Nadine Dobrovolskaïa-Zavadskaïa and the dawn of developmental genetics

Vladimir Korzh[1]* and David Grunwald[2]

Summary

In one of the first genetic screens aimed at identifying induced developmental mutants, Nadine Dobrovolskaïa-Zavadskaïa, working at the Pasteur Laboratory in the 1920s, isolated and characterized a mutation affecting *Brachyury*, a gene that regulates tail and axial development in the mouse. Dobrovolskaïa-Zavadskaïa's analysis of *Brachyury* and other mutations affecting tail development were among the earliest attempts to link gene action with a tissue-specific developmental process in a vertebrate. Her analyses of genes that interacted with *Brachyury* led to the discovery of the *t*-haplotype chromosome of mouse. After 70 years, *Brachyury* and the multiple genes with which it interacts continue to occupy a prominent focus in developmental biology research. A goal of this review is to identify the contributions that Dobrovolskaïa-Zavadskaïa made to our current thinking about *Brachyury* and how she helped to shape the dawn of the field of developmental genetics. *BioEssays* 23:365–371, 2001.

Introduction

From the rediscovery of Mendel's laws by De Vries and others in 1900 to the ongoing efforts of the multiple genome projects, biological research in the twentieth century has been largely dominated by studies aimed at understanding how the characteristics of living organisms are regulated by a genetic code. The study of how genetic alterations produce variant forms within a species and contribute to the evolution of species has found a focus in the resurgence of the integrative discipline of developmental genetics.[1–4]

In some regards, the origin of the modern era of vertebrate developmental genetics can be traced to studies of a gene — *Brachyury* — that controls tail development. A loss-of-function mutation in the mouse *Brachyury* gene was first described in detail by Nadine Dobrovolskaïa-Zavadskaïa,[5] who isolated it in the course of a screen for induced developmental mutants. In heterozygous state, the *Brachyury* mutation results in mice with short tails; in homozygous state, the mutation is lethal, resulting in embryos that lack the notochord and posterior mesoderm.[6] The remarkable position of the *Brachyury* gene in the history of developmental genetics is underscored by its continued study into the present time. Perhaps because of its pivotal role in regulating the development of the notochord, the defining feature of the vertebrate, the *Brachyury* gene was the focus of one of the earliest positional cloning efforts in the mouse.[7] Similarly, the striking phenotype of the *Brachyury* mutant meant that, once a homologous mutant was recovered in the zebrafish, where it is called *no tail*, it became one of the first zebrafish mutants to be characterized in detail[8] and the first zebrafish mutation to be molecularly identified.[9] Here, we revisit the origins of studies of the *Brachyury* gene, examining the contributions of Nadine Dobrovolskaïa-Zavadskaïa (1878–1954), whose work formalized a link between genes and development. Although her discovery of *Brachyury*

Nadine Dobrovolskaïa-Zavadskaïa, 1948.

[1]The Institute of Molecular Agrobiology, National University of Singapore.
[2]Department of Human Genetics, University of Utah.
Funding agencies: The National Science and Technology Board of Singapore; NIH.
*Correspondence to: Vladimir Korzh, The Institute of Molecular Agrobiology, 1 Research Link, National University of Singapore, Singapore 117604. E-mail: vlad@ima.org.sg

is often cited, it is likely that few contemporary researchers are familiar with the published works of Dobrovolskaïa-Zavadskaïa. Our goal is to review the nature of the contributions of the first proponent of the importance of *Brachyury*, and in doing so we hope to rediscover some perspectives on the forces, ideas, and people who shaped the dawn of the field of developmental genetics.

Russia (1878–1920)

Although very little is known about the early years of Dobrovolskaïa-Zavadskaïa, her professional life in Russia and her later scientific pursuits in France were sculpted by ideological revolutions that dominated the early 20th century. Nadine Dobrovolskaïa-Zavadskaïa, as she was known in the Institute Curie in Paris, was born in Kiev as Nadezhda (meaning ''Hope'') Aleksandrovna Dobrovolskaïa (meaning ''Good-willed''). She studied medicine in St. Petersburg and became a surgeon. Through marriage to A.M Zavadsky (1879–194?) she entered a family of biologists, and it is thus likely she was exposed to the emerging concepts of genetics early in her career. Zavadsky was a biologist at the Kazan University before the Russian Revolution. After the Revolution he worked in Samarkand (now Uzbekistan) and after the Second World War in Kishinev (now Kishiney), Moldavia. His nephew, K.M. Zavadsky became a professor of plant biology at the Leningrad University (E.I. Kolchinsky, personal communication). Since she kept the family name of her husband until the end of her life, she probably never married again. It seems that, at the end of her life, she discussed plans to pass all her archives to the USSR Academy of Sciences in Leningrad and may have even succeeded in this endeavor, since very few papers about her still exist in the archives of the Institute Curie (Ilana Löwy, personal communication). Unfortunately, the search for her archives in Saint-Petersburg has been fruitless (E.I. Kolchinsky, personal communication), and her scientific achievements remain unrecognized in her motherland.

