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Составители: ***В. Л. Корогодина, Н. И. Дубровина***

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Edited by ***V. I. Korogodin***
Composed by ***V. L. Korogodina, N. I. Dubrovina***

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THE SCIENTIFIC RESEARCH OF N.W. TIMOFÉEFF-RESSOVSKY IN 1930–1945 AND ITS TRADITION IN BERLIN-BUCH

D. Ganten, H. Bielka

Max-Delbrück-Center for Molecular Medicine, D-13125 Berlin-Buch, Germany

Timoféeff-Ressovsky's move from Moscow to Berlin in 1925

In February 1925, Professor Oskar Vogt, Director of the Kaiser Wilhelm Institute for Brain Research went to Moscow to prepare "scientific investigations" on the brain of V.I. Lenin who had died the year before. He also used his time there to recruit a Russian geneticist for his own institute in Berlin. Oskar Vogt was interested in genetic problems in relation to evolutionary biology, variations in the cytostructure of the cerebral cortex and inherited neurological diseases. He chose the young N.W. Timoféeff-Ressovsky from the Moscow Institute of Experimental Biology headed by Professor N.K. Koltzoff. Timoféeff-Ressovsky had worked there in the Department of Genetics with the father of Russian population genetics, Professor S.S. Tschetverikoff. On July 1st, 1925, N.W. Timoféeff-Ressovsky with his wife Elena, who also worked as a geneticist in Koltzoff's institute, arrived in Berlin. The move by Timoféeff from Moscow to Berlin was made possible by a scientific exchange program which had been set up between Germany and the Soviet Union in 1924. Vogt's Institute for Brain Research was then located in the center of Berlin, where Timoféeff-Ressovsky established a department of experimental genetics. He became head of this department in 1929.

In 1930, a new building with a genetic vivarium was completed in Buch, a suburb to the north-east of Berlin, for the Kaiser Wilhelm Institute for Brain Research. Until 1945, this was where Timoféeff worked in Berlin-Buch and he lived there with his family on the campus of the Institute. A commemorative plaque in this building is dedicated to him; it says: "Nikolai Vladimirovich Timoféeff-Ressovsky. 1900–1981. Russian geneticist, biophysicist and pioneer of molecular genetics lived and worked in the Kaiser Wilhelm Institute for Brain Research in Berlin-Buch from 1930–1945".

Timoféeff's scientific research in Berlin

Timoféeff's genetic and biophysical research in Berlin concentrated mainly on four areas, namely, population genetics, phenogenetics, radiobiology (radiation genetics) as well as his later research on the application of radioisotopes in biology and medicine.

In conjunction with his wife Elena he carried out investigations into population genetics analyzing mutations and alterations in the temporal and spatial distribution of the fruit fly Drosophila (which had been introduced into genetic research in 1906 by W.E. Castle and in which one year later T.H. Morgan was able to show that the paired chromosomes are carriers of inherited material) and the ladybird Epilachna chrysomelina under laboratory conditions (in the genetic vivarium of the institute) as well as under panmictic conditions in the wild (in the park of the institute's campus). Due to differences in the alterations in the number of individuals within certain lifespan and time periods, as well as increased mutation rates in the laboratory populations in comparison with the wild populations, they concluded that the abolition of natural selection in closed populations led to an increase in mutations, including pathogenic and lethal mutations. In addition, according to Timoféeff, in natural populations with mixed inherited characteristics in recessive mutations there was a great potential for genetic variability in species developments. This allowed the two Timoféeffs to make a significant contribution in the 1930s and 1940s to the unification of Mendel's teaching on genetics and Darwin's classical theory of the origin of species and hence to the development of the "synthetic theory of evolution".

