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

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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.[1] 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."[2] Another "gene meeting" was planned following the International Congress of Genetics in Edinburgh in September 1939.[3] 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.[4] 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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1 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)

2 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.

3 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, Plough, 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.)

4 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.[5]

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.[6] 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.[7] 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.[8] 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.[9] 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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5 Stubbe 1938, p. 315, cf. also pp. 316-320 (trans. AS).
6 For instance, see Timoféeff-Ressovsky 1937, p. 58.
7 Schwerin 2010.
8 K. Wirtz: Biophysikalische Konferenz im Max Planck-Institut für Physik, Göttingen, Januar 1947, Lilly Library, Indiana University Bloomington, Muller Mss., series III, box 1.
9 Correspondence with Garland Allen.

figure — although, unfortunately, there has been no thorough analysis thus far.[10] 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 genetico-biophysical model of mutagenesis at that time.[11]

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.[12] Thus far historians have been fascinated by and focused on the crucial influence of the physicist Max Delbrück.[13] 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 genetico-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 genetico-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 genetico-biophysical adaptation. (2) It has not yet been considered that these early approaches did not end when the genetico-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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[10] See for example Fischer 1985 and several portraits in Pasternak 1994.

[11] 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.

[12] 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.

[13] 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.[14] Since the 1910s radiologists had come to rely more and more on the help of physicists able to handle X-ray apparatuses and dosimeters.[15] 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.[16] 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.[17]

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.[18] 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*).[19] 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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[14] There were similar approaches developed quite independently in United Kingdom, France, and Germany. This account deals only with the German conditions.
[15] Dommann 2003.
[16] Schwerin 2009.
[17] Dessauer/Vierheller 1921, p. 656 (trans. AS).
[18] Dessauer 1921, pp. 1155-1156.
[19] Dessauer 1922; Dessauer 1923.

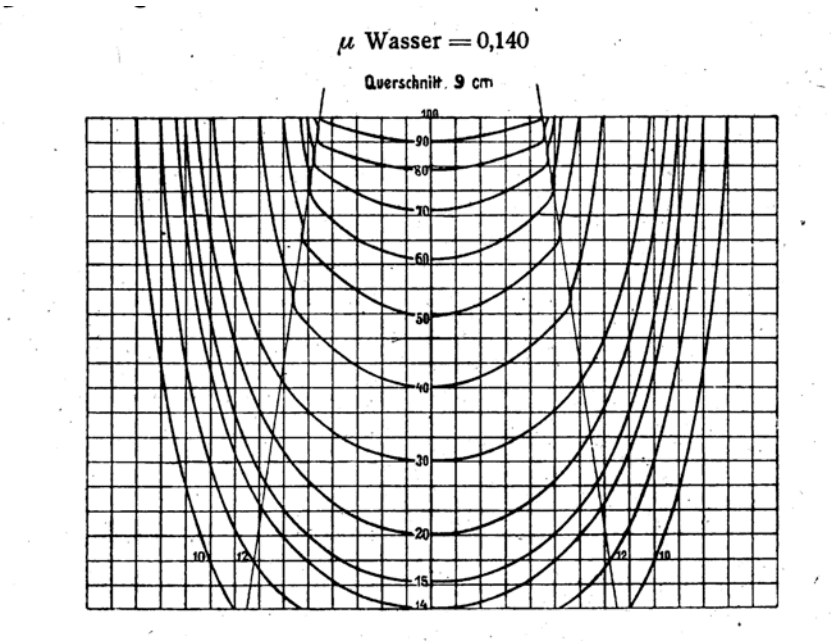

Fig. 1: The distribution of radiation within water. From: Dessauer 1923, p. 12.

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.[20] 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.[21] 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

[20] Dessauer 1922, p. 42.
[21] 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.[22]

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."[23] 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*).