When the First World War started, she worked in military hospitals until 1917, when the Revolution dramatically changed the fate of Russia and all Russians. Soon after the Revolution, the Civil War began between the followers of the old tsarist regime, the ''Whites'', and the followers of the bolsheviks, the ''Reds''. At this point, many Russians were forcibly conscripted into the services of one side or the other. How Dobrovolskaïa-Zavadskaïa came to serve during the civil war is unknown but, at its conclusion, she was working in the White Army hospitals of General Wrangel on the Crimean Peninsula. Surrounded by the Black Sea, this was the last fortress of the Whites in the European part of Russia. When Wrangel was defeated in Crimea in 1920, Dobrovolskaïa-Zavadskaïa left Russia and went into exile. Like many other Russian emigres of this era, she fled to Paris, arriving there via Turkey and Egypt.

France (1921–1954)

In Paris Dobrovolskaïa-Zavadskaïa initiated a new scientific career at the age of 43. On the First of October 1921, she joined Professor Claudius Regaud at the Pasteur Laboratory.[10] The Pasteur Laboratory was established jointly by the Institute Pasteur and the Institute of Radium (currently the Institute Curie) to study the biological effects of radioactivity, making it one of the first research institutions committed to radiobiological studies. Her first published works from this period described the effects of X-rays on muscle and testicular tissues.[11,12] However, soon she turned her attention to the questions of whether radiation effects could be transmitted hereditarily in mice and the organ-specific role of genes in development and cancer.

The new direction of her studies was a natural outgrowth of the times and her immediate surroundings. In the first two decades of the century, the widespread applicability of the laws of Mendel had been confirmed, the gene as the unit of inheritance had been established and, in 1916, Bridges[13] had provided concrete evidence that chromosomes were the subcellular structures that carried the hereditary information, thereby confirming the hypotheses of Boveri and Sutton. By the early 1920s, there was intense interest in determining the nature of the gene, establishing the types of characteristics that were governed by genes, and examining how genetic variation might contribute to evolution. To better understand the types of phenotypic changes brought about by gene mutations, a number of pioneering scientists attempted to generate genetic variants at measurable frequencies in the laboratory under controlled conditions. In the early 1920s, Mavor,[14–16] Bagg and Little,[17] and Nadson and Philippov[18] attempted to induce mutations with X-irradiation in fruit flies, mice, and fungi, respectively. Although the results of these early efforts were ambiguous, Dobrovolskaïa-Zavadskaïa appreciated their importance and the potential implications of their success.[19,20] Given her mentor's work over the previous 15 years on the nature of the effects of irradiation on the viability and developmental potential of germ cells,[21,22] she was well-situated to develop her own research program in the field. As she testified herself: ''In 1923 Professor Regaud directed my attention to the desirability of studying the influence of the modifications produced by X-rays in the testicles on heredity in mice, and I have since been pursuing this inquiry''.[20] What followed was one of the first successful genetic screens for developmental mutants, the analyses of which would occupy Dobrovolskaïa-Zavadskaïa's studies for the next 10 years.

In her initial studies, Dobrovolskaïa-Zavadskaïa irradiated 48 male and 2–3 female mice and recovered offspring from 35 of the treated animals.[19,20] Using a combination of backcrosses and brother–sister matings she produced about 3000 mice across three or four generations of breeding. Among these crosses, she found evidence for the inheritance of only

two clear-cut mutant phenotypes, *waltzing* and *short-tail.* She established true-breeding lines of *waltzing*, which she concluded was due to a recessive viable mutation, but she was unable to establish a true-breeding line that produced only *short-tail* offspring. She demonstrated that *short-tail* was caused by a dominant mutation,[19,23] which she called *T*.[24] Intercrosses between *T*/+ heterozygotes yielded a 2:1 ratio of mutant to wild-type progeny, and had a small but significant reduction in litter size.[20,23] Noting the previous work of Cuenot in 1905[25] and Castle and Little in 1910[26] with lethal mutations in mice, she surmised that the deviation from a Mendelian ratio of progeny types resulted from the fact that the *T* mutation was lethal when homozygous. In support of this hypothesis she found that approximately one-fourth of the dissected conceptuses from breedings between heterozygotes contained degenerated fetuses.[23] Thus, by 1930, Dobrovolskaïa-Zavadskaïa's work had solidly established the genetics of the *T* mutation. It was not until the work in L.C. Dunn's laboratory of Paul Chesley in 1935[6] and later Salome Gluecksohn-Schoenheimer in 1944[27] that the developmental defect leading to death of the *T/T* homozygotes was eventually clarified.

