Nikolai V. Timoféeff-Ressovsky

Controversy surrounds this Russian-born geneticist, whose major scientific achievements were made in Nazi Germany and who was later convicted of treason by the Soviet Union

by Diane B. Paul and Costas B. Krimbas

In 1925 Oskar Vogt, the director of the Kaiser Wilhelm Institute for Brain Research in Berlin, invited a promising young Russian researcher named Nikolai V. Timoféeff-Ressovsky to organize a department of experimental genetics there. Timoféeff, who was 25, did not even possess an undergraduate degree at the time. Yet within a few years, he was to become director of the new department and a leading figure in the fields of population and radiation genetics.

Specifically, Timoféeff helped to develop an influential theory of how mutations occur, he made the first measurement of a gene, and he established that much of the genetic diversity in a wild population is hidden in the form of recessive mutations. Although histories of genetics hardly mention Timoféeff, he significantly influenced genetic research not only through his own work but also by transmitting Russian ideas about the mechanism of evolution to the West.

These achievements were all the more remarkable given the troubled, paradoxical political circumstances of his life. He was a Russian patriot, but Timoféeff's most scientifically productive years were spent in Germany before and during the Nazi era. When Soviet troops entered Berlin at the end of World War II, he was imprisoned. Because of his expertise in radiation biology, he was allowed to continue his genetic studies in a military laboratory at a time when such research had been publicly banned in the U.S.S.R. Nevertheless, he was hounded by political opponents for the rest of his life and has never been rehabilitated.

Timoféeff's life poses difficult questions: How could a scientist work honestly in an environment of ideological and physical warfare? Was it possible to be a geneticist in Nazi Germany without being morally compromised? And how can one distinguish an independent researcher from a discreet collaborator? We set out to investigate these issues and to learn more about Timoféeff's fascinating political and intellectual life.

Political upheaval interfered with Timoféeff's research from the start. The October Revolution erupted while he was a biology student at Moscow University. Timoféeff left school to fight with the anarchists and later with the Red Army (he did not formally complete his doctorate until 1964). In 1922 he returned to the university, where he studied with Sergei S. Chetverikov, the founder of Russian population genetics. Chetverikov instilled in Timoféeff an abiding interest in the genetic basis of evolution. At the same time, Timoféeff began working with Nikolai K. Kol'tsov, the head of the Research Institute for Experimental Biology. Kol'tsov grounded the young Timoféeff in the methods of comparative anatomy, morphology and systematics. This intellectual mixture proved instrumental in guiding Timoféeff's later scientific work.

A curious set of circumstances prompted Timoféeff to leave Russia and move to Berlin in 1926. After Lenin's death in 1924, the Soviet government arranged for a microscopic study of its deceased leader's brain, ostensibly to uncover the material basis for his genius. The Soviets invited Vogt, a noted German psychiatrist and neurophysiologist, to direct the work.

While in Russia, Vogt learned that Timoféeff and his wife, Helena Aleksandrovna, had found a mutation in the fruit fly species *Drosophila funebris* that produced highly variable deformations in a vein in the fly's wings. At the time, Vogt was trying to determine why certain inherited neurologic disorders vary tremendously in frequency and severity. The discovery that a single kind of mutation could produce many different wing morphologies therefore caught Vogt's attention.

He invited Timoféeff to organize a new genetics laboratory being started at Vogt's institute. Despite his strong emotional ties to Kol'tsov and to his homeland, Timoféeff accepted and moved to Berlin. At that point, he had published a few papers but was essentially unknown outside of a small circle of Russian biologists. In the years between his arrival in Berlin and the outbreak of war, Timoféeff produced nearly all the work on which his scientific reputation rests.

Timoféeff's primary interest lay in understanding the process of evolution. When he moved to Berlin, he brought to Germany and western Europe the ideas of Chetverikov, who had developed an innovative synthesis of Mendelian genetics and classical Darwinism. Chetverikov arrived at his ideas independently of the British geneticists Sir Ronald A. Fisher and J.B.S. Haldane and the American Sewall Wright, who in the West are considered the founders of the neo-Darwinian school. The American evolutionist Ernst Mayr states that Timoféeff was largely responsible for the evolutionary synthesis that occurred in Germany in the 1930s.

