Polyploidy as a Method of Breeding Crop Plants,” p. 347.

<sup>57</sup> *Ibid.*, p. 362.

and bulb portion of the Burbank estate. Burpee had officially entered the seed business in 1914 at the age of twenty-two. That year he dropped out of Cornell University, where he had completed only one semester of coursework, to run the W. Atlee Burpee Company after his father's death. The father, W. Atlee, had founded the business in 1878, first offering for sale farm birds, animals, and seeds; the seed end of the business grew from a sideline to the centerpiece. When David Burpee took over, the company was among the largest mail-order seed companies in the world. In the decades that followed, Burpee became well known for his keen business sense, his relentless promotion of Burpee products, and his vigorous pursuit of new and better plant varieties.<sup>58</sup>

With the 1931 transfer of the Burbank seed collection, Burpee also arguably took Burbank's place as the most prominent American horticulturalist. Burbank had captured international attention at the turn of the twentieth century through his ability to create impressive new varieties of crop and flower plants, especially fruit.<sup>59</sup> His basic techniques included crossing imported varieties with traditional types and the careful selection of progeny. Although scientists later contested his standing as a member of the scientific community, Burbank was widely celebrated as a scientific hero among the general public and always spoke of his successes as the consequence of his experimentation and application of scientific principles.<sup>60</sup> David Burpee willingly assumed this mantle of scientific investigation from Burbank. As *Time* reported that year, "It has long been the ambition of David Burpee to take over the unfinished work of Luther Burbank. And that work he will carry on, he says, as Burbank did: in a scientific spirit, not a commercial one, in the interest of mankind. Also he hopes to bring greater resources to the experiments than Burbank was able to command."<sup>61</sup>

The popular press often linked Burpee's activities with those of the archetypical scientific horticulturalist Burbank in the years that followed, but — much like the reporter from *Time* — they also noted that the game had changed between these two generations. Burpee was represented (and represented himself) as more scientifically advanced than his predecessor. For example, Frank Taylor, a reporter who wrote a number of pieces on Burpee in the 1930s and 1940s for various magazines, noted that researchers at seed companies such as Burpee's "were typical of the Luther Burbanks who cook up your next year's flowers." Except, however, that they could do better, as Taylor confirmed, "perform[ing] tricks of horticultural wizardry never dreamed of by Burbank."<sup>62</sup> Where Burbank's work had been limited to crossing and selection, then the mainstays of theoretical and practical breeding, Burpee took up, as quickly as they emerged, even more interventionist techniques that promised faster results. Luther Burbank had made it clear in public interviews that he was powerless to go beyond the materials provided by nature. He had sought out plants with desirable traits and used selection and hybridization to combine these traits into individual plants and amplify them over time.<sup>63</sup> Burpee, with access to mutation-inducing chemicals and techniques developed in academic laboratories or at agricultural research stations, sought to induce in plants the traits he and his customers desired.

Consider Burpee's understanding of the implications of colchicine for the commercial

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<sup>58</sup> Ken Kraft provides a history of the company in Ken Kraft, *Garden to Order*, 1st. ed. (Garden City, N.Y.: Doubleday, 1963).

<sup>59</sup> For a biography of Burbank, see Peter Dreyer, *A Gardener Touched with Genius: The Life of Luther Burbank*, Rev. ed. (Berkeley: University of California Press, 1985).

<sup>60</sup> See Paolo Palladino, "Wizards and Devotees"; Pandora, "Knowledge Held in Common"; Marcel C. LaFollette, *Making Science Our Own* (University of Chicago Press, 1990).

<sup>61</sup> "Burpee for Burbank," *Time*, September 21, 1931.

<sup>62</sup> Frank J. Taylor, "How Your Flowers Are Remodeled," *Saturday Evening Post* (March 1, 1947).

breeder. In 1940, he described how “Every good flower in your garden has been bred from a sport that occurred somewhere, a plant with unusual characteristics that gave some plant hybridizer new blood with which to breed new shades, more vigor, better form into flowers.” He continued, suggesting that a dramatic shift had recently occurred, “In my father’s time a ‘break,’ as the plant breeder usually calls a sport, was supposed to occur once in every 900,000 plants. But now, by artificial stimulants, we can turn them out once in every 900 plants. Or oftener.”<sup>64</sup> Colchicine, Burpee argued, would free the breeder from the hunt for the random mutations that often became market successes, by increasing these mutations “a thousandfold.”<sup>65</sup> To him, it marked a turning point from the old fashioned techniques of his father (from whom he had inherited the business) and his father’s contemporary Luther Burbank. Burpee linked colchicine to other new tools of the trade, many of which we intended to speed up mutation, “Yesterday we were using the old established catch-as-catch-can methods. Tomorrow we will work in a laboratory as scientifically equipped as that of a chemist or physicist, and our experiments will be systematically planned in advance ... through the use of X rays, light rays, aging, mutilation, and chemicals we may induce mutations almost at will.”<sup>66</sup>

For Burpee, the need to induce nature into producing new varieties more quickly resulted in part from the demands of the commercial marketplace. During the 1930s the United States provided no intellectual property protection for seeded plants.<sup>67</sup> When a new variety was introduced to market, its seeds could immediately be planted, harvested, and sold by any company, not just the company that had developed the variety. This appropriation of newly introduced varieties, no matter how long they had been in development by the originating company, was not considered to be unethical; rather, it was standard industry practice.<sup>68</sup> In this context, a successful business model for a commercial seedhouse — most of whose products would grow to be fertile, seed-producing plants — entailed developing a new variety, promoting it heavily for no more than a few years to draw a maximum profit before others had time to grow and sell it in bulk. In time, the originating company would let the plant drop (in price and in catalog placement) in favor of other, newer varieties.<sup>69</sup> An alternative to this was to develop first-generation hybrids, the offspring of two purebred strains. These sometimes made for better plants, but, more important, the fact that they were sterile provided what the Burpee biographer Ken Kraft called “a kind of grow-your-own patent protection” in which seed had to be obtained from the company maintaining the two parent lines of plants.<sup>70</sup>

This highly competitive market in which the only property protection to be found was that which was biologically conferred (i.e., by hybridization that produced sterile offspring) resulted in the relentless pursuit of novel varieties. It was in this context that commercial horticulturalists such

<sup>63</sup> Dreyer, *A Gardener Touched with Genius*, chap. 1.

<sup>64</sup> David Burpee and Frank J. Taylor, “So We Shocked Mother Nature,” *Rotarian* 57 (1940), p. 15.

<sup>65</sup> *Ibid.*, p. 16.

<sup>66</sup> *Ibid.*, p. 17.

<sup>67</sup> It was not until the passage of the Plant Variety Protection Act in 1970 that the United States government offered intellectual property protection for seeded plants. On the history of intellectual property in plant, see Glenn E. Bugos and Daniel J. Kevles, “Plants as Intellectual Property: American Practice, Law, and Policy in World Context.”

<sup>68</sup> Taylor, “How Your Flowers Are Remodeled,” p. 54.

<sup>69</sup> Taylor discusses this problem at length, in the specific context of the Burpee company and their practices. See Taylor, “How Your Flowers Are Remodeled.” The more general history of intellectual property in plants and its role in the commercial seed industry can be found in Bugos and Kevles, “Plants as Intellectual Property” and Kloppenburg, *First the Seed*.

<sup>70</sup> Kraft, *Garden to Order*, quotation 73.

as Burpee embraced any technique or process that promised to bring a more rapid appearance of new traits. The long-term success of his business depended on a steady stream of new plants, and waiting around for nature to produce them was a poor business strategy. In 1940, after only a couple years of colchicine's use, a reporter described how "Mr. Little [the head breeder] at Burpee's will show you a small moonbeam petunia which after colchicine treatment produced huge leaves and flowers. A snapdragon, instead of growing blossoms on spikes in the normal manner, produced flowers irregularly above the leaves all along the stalk. An inch has been added to zinnias. A large orange cosmos blossoms three weeks ahead of normal ..."71 Such results, after only a short time and in the context of a market structured like that of the commercial seed market, helps to explain the enthusiasm demonstrated by David Burpee and others for colchicine.

And that enthusiasm extended to other techniques of inducing mutation. Burpee prodded plants into producing new forms using a range of methods, including chemicals such as colchicine, X rays, mutilation, seed aging, hydroponics, and ultraviolet radiation, among others.72 For example, in 1942, Burpee introduced the "X-Ray Twins," a pair of *Calendula* varieties produced from seed that had been exposed to X rays by the geneticist Ernest Brown Babcock of the University of California in 1933.73 Sometimes producing the desired results led to the combination of multiple techniques, as in the case of David Burpee's work with the zinnia. "Mr. Burpee decided to 'change the living organism of the zinnia,'" Frank Taylor reported to readers of the *Saturday Evening Post*. Taylor described the methods used in this process, "[Burpee] sent a batch of zinnia seeds to college, having them bombarded with X rays at the University of California laboratories. When this exposure to modern campus life failed to do the trick, he had the zinnia patch fertilized with radioactive phosphorus. Then he had the trial gardens sprayed with colchicine, which ordinarily has the same effect on plant life as spraying a New Year's Eve house party with 100-proof Scotch ..." The last process was the one to result in the desired effects, the colchicine causing "an explosion out of which came several new strains."74

This last comment points to an important distinction between the enthusiasm of Burpee for the use of colchicine and those of his contemporaries in the laboratory — such as Blakeslee, Nebel, Ruttler, and Eigsti. Burpee and his staff in many cases were not using the chemical to enhance their ability to direct the processes of variation and evolution, except in the straightforward sense of speeding it up. And although the Burpee company offered a number of enlarged tetraploid flower varieties in the 1940s and 1950s, this did not become the standard use of the chemical; after all, once a tetraploid variety was produced, it too would be subject to usurpation by other companies. Thus it was not necessarily control that these commercial breeders sought, but rather the opposite — "a shakeup," "a bust-up," or an "explosion" of new strains via the generation of random mutations.

Blakeslee and Avery had noted in their 1937 article the possibility that colchicine caused

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71 Frank J. Taylor, "Speeding up Nature," *Reader's Digest*, May 1940, p. 70.

72 Burpee and Taylor, "So We Shocked Mother Nature." The following examples draw from Burpee, but other prominent seed houses participated in similar work. See for example the companies discussed in Taylor, "How Your Flowers are Remodeled" and Edwin Way Teale, "Test-tube Magic Creates Amazing New Flowers," *Popular Science* (May 1940).