Despite its dominant effects, Dobrovolskaïa-Zavadskaïa interpreted the *T* mutation as causing loss of function of the *Brachyury* gene, going so far as to suggest that perhaps "the rays produced....a kind of inactivation or elimination of a small portion of chromatin".[20] This intuitive interpretation was confirmed after the gene had been cloned, when it was shown that the original *T* mutation was a deletion of 160–200 kbp.[7]

Chasing the tail: the roles of genes in development

Dobrovolskaïa-Zavadskaïa was fascinated by the tail phenotype and she went about studying it with a surgeon's precision, employing radiographic analyses to measure quantitatively the form and number of vertebrae that were produced in the offspring of her mice.[28] Her meticulous analyses together with her naturalist penchant for asking whether similar mutations were already segregating in mice populations led her to recover from laboratory stocks and mice in the wild a variety of existing mutations that affected tail development. Some of these, such as *kinked tail* (probably the *FuKi* mutation), which she recovered from laboratory stocks, had effects independent of the action of the *T* mutation on mice;[27] others, such as the *tailless* mutation, which she recovered from a wild mouse trapped in Spain, expressed their tail effects only when present in combination with *T*.[29–32] From her analyses of the tail mutants, Dobrovolskaïa-Zavadskaïa formulated theories about the role of the *T* gene in development. She viewed the T gene as a primary determinant of the development of the spine and tail; the *T* mutation itself was a factor that caused an organ-specific "non-viable character", to be contrasted with mutations that acted as general lethal factors.[5,19,20] Furthermore, she interpreted her findings as indicating that, whereas *T* might be one of the few primary determinants of the development of the tail organ, a large set of genes function to modify the character or form of the tail.[28] Without a clear resolution of the problem, she attempted to fit these genes into a model to account for the evolution of tailed and tailless species. The theoretical importance of the *Brachyury* mutation in her view was clear: "..the "short tail" mutation, which concerns the organ with differentiated structure gives us a chance to ask the question of which genetic mechanism assures the consistency of ontogenetic development of a formation such as the tail. The morphological study of deviations from the normal type has allowed a new hypothesis to be formed, according to which there would be genes or special regulatory centers for the specific size, and for the formative dispositions of the organ. These main regulatory genes would be functioning in collaboration with accessory and modifying genes" (our emphasis).[28] In contemporary terms, she made the distinction between the functions of genes that specify the development of a structure and those that regulate its growth or shape characteristics. For example, we might imagine that genes that initiate formation of a limb would be conserved between mouse, bat, and whale, but genes that regulate growth and morphogenesis of the limb are likely to have diverged, if only in terms of quantitative parameters.[33]

Although her emphasis on the specificity of gene action during development is widely embraced today, it was a novel and undervalued insight at the time. As noted by many historians and workers in the field of developmental genetics,[34–36] for much of this century there was a nearly complete separation between the study of gene action and the study of cell behavior during embryonic development. Reconciliation of the profound intellectual chasm between these two disciplines came about slowly, largely as a consequence of the use of mutants to study developmental processes in *Drosophila*.

Whereas the *short-tail* mutant formed the springboard for Dobrovolskaïa-Zavadskaïa's ideas that individual genes act with great tissue specificity to guide developmental processes, her ability to proselytize on behalf of the mutant led to its use for many additional purposes. In France, Boris Ephrussi established the cell-lineage-specific lethal action of *Brachyury*.[37,38] At Columbia University, Paul Chesley's work with the mutant helped to elucidate the inductive influences of the notochord in mouse development. Specifically, Chesley suggested that the neural tube and somite defects seen in *Brachyury* mutants arose secondarily to loss of the notochord. He concluded that: "abnormality of the notochord is one of the more fundamental of the disorders involved, and that the condition of the neural tube is either wholly or in part due to the abnormality of the notochord".[6] This remarkable insight has been confirmed many times over the past decade (reviewed in Refs. 39 and