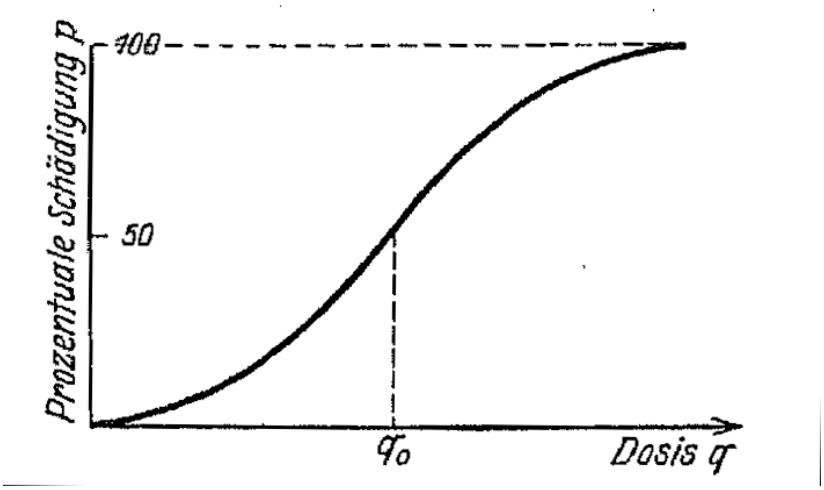

Fig. 2: The principle of the damage curve (*Schädigungskurve*): with the increase in dose (x-axis), the percentage of damaged objects (eggs, dead organisms, etc.) changes — normally in an increasing fashion. The experimenter tries to conclude something about the mechanisms from the exact form of the 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.[24] 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."[25]

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

[22] Glocker 1932. For the approach of Jordan see Beyler 1996.
[23] Glocker/Hayer/Jüngling 1929, p. 37.
[24] 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.
[25] Glocker 1932, p. 653.

Germany, the biophysicists dominated this discussion, but, radiologists were also involved, in particular, Hermann Holthusen and Hans Holfelder.[26] 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.[27] 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 genetico-biophysical target theory. This conjunction, which I will discuss only briefly here,[28] 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.[29]

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[26] Glocker (1932) gives here a short historic overview of the target theory and different approaches. See also Schwerin 2010.

[27] Glocker 1929, p. 112.

[28] This analysis is the result of research on German genetics that was done by both Bernd Gausemeier and me in recent years.

[29] Timoféeff-Ressovsky 1934a, p. 475; Timoféeff-Ressovsky 1934b, p. 420.

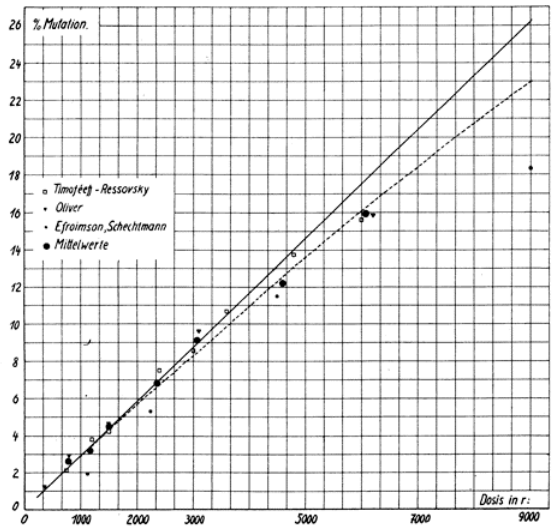

Fig. 3: This often-repeated figure shows the relation between dose and mutation rate. This version was printed in the initial paper of Timoféeff-Ressovsky, Zimmer, Delbrück (later called the "Three-Man Paper") in 1935. It showed the linear progression of the mutation rate — a key feature of the genetico-biophysical 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.[30] 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.[31] 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.[32]

[30] Timoféeff-Ressovsky, Zimmer, Delbrück 1935, p. 222.
[31] Timoféeff-Ressovsky, Zimmer, Delbrück 1935, p. 222.
[32] 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.[33]

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.[34] 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.[35]

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.[36] The commission involved radiologists (including the radiologist Hermann Holthusen), medical physicists (including Richard Glocker), and geneticists (including N. Timoféeff-Ressovsky). Even the compilation of the commission members indicates a new conjunction.[37]

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).[38] 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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[33] Timoféeff-Ressovsky, Zimmer 1947, p. 5.
[34] Timoféeff-Ressovsky 1934a, p. 475.
[35] Timoféeff-Ressovsky 1934b, p. 445.
[36] Schwerin 2004, p. 125; Gausemeier 2005, p. 167; in more detail Schwerin 2010.
[37] In Germany, the radiologist Hermann Holthusen was involved in the discussion on the target theory and contributed significant result.
[38] 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.[39] 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."[40] 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 genetico-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.[41] 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.[42]

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).[43] Hanns

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[39] 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.

[40] 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.

[41] For a more thorough account, see Schwerin 2009.

[42] Maier 2007, pp. 387ff.

[43] 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.[44]

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.[45]

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.[46]

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.[47] 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.[48] 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.[49]

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[44] Langendorff/Sommermeyer 1940, p. 196.
[45] Rajewsky, Theorie 1935, p. 76.
[46] Jüngling/Langendorff 1932; for experiments with spermatogonia of mice, see Langendorff 1936, p. 71.
[47] Langendorff/Langendorff 1931, p. 97; for the Hertwigs see Schwerin 2004, pp. 123.
[48] Langendorff/Langendorff 1931, p. 101.
[49] Langendorf 1936; Langendorff 1937: Langendorff 1938; For Paula Hertwig, see Schwerin 2004, pp. 122ff.