73 "New Flowers by X-Rays," *Time*, February 2, 1942. Rival seed companies also sought university aid to "X-ray" recalcitrant varieties into showing new forms; For the example of seedsman Frank Reinelt, see Taylor, "How Your Flowers Are Remodeled," p. 55; for the example of Bodger Seed Company, see Teale, "Test-Tube Magic Creates Amazing New Flowers."

74 Frank J. Taylor, "They've Grown Some New Posies for the Ladies," *Saturday Evening Post* (March 17, 1951), p. 135.

hereditary changes that were not related to polyploidy. “Some of the plants from treated seeds were suspected of carrying deficiencies on account of their abnormal appearance,” they wrote, acknowledging both that cytological evidence confirmed such changes and that other evidence of increased “pollen lethal mutations” had been discovered.<sup>75</sup> The mention of these other mutative effects called attention away from the effect of polyploidy (and in addition carried implications for the predictability of colchicine’s effects), however, and the authors did not dwell on it at length in early papers. It lay for commercial plant producers such as Burpee to make such effects a central aim of colchicine application.

### *Backyard Mutation*

The desire for faster production complemented another aspect of the commercial appeal of new technologies in breeding to David Burpee — the opportunity to incorporate them into his advertising of new high-tech varieties to his customers. Burpee described his seed farm, Floradale, located in Lompoc, California, as a place “where we build new flowers,”<sup>76</sup> and he often sold his products as the creations of his farm’s laboratories. In the 1930s and 40s, his catalog detailed the ongoing experimental labors of his breeders and the processes at work in the production of new varieties, supplementing these with images of scientists in labs and at work in the fields. And the scientific sales pitch encompassed specific flower products as well. Advertising copy for the Tetra Marigold and other tetraploid plants were replete with references to their chromosome count, in addition to their more perceptible benefits such as increased size and hardiness.<sup>77</sup> Burpee’s strategies for developing seeds might best be understood not simply as the application of scientific research to commercial horticulture but as part of a larger marketing strategy that took advantage of mid-century enthusiasm for new technologies.<sup>78</sup>

It may seem surprising that a seed company would choose to emphasize the origins of its plants in scientific processes in its sales pitches. Wouldn’t gardeners have been more pleased to know that their flowers were all natural, hand selected over many generations, and time-tested to be reliable, attractive plants, than to hear that a plant had been swirled in chemicals last year, or recently bombarded with radiation? Evidently not, for both general interest in novelties and public respect (and enthusiasm) for science helped determine Burpee’s research and advertising strategies. As Burpee once described in an interview, “One of the surprising things I have found out about people lately ... is that even in hard times they will pay several times the usual price for something

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<sup>75</sup> Blakeslee and Avery, “Methods of Inducing Chromosome Doubling in Plants – by Treatment with Colchicine,” p. 409.

<sup>76</sup> David Burpee, “The Missionary and Mary’s Gold,” *Saturday Evening Post* (March 12, 1938), p. 21.

<sup>77</sup> For example, an ad in one horticultural magazine proclaimed, “Giant Tetra is the result of doubling the chromosomes which govern heredity, in Guinea Gold Marigold, by using Colchicine, thus creating this new tetraploid Marigold. This man-made miracle has resulted in both greater size and more vigorous plants”; see advertisement, *Flower Grower* (March 1940). Another example, this from the 1949 Burpee Catalog description of tetraploid snapdragons is equally illustrative: “Genetically, Tetra Snaps are known as tetraploid snapdragons for, when examined under the microscope, they have twice the number of chromosomes in their cells as regular or diploid snapdragons...” *Burpee Seeds for 1940* (Catalog), W. Atlee Burpee Co., Philadelphia, Penn., 16. Collected in TLC-NMAH, Smithsonian Institution, Washington DC.

<sup>78</sup> On the idea of technological enthusiasm in the United States in the years leading up to World War II, see Thomas P. Hughes, *American Genesis: A Century of Invention and Technological Enthusiasm, 1870-1970* (Chicago: University of Chicago Press, 2004 [1989]), pp. 2-3.

very special and unusual.”<sup>79</sup> Novelty was not necessarily a result of the market structure alone, but a product of consumers’ own desires and preferences; if the degree of novelty could be implied through a discussion of how a plant came into existence, such as through the use of X rays, then this might only add to the unusual nature of the plant and to customers’ interest in purchasing it. Furthermore, Americans of the early twentieth century accepted and celebrated the benefits of science and technology, including many things now understood to be dangerous.<sup>80</sup> Physicians employed radium medicine in the teens and twenties, just as radioactive materials were put to use in watch dials and other glow-in-the-dark objects; physicians, as well as writers, artists, and the popular press, celebrated the X ray as a largely benign technology through the end of World War II; and chemical companies grown fat off war touted the healing properties of chlorine gas during the interwar years.<sup>81</sup> The enthusiasm for the application of new technologies to the production of plant varieties should be understood in this context.

Burpee’s frequent use of a science-linked sales pitch suggests that he believed his customers would be influenced not only by the promise of superior seeds but also by knowledge of the processes of their creation. In the case of colchicine, Burpee appears to have been correct. By and large, gardeners reacted favorably to the products of colchicine breeding, understanding them to be superior plants. L. C. Grove, representing a group of Iowa gardeners, reported positively of the Tetra marigold in 1941 that it “was found to produce a larger flower of a more brilliant color” and “bloomed consistently until frost”; the only downside reported was that the stems were too weak to hold the extra-large, and therefore extra-heavy, flowerheads — they often split when exposed to wind.<sup>82</sup> The sale of snapdragons shot upwards after the introduction of tetraploid varieties by Burpee in 1946; by 1963 they were by virtue of their size and hardiness, as one author commented, “not surprisingly, the most popular snapdragons on the market.”<sup>83</sup> Other varieties gained popular approval in the 1940s and 1950s. One 1956 report on the advances in flower varieties produced by modern horticultural science singled out a number of colchicine-induced tetraploids for specific mention.<sup>84</sup> This is not to say the pleasure was universal. In the late 1950s, the American author Katherine White in a *New Yorker* column wrote with relief, “It is encouraging to find Burpee ... somewhat less preoccupied with chromosomes. Last year, everything was ‘triploid’ or ‘tetraploid.’”<sup>85</sup> Yet White appears to have been the minority in her evaluation of the colchicine varieties. Many gardeners and others in the broader public also appear to have been interested in the

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<sup>79</sup> Waldron Webb, “Turnips or Tulips: Which Are You Planting?” *The American Magazine* (March 1933) p. 140.

<sup>80</sup> On the celebration of science and technology in the interwar years, especially as it relates to science in the popular press, see Daniel Kevles, *The Physicists, The History of a Scientific Community in Modern America* (Cambridge, Mass.: Harvard University Press, 1995 [1977]), chapter XII; and on popular images of chemistry in particular see Marcel C. LaFollette, “Taking Science to the Marketplace: Examples of Science Service’s Presentation of Chemistry During the 1930s,” in *The Public Image of Chemistry*, ed. Joachim Schummer, Bernadette Bensusade-Vincent, and Brigitte Van Tiggelen (Tuck Link, Singapore: World Scientific Publishing, 2007).

<sup>81</sup> Bettyann Kevles, *Naked to the Bone: Medical Imaging in the Twentieth Century* (New Brunswick, N.J.: Rutgers University Press, 1997); Claudia Clark, *Radium Girls, Women and Industrial Health Reform: 1910-1935* (Chapel Hill, NC: University of North Carolina Press, 1997), ch. 2; Edmund Russell, *War and Nature: Fighting Humans and Insects with Chemicals from World War I to Silent Spring* (Cambridge: Cambridge University Press, 2001), pp. 62-3.

<sup>82</sup> L. C. Grove, “Iowa Marigold Test Report,” *Horticulture* (April 1, 1941), 1p. 81

<sup>83</sup> Kraft, *Garden to Order*, p. 94, p. 97.

<sup>84</sup> Gordon Morrison, “Science Brings Better Plants Thru Research,” *Chicago Daily Tribune*, April 5, 1956.

<sup>85</sup> Katharine Sergeant Angell White, *Onward and Upward in the Garden* (New York: Farrar, Straus, Giroux, 1979), p. 28.

technologies behind the production of these new varieties. Popular media coverage celebrated the means of production equally vigorously, if not more vigorously, than the end products.<sup>86</sup> A 1940 article in *Popular Mechanics* reported on “modern plant engineers” who in colchicine “have found a chemical ... which completely upsets long-established laws of heredity.” The results seemed almost unbelievable, and the author provided a list of new “super-giant” varieties, noting that “Most of this chemical plant growing is in the experimental stage but enough has come from the laboratories to assure us that the era of the chemical plant engineer is here.”<sup>87</sup> Edwin Way Teale described the “1940 plant wizard” who uses “tiny vials of potent drugs, X rays, and amazing synthetic foods,” and who finds that “By the new methods of the laboratory, the work of years [in cross-breeding and selection] can be telescoped into the space of a single season.”<sup>88</sup> Of all these methods, Teale suggested that colchicine was by far the most exciting.<sup>89</sup>

That the public interest in the effects of colchicine was not linked specifically to particular plant creations was evidenced by the visibility of colchicine mutation research in the popular press. In a short note following the 1937 article on colchicine and diploidy by Blakeslee and Avery, the editors of the *Journal of Heredity* warned their readers, “Colchicine is not a ‘growth elixer [sic],’ and evidence is lacking as to its effects on animal chromosomes, so that doctors may still make their calls safe from attack by giant rats, and ladies are in no danger of being gobbled up by caterpillars suddenly gone carnivorous.”<sup>90</sup> The letter appeared in response to a piece published in Hearst newspapers that November, and it indicates the interest regarding the effects of colchicine that existed beyond the walls of the laboratory. Blakeslee and Avery also felt the need to address these overblown expectations. “Some appear to expect too much from doubling chromosomes by use of colchicine,” they wrote. “One correspondent asks ‘If it will grow better plants, is it good for hair on the head?’ and similar questions have been asked by others.”<sup>91</sup> Blakeslee and Avery offered a more sober (though still quite enthusiastic) assessment of the narrow range of applications of their research.