40). Similarly, Dunn and Gluecksohn-Schoenheimer showed that urogenital defects were seen commonly in *T*-bearing animals, suggesting that this defect was secondary to a loss of posterior notochord development.[41] In the zebrafish too, the *Brachyury* mutant, *no tail*, has been used to show the roles of the notochord in influencing the differentiation of the neighboring mesoderm and nervous system and establishing left/right asymmetries in the body.[8,42–44] Thus from shortly after its initial characterization to the present time, analyses of the *Brachyury* mutant have had significant influence on thinking in developmental biology.[45]

Mutant tails lead to complexes

Dobrovolskaïa-Zavadskaïa recovered several tail mutations and *T*-interacting factors that were linked to *T*, leading her to speculate as early as 1928 that the chromosomal region containing *Brachyury* constituted a complex of genes regulating tail development.[19,46] From a wild mouse, she isolated a *T*-interacting mutation, now called a *t* mutant haplotype, that was associated with several unusual genetic behaviors, including effects on inheritance of the mutation (transmission distortion)[29,30] (reviewed in Refs. 31, 32, and 47). Although breedings between mice harboring the wild "*t*" mutation did not yield mice with aberrant tails, *T/t* heterozygotes lacked tails altogether and could be used to establish a true-breeding line of tailless offspring due to the failure of both *T/T* and *t/t* homozygotes to develop.[48] Dobrovolskaïa-Zavadskaïa's ideas about the nature of the *t*-complex were vague, being espoused at the time that similar ideas were first emerging from geneticists working on the *Drosophila scute* complex.[49–53] Dobrovolskaïa-Zavadskaïa wrote: "We named this complex formation in the hereditary substance, corresponding to the mutable tail in our mice, a 'mutable factor', reserving the term 'gene' for the real units, or simple Mendelian characters. For those atoms of heredity which constitute a 'mutable factor' the name of 'gene elements' may be maintained. The existence of smaller units [true genes] in our case reveals itself in the possibility of being able to reproduce many of the particular forms of abnormal tail in succeeding generations; our next problem is to extract at least some of them as pure as possible".[20] Dobrovolskaïa-Zavadskaïa failed to make headway dissecting the complex of mutations harbored by the wild "*t*" chromosome, but she was sufficiently intrigued by the importance of the problem that, as Chesley and Dunn acknowledged in their papers,[48] she passed the *T* and *t* (later known as t°) mutations to the Dunn laboratory at Columbia University in 1933. At this point in time, Dobrovolskaïa-Zavadskaïa and Kobozieff suspected that *T* and *t* were components of a balanced lethal system. Chesley and Dunn described the results of their own $T/t \times T/t$ crosses as confirming that taillessness bred true and that these crosses produced discernibly small litters. Further, they went on to prove that each mutation in isolation acted as a recessive lethal.[48]

Dunn and his laboratory's descendants eventually expended large portions of their careers identifying the immense variety of *t*-haplotypes that prevail in the wild, deducing the individual functions controlled by the genes of the *t*-complex, and examining the strange effects these chromosomes had on recombination and transmission (reviewed in Refs. 31, 47, and 53). It is now clear why the analysis of the "*t* mutations" was so difficult for Dobrovolskaïa-Zavadskaïa and Kobozieff. The *t* mutations being studied involved complex chromosomal rearrangements covering a sizable portion of chromosome 17. These *t*-haplotypes harbored multiple mutations that usually segregated as a single inheritance unit because of the local suppression of recombination that resulted from inversions within the *t*-chromosomes. Even now, as genes responsible for individual characteristics of *t*-haplotypes are being defined,[54] understanding the *t*-complex remains a formidable challenge for geneticists and developmental biologists.

Mouse genetics, development and cancer

In addition to her studies of the genes regulating tail development, Dobrovolskaïa-Zavadskaïa was noted for her contributions in mouse husbandry and cancer biology. Previous studies of the *T* mutation, which had been seen in laboratory stocks prior to her work, had been confounded by the poor viability of the *short-tail* animals. Perhaps because of her life-long interest in the interactions between environment and genes, she established rigorous standards of animal husbandry, which resulted for the first time in a robust line of *T*-bearing mice.

In 1926 she initiated a study of hereditary factors associated with the formation of tumors in mice, a field in which she worked continuously for almost 30 years. As for her theory of the organ-specific action of genes in development, she suggested that genes could confer cancer susceptibility in an organ-specific manner, and she suggested the existence of several organ-specific recessive genes in the genesis of cancer.[55,56] She generated several lines of mice, some of which had a high incidence of cancer and others that were cancer-free. Her work on mammary tumors was influential.[10] For example, her RIII line, which developed high levels of spontaneous mammary tumors, was employed in the 1930s and 1940s in several leading laboratories to isolate mouse mammary carcinoma virus.[57] Through her studies of the consequences of carcinogen application to these lines of mice, she came to the conclusion that cancer is a multifactorial disease that develops through a specific interaction between external factors and genetic predispositions[55,56] (reviewed in Ref. 58).