From 1925 till 1935, Elena and Nikolai W. Timoféeff-Ressovsky also worked in Berlin on phenogenetics, i.e. the phenomenon of polyphenic gene effects described by T.H. Morgan, which they had also been working on in Moscow. They investigated the effect of a gene or the action of a gene in terms of manifestation in the phenotype by environmental factors as well as by other genes of the genome of the same individual or other individuals in a given population. This work showed that the expression of a characteristic can be affected by several genes and that the action of different mutated genes in the phenotype is not completely predictable from the single effects of the genes.

From 1929/30 on, the main research of N.W.Timoféeff-Ressovsky involved radiobiology, which he also called radiation genetics. This research involved investigating the production of mutations, especially the relationships between dose and effect which had been described in 1926 by the American geneticist Hermann Joseph Muller (Nobel Prize winner in 1946) who studied the mutagenic action of X-rays. Again, he chose Drosophila as the subject for most of his experiments. Timoféeff reported his observed effects in his research publications as "Genetic Variations due to X-rays". Due to these investigations, H.J. Muller visited Timoféeff's laboratory in Berlin-Buch in 1932, but he left in 1933 after the National Socialists came to power in Germany and then went to Moscow to the University's Institute of Genetics. Another scientist who was impressed by Timoféeff's research was the young physicist Dr. Max Delbrück, who at that time worked as an assistant to Lise Meitner in the Kaiser Wilhelm Institute of Chemistry in Berlin-Dahlem. Delbrück was involved in a number of areas of research including the concept of complementarity which came from atomic physics. In this context, he was also interested in doubling of genetic material. So, Delbrück made contact with Timoféeff in Berlin-Buch and invited him to his private seminars in his parents' home. In his Nobel Lecture in 1969 on "A Physicist's Renewed Look at Biology: Twenty Years Later" (Science, 1970, Vol.168, P.1312-1315) Max Delbrück commented: "Our principal teacher in the latter area [biology] was geneticist Timoféeff-Ressovsky, who, together with physicist K.G. Zimmer, at that time was doing by far the best work in the area of quantitative mutation research". This led to a fruitful collaboration resulting in the celebrated paper "On the Nature of Gene Mutation and Gene Structure" by N.W. Timoféeff-Ressovsky, K.G. Zimmer and M. Delbrück, published in 1935 in the "Nachrichten der Gesellschaft für Wissenschaften zu Göttingen" (Volume 1, No. 13, P. 189-245).

Timoféeff and his collaborators physicists K.G. Zimmer and M. Delbrück analyzed the findings on the linear relationship between the dose and the mutagenic effect of X-rays using the hit theory proposed in 1922 by Friedrich Dessauer, i.e. a mathematical description of the biological effects of X-rays in biological systems. They obtained results which showed that a mutation is the consequence of a one-hit event, which comes about by a single ray-determined effect. From this they concluded that mutations are atomic transitions and that such a molecule could be a gene or a part of a gene. So, they defined a gene as a stable structure built of atoms, whereby the gene, until then an abstract concept, took on a material form and physical dimensions. In looking back on this work, Max Delbrück in his article in “Science”, cited earlier, commented: "Genes at that time were algebraic units of the combinatorial sciences of genetics, and it was anything but clear that these units were molecules analyzable in terms of structural chemistry".

The importance of the publication by Timoféeff-Ressovsky, Zimmer and Delbrück was really only properly recognized and appreciated some 10 years later, in particular by the physicist Erwin Schrödinger in his essay published in 1944 "What is Life?" In that book, where Schrödinger tried to answer the question of whether life could be explained by the laws of physics, he also described model images of the structure of genes and referred to the "research by the trio" of Timoféeff et al. The particular importance of Timoféeff in relation to this work, due to his experimental investigations, was acknowledged by Robert Olby in his book published in 1974 entitled "The Path to the Double Helix", in which he wrote: "Perhaps molecular biology owes more to the geneticist who began that work – Timoféeff-Ressovsky – than has so far been admitted".