Scientists anticipated from the start that non-experts would take up their colchicine-based improvement techniques. Blakeslee and Avery positioned the use of colchicine as a method best left to experts but did not exclude the possibility of its use in other circumstances. “Juggling chromosomes for the betterment of plant-kind is primarily a matter for the trained genetics engineer who knows the chromosomes with which he is working,” they emphasized. But they left the door open, suggesting specifically that amateur gardeners might have reason to use the chemical. The authors explained how one could obtain colchicine, how much it cost, and warned users of its toxicity to humans, in addition describing how to identify a tetraploid by examining the pollen under a microscope.<sup>92</sup> Their stance on the importance of being “a trained genetics engineer” was

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<sup>86</sup> It is important to note that in part the reporting followed in a more general pattern of viewing horticulture as an area of scientific research. The popular press celebrated the science and “wizardry” of commercial horticulture and the new varieties of plants that it introduced to yards and gardens. Historians have by and large approached gardening in the twentieth century as either a hobby or as an art form, and sought to understand its history in this light. However, the development of ornamental plants was discussed in popular media much as Burpee presented it, an activity requiring scientific expertise and as a field that took advantage of advances in basic research and technological developments.

<sup>87</sup> “Growing ‘Em Bigger with Chemicals,” *Popular Mechanics* (November 1940), p. 680.

<sup>88</sup> Teale, “Test-Tube Magic Creates Amazing New Flowers,” p. 58.

<sup>89</sup> *Ibid.*, p. 227.

<sup>90</sup> “Colchicine and Double Diploids,” *Journal of Heredity* 28, no. 12 (1937), p. 411.

<sup>91</sup> Blakeslee and Avery, “Methods of Inducing Doubling of Chromosomes in Plants - by Treatment with Colchicine,” p. 404.

<sup>92</sup> *Ibid.*

contradicted by their equal insistence that “Any high school biology teacher should be in position to help one in getting familiar with the relatively simple methods which are involved in the use of a microscope for examination of pollen.”<sup>93</sup>

Gardeners’ interest in the use of colchicine to produce changes in plants is perhaps exemplified in their application of the chemical to their own flowers. In January of 1940 a reader of *Horticulture* wrote to the publication to describe the challenges of colchicine experimentation. Kenneth Houghton of Dedham, Massachusetts, had in the year prior tested its effects on lupins, shasta daisies, and gladioli. Though he had not produced anything of interest, he thought “the difficulties encountered may be of interest” to other readers. Houghton had found colchicine to be considerably more expensive than he had been led to believe by the “numerous articles” he had read, the chemical difficult to apply to the plant in some cases, and mortality rates among his plants to be shockingly high — all of his daisies and all but one of the lupins died, though the gladioli fared better.<sup>94</sup> Houghton’s report of difficulties prompted at least one response. A representative of the Empire State Gladiolus Society wrote to *Horticulture* to affirm of the society’s determination to “lend its support in a wholehearted way to the amateur breeders of the state” in their experimentation with colchicine. The society itself had been undertaking studies on how to use the chemical and what results might be expected, with the aim of alleviating the situation experienced by Houghton in which “each worker will have to work out his own methods of application.”<sup>95</sup>

The interest of gardeners in experimentation with colchicine is also well illustrated by the response to a study first initiated by Eigsti at the University of Oklahoma in 1939 that involved distribution of colchicine and instructions for its use to amateur gardeners in exchange for information about the results obtained. An article in the university magazine described the project’s origins. Eigsti was curious about the range of agricultural products that colchicine could be used to improve, but lacked space in which to make these tests. According to the article, a “small story was given the news agencies, which told of Dr. Eigsti’s work. A picture showed him at work in the crowded quarters of a small greenhouse on the campus. Letters poured in. A prominent lawyer in Oklahoma said his farm could be used. A pecan grower wants to experiment with his pecan trees. A science teacher in a large state high school wants to help. Loyal Sooners have solved the problems of space and help ...”<sup>96</sup> The project soon turned into a more elaborate scheme in which volunteers were recruited and tracked, and a graduate assistant, Barbara Tenney, coordinated the effort.<sup>97</sup>

A small pamphlet produced as a summary of the project described the results of experiments undertaken by 327 volunteers in 38 states. Here Eigsti and Tenney concluded that “laymen” did not produce any economically valuable results.<sup>98</sup> They recommended instead that colchicine experimentation made a good project for garden clubs and student groups because the “work stimulates the latent inquisitiveness of amateur gardeners and their desire to improve the plants they raise.”<sup>99</sup> These were modest results for a project whose stated goal had been to engage non-scientists in identifying the species most responsive to colchicine and thus eventually to produce

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<sup>93</sup> Ibid., p. 405.

<sup>94</sup> Kenneth W. Houghton, “Experiments With Colchicine,” *Horticulture* (January 1, 1940), p. 16.

<sup>95</sup> G. A. Blanchard, “Colchicine in Gladiolus Breeding,” *Horticulture* (March 1, 1940), p. 100.

<sup>96</sup> Glenn Couch, “A Botanist Upsets Heredity,” *The Sooner* (January 1939), p. 11.

<sup>97</sup> Eigsti and Tenney, *A Report on Experiments with Colchicine by Laymen Scientists During 1941*; Barbara Tenney, “A Report on Experiments with Colchicine by Lay Scientists,” *Proceedings of the Oklahoma Academy of Science* 22 (1942).

<sup>98</sup> Eigsti and Tenney, *A Report on Experiments with Colchicine by Laymen Scientists During 1941*, p. 25.

<sup>99</sup> Ibid.

improved plant varieties.<sup>100</sup> Yet given the nature of the work required to produce a useful improvement from colchicine, well known to Eigsti and others, this outcome could not have been unexpected.

The more interesting information presented by the project summary is the enthusiasm of the participants as evidenced by the extent of the study and as described by the authors. The authors believed it was natural that so many would be interested in the project, for “Many laymen scientists were already engaged in work with hormones, vitamins, and chemicals for soilless farming. The announcement of colchicine as a ‘magic’ substance with ‘mysterious’ powers was received with great enthusiasm ...” Eigsti, rather than turning away the amateurs “knocking at the door of the scientist’s laboratory,” instead turned them into experimenters like himself, providing access to materials and information. “Practically every participant has definitely expressed a desire to be included in the project next year,” the report concluded, this despite the fact that far less than half had produced results of any kind, let alone improved upon a plant variety.<sup>101</sup> Amateurs did not appear to be discouraged by the near impossibility of generating the impressive new varieties described in popular media.

Not all gardeners were enthused about these kinds of activities. A letter to the editor of *Horticulture* by Richard Wright of New York City in 1941 complained of the “penetrating and often morbid curiosity” among garden club members regarding the application of chemicals in their gardens. “Otherwise normal housewives speak glibly of colchicine, potassium naphthaleneacetate, Vitamin B1, and indolebutyric acid ...,” the writer complained. “Has gardening in this country gone too chemical? Must our tool sheds be turned into laboratories?”<sup>102</sup> But other readers quickly attacked Wright’s position. Mrs. R. L. Ross of Tallmadge, Ohio, a self-declared housewife, wrote in retaliation, “Mr. Wright need have no worry about housewives. A good one does not necessarily cook only by old recipes but rather is ever happy to try new ones.” Ross offered the newly introduced Tetra marigold as a prime example of the benefits to be anticipated from chemical gardening and stated her position that “if the men offering these new chemicals are sincere, they deserve whatever expenditure or time we care to give to them.”<sup>103</sup> Berenice Nulsen of Missouri echoed Ross’s sentiments, noting also that the experimentation itself would be of value. “Even if nothing comes of all the stench” associated with chemicals in the garden, Nulsen argued, “we garden club women will have had months of stimulating study and as much satisfaction in finding a proper blue in the phosphate test as any one can have in a long-sought blue flower.”<sup>104</sup> Trying new techniques and learning by experimentation alone were reason enough for some to put colchicine to work in the garden.

Reporters such as Glenn Couch, who covered Eigsti and Tenney’s work for the University of Oklahoma, likely encouraged the amateur enthusiasm displayed by readers of *Horticulture* such as Nulsen, Ross, and Kenneth Houghton, and other gardeners. Couch suggested, naively, to his readers that “If you have ever done any gardening, you might have an urge to try your own hand at changing chromosomes. There is no secret about it ... In contrast to many scientific experiments, this one is easy to perform. Here is the way to try it in your own back yard ...” Couch continued with specific instructions for both soaking seeds in colchicine dilutions and applying colchicine

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<sup>100</sup> Ibid., p. 6.

<sup>101</sup> Ibid., pp. 4-5, p. 25.

<sup>102</sup> Richard Wright, “Richard Wright Asks A Question,” (January 1, 1940), p. 12.

<sup>103</sup> R. L. Ross, “A Housewife’s Answer to Mr. Wright,” *Horticulture* (February 1, 1940), p. 55.

<sup>104</sup> Berenice M. Nulsen, “Women Who Like to Experiment,” *Horticulture* (February 1, 1940), p. 55.

directly to the flower buds of full-grown plants.<sup>105</sup> In 1961, more than twenty years after news of colchicine's effects were first published, amateurs were still being instructed on how to put it to use in the home garden and about genetic manipulation, and the expectations for what an amateur might produce appear to have changed very little. An article in *Popular Mechanics* detailed for readers how colchicine might be used in "the experimentations of serious amateur gardeners." Though the author suggested to readers that "it's a good idea to read a book or two about genetics," the method was as simple as ordering some colchicine from a pharmaceutical company and applying it to germinating seeds. The author did not promise improvement, however, only effect, "You can be sure of one thing when you try it: Good or bad, you'll get *changes* in plants."<sup>106</sup> Changes, and not necessarily improvement, were the central object of interest.

## Conclusion

The examination of public interest in experimenting with colchicine and its use by amateur gardeners expands the history of colchicine to include not only geneticists with garden plants but also gardeners with genetic techniques. The use of colchicine traveled the length of the spectrum of empirical inquiry, from the realm of basic research in cytology and genetics, to applied science at agricultural research stations, commercial flower development, and the amateur experiments of the home gardener. The transfer of techniques among these various groups suggests the channels of communication and exchange among them, and points especially to the overlap in their hopes of utilizing genetic manipulation via mutation to produce new varieties of plants.

Although the production of mutations via the chemical agent colchicine was a central aim of the many horticulturalists discussed here, their motivations for doing so and the ways in which they went about it were not necessarily the same. Colchicine's ability to produce either polyploidy or other spontaneous mutations, and its wide availability and ease of use, meant to could be deployed to different ends. For professional breeders at research stations and academic institutions, colchicine promised primarily to become a tool for increased control over the evolution of improved varieties via chromosomal mutations; for commercial horticulturalists, it was also (and more often) a way to rapidly unleash mutations of all kinds, and thus to produce profitable new varieties at a faster pace; for home gardeners, it was not only the source of new plant varieties on the market, but also a chance to become a part of technological progress via "juggling of chromosomes" at home. This last context is perhaps most interesting from the perspective of the historian of science, for it suggests the home, and more specifically the garden, as a space for experimentation and knowledge creation apart from the research laboratory or the experimental agricultural station. Ornamental horticulture provided, in at least this instance, a unique space for collaboration in research and experiment among distinct communities.