A promising beginning, a lasting legacy

The accomplishments and lasting influences of Nadine Dobrovolskaïa-Zavadskaïa are truly spectacular when viewed from any of several different vantage points. A refuge of war,

she began her career as a "bench scientist" when she was a middle-aged woman. She undertook a pioneering and unproven line of biological research and emerged with a novel way of thinking about gene action during embryonic development. She focused attention on a phenotype and a gene whose cloning was described as bringing the field to "the crossroads of developmental genetics".[59] She developed her insights during an era when there was almost no intersection between the fields of developmental mechanics and heredity, in scientific environment, where the importance and applicability of the principles of genetics were tremendously undervalued,[60] and at a time when the contributions of women scientists worldwide were rarely recognized and their ability to develop independent research programs was constrained (see for example the career of Salome Waelsch, Ref. 61). It is reasonable to assume that some of these factors may have limited her development as a scientist and the past recognition of her contributions.

In addition, several factors detracted from her legacy as a pioneering mouse geneticist. One of them was the difficulty Dobrovolskaïa-Zavadskaïa had in interpreting the origin of the mutations recovered in her initial mutant screen. Noting that the only mutants she recovered were phenotypes that had been described previously in mice, she candidly questioned whether the mutations she isolated were induced by the X-rays, since she found that one of the founder males carried a natural mutation of Brachyury.[19,20,28] She was frustrated by the low incidence of induced mutations with visible effects, commenting that all of the early workers in the field had only recovered sporadic mutants and that they were unable to produce similar mutants in repeated mutagenesis experiments. Indeed, even Herrmann Muller[62] in his famous paper linking the physical action of X-rays on a gene to the induction of mutations, summarized the field by saying: "The work has been done in such a way that the meaning of the data, as analyzed from a modern genetic standpoint, has been highly disputatious at best; moreover what were apparently the clearest cases have given negative or contrary results on repetition." It is important to realize that the fundamental breakthrough in this area by Muller relied on procedures that were not technically feasible in mice. Muller's brilliant experiments relied on very large breeding programs that allowed him to establish the spontaneous or background frequency of lethal mutations in flies and thus measure the dose-dependent induction of lethals by X-irradiation. In hindsight, it is clear that, in the early 1920s, with the limited number of mutations available in mice to mark the transmission of chromosomes, small-scale mutagenesis studies could only have yielded equivocal results. Nevertheless, Dobrovolskaïa-Zavadskaïa, remained steadfast in her attempts to extrapolate from her limited studies, and throughout the almost 10 years that she worked on T, she continued to question whether irradiation was responsible for the induction of new mutations.

More than 70 years after Dobrovolskaïa-Zavadskaïa's discovery of *Brachyury*, it is impossible to resolve the question of whether the initial *Brachyury* mutation was induced by X-ray treatment. Perhaps the question should be rephrased: "Could irradiation have induced the original *T* mutation?". The answer is clearly positive, since multiple mutant alleles of *Brachyury* have been subsequently induced in both the mouse and the zebrafish following irradiation.[9,63,64] Like the original *T* allele, the later mouse and zebrafish mutations were deletion mutations with a homozygous phenotype of loss of notochord and posterior mesodermal differentiation. It is to her credit that Dobrovolskaïa-Zavadskaïa recognized that she could not conclude that the *T* mutation was induced, given the existence of spontaneous variants with altered tail development in her laboratory colony.

In this brief essay, we have attempted to capture some of the lasting aspects of the legacy of Nadine Dobrovolskaïa-Zavadskaïa. Much of Dobrovolskaïa-Zavadskaïa's work seems richly contemporary, including her screen for developmental mutants, her attempt to relate laboratory-induced variants to variation in the wild, and her attempt to identify hierarchical genetic interactions that govern a complex developmental process. She was a gutsy pioneering biologist who attacked issues of her day that were important and yet completely unresolved. Her ideas about the organ-specific function of *T* and the hierarchy of gene functions that contribute to variations in adult forms are ideas that are commonplace today. Perhaps even more important to her legacy are other qualities that have made her such a common feature in the cited literature more than 70 years after her discovery of *T*. Her insight into the significance of the mutant phenotypes associated with *T* and *tailless*, her ability to proselytize her results, and her willingness to share her reagents, have left us with an extensive array of unresolved and fascinating problems, still under study today. The recent discovery of a large family of genes related to *Brachyury*,[65,66] some of which, like *Brachyury*, are involved in formation of the early mesoderm,[67–71] and others of which somehow work to distinguish forelimbs from hindlimbs,[72–74] is leading to a new series of investigations of the primary function of *Brachyury*. It appears likely that Dobrovolskaïa-Zavadskaïa's *short-tail* mutation will spend over 100 years as one of the centerpieces of vertebrate developmental genetic studies.