A year before the work of the trio, Timoféeff published a remarkable piece of work in the highly regarded journal "Biological Review of the Cambridge Philosophical Society" (1934, Vol.9, P.411-457), entitled "The Experimental Production of Mutations". In it, for the first time, the concept of "genetic engineering" was formulated and explained. Timoféeff wrote that this concept "makes the application of radiation genetic methods most valuable for analytical genetic studies, for instance, in comparative genetics of related species, in quantitative studies of the mutabilities in different species and of different individual genes, in cytogenetics, and in «genetic engineering» (i.e. the synthesis of new genotypes and races)". So, the concept and research aims of "genetic engineering" were first formulated by Timoféeff in Berlin-Buch in 1934, even if at this time they related mainly to methods of breeding and induced mutations.

In 1944, N.W. Timoféeff-Ressovsky and K.G. Zimmer summarized the results of their investigations on hit theory, which from 1939 on also included neutron radiation, in the book "The Hit Principle in Biology". Due to the war, this book first appeared following its approval by the Soviet military administration in 1947 and was published by S. Hirzel Verlag in Leipzig. In 1972 the book "The Application of the Hit Principle in Radiation Biology" by

N.W. Timoféeff-Ressovsky, V.I. Ivanow and V.I. Korogodin was published by Fischer Verlag in Jena.

To further support the hit principle of the effect of radiation, from 1939 on, work was also carried out using neutron radiation. To help this work, a biophysical laboratory was established in 1938 in the Department of Genetics and a Philips neutron generator was installed so that radioactive isotopes could also be prepared. This also led to work using radioactive isotopes. Whether radiation of radioactive isotopes was initially also planned as part of the mutation experiments cannot be determined from research plans and publications. However, comprehensive experiments were carried out on the distribution of radioactive elements in mammals. This work involved a large number of contributions to the use of the indicator method established by George v. Hevesy and its application to biology and medicine. Others taking part in this work were H.J. Born and P.M. Wolf and, above all, Timoféeff's wife Elena. Some of the most significant work from this large volume of research included the determination of the circulation time in humans with the help of Thorium X (Ra-224), the application of Thorotrast (Thorium dioxide sol) as a contrast agent in X-ray diagnostics as well as the first labeling of the tobacco mosaic virus (TMV) using radioactive phosphate for research in virology.

Timoféeff's fate in 1945

As early as 1944, the transfer of the scientific departments of the Kaiser Wilhelm Institute for Brain Research to the western part of the "German Reich" started. When Soviet troops marched into Berlin-Buch on April 21st, 1945, the only people left at the Institute for Brain Research were Timoféeff-Ressovsky with many of his colleagues and a number of guest researchers. The institute was placed under the control of the Soviet military administration and renamed "Institute of Genetics and Biophysics" and Timoféeff-Ressovsky, as a Soviet citizen, was made Director in May 1945. He was then allowed to continue with his scientific research there under the special protection of the Commissar for Internal Affairs of the Soviet Union, A. P. Savenyagin. He was also allowed to be assisted by German scientists such as the physician and biochemist Karl Lohmann and the physicists Robert Rompe and Friedrich Möglich.

On September 14th, 1945, Timoféeff-Ressovsky was arrested in Berlin-Buch and deported by the Soviet authorities. Elena Timoféeff remained in Berlin-Buch and, initially, she was without a job but received financial help from American colleagues via an accommodation address in West Berlin. Among these involved were the geneticists Milislav Demerec and Herrman Muller. From May 1st, 1946, until June 30th, 1947, Elena Timoféeff worked with the well-known geneticist Professor Hans Nachtsheim at the Zoology Institute of the University of Berlin. After receiving news from her husband from the Urals, she returned to the Soviet Union. This marked the end of 22 years of the Timoféeffs and "Timoféeff genetics" in Berlin, 17 of these years being spent in Berlin-Buch.