Giving attention to the range of groups interested in these processes brings their differing responses to and hopes for technologies of genetic manipulation into sharp relief. Colchicine was — and is — part of the constellation of tools and practices that fall under the umbrella term of mutation breeding. As mentioned at the outset, the use of colchicine in mutation breeding illuminates both the frustration felt by some researchers at mid-century with the slow pace of Mendelian breeding. More so, it demonstrates the widely held belief that improved varieties would

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<sup>105</sup> Couch, "A Botanist Upsets Heredity," 11, p. 27.

<sup>106</sup> A. B. Kennerly, "New Plants on Order," *Popular Mechanics* (June 1961), p. 132

result from genetic manipulation through technological intervention. This suggests that the history of mutation breeding more broadly may highlight the challenges and hopes encountered in plant breeding in the period between the heyday of hybridization (in the mid-1930s) and the first uses of genetic modification (GM) technologies in plants (beginning in the early 1980s) — two periods about which we know comparatively more.<sup>107</sup> In addition, if the case study of colchicine use is any guide, such a history must give attention to the interests of the commercial and amateur ornamental horticulturalists, in addition to agriculturalists and academic or governmental researchers, for the mode and meaning of mutation breeding was not uniform across these groups.

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<sup>107</sup> See footnote 10.

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## *The Political Life of Mutagens: A History of the Ames Test*<sup>1</sup>

Angela N. H. Creager

In 1973, Bruce N. Ames, a professor of biochemistry at the University of California, Berkeley, introduced a new assay for use in evaluating carcinogenicity. The test relied on four mutant strains of *Salmonella* that Ames's group had customized, drawing on years of experience using such strains in studies of metabolism and mutagenesis. Each could be used to genetically screen compounds inducing a specific kind of mutation in the DNA sequence, thereby registering them as back-mutations to the phenotype. (For these strains, such reverse mutations meant the cells no longer required the amino acid histidine in the medium.) The four *Salmonella* strains were further customized with additional mutations that made the cells more permeable to large molecules and eliminated some kinds of DNA repair. Ames showed that his test could identify nearly all known chemical carcinogens and he advocated its utilization in assessing the cancer risks posed by both new substances. Companies immediately began adopting the Ames test as a way to undertake routine chemical screening; the new method was both quicker and less expensive way than traditional animal testing. (Facilitating the adoption of his test method, Ames made his strains freely available.) Environmental groups were equally enthusiastic about the test, particularly once Ames identified as likely carcinogens a new food preservative and a flame retardant being incorporated into children's pajamas.

The value of Ames test, which was embraced by industry and environmentalists in the 1970s, relied on two powerful but vulnerable assumptions. First, as Ames put it, a carcinogen is a mutagen. Human cancer, in this view, is caused principally by exposure to environmental mutagens. Compounds that do not induce mutations were presumed to not cause cancer, either. Second, he assumed that a microbe was a suitable model organism for assaying mutagenicity as it occurred in human cells. Many toxicologists and cancer biologists objected to Ames's simplifying assumptions. But these objections were minor compared to the political controversy that developed around the test in the 1980s, after Ames decided to begin testing natural substances, such as extracts of vegetables and caffeine. His assays showed many foods and beverages to be just as carcinogenic as synthetic chemicals. On this basis he began arguing against new industry regulations, even as he was being appointed to government panels to interpret and implement safety standards. Environmentalists felt betrayed.

This paper situates the invention of the Ames test in terms of his experimental trajectory as a biochemist in the broader context of postwar radiation genetics and environmentalism. In particular, the reconceptualization in the 1960s of the "somatic" (including cancer-causing) effects of radiation in terms of mutation enabled scientists to directly connect the mutagenicity and carcinogenicity of radiation, and, by extension, synthetic chemicals. I aim to answer the question of why and how microbial *mutations* became a key means for visualizing the cancer-causing dangers of environmental substances, and how Ames's attempt to rationalize and rank cancer risks in this way

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met with opposition from cancer biologists and environmentalists.

### *Radiation, Mutation, and Cancer*

The Ames test relied on equating mutagenicity with carcinogenicity, i.e., that the mutagenizing ability of a chemical substance or radiation was responsible for inducing cancer. This idea, which brought together two distinct conceptions of radiation effects, did not gain wide currency until the 1960s, for reasons that had nothing to do with the double helix or molecular biology. H. J. Muller had demonstrated in 1927 that X-rays could induce mutations and this finding was rapidly extended to other forms of radiation (Muller 1927). Radiation had also been correlated with the appearance of cancer (especially leukemia) from early observations of the hazards of radium exposure in the 1920s and 1930s.<sup>2</sup> However, these two consequences of radiation were not causally linked. The elevated risk of cancer consequent to irradiation was considered a *somatic* effect of radiation, as opposed to its *genetic* effects — principally mutations. Somatic effects could directly affect the health of the individual; these were effects on the body. Genetic effects — the consequences for one's gametes — were seen in one's offspring, or through decreased fertility. Through World War II, radiation safety standards were based on the notion of a threshold below which somatic damage was thought to be negligible (Walker 2000). By contrast, geneticists did not recognize a lower threshold for the mutational effects of radiation.

The extension of the realm of mutagens to include chemical agents did not change these perceptions. The pathbreaking work of Charlotte Auerbach and her colleagues on the chemical production of mutations was not oriented to carcinogenesis, but aimed at showing that mustard gas derivatives caused mutation like sources of ionizing radiation. In the estimation of one of the few historians who has written on this topic, most retrospective accounts “fail to understand the lukewarm reception that geneticists gave chemical mutagenesis and the uneven incorporation of chemical mutagens into standard genetics practices over the next three decades” (Frickel 2004, p. 29).<sup>3</sup>

What about interest from the side of cancer researchers? There certainly was interest in the role of heredity in cancer — one thinks of C. C. Little's development of mouse genetics in order to study this question — yet this trajectory of research did not connect to literature about the mutagenicity of radiation (Löwy and Gaudilliere 1998; Rader 2004). During the 1930s and 1940s cancer causation tended to be attributed to external factors, such as tissue irritation (such as through exposure to coal tars) and viruses (Creager and Gaudillière 2001). Neoplasms caused by exposure to ionizing radiation also supported the exogenous theory of cancer causation. Other researchers argued for the role of endogenous factors; genetic studies of cancer tended to focus on its prevalence in families or animal strains (Gaudilliere 1999; Comfort 2006). While scientists acknowledged that these different factors might combine to incite tumor formation, radiation and heredity fell on different sides of the exogenous/endogenous divide in cancer etiology.

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<sup>2</sup> Similar observations were made with X-ray exposure; there were 94 cases of X-ray induced skin cancer in the medical literature by 1911. On this and on early observations of radium-induced cancer, see Kathren (1996).

<sup>3</sup> This appraisal does not accord with the perspective of all geneticists; Evelyn Witkin, a bacterial geneticist working at Cold Spring Harbor in the 1940s, remembers avid interest there in Auerbach's work and a rapid incorporation of chemical mutagenesis (personal communication, 23 April 2009).

The construction of a massive atomic energy infrastructure in the American bomb project made the role of radiation in cancer incidence a matter of occupational safety for the U.S. government, particularly after the war, when the facilities were transferred from military to civilian control by the Atomic Energy Commission (AEC) (Hacker 1987). Conflicts between geneticists and health physicists over the hazards of low-level radiation surfaced by 1949 (Jolly 2003, ch. 3 and 4). Robley Evans, a physicist known for his studies of the radium dial painters, published an article entitled “Quantitative Inferences Concerning the Genetic Effects of Radiation on Human Beings” (Evans 1949). Evans presented a reassuring picture of the genetic consequences of radiation exposure, arguing that exposure at or under the government’s permissible dose level would not significantly increase the mutation rate beyond its spontaneous level. However, geneticists regarded his estimate for the spontaneous mutation rate in humans,  $10^{-5}$ , to be two orders of magnitude too high. Using a lower estimate for the spontaneous mutation rate, based on experiments with *Drosophila* rather than extrapolated from the incidence of rare human genetic diseases such as hemophilia, Sewell Wright calculated that exposures within the permissible dose could, in fact, alter the incidence of mutations significantly (but perhaps not detectably, as most mutations are recessive) (Wright 1950).<sup>4</sup>

In the end, new research, much of it sponsored by the AEC, bolstered the geneticists’s viewpoint that low-level radiation exposure entailed human mutation risk. Alexander Hollaender, who headed radiobiology research at the AEC’s Oak Ridge National Laboratory, was a major contributor to this development, by supporting research programs and organizing conferences aimed at resolving these issues (Rader 2006). He held an Information Meeting on the Cytological and Genetical Effects of Radiation in March 1948 at Oak Ridge; this was the origin of Wright’s 1950 paper that critiqued Evans. Muller’s paper for this conference advanced his concern that a large segment of the population would suffer genetic damage due to occupational and medical exposure to radiation.<sup>5</sup> He also suggested that mutations in the somatic cells were responsible for some of the known long-term effects of radiation, such as cancer (Muller 1950a). Concurrently, William and Lianne Russell’s “mega-mouse” study was launched at Oak Ridge National Laboratory to help provide a better estimate of both the spontaneous mammalian mutation rate and the human genetic hazard from low-level exposure to ionizing radiation. Their results by early 1951 suggested that the mammalian spontaneous mutation rate might be an order of magnitude lower than that for *Drosophila* (Jolly 2003, p. 112). The growing consensus among geneticists was that mutational damage from ionizing radiation was linear, cumulative, and deleterious, a perspective the AEC leadership was reluctant to accept.

In addition, the studies of the Atomic Bomb Casualty Commission (ABCC) ended up focusing attention on the genetic damage associated with radiation exposure in survivors of Hiroshima and Nagasaki. As Susan Lindee has argued, defining what phenotypes qualified as mutations in the evaluation of children of these survivors was not straightforward, and the ABCC’s guidelines reflected social realities and criteria as well as scientific ones (Lindee 1992 and 1994). In 1955, the genetics project released their results, which were “negative” — or inconclusive (Beatty 1991).