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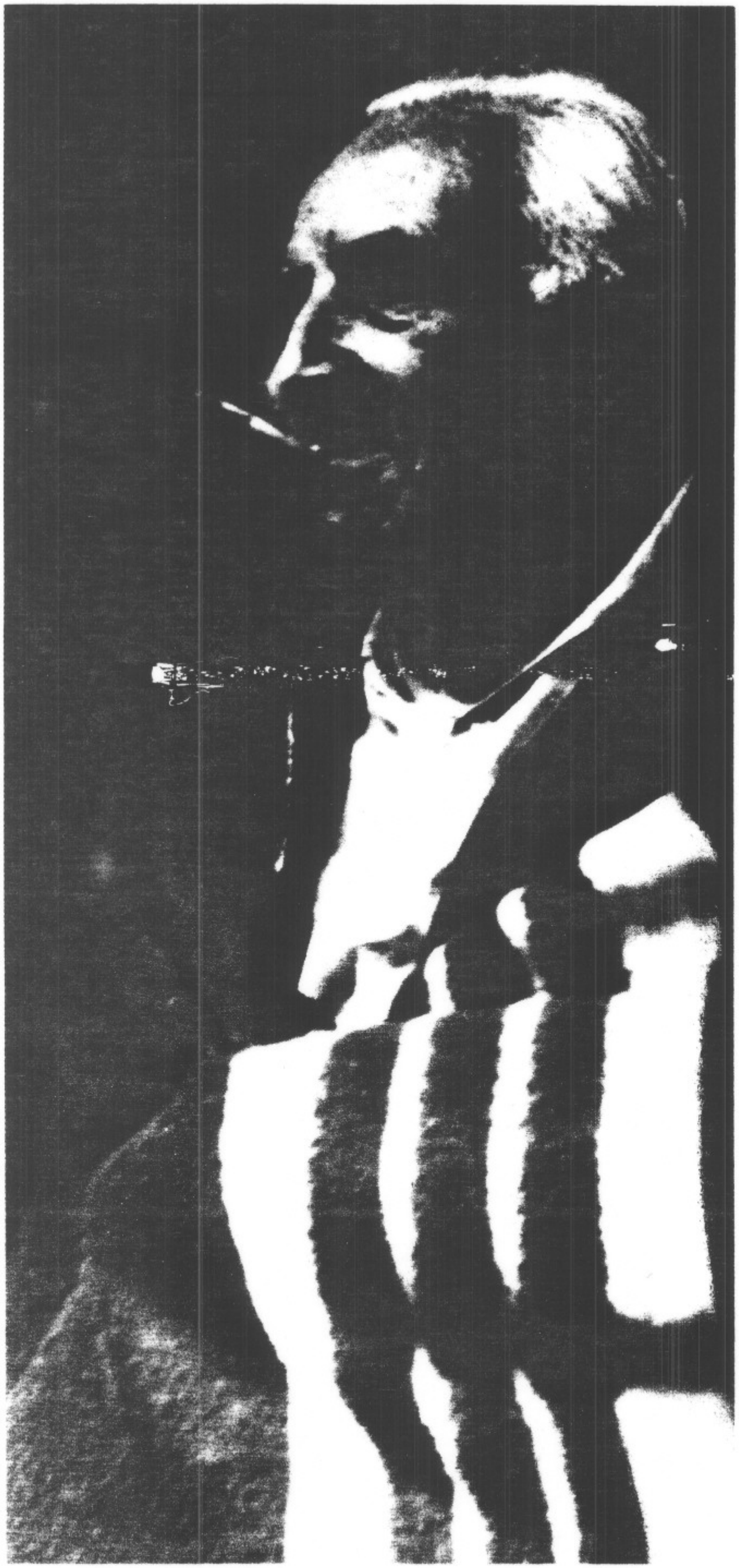
TIMOFÉEFF-RESSOVSKY remained scientifically active throughout his tumultuous life. Here he is seen between lectures at Lake Miassovo in the 1960s.



Timoféeff's research group at the institute included prominent Russian, German, Romanian and Greek geneticists, who helped spread his influence. He also received a number of notable visitors, among them the population geneticist Adriano Buzzati-Traverso, who once brought along his students Luigi Luca Cavalli-Sforza (now a geneticist at Stanford University) and G. E. Magni (now at the University of Pavia in Italy). Buzzati-Traverso in turn influenced Antonio Prevosti of the University of Barcelona and, through him, a significant group of Spanish population geneticists.

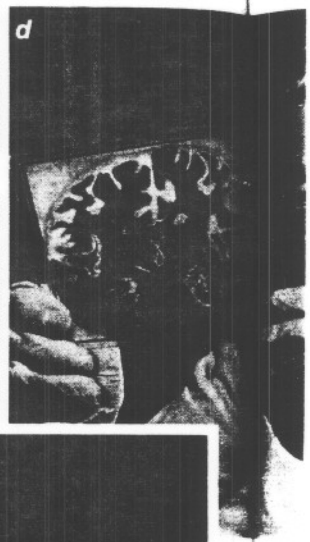
According to the neo-Darwinian view that shaped Timoféeff's work, natural selection can act only when genetic variability—which is generated by mutations—is present. Members of a population, whether birch trees, sparrows or fruit flies, usually show remarkable morphological constancy. Genetic variability is concealed because each individual has two sets of genes, one inherited from the male, the other from the female parent. Most mutations are recessive and therefore are not manifested in individuals who also possess a normal ("wild type") form of the gene. Chetverikov understood that because of this hidden store of variability, selection need not wait for the appearance of new mutations; they are already present in recessive genes in the population.