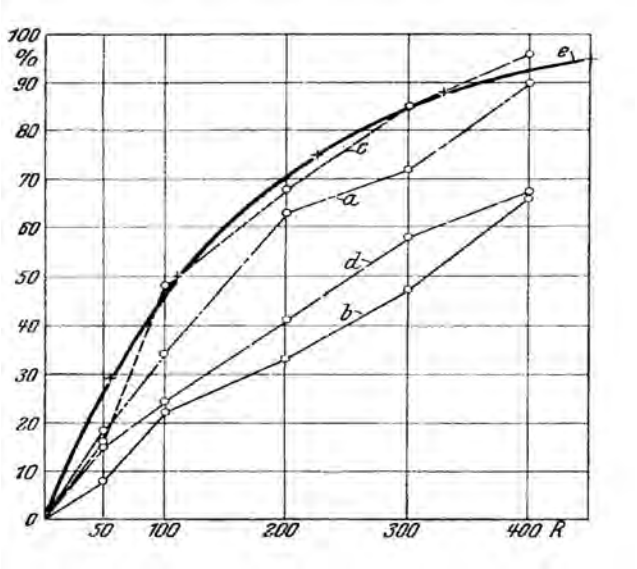

Fig. 4: The damage curve (*Schädigungskurve*) as depicted in the experiments of M. and H. Langendorff. The x-axis shows the X-ray doses; the y-axis shows the percentage of damaged objects. The single curves (a-e) show the effects on different objects (eggs and sperm of sea urchin). From: Langendorff/Langendorff 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.[50] 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.[51] 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.[52]

[50] Langendorff 1942, p. 275.
[51] Cf. Schwerin 2010.
[52] 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 genetico-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.[53]

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 genetico-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 genetico-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 genetico-biophysicists such as Zimmer and Timoféeff-Ressovsky.[54] 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.[55] 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."[56] 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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[53] Langendorff/Sommermeyer 1940a, p. 196 (trans. AS).

[54] Langendorff/Sommermeyer 1940a, pp. 203-204.

[55] 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)

[56] 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 genetico-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.[57]

Obviously, there was a non-physical factor that influenced the effects of radiation on both the biological *and* genetic side.[58] 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.[59]

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 genetico-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 genetico-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.[60]

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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[57] 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)

[58] 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.

[59] 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)

[60] 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 genetico-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.[61] 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 genetico-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 genetico-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" genetico-biophysical dose-response curve.[62]

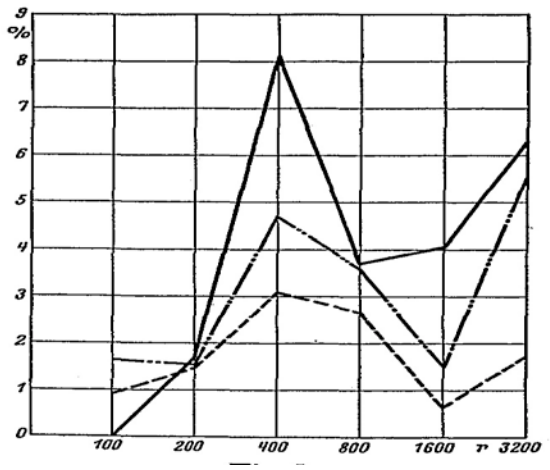

Fig. 5: The experiments of the geneticist Hans Stubbe contradicted the basic assumption of genetic mutation and target theory that mutagenesis was a physical process that showed linearity in the measured relation of external disturbance (radiation, trigger) and effects (hits, mutations). From: Stubbe 1932, p. 189.

[61] 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).

[62] 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.[63] 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.[64] 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 genetico-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.[65] 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.[66] 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).[67] 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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[63] In the case of Stubbe, see Timoféeff-Ressovsky 1934a, p. 463; Timoféeff-Ressovsky 1934b, pp. 420-421.
[64] Deichmann 1995, pp. 93-105, 98-100 and the charts with tabulated information on pp. 78 and 84; Harwood 1993, passim.
[65] Harwood 1993, pp. 79-80; Sander 1995.
[66] Deichmann 1995, p. 93.
[67] 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 understand 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.[68] 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.[69] 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.[70] 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 genetico-biophysical approach was able to describe the energetic side of the effects of X-rays and to propose a biophysical view on mutations.[71] However, the cost was a limited horizon because the genetico-biophysicists only considered "so-called gene mutations" within a very special experimental design.[72] 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.[73]

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."[74] Like other chromosome researchers, Marquardt distinguished phenomenologically different classes of chromosome