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<sup>4</sup> Evans calculated the radiation level that would cause a doubling of the spontaneous mutation rate, or doubling dose, of 300 roentgens. Adjusting the spontaneous mutation rate by two orders of magnitude also reduced this estimate to a much more worrisome level (in terms of occupational exposures among workers in atomic energy facilities and also clinics), 3 roentgens. Jolly 2003, p. 98.

<sup>5</sup> As Jolly notes (2003, pp. 90–93), Muller’s idea of “genetic death,” introduced here, was developed more fully in “Our Load of Mutations” (Muller 1950b).

Even though the final report denied that exposure had detectably increased mutation rate, the studies provided a platform from which geneticists could shift public health guidelines for radiation exposure from an exclusive focus on somatic effects to attention to genetic effects.

Public concern about the dangers of radioactive fallout in the 1950s made technical debates about the biological effects of low-level radiation both more visible and more consequential. Recently-developed hydrogen bombs released significantly greater amounts of radioactive contamination into the environment, and the AEC's decision to test many of their devices in a proving ground in Nevada meant that fallout could reach many ordinary Americans (Hacker 1994). In March 1954, the AEC conducted a test of its thermonuclear weapon on the Pacific proving ground. Fallout from the "Bravo" shot of this Castle testing series fell on a Japanese fishing boat, the "Lucky Dragon." Nearly two dozen fishermen suffered injuries from the radiation exposure and one eventually died; these casualties received extensive media coverage in the U.S. as well as Japan. The U.S. government made no concessions to critics. Lewis Strauss, the Chair of the AEC, publicly denied that the fallout was harmful to humans, animals, or crops (Strauss 1954; Kopp 1979). Geneticist A. H. Sturtevant rebutted Strauss in his presidential address at a meeting of the Pacific Division of the American Association for the Advancement of Science, which then appeared in *Science*. In recounting the hazards of radiation exposure, Sturtevant connected mutagenicity with so-called somatic effects, "There is reason to suppose that gene mutations, induced in an exposed individual, also constitute a hazard to that individual — especially in an increase in the probability of malignant growths, perhaps years after the exposure." He concluded that "there is, in fact, no clearly safe dosage."<sup>6</sup> In the year that followed, open debate between the AEC and a number of scientists reinforced the growing public alarm (Jolly 2003).

In part to provide an independent assessment, the U.S. National Academy of Sciences appointed six committees to address different aspects of the Biological Effects of Atomic Radiation. The report of the genetics committee, published along with those from the other five committees in June 1956 (as the "BEAR Report") focused on the hazards of low-level radiation exposure (Beatty 1987, 1991; Lindee 1994; Hamblin 2007). The report from the Pathology Committee addressed cancer risk, and was more reassuring. Their main task was to evaluate concerns about whether the level of contamination of strontium-90 in milk and vegetables might lead to its concentration in human bones at hazardous levels. They acknowledged a possible link between radiation from internal emitters such as strontium-90 and leukemia incidence.<sup>7</sup> Despite the Pathology Committee's conclusion that current levels "are not considered to produce harmful effects," scientists such as Ralph Lapp published criticisms of the official interpretation, and Linus Pauling cited the link between strontium-90 and cancer in a 1959 letter in *The New York Times* (Lapp 1957; Pauling 1959).

In this way, the connections between radiation, mutation, and cancer were consolidated during the fallout controversy, particularly through the public statements of scientists who dissented from the AEC's position. At the same time, and despite its public stance, the AEC supported

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<sup>6</sup> Sturtevant 1954, p. 406.

<sup>7</sup> Strengthening the plausibility of this connection were studies published in 1956 and 1957 showing a statistically significant correlation between clinical radiation exposure and subsequent leukemia incidence. See de Chadarevian, "Mutations in the Nuclear Age," this volume, and Dry 2006.

much of the research that substantiated a new understanding of how radiation caused cancer through genetic damage. For example, the work of AEC Laboratory Director John Gofman of chromosomal aberrations caused by cell irradiation offered a way of understanding somatic effects including tumorigenesis as *genetic*, even when the cells affected were not gametes (Semendeferi 2008). This reflected not only new cytogenetic data but also an emerging molecular biological understanding of cancer as mutational in origin. Thus low-level radiation might lead, through similar genetic mechanisms, to cancer in an individual and to deleterious mutations in his or her offspring.

### *Ames's Path to Chemical Mutagens*

Bruce Ames came into these debates through a background in biochemical genetics. He earned his Ph.D. at Caltech in 1953, using metabolic mutants *Neurospora* isolated by his advisor Herschel Mitchell (a former postdoctoral fellow of George Beadle's) to study the biosynthesis of the amino acid histidine.<sup>8</sup> Ames went on to a postdoctoral fellowship at the National Institutes of Health (NIH), in the laboratory of Bernard Horecker, because "I knew I needed to learn enzymology" (Ames 2002, p. 4370). The NIH was indeed a great center of enzymology — and biochemistry more generally — in the 1950s, with laboratories headed by Arthur Kornberg (Nobel Prize 1959), Earl Stadtman, Leon Heppel, Marshall Nirenberg (Nobel Prize 1968), and Martin Rodbell (Nobel Prize 1994).<sup>9</sup> After one year Ames became a section chief in Gordon Tomkins's unit at the NIH, the Laboratory of Molecular Biology. Ames stayed until 1967.

After arriving in Bethesda, Ames continued to study histidine biosynthesis, but shifted organism to *Salmonella typhimurium*. In this way he could take advantage of an extensive set of histidine-requiring mutants that had been isolated by Philip Hartman at the Carnegie Institution of Washington. Hartman had already isolated and genetically mapped hundreds of histidine mutants in *Salmonella* (eventually it would be thousands), creating a remarkable repertoire of mutants available for work on this biosynthetic pathway. Ames and his coworkers showed that histidine regulated the synthesis of each enzyme in this biosynthetic pathway; they dubbed this kind of regulation "coordinate repression." Hartman had previously shown that these enzymes mapped to the same location of the *Salmonella* chromosome. In fact, the sequence of genes encoding these enzymes on the chromosome was the same as the sequence of enzymatic steps in the biosynthetic pathway. Based on this finding, Ames and his coworkers suggested that histidine regulated its own biosynthesis at the gene level, by repressing "the synthesis of all of the biosynthetic enzymes together" (Ames and Garry 1959, p. 1459).

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<sup>8</sup> Drawing on both biochemical techniques and genetics, Ames used chromatography to separate the precursors of histidine (imidazole intermediates), and made double mutants to determine the order of metabolic steps in the pathway (Ames and Mitchell 1952; Haas et al. 1952; Ames, Mitchell, and Mitchell 1953).

<sup>9</sup> For more on the NIH intramural program in biochemistry in the 1950s, see Kay 2000; Park 2003; Creager 2008, and essays in Hannaway 2008.

In the late 1950s and early 1960s, Ames was among a dozen or so prominent biochemists that were engaged in studies of metabolic responses to physiological or environmental stimuli by measuring changes of enzymatic activities at the cellular level. Papers on “feedback inhibition” of metabolic pathways emerged from members of this loose international network of researchers, which featured in both the 1959 Ciba Foundation Symposium on the Regulation of Cell Metabolism and the 1961 Cold Spring Harbor Symposium on Cellular Regulatory Mechanisms.<sup>10</sup> Ames’ research on histidine biosynthesis epitomized this trend, which brought together biochemistry and bacterial genetics and contributed to the vibrancy of molecular biology as it was emerging as a new field during this period. Continuing his affiliation with vanguard institutional niches, Ames took a year-long sabbatical from the NIH in 1961 and split the time between the laboratories of Francis Crick at the Laboratory of Molecular Biology in Cambridge and the laboratory of François Jacob at the Institut Pasteur.

Ames recalls, “Sometime in 1964, I read the list of ingredients on a box of potato chips and began to wonder whether preservatives and other chemicals could cause genetic damage to humans” (Ames 2002, p. 4371). The thousands of histidine-requiring mutants he had at hand (through collaborator Hartman) provided ready test material for investigating mutagens. The early phase of this work involved classifying mutants with an eye towards studying mutagenesis. At the 1966 Cold Spring Harbor Symposium on Quantitative Biology on the Genetic Code, Ames and laboratory member Harvey Whitfield presented evidence that a group of acridine-like compounds, developed as potential anti-tumor agents and powerfully mutagenic, added or deleted nucleotides from DNA. They identified a class of mutants that were not mutable by standard mutagens, and showed them to be mutable by one of these compounds, ICR 170. The authors inferred that these mutant strains were frameshift mutants, in which the addition or deletion of a base disrupted the reading frame of triplet bases and so yielded an incorrect sequence of amino acids (Ames and Whitfield 1966; Whitfield, Martin, and Ames 1966).

In effect, Ames and Whitfield were able to use current knowledge about mutagens and mutant strains to classify both. For example, the authors used one of the frameshift mutants to test quinacrine, an antimalarial drug. It was a weak mutagen of the strain. As the author commented, “This raises the possibility that the standard antimalarials chloroquine, quinine, and quinacrine, which are known to bind to DNA strongly, are causing frameshift mutations in the human population” (Ames and Whitfield 1966, p. 225). Ames’s eponymous test would build on this practice of using known mutant strains to detect and classify mutagens. After moving to Berkeley in 1967, Ames sought funding for the ongoing project on mutagens. His application to the National Cancer Institute was turned down (as he puts it, “they did not think bacteria could teach us much about cancer”), but supported by the AEC (Ames 2002, p. 4372).

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<sup>10</sup> Jean-Paul Gaudillière and I have called this international scientific community, of which Ames was an obvious participant, “cell regulationists.” We identify the following core group as representative of the trend: Bruce Ames, Earl Stadtman, and Gordon Tomkins at NIH; Boris Magasanik, Bernard Davis, Luigi Gorini, Harold Amos, and H. Edwin Umbarger at Harvard Medical School; Jacques Monod and Georges Cohen at the Institut Pasteur; Arthur Pardee at the University of California, Berkeley; Aaron Novick at the University of Oregon; Werner Maas at New York University; and Melvin Cohn at Stanford University (until he turned his attention to immunology). Enzyme formation and enzyme adaptation were key problems, alongside regulation of amino acid metabolism. Creager and Gaudillière 1996, pp. 6–15.