Timoféeff and his wife studied a natural population of the fruit fly *Drosophila melanogaster* to prove experimentally what their teacher had surmised. By inbreeding flies caught in nature, they produced individuals in which both genes encoded the recessive mutant trait. Their paper, published in 1927, offered the first proof of the existence of significant amounts of concealed genetic variability.

Timoféeff was guided to another important area of research by the Russian neo-Darwinian school's emphasis on the relation between genotype (the genetic constitution of an individual) and phenotype (its observable morphology, physiology and behavior). Being good naturalists, the Russians knew that natural selection targets the phenotype. Its relation to the genotype therefore is of primary importance for understanding how genetic changes occur in a population. Timoféeff and his wife, along with the Russian-born American geneticist Theodosius Dobzhansky, were among the first to study phenomena such as pleiotropy (the manifestation of a gene in more than one characteristic), as well as penetrance and expressivity (the frequency and degree, respectively, to which a gene is manifested).

These studies bolstered the view that

The Strange Career of Timoféeff-Ressovsky



The young **Timoféeff** (*a*) benefited from an education that prepared him both as a field naturalist and as a mathematical population geneticist. His teacher **Chetverikov** (*b*) helped him to recognize the connection between mutations, genetic variability and natural selection. The death of **Lenin** (*c*) in 1924 signaled a turning point in Timoféeff's career. **Vogt**, seen here with his wife (*d*), came from Germany to the Soviet Union to study Lenin's brain. There he met Timoféeff and offered him a position at the Kaiser Wilhelm Institute for Brain Research in Berlin. In 1926 Timoféeff moved to Germany, where he conducted his most significant research. Much of his work focused on understanding the nature of genetic variation; to this end he worked extensively with X rays. At one point, he collaborated with **Muller** (*e*), who later won the Nobel Prize for his discovery that X rays produce mutations.

several genes can influence the same characteristic, such as fecundity, and that the combined action of two mutant genes cannot necessarily be predicted by their actions when only one is present. Thus, geneticists came to realize that the genetic variability of a population should be viewed not as a group of noninteracting genetic entities (a model labeled "bean bag" genetics by Mayr) but as an integrated, cohesive whole.

Early in the 20th century many geneticists, following the ideas of the British biologist William Bateson, believed that recessive mutations resulted from irreversible genetic damage or loss. This view implied that evolution could not proceed further, because all mutations would lead to a reduction and loss of usable genetic material. Timoféeff demonstrated that mutant strains can undergo additional mutations, eventually reverting to dominant, wild-type forms. These so-called back mutations would be impossible if the appearance of a mutant were caused by a loss of genetic material.

One way to increase mutation rates is to irradiate organisms with X rays, a phenomenon first documented in 1927 by the American geneticist Hermann J. Muller. As a result of his student years in Russia, Timoféeff was inclined to use experimental techniques; he readily incorporated X ray-driven mutations in his studies. Some of his most important scientific achievements derived from his efforts to understand how X rays cause mutations.

Timoféeff's principal discovery was his observation of a linear relation between the total radiation dose and the number of mutations. Whether the dose was administered in a single shot, in several fractions or continuously at a low level over an extended period appeared irrelevant. The intensity of the dose did not affect the number of mutations produced. He also found no minimum dose below which mutations were not generated.

These properties suggested that X rays produce mutations much like bombs hitting targets. Timoféeff, along with his German co-workers Karl G. Zimmer and Max Delbrück, set out the target—or hit—theory based on this analogy. The classic "three-man paper" describing their work inspired Erwin Schrödinger to deliver his 1943 course of lectures, later published as the book *What Is Life?*, which helped draw many physicists to molecular biology.

In the target model, an X-ray photon expels electrons from atoms. These unbound electrons hit other atoms, dislocating more electrons, and so on. The free electrons eventually settle in the electron shells of other atoms. In this way, an X ray creates positively charged ions (atoms missing electrons) and negatively charged ones (atoms having a surplus of electrons). One ionization in a gene causes a mutation.

Timoféeff and his collaborators set out to estimate the size of a single gene by calculating the number of ionizations produced in a certain volume of tissue and by recording the increased number of mutations of a particular gene in that tissue. Timoféeff and his co-workers found the gene to be a sphere one to 10 microns across.

However crude this estimate may now seem, it had a tremendous conceptual impact at the time. Thomas H. Morgan's group at Columbia University demonstrated in 1910 that genes are located at fixed positions on chromosomes. Timoféeff rendered this description more precise: the gene has the dimensions of a large organic molecule.