Genetics in Berlin-Buch after Timoféeff-Ressovsky's departure:
Genetic and biophysical research in the Academic Institute of Medicine and Biology

In 1947, the Soviet military administration in Germany handed over the former Kaiser Wilhelm Institute for Brain Research to the German Academy of Sciences in Berlin, formerly the Prussian Academy of Sciences. Associated with this was the foundation of an Institute of Medicine and Biology for the investigation of problems in theoretical and clinical medicine, particularly cancer. Not surprisingly, genetic research was also carried out in a department set up specially for this. It was headed by the geneticist Professor Herbert Lüers, who had being collaborated with Timoféeff-Ressovsky in Berlin-Buch since 1935. This allowed a continuation of "Timoféeff genetics" in Buch and its tradition, and research interests also made use of models such as Drosophila. Furthermore, at the heart of this was an interest in mutation research, in particular investigations of the mutagenic effects of chemical carcinogens as well as contact insecticides and the genetic basis for the development of insecticide resistance. The research on chemical carcinogens pseudo-tumors in Drosophila was associated with problems involving cancer research. In a continuation of his research with Timoféeff on the influence of the expression of vision systems in Drosophila due to genetic factors, analyzed in transplant experiments, Lüers also worked in the Buch Institute of Medicine and Biology on the analysis of neurosecretory centers in Drosophila.

Also, the research with radioactive isotopes continued after the Second World War at the Institute of Medicine and Biology in Buch, and this was carried out in the Department of Applied Isotope Research under the leadership of Otto Hahn's student, Professor Hans-

Joachim Born. Born had also worked in Timoféeff's department and, since 1940, he had collaborated with Elena Timoféeff, K.G. Zimmer and others. While in Timoféeff's department, Born had been mainly engaged in the behavior of radioisotopes in mammals. This research was continued in the Department of Isotope Research in Buch after the Second World War using the methods that had been used in Timoféeff's department, namely looking at the application of radioactive isotopes for diagnostic and therapeutic purposes in medicine, from then on particularly in relation to combating tumors, as well as for biological research purposes.

With the development of the doctrinaire, politically motivated, pseudogenetics of Lyssenko in the Soviet Union, from the end of the 1940s onwards, genetic research and teaching in the GDR was markedly impeded. As a protest against these developments, Professor Herbert Lüers left Berlin-Buch in 1953 and moved to the Free University at Berlin-Dahlem as the successor to the geneticist Professor Hans Nachtsheim. This brought the tradition of Timoféeff genetics in Berlin-Buch to an end. By 1948, Hans Nachtsheim had his post at the German Academy of Sciences as a member of the Buch Institute of Medicine and Biology terminated, since he believed "that German geneticists too are no longer able to undertake research in a free atmosphere while the Soviets occupy German territory".

Genetics in the Max Delbrück Center for Molecular Medicine

After the re-unification of the two Germanys, the Max Delbrück Center for Molecular Medicine (MDC) was founded on January 1st, 1992, in Berlin-Buch, on the campus of the Institutes of the former GDR Academy of Sciences. The main aims of the MDC were laid down following the recommendations of the Scientific Council and the Founders Committee that they should pursue medical and clinical research using methods of molecular biology and genetics. At the forefront of these activities is the investigation of cardiovascular diseases and cancer. The neurosciences represent another major topic of research.

Many research groups at the MDC are involved in genetics, since lots of human diseases have at least a genetic component in their pathogenesis. One of the central tasks of these research groups is the identification of the genes that are involved in causing disease. To do this, researchers need to carry out genetic mapping and subsequent cloning to identify and characterize the functions of candidate genes for monogenic and complex inherited conditions.

Further examples of genetic research at the MDC include investigations of the gene fragments, from which DNA synthesis starts, as well as investigations of genetic trigger elements (transposons). These are normally inactive but can be activated by mutations giving them the ability to incorporate themselves in other sites in the genome.

This variety of topics at the present MDC is based on the research of Timoféeff and his understanding of phenogenetics. In the future, we predict that the area of functional genome research will increase in importance and have very a significant effect on our understanding of physiological and pathological processes.