Ames first presented his mutagen tester strains at The Conference on Evaluating the Mutagenicity of Drugs and Other Chemical Agents, which took place in Washington D.C. on November 4-6, 1970. According to the report in *Science*, the event was prompted by concern among researchers about the potential hazards of synthetic chemicals, which were becoming ubiquitous (Harris 1971). It was not only scientists who were concerned, of course: Rachel Carson's *Silent Spring*, which appeared in 1962, built on the public fear of radioactive contamination generated by the fallout debates to draw attention to the unseen hazards of pesticides and other synthetic chemicals (Lutts 1985). At this 1970 meeting, six months after the first Earth Day, biologists drew on their familiarity with mutagenesis as a laboratory tool to consider the parallel hazards of ionizing radiation and chemical mutagens in everyday life:

Using a variety of well-characterized mutagens, scientists have been able to manipulate microorganisms in particular to produce selective mutations in the genes. Their methods are sophisticated enough to produce mutations in the genes governing the synthesis of the macromolecules involved in chromosome duplication (DNA synthesis) and gene expression (RNA and protein synthesis). With these advances has come the realization that similar mutations may be occurring in man by way of less controlled process, such as radiation damage and alteration of chromosomes by chemicals and drugs. Many workers believe that chemical damage is now a more important problem than radiation hazard (Harris 1971, p. 51).

Toxicological and environmental problems could now be understood in molecular biological terms. A major pharmaceutical trade association was one of the sponsors of the conference, and scientists in attendance called on them to address the new hazards. As the reporter for *Science* observed, geneticists James Neel and Jim Crow felt "that a burden of responsibility rests on the pharmaceutical industry, even though they are not the major producers of potential mutagens, and called on them to lead the way toward testing before use by the human population" (Harris 1971, p. 52).

Researchers at the meeting presented work on the most up-to-date methods for assessing mutagenicity as well as for detecting the rate of mutations in human populations. In describing his own assay, Bruce Ames acknowledged the limitations of a bacterial test, admitting it is "absurd to extrapolate from bacteria to humans," even as he defended the concept:

But DNA has the same double helical structure and the same four nucleotides in all organisms, and it is logical to believe that mutagens of *Escherichia coli* DNA will also be mutagenic for animal DNA. In general, mutagens for higher organisms are mutagens for bacteria also. More than half of the mutagenic agents for bacteria are carcinogenic for animals (Ames, as quoted in Harris 1971, 52).

Other researchers were attempting to develop laboratory tests using mammalian cells in tissue culture. The 1960s had seen the development of a variety of tissue culture lines, often developed for work with animal viruses, modeled on the investigation of bacteriophages using bacterial cultures. However, the tissue culture systems for scoring carcinogens apparently did not develop as quickly as Ames's bacterial system.<sup>11</sup>

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<sup>11</sup> Harris (Harris 1971, p. 52) does not mention researchers by name when making reference to these attempts, but simply states that "Procedures are now being developed by several laboratories by which genetic analysis of mammalian cells in tissue culture can be performed as easily as bacterial tests." The Ames test is compared to some of these mammalian cell culture test systems by U.S. Interagency Staff Group on Carcinogens 1986, p. 227.

Not all the proposals at this meeting concerned laboratory screening of compounds. James Neel, who had previously participated in the ABCC investigations in Japan, was encouraging the implementation of mass human screening for mutations, along the lines of the screening of infants for phenylketonuria. By using electrophoresis testing of ten proteins in blood samples, such a screening project could detect a “50 percent increase in human mutation rate” (Harris 1972, 52). The cause of a rise in mutation rate could not be determined by such a screen, but it could serve as a “public health warning system.”<sup>12</sup>

The participation of geneticists like Neel in efforts to evaluate and regulate new chemical mutagens carried over directly from early studies of radiation.<sup>13</sup> Alexander Hollaender, who had presided over the growth of radiobiology research at Oak Ridge, attended the 1970 meeting, and reminded other participants that “the research effort directed toward the investigation of radiation hazards was made possible only by long-range guaranteed support [i.e., of the AEC]” (Hollaender, as quoted in Harris 1971, p. 52). In fact, the attempt to connect advances in molecular biology, particularly the growing understanding of DNA replication, transcription, and causes of mutation in bacteria, to evaluations of human carcinogenesis was a trend that the AEC had specifically fostered.

The Ames test involved the use of four strains (Ames et al. 1972). (For an illustration of what the plates look like, see Figure 1) Three of the strains (originally TA1531, TA1532, and TA1534) were designed to detect different kinds of frameshift mutagens.<sup>14</sup> The fourth strain, TA1530, contained a base-pair change, and so it would detect mutations that involve base-pair substitutions.<sup>15</sup> In addition, all four tester strains included a mutation in the *uvrB* gene that disabled DNA excision repair, making them more sensitive to mutagens whose effects would be corrected by this system. Ames’s group soon added two additional features to the system, to improve its sensitivity to mutagens. The first was the incorporation of an additional mutation in the strains that resulted in a deficient lipopolysaccharide (Ames, Lee, and Durston 1973). This compound normally coats the bacterium and poses a barrier to the penetration of large molecules into the cell. The mutation rendered the cells able to take up a wide range of large chemical compounds. Second, Ames’s group showed that spreading an extract of rat or human liver with the carcinogen on the Petri dish allowed testing of metabolic derivatives of the compound being tested (Ames et al. 1973). It was known that mammalian microsomal hydrolase activated many classes of carcinogens and mutagens, including aflatoxin, aromatic amines, and polycyclic hydrocarbons (Ames 1973, p. 116).

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<sup>12</sup> Neel estimated that reliable results could be obtained from blood samples of 350,000 people a year (Harris 1971, p. 52). On the development of genetic screening programs, see Lindee 2005.

<sup>13</sup> Neel was an architect of the genetics project of the Atomic Bomb Casualty Commission (Beatty 1991).

<sup>14</sup> Each of these included a frameshift mutation in one of the genes of the histidine operon.

<sup>15</sup> The strain to detect base-pair substitutions contained mutation in the in the histidine G gene.

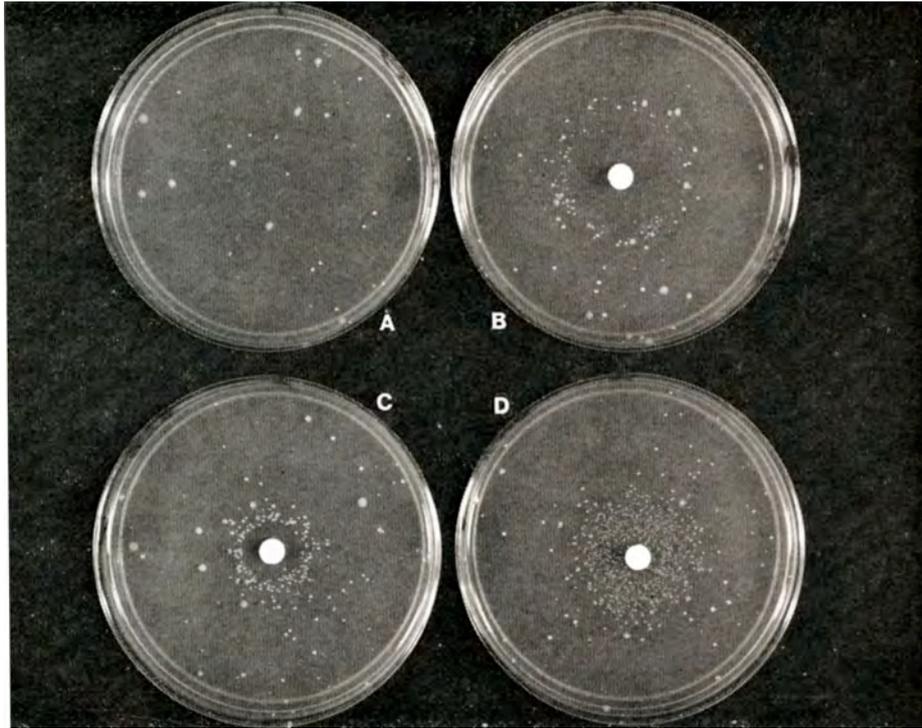


Fig. 1: Pictures of Ames Tests for (A) Spontaneous Revertants and exposure to (B) Furfurylformamide, (C) Aflatoxin B1, and (D) 2-Aminofluorene. The mutagenic compounds in B, C, and D were applied to the 6 mm filter disk in the center of each plate. Each Petri plate contains cells of the tester strain in a thin overlay of top agar. (The strain used here is TA98, derived by adding a resistance transfer factor to a *Salmonella* tester strain, mutant hisD3052, that scores frameshift mutations.) Plates C and D contain, additionally, a liver microsomal activation system isolated from rats. The spontaneous or compound-induced revertants, each of which reflects a mutational event, appear in a ring as spots around the paper disk (Ames, McCann, and Yamasaki 1975, 358).

As Ames readily admitted, the idea of using microbes to screen compounds had not originated with him. Following Evelyn Witkin's 1947 demonstration that a wide variety of chemical compounds could serve as mutagens in *E. coli*, Milislav Demerec, Giuseppe Bertani, and J. Flint published an article in which they tested a variety of chemicals for mutagenicity in a streptomycin-dependent strain of *E. coli* (Witkin 1947; Demerec, Bertani, and Flint 1951). The system registered mutagenicity by scoring colony growth from back-mutations. This meant they could score low-frequency mutagenic events through the screening of up to five hundred million bacteria (Demerec 1954, p. 319). Nineteen of the thirty-one compounds tested proved to be mutagenic. It was a chemically diverse group, including boric acid, ammonia, hydrogen peroxide, copper sulfate, acetic acid, formaldehyde, and phenol.

Waclaw Szybalski's laboratory further refined the use of bacterial strains to detect chemical mutagens in the late 1950s, screening over 400 compounds (Iyer and Szybalski 1958; Szybalski 1958).<sup>16</sup> His technique included the paper disk method for screening mutagens, in which the

<sup>16</sup> The list of publications on Professor Szybalski's website is annotated, and the note about these two publications is telling: "Dr. Szybalski and his collaborators studied the mechanism of mutagenesis. First,

substance was placed on the Petri dish on a small circular piece of filter paper, causing revertants to appear in a ring around the substance as it diffused out. (See figure 2) Szybalski noted a strong correlation between carcinogenicity and mutagenicity, “These studies demonstrated a close correlation between the carcinogenic effect in mammals and the mutagenic effect on bacteria, stimulating a wide interest in this field.”<sup>17</sup> But that was not the principal motivation for his screen, which was aimed at identifying anti-tumor agents (Zeiger 2004). Why not see the genetic consequences of these compounds as key to explaining their carcinogenicity, too?