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[68] See Campos, "Mutant Sexuality: The Private Life of a Plant" in this volume.
[69] Falk 2004.
[70] Marquardt 1938a, p. 108.
[71] Marquardt 1938a, p. 110.
[72] Marquardt 1938a, pp. 110-111.
[73] Marquardt 1949, p. 31.
[74] 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 genetico-biophysical model — but in quality, too. From 1941 on, Marquardt argued that there were at least two kinds of targets — "Restitutionstreffer" and "Fragmentationstreffer."[75] 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.[76] Lea had suggested that some special substances emerged after irradiation that led to variable disruptions of chromosomal function.[77] 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).[78] He saw all of these results and pieces of circumstantial evidence as contradicting the genetico-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.[79]

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.[80] 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.[81]

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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[75] Marquardt 1941; Marquardt 1949, pp. 42-43.
[76] Marquardt 1949, p. 32.
[77] Marquardt 1949, p. 34.
[78] Marquardt referred to experiments of Mitchell and v. Hevesy on the changes in metabolism after irradiation. (Marquardt 1950, p. 417)
[79] Marquardt 1950, p. 438 (trans. AS).
[80] Marquardt 1938a, p. 111.
[81] Marquardt 1950, p. 416 (trans. AS).

genetic target theory.[82] 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.[83] 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 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.[84]

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.[85] 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.[86] 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.[87] Wettstein recognized the originality of Knapp and fostered his talent; nevertheless Knapp was one of the few who did not recognize recognize Wettstein's politically liberal management of the institute, but openly pronounced himself for the "new state," i.e., the Nazi regime.[88]

Like Marquardt, Knapp aimed to bridge the gap between genetics and cytology with "cytologic-genetic studies of the genome."[89] 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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[82] Bauer 1942; Marquardt 1942.
[83] Bauer 1939, p. 386.
[84] Marquardt 1949, p. 43 (trans. AS).
[85] Heim 2003, pp. 33-49.
[86] For Stubbe see Heim 2003, pp. 200-246; for the KWI before 1933 see Harwood 1993, pp. 195-226.
[87] Gausemeier 2005, p. 134.
[88] Gau-Dozentenbundführer to Reichsministerium für Wisenschaft, Unterricht und Volksbildung, Bundsarchiv Berlin-Dahlwitz, 4.11.1936, ZB II, 1979, A.10.
[89] Knapp an DFG, 9.1.1942, BAK, R 73, 12199.

terms of mutability within a "bigger work programme."[90] Additionally, Knapp established a good working cooperation with the biophysical institute of Walter Friedrich in Berlin.[91] One of his assistants was the geneticist and plant physiologist Reinhard Kaplan who later formulated a mathematically informed critique of the genetic target theory.[92] 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.[93] 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.[94] 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.[95] The findings were a kind of precedent showing that the inconsistencies of the dose-effects curves of the genetico-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.[96]

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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90 Knapp/Kaplan 1942, p. 503.
91 Knapp an DFG, 9.1.1942, BAK, R 73, 12199.
92 Kaplan 1950.
93 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.
94 Knapp 1939, p. 839.
95 Knapp carefully followed the cytological research on the structure of chromosomes and chromosomal changes. (BAK, R 73, 12199)
96 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.[97]

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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[97] 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 reconfigurations 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.[98]) 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.[99] 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 genetico-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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[98] For a detailed analysis see Maier 2007, pp. 235-243.

[99] 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.[100] 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 genetico-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.

[100] 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.[101] Less well known is that Friedrich Oehlkers achieved the same result with *Oenothera* at the same time — using inorganic substances, alkaloids, and narcotics.[102] 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.[103] 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.[104] 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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[101] The results of this research were kept secret until the end of the war. Auerbach 1949.
[102] Auerbach 1976, p. 346.
[103] The physiological approach was a quite different question than that of "Dauermodifikationen; it aimed at the nature of genetic mutations.
[104] Kimball in Wolstenholm 1969, p. 1; Auerbach 1976, p. 11.

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Luis Campos and Alexander von Schwerin (eds.)

Making Mutations: Objects, Practices, Contexts

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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?

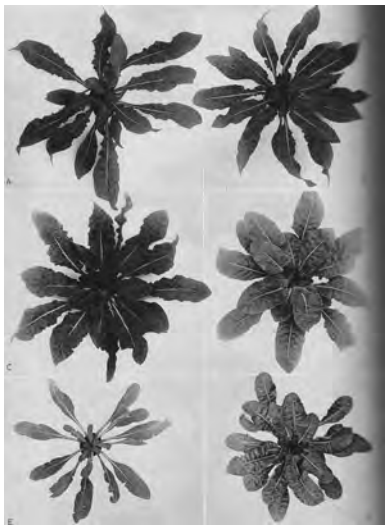

Fig 1: Six rosettes of *Oenothera lamarckiana* and its various mutants – but which is which? Photo by G. H. Shull.

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

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