Acknowledgments

The authors are indebted to Dr. Daniel Louvard, Ms. Christine Tarenne, Ms. Marie-Claude Moutier and Mr. Daniel Meur from the Institute Curie in Paris, Drs. Ilya Ruvinsky, Lee Silver (Princeton University, USA), Karen Artzt (University of Texas in Austin), Ilana Löwy (INSERM, Paris), and E. I. Kolchinsky (Institute of the History of Science and Technology, St-Petersburg, Russia) for their generous help in finding information used in this essay. Drs. Isabelle Desjeux and Christiane

Fauron kindly helped with translations from the French. Drs. Michael Richardson, V. Sundaresan and Ellen Wilson critically read this manuscript. The authors are thankful to an anonymous reviewer and Dr. Adam Wilkins for their comments on manuscript.

References

1. Slack JMW, Holland PWH, Graham CF. The zootype and the phylotypic stage. Nature 1993;361:490–492.
2. Raff RA. The Shape of Life. Chicago: Chicago University Press; 1996.
3. Gerhart J, Kirschner M. Cells, Embryos, and Evolution. Malden, Mass: Blackwell Science, Inc.; 1997.
4. Shubin N, Tabin , Carroll S. Fossils, genes and the evolution of animal limbs. Nature 1997;388:639–648.
5. Dobrovolskaïa-Zavadskaïa N. Sur la mortification spontanee de la chez la souris nouveau-nee et sur l'existence d'un caractere (facteur) hereditaire, non-viable. Crit Rev Soc Biol 1927;97:114–116.
6. Chesley P. Development of the short-tailed mutant in the house mouse. J Exp Zool 1935;70:429–459.
7. Herrmann B, Labeit S, Poustka A, King T, Lehrach H. Cloning of *T* gene required in mesoderm formation in the mouse. Nature 1990;343:617–622.
8. Halpern ME, Ho RK, Walker C, Kimmel CB. Induction of muscle pioneers and floor plate is distinguished by the zebrafish *no tail* mutation. Cell 1993;75:99–111.
9. Schulte-Merker S, van Eeden FJM, Halpern ME, Kimmel CB, Nusslein-Volhard C. No tail (ntl) is the zebrafish homologue of the mouse *T* (*Brachyury*) gene. Development 1994;120:1009–1015.
10. Chaine J. Madame Dobrovolskaïa-Zavadskaïa, 1878–1954. Bulletin du Cancer 1954;41:508–509.
11. Dobrovolskaïa-Zavadskaïa N. Modifications des fibres striees sous l'influence d'irradiations prolongees au moyen de foyers radiferes introduits dans les muscles. J de Radiol et d'Electr 1924;2:49–61.
12. Dobrovolskaïa-Zavadskaïa N. Etudes sur les effets produits par les rayons X dans le testicule de la Souris. Arch d.Anat micr 1927;23:396–438.
13. Bridges CB. Non-disjunction as proof of the chromosome theory of heredity. Genetics 1916;1:107–163.
14. Mavor JW. The production of non-disjunction by X-rays. Science 1922; 55:1420.
15. Mavor JW. Studies on the biological effects of X-rays. Am J Roentg and Rad Ther 1923;10:968–974.
16. Mavor JW. The attack on the gene. Sci Monthly 1925;21:355–363.
17. Bagg HJ, Little CC. Hereditary structural defects in the descendants of mice exposed to Röntgen ray irradiation. Am J Anat 1924;33:119–145.
18. Nadson GA, Philippov GS. Influence des rayons X sur la sexualite et la formation des mutantes chez les champignons inferieurs (Mucorinees). C R Soc Biol 1925;93: 473.
19. Dobrovolskaïa-Zavadskaïa N. L'irradiation des testicules et l'heredite chez les souris. Arch de Biologie 1928;38:457–501.
20. Dobrovolskaïa-Zavadskaïa N. The problem of species in view of the origin of some new forms in mice. Biol Rev 1929;4:327–351.
21. Regaud C, Blanc J. Actions des rayons X sur les diverses generations de la lignee spermatique. Extreme sensibilite des spermatogonies a ced rayons. C R Soc Biol 1906;61:163.
22. Regaud C, Dubreuil G. Perturbation dans le developpement des oeufs fecondes des spermatozoides roentenises chez le Lapin. C R Soc Biol 1908;64:1014.
23. Dobrovolskaïa-Zavadskaïa N, Kobozieff N. Sur le facteur lethal accompagnant l'anurie et la brachyurie chez la souris. C R de l'Acad des Sci 1930;191:352–355.
24. Dobrovolskaïa-Zavadskaïa N. Preliminary symbols for a tail-mutation in mice. Amer Natur 1933;47:186–188.
25. Cuenot L. Les races pures et leurs combinaisons chez les Souris. Arch Zool Exper 1905; 3, 4^{e} ser., Notes de Revues: p 123.
26. Castle WE, Little CC. On a modified mendelian ratio among yellow mice. Science 1910;32:868–870.