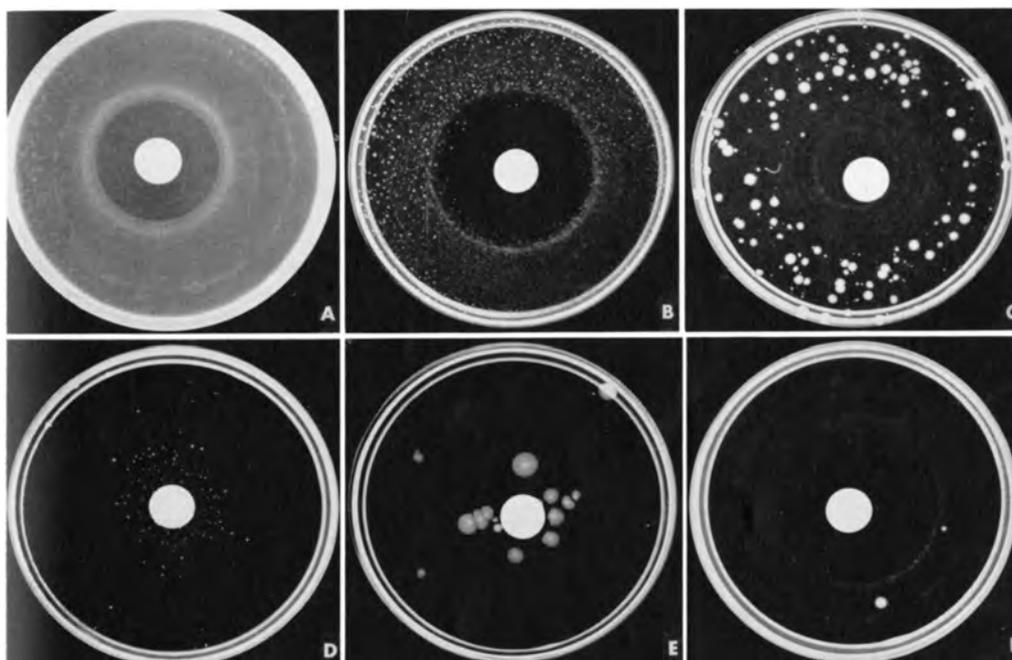


Fig. 2: Paper Disk Method for Screening Mutagens. Assay tests for mutagenicity at the streptomycin-dependence locus of *Escherichia coli* strain Sd4-73. Plates A-C show the mutagenic effect of beta-propiolactone, 10 mg per disc. (A) Control Plate with high inoculum (109) cells + 100 µg per ml streptomycin; shows inhibition zone. (B) Appearance of mutant colonies with high inoculum. (C) Appearance of mutant colonies with ten-fold lower inoculum (108) of cells. Plates D-E show the mutagenic effect of azaserine at 100 µg per ml. (D) Formation of mutant colonies in proximity of disk with a high inoculum cells. (E) Formation of mutant cells in proximity of disk with a ten-fold lower inoculum (108) of cells. (F) Control plate for spontaneous formation of streptomycin-independent colonies; 0.1 ml distilled water added to disk (Iyer and Szybalski 1958, p. 25).

Demerec assumed that chemical agents induced mutations in an *indirect* way — that “mutagenic treatment brings about some change in either the cytoplasm or nucleus which in turns affects certain physiological processes of the cell, and thereby influences genes” (Demerec 1954, pp. 321-322). In other words, “treatment with a mutagen does not affect genes directly” (Hemmerly and Demerec 1955, 74). Joshua Lederberg also emphasized the complications of indirect effects with chemical mutagens:

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they developed the ‘paper disc mutagenicity test,’ which was later adopted in [the] so-called ‘Ames test.’”  
<http://mcardle.oncology.wisc.edu/faculty/bio/WSPubl.html>.

[We] must be very cautious in interpreting chemical mutagenesis as a direct chemical reaction with the gene. Cells, including bacteria, react in a very complex pattern to treatment with mutagenic agents. The possibility cannot be excluded that some mutations are produced indirectly as a consequence of accidents during recovery or of non-specific and non-localized disturbances of nuclear structure (Lederberg 1951, p. 275).

Bacterial screens of chemical mutagens, then, were not thought to shed direct light on the nature of mutation.

Lederberg himself noted that the interest in chemical mutagens might have translated into an earlier engagement with toxicology and public health (Lederberg 1997). Based on his own work on “radiomimetic” chemical mutagens, Lederberg wrote H. J. Muller in 1950 expressing concern that a wide range of common organic reagents might pose a significant genetic hazard to individuals exposed, similar to and even greater than sources of ionizing radiation. He suggested that the problem be brought to the attention of the National Research Council. Muller, who certainly did not hesitate to enter into debates about genetics and public safety, felt the evidence was not strong enough to warrant the NRC’s involvement. In broaching the topic of who would pay for large-scale investigation, he warned, “It is not right that mutation work should have to be a tail to the cancer kite.”<sup>18</sup> Here again, we see the tendency to differentiate somatic effects — namely cancer — from questions of genetics. Muller wanted to make sure that work on mutation did not become subordinate.

Any hesitancy to hitch chemical mutagenesis studies to the cancer kite evaporated by the 1970s. Instead, the well-established correlation between mutagenicity and carcinogenicity was increasingly taken by scientists such as Ames as causal rather than coincidental. And there was not longer any sense of rivalry between focusing on somatic vs. genetic effects. Ames published an overview of his method in *Environmental Health Perspectives* that put the new premise succinctly, “Carcinogens are Somatic Mutagens” (Ames 1973). Here and in his other publications, Ames drew on recent work on both the genetic code and on the chemical nature of DNA damage, much of which had been funded through the AEC. In contrast to Demerec’s perspective that mutation was an indirect consequence of exposure to these agents, biochemists studying DNA damage conceived of direct action, such as intercalation between the base pairs of the double helix.

Let me return to the question I posed at the outset — how and why did *mutations* in bacteria become a key means for visualizing the cancer-causing dangers of chemicals? The answer is not principally technological — microbial screens for chemicals dated to the 1950s — but reflects a convergence of new ideas about genetic damage and cancer with political and institutional developments. Scott Frickel has argued that political engagement and activism on the part of scientists was critical to the founding of the field of genetic toxicology in the late 1960s and early 1970s (Frickel 2004). Exemplifying this trend were the founding of the Environmental Mutagen Society and the establishment of the federal government’s National Institute of Environmental Health, both in 1969.

This time period also saw the reorientation of molecular biologists to the challenges of eukaryotic biology, what Michel Morange has termed the “mass migration” of molecular biologists in the 1960s and 1970s from simple microbial systems to eukaryotic organisms and biological problems, such as immunology, development, and, not least, cancer biology (Morange 1997). As Doogab Yi has recently argued, this trend was driven by new political pressures on scientists in the

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<sup>17</sup> Iyer and Sybalski 1958, p. 23.

<sup>18</sup> H. J. Muller to Joshua Lederberg, 16 March 1950, reprinted in Lederberg 1997, p. 7.

late 1960s and early 1970s to demonstrate that taxpayer-funded research was improving health (Yi 2008a, 2008b). Environmental health and cancer research were both important venues in which experimental biologists could demonstrate the utility of their knowledge. Lastly, the shift in studies of genetic damage from chromosomes to DNA positioned molecular biologists and biochemists to provide principal support for the mutational theory of cancer. The Ames test registered the convergence of these political, institutional, and disciplinary changes.

By 1976 the Ames test was being used by 60 or 70 major companies. As Gina Kolata observed in *Science*, “This has led to a curious situation in which industries are implicitly endorsing the tests at the same time that scientists and legislators deliberate over whether companies should be forced to use them” (Kolata 1976, p. 1215). Ames made the tester strains freely available, asking only that recipients request them directly from him rather than from secondary sources (Ames, McCann, and Yamasaki 1975, p. 350,). Companies often contracted with commercial laboratories to conduct their toxicological screening, and Kolata noted that one such outfit, Litton Bionetics in Maryland, had already seen an increase of contracts for screening chemicals. The Ames test was almost always performed first — it cost only \$200 per chemical — and if a compound proved mutagenic in the Ames test, other tests (including other quick tests) could be ordered.

In general, and despite its rapid adoption by industry, the early uses of the Ames test reinforced the conjunction of environmentalism and scientific research. Within a few years, the Ames test had identified as worrisome a number of widely used industrial products. By 1975, Ames’s laboratory had used its test to demonstrate the mutagenicity of chloroacetaldehyde (a possible metabolic product of vinyl chloride, a commonly used synthetic chemical), cigarette smoke condensate, and hydrogen peroxide-based hair dyes (Kier, Yamasaki, and Ames, 1974; McCann, Simmon, ... et al., 1975; Ames, Kammen, and Yamasaki, 1975). The Ames test also showed the Japanese-developed preservative furofuramide to be mutagenic, and the compound was banned in Japan (Kolata 1976, p. 1217). More controversially, Arlene Blum and Ames showed that the most commonly-used flame retardant for children’s pajama, tris(2,3-dibromopropyl) phosphate, also called Tris, was a mutagen (Blum and Ames 1977). In response, toxicologists undertook animal experiments and found that Tris could cause kidney cancer in mice and rats. Other studies showed that Tris could be absorbed through the skin.<sup>19</sup> Soon thereafter, in April 1977, the government banned the sale of Tris-treated garments. The compound was only used a few years, introduced to meet 1973 federal regulations for decreased flammability.

With the newly-evident potential of the Ames test to shape government regulation and policy, critics raised doubts about the premise of the test, that cancer should be regarded as a disease induced by mutagens. Harry Rubin, a virologist at Berkeley, voiced his skepticism in a letter to *Science*:

Acceptance of screening for carcinogenicity by determining mutagenicity lends tacit support to the hypothesis that malignant transformation of cells is caused by somatic mutation. This hypothesis has been tested explicitly in several experiments and has been found wanting in each case. ... Excessive application of normal steroid hormones causes cancer, as does the simple transplantation of some endocrine organs into the spleen of the same animal. It is difficult to accept mutagenesis as the origin of these cancers (Rubin 1976, p. 241).<sup>20</sup>

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<sup>19</sup> Animal studies before the ban were followed by a study of human absorption published after the ban (Blum et al. 1978).

<sup>20</sup> One study cited for demonstrating a non-mutational basis for transformation to malignancy was Mintz and Illmensee (1975).