27. Gluecksohn-Schoenheimer S. The development of normal and homozygous Brachy (T/T) mouse embryos in the extraembryonic coelom of the chick. Proc Nat Acad Sci USA 1944;30:134–140.
28. Dobrovolskaïa-Zavadskaïa N, Kobozieff N, and Veretennikoff S. Etude morphologique et genetique de la brachyourie chez les descendants de souris a testicules irradies. Arch de Zool Exp 1934;76:249–358.
29. Dobrovolskaïa-Zavadskaïa N, Kobozieff N. Sur la reproduction des souris anoures. C R Soc Biol 1927;97:116–118.
30. Dobrovolskaïa-Zavadskaïa N, Kobozieff N. Les souris anoures et a queue filiforme qui se reproduisent entre elles sans disjonction. C R Soc Biol 1932;110:782–784.
31. Gluecksohn-Waelsch S, Erickson RP. The T-locus of the mouse: implications for mechanisms of development. Curr Top Dev Biol 1970;5:281–316.
32. Bennett D. The T-locus of the mouse. Cell 1975;6:441–454.
33. Wolpert L. Principles of Development. Oxford: Oxford University Press; 1998, p. 444–450.
34. Monroy A. Developmental biology and genetics: a plea for cooperation. Curr Top Dev Biol 1970;5:xvii-xxi.
35. Saap J. Beyond the gene. Cytoplasmic inheritance and the struggle for authority in genetics. New York, Oxford: Oxford University Press. 1987.
36. Gilbert S. Induction and the origins of developmental genetics. In Gilbert S. ed; A Conceptual History of Modern Embryology. New York: Plenum Press. 1991. pp. 181–206.
37. Ephrussi B. Sur le factour lethal des souris brachyures. C R Acad Sci 1933;197:96–98.
38. Ephrussi B. The behaviour in vitro of tissues from lethal embryos. J Exp Zool 1935;70:197–204.
39. Bumcrot D, McMahon A. Sonic signals somites. Curr Biol 1995; 5: 612-614.
40. Placzek M. The role of the notochord and floor plate in inductive interactions. Curr Opin Gen Dev 1995;5:499–506.
41. Dunn LC, Gluecksohn-Schoenheimer S. A specific abnormality associated with a variety of genotypes. Proc Nat Acad Sci USA 1944;30:173–176.
42. Griffin K, Patient R, Holder N. Analysis of FGF function in normal and no tail zebrafish embryos reveals separate mechanisms for formation of the trunk and the tail. Development 1995;121:2983–2994.
43. Halpern ME, Hatta K, Amacher SL, Talbot WS, Yan Y-L, Thisse B, Thisse C, Postlethwait JH, Kimmel CB. Genetic interactions in zebrafish midline development. Dev Biol 1997;187:154–170.
44. Danos MC, Yost HJ. Role of notochord in specification of cardiac left-right orientation in zebrafish and *Xenopus*. Dev Biol 1996;177:96–103.
45. Smith J. *Brachyury* and the T-box genes. Curr Opin Gen Dev 1997;7: 474–480.
46. Dobrovolskaïa-Zavadskaïa N. (1928b) Contribution a l'etude de la structure genetique d'un organ. C R Soc de Biol 1928;99:1140–1143.
47. Silver LM. Mouse *t* haplotypes. Annu Rev Genet 1985;19:179–208.
48. Chesley P, Dunn LC. The inheritance of taillessness (anury) in the house mouse. Genetics 1936;21:525–536.
49. Dubinin N. Allelomorphentreppen bei *Drosophila melanogaster*. Biol Zentr 1929;49:328–339.
50. Dubinin N. Step-allelomorphism and the theory of centres of the gene achaete-scute. J Genet 1932;26:37–58.
51. Serebrovsky A. A general scheme for the origin of mutations. Am Nat 1929;63:374–378.
52. Agol I. Evidence of the divisibility of the gene; abstract. Anat Rec 1930; 47:385.
53. Bennett D. L.C.Dunn and his contribution to *t*-locus genetics. Ann Rev Genet 1977;11:1–12.
54. Herrmann B, Koschorz B, Wertz K, McLaughlin KJ, Kispert A. A protein kinase encoded by the *t complex responder* gene causes non-mendelian inheritance. Nature 1999;402:141–146.
55. Dobrovolskaïa-Zavadskaïa N. Heredity of Cancer. Am J Cancer 1933; 18:357–379.
56. Dobrovolskaïa-Zavadskaïa N. Hereditary and environmental factors in the origin of different cancers. J Genet 1940;40:157–170.
57. Graff S, Moore CH, Stanley WM, Randall H, Haagensen C. Isolation of mouse mammary carcinoma virus. Cancer 1949;2:755–762.
58. Löwy I and Gaudilliere J-P. Disciplining cancer: mice and the practice of genetic purity. In Gaudilliere J-P and Löwy I. ed; The Invisible Industrialist. Manufacturers and the Production of Scientific Knowledge. London: Macmillan. 1988, pp. 209–249.