In the assessment of another critic, “The mutation origin of cancers remains an unproven hypothesis, with a substantial body of evidence in support of other mechanisms” (Sivak 1976, 273). Ames’s main response was to point to the power of correlation. His laboratory had demonstrated that 90% of *Salmonella* mutagens were also rodent carcinogens, and that 89% of animal test carcinogens were also bacterial mutagens (Zeiger 2004, p. 364). Of more than 109 “non-carcinogens” tested, none proved to be mutagens. In effect, supporters of the Ames test pointed to the strong correspondence among compounds that screened as mutagenic and that proved carcinogenic in animal tests as proof enough of the basic principle. As a side benefit, noted by a professor of veterinary medicine, the Ames test could reduce the number of animals consumed in toxicological safety tests (Loew 1976).

### *Salmonella Strains in Industrial Testing and Government Regulation*

In the late 1970s, the Occupational Safety and Health Administration proposed new legislation regulating carcinogens in the workplace. American industry reacted strongly against the threat of regulation, even as they tried to take advantage of less expensive testing methods. Toxicological testing companies routinely used the Ames test alongside several other rapid screens to identify those compounds that warranted further testing.<sup>21</sup> In addition, companies such as DuPont and American Cyanamid routinely used it to test new products before deciding whether to bring them to market. According to Ames, DuPont decided not to produce two Freon propellants because they were found to be mutagenic in *Salmonella* tests (Ames 1979, 593n21). The government’s own screening program was not extensive enough to provide data on the range of chemicals on the market — the National Cancer Institute screened about 100 compounds a year, out of the 63,000 chemicals being commonly used in the U.S. (Maugh 1978, p. 1202).

Environmentalists tended to view the Ames test as allied with the cause of greater industrial regulation. The high-profile identification by Ames and his coworkers of the preservative furofuranamide, hair dyes, and especially Tris as potent mutagens bolstered public concern about the safety of chemicals — and, in the case of both furofuranamide and Tris, led to their ban. However, the apparent alliance between molecular biologists and environmental organizations was already becoming unraveled in the late 1970s over disagreements about the safety of recombinant DNA. As a journalist for *Science* put it in 1978:

Among those who doubt the environmentalists’ good faith are National Institutes of Health (NIH) researchers Malcolm Wallace Rowe, and Maxine Singer. ... Paul Berg of Stanford, Bruce Ames of the University of California at Berkeley, and Norton Zinder of Rockefeller University as well as others not directly involved in the politics of DNA have told the environmentalists that they are flatly wrong in the recombinant DNA case (Marshall 1978, p. 1265).

The direction that Ames took next in put him further at odds with environmentalists.

Ames became interested in how the risks of somatic mutation from synthetic chemicals compared to those from “natural” sources, particularly prepared food (Ames 1979). Others had already taken his microbial test in this direction. Japanese researcher Takashi Sugimura had first

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<sup>21</sup> As reported in *Science* magazine, Litton routinely employed four tests: “the Ames test, a test for gene mutation in mouse cells, the SCE test, and an in vitro transformation test” (Maugh 1978, p. 1204).

applied the Ames test to screen naturally occurring agents in the mid-1970s, building on a few identified early on by Ames, such as aflatoxin. Sugimura found that plants were a major source of mutagens (Nagao, Sugimura, and Matsushima 1978).<sup>22</sup> Sugimura also pointed to differences in food preparation in explaining the higher incidence of stomach cancer in Japan as compared to the U.S. (Abelson 1979). Along similar lines, Barry Commoner's laboratory demonstrated that fried hamburger showed mutagenic activity in the *Salmonella* test (Commoner et al. 1978). Many of these naturally occurring compounds were just as potent mutagens as synthetic chemicals — and animal tests showed some to be just as carcinogenic. While this line of research enlarged the scope of materials that might be tested for mutagenicity, in order to limit exposure, the attention to the risks of exposure to natural agents actually subverted the rationale for increased government regulation. As the editor of *Science*, Philip Abelson, put it in an editorial, "The effort to prove a big role for industrial chemicals diverts attention from what is probably the best hope for reducing cancer incidence — careful study of foods and effects of cooking" (Abelson 1979, p. 11).

By the mid-1980s, Ames had become convinced that the greatest danger to human health came from diet and metabolism. Alvin Weinberg was among those scientists who supported Ames's viewpoint, "Cancer is essentially a natural aging process. No matter what we eat, the huge flood of oxygen radicals produced in many metabolic processes overwhelms all but the most heavy external carcinogens, such as tobacco in heavy smokers. To be sure, anticarcinogenic substances are of benefit, but to choose a noncarcinogenic diet would probably be equivalent to starving to death" (Weinberg 1984, p. 659). Ames was not so defeatist and advocated the ingestion of vitamins and nutrient-rich foods to counteract mutagenicity in foods and chemicals (Ames 1983).

But it was not his touting of nutritional supplements that was controversial. Ames strongly questioned whether cancer rates were increasing in the industrialized world, and was suspicious of putative links between industrial pollutants and cancer incidence, arguing that smoking and poor nutrition could account for much observed cancer. He also observed that in both number and amount, we ingested more carcinogens "of natural pesticides and other natural toxic molecules than we do of manmade substances" (Ames 1984, p. 758). Thus activists who focused on cancer as a "corporate problem" were misguided, in Ames's view — they should be stopping subsidies to tobacco farmers and improving the diet of ordinary Americans. Pollution and occupational exposure were already sufficiently regulated by the government, given their smaller role in cancer incidence. As he put it, "the preoccupation with tiny amounts of man-made pollution has been blown up out of proportion" (Ames 1984, p. 668). Needless to say, this viewpoint outraged environmental groups. To add insult to injury, Ames was awarded a major ecology prize in 1985.<sup>23</sup>

In 1987, Ames campaigned against Proposition 65, a "citizens' enforcement law" in California that imposed stringent new regulations on chemical users. The law passed, by a margin of two to one, and Ames was then appointed to a regulatory group to help implement the law. This provoked outrage from the mainline environmentalist groups who had supported the proposition. As Carl Pope of the Sierra Club put it to a writer for *Science*, "I've never seen a clearer fox-in-the-chicken-coop situation" (Marshall 1987, p. 1459).

In the end, Ames and his coworkers attempted to lighten the corporate burden of responsibility for

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<sup>22</sup> The importance of Japanese workers in this arena is attested by an international conference held in Tokyo in 1979, "Naturally Occurring Carcinogens-Mutagens and Modulators of Carcinogenesis," which was attended by a number of American and European researchers (including Bruce Ames) as well as many Japanese scientists.

<sup>23</sup> It was the John and Alice Tyler Ecology-Energy Prize, administered by University of Southern California (Dye, 1985, p. 20).

cancer prevention on the grounds of scientific uncertainty:

In the modern context of being able to measure parts-per-billion and parts-per-trillion levels of substances and the realization that there is universal human exposure to rodent carcinogens of natural origin, it is first important to prioritize among the plethora of possible hazards in order to avoid being distracted from working on the more important problems. The enormous uncertainties in the use of animal data to assess human risk and our lack of knowledge about the mechanisms of carcinogenesis make policy-making especially difficult; however, we do not imply that all problems should be passed over until the last smoker lays down his cigarette (Ames, Magaw, and Gold 1987, 235).

As Robert Proctor and Naomi Oreskes have shown, scientific uncertainty was increasingly used by politicians and industry representatives (including some prominent scientists) in the 1970s and 1980s to derail or slow government regulation (Proctor 1995; Oreskes, Conway, and Shindell 2008). Ames played right into this mindset.<sup>24</sup> While Ames was vocal about not being supported by corporate interests, his skepticism about the role of industrial pollution in causing cancer reinforced the conservative cause of halting government regulations, and was picked up by anti-environmentalists in their polemics (Ephron 1984).<sup>25</sup>

### *Concluding Reflections*

I have stressed two aspects of the history of the Ames test. One is the way in which its conception of carcinogenicity built on earlier research about the role of radiation in cancer. I am not the first to note how research into chemical carcinogens followed the tracks — conceptual, experimental, and institutional — of radiation genetics.<sup>26</sup> The important role of the AEC in funding work such as Ames, and the establishment of a computer registry for carcinogens at Oak Ridge, attest to the way in which institutions established to investigate the biological effects of radiation took in the field of chemical mutagenesis as well.<sup>27</sup> Indeed, the two aspects taken together comprised much of what came to be identified under the rubric “genetic toxicology” in the 1960s, as Frick has shown (Frick 2004). It is worth considering how this shaped the understanding of chemical agents as mutagens and carcinogens. Charlotte Auerbach has argued that it was hard for researchers to come up with mechanisms that would explain the action of both ionizing radiation and chemical agents, and this put the two lines of mutation research in competition. “Sweeping attacks on target theory were made soon after the discovery of chemical mutagens. The fact that chemicals can produce many of the same effects as X-rays was taken to indicate that X-rays, too, must act by chemical intermediates” (Auerbach 1967, p. 71). In a sense, the shift from studies of chromosomal damage to the biochemistry of DNA damage provided a substrate, or even boundary object, in which the actions of the two classes of mutagens could be brought into correspondence. Biochemists and molecular biologists such as Ames were also eager to promote the understanding of cancer in terms of DNA damage (though, interestingly, not in terms of particular genes), but this raised the ire of

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<sup>24</sup> Though I would not follow Proctor as far as referring to Ames as “the most powerful anti-environmentalist of the century” (Proctor 1995, p. 133). On the corporate use of scientific uncertainty, also see Michaels (2008).

<sup>25</sup> On the antiregulatory movement, see Hays (1987).

<sup>26</sup> As Frickel (2004, p. 42) puts it, “chemical mutagenesis remained indelibly intertwined with and to a large extent institutionally dependent on radiation biology.”

<sup>27</sup> On the Environmental Mutagen Information Center, see Frickel 2004, pp. 58–59.

cancer specialists who regarded tumorigenesis as a more complex biological affair.

The second issue concerns how the development and adoption of the Ames test intersected with changing currents in American politics. The Ames test was introduced during a time of popular environmentalism, and Ames himself applied his test to identify dangerous new synthetic chemicals, informing government regulation. However, Ames's subsequent tests of the carcinogenicity of natural substances put him at odds with environmentalist, and more specifically, anti-industrial groups. Before this shift, the early years of use of the Ames test were turbulent ones for biologists — the concerns about the safety of recombinant DNA and the conflicts over sociobiology involved molecular biologists and biochemists in acrimonious, public debates about whether science was serving society, and whether it should. One senses in Ames's changing views his discomfiture with the leftist orientation of a handful of vocal biologists. Was his skepticism representative of a broader shift within the research community? Examining disputes about the Ames test may help historians assay the changing political attitudes of molecular biologists at the beginning of the age of biotechnology.

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