59. Silver LM. At the crossroads of developmental genetics: the cloning of the classical mouse *T* locus. Bioessays 1990;12:377–380.
60. Burian RM, Gayon J. The French school of genetics: from physiological and population genetics to regulatory molecular genetics. Ann Rev Genet 1999;33:313–349.
61. Silver LM. The 1999 Thomas Hunt Morgan Medal: Salome G. Waelsch. Genetics 2000;154:1–2.
62. Muller HJ. Artificial transmutation of the gene. Science 1927;66:84–87.
63. Kimmel CB, Hatta K, Eisen JS. Genetic control of primary neuronal development in zebrafish. Development (Suppl.) 1992;2:47–57.
64. Bennett D, Dunn LC, Spiegelman M, Artzt K, Cookingham J, Schermerhorn, E. Observations on a set of radiation-induced dominant T-like mutations in the mouse. Genet Res 1975;26:95–108.
65. Bollag RJ, Siegfried Z, Cebra-Thomas JA, Garvey N, Davison EM, Silver LM. An ancient family of embryonically expressed mouse genes sharing a conserved protein m/otif with the *T* locus. Nat Genet 1994;7:383–389.
66. Papaioannou VE, Silver LM. The T-box gene family. Bioessays 1998;20: 9–19.
67. Dheen ST, Sleptsova-Friedrich I, Xu Y, Clark M, Gong Z, Lehrach H, Korzh V. Zebrafish tbx-c functions during formation of midline structures. Development 1999;126:2703–2713.
68. Hug B, Walter V, Grunwald DJ. tbx6, a brachyury-related gene expressed by ventral mesendodermal precursors in the zebrafish embryo. Dev Biol 1997;183:61–73.
69. Chapman DL, Papaioannou VE. Three neural tubes in mouse embryos bearing mutations in the T-box gene Tbx6. Nature 1998;391:695–697.
70. Griffin K, Amacher S, Kimmel C and Kimelman D. Molecular identification of spadetail: regulation of zebrafish trunk and tail mesoderm formation by T-box genes. Development 1998;125:3379–3388.
71. Smith J. T-box genes: what they do and how they do it. Trends Genet 1999;15:154–158.
72. Gibson-Brown JJ, Agulnik S, Chapman DL, Alexiou M, Garvey N, Silver LM, Papaioannou VE. Evidence of a role for T-box genes in the evolution of limb morphogenesis and the specification of the forelimb/hindlimb identity. Mech Dev 1996;56:93–101.
73. Takeuchi JK, Koshiba-Takeuchi K, Matsumoto K, Vogel-Hopker A, Naitoh-Matsuo M, Ogura K, Takahashi N, Yasuda K, Ogura T. Tbx5 and Tbx4 genes determine the wing/leg identity of limb buds. Nature 1999;398:810–814.
74. Rodriguez-Esteban C, Tsukui T, Yonei S, Magallon J, Tamura K, Izpisua-Belmonte JC. The T-box genes Tbx4 and Tbx5 regulate limb outgrowth and identity. Nature 1999;398:814–818.