One might expect that Timoféeff's group would have identified the hereditary molecule as being DNA. Investigators studying mutations caused by ultraviolet rays had already uncovered evidence pointing in that direction. Ultraviolet rays vary in their ability to cause mutations depending on their wavelength. Different substances have their own specific spectrum of absorption of ultraviolet rays. Starting in the mid-1930s in Germany and in the early

Political turmoil forced Timoféeff to make difficult decisions during the 1930s and 1940s. In Germany, the Nazis (*f*) provided generous funding for science but aggressively pursued eugenics and atomic weapons development. Meanwhile **Stalin** (*g*) ordered a series of repressive purges in the Soviet Union, and classical genetics was denounced. In 1937 Timoféeff refused an order to return to his homeland.

1940s in the U.S., researchers found that the ultraviolet wavelengths that most efficiently caused mutations corresponded to the absorption spectrum of DNA.

Biologists knew that chromosomes consisted of DNA and proteins. But nobody, Timoféeff included, suggested that the gene might be composed of DNA. Instead proteins were the favorite candidate for the molecule making up the gene. Two reasons led to that confusion. First, chemists at the time thought DNA had an invariant molecular structure. It seemed impossible that such a molecule could form the enormous range of genetic entities.

Second, in Germany knowledge of the chemistry of proteins was far more advanced than that of nucleic acids. By the 1930s many aspects of protein structure were understood. Geneticists knew that many different proteins could be constructed by combining the 20 kinds of amino acids in various linear assemblies. In 1932 the organic chemists Max Bergmann and Leonidas Zervas invented a method for synthesizing any small sequence of amino acids.

These prejudices and misconceptions prevented Timoféeff from recognizing the significance of the ultraviolet absorption spectrum of DNA. Until the fall of Berlin in 1945, his student Anton Kanellis worked on the relation between dose and number of mutations produced by ultraviolet rays but did not look at the effect of wavelength.

It is worth noting, however, that James Watson, who along with Francis Crick co-discovered the double-helix structure of DNA, was a student of Salvador E. Luria. Luria in turn closely collaborated with Delbrück, Timoféeff's co-author on the three-man paper. Thus, Timoféeff's intellectual legacy eventually contributed to the greatest biological discovery in this century.

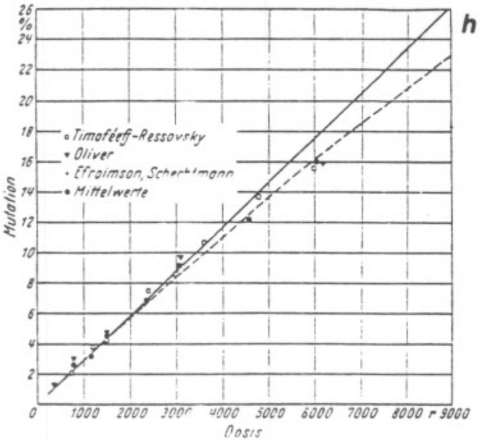
Timoféeff's scientific productivity during his years in Germany belies the difficult decisions forced on him by the political situation there and in the Soviet Union during the 1930s and 1940s. After the Nazis assumed power in 1933, they expanded support for genetic research but also required obeisance to the new regime. During the same period, Soviet officials had suggested several times that Timoféeff should return home. In 1937 they ordered him to do so. Timoféeff refused.

His decision in part reflected the deteriorating situation in the Soviet Union. Under the peasant agronomist Trofim D. Lysenko, the study of Mendelian genetics was outlawed in favor of his own belief that evolution occurs primarily through the inheritance of acquired traits. Kol'tsov had been dismissed as director of his institute, and Chetverikov had been arrested and exiled. The wider Stalinist terror was also well under way. In the mid-1930s two of Timoféeff's younger brothers and many of his wife's relatives were arrested; one of his brothers was executed. Thinking that Timoféeff might obey the order to return, Kol'tsov reportedly warned him, "Of all the methods of suicide, you have chosen the most agonizing and difficult. And this not only for yourself, but also for your family."

Timoféeff had other options, including an opportunity to work in the U.S. The Institute for Brain Research had long-standing ties to the Rockefeller Foundation. When informed that Timoféeff might be considering leaving Nazi Germany, the foundation helped to negotiate an offer of a position with the Carnegie Institution in Cold Spring Harbor on Long Island. To their surprise, he declined.

Timoféeff cited his responsibilities to co-workers and technical assistants who would lose their jobs if he left, qualms over moving his family and the inferior technical support—and social status—accorded to professors in America. "I heard that America too is getting chauvinistic," he added. He had commented to the French physicist Charles Peyrou that the working conditions of scientists in the U.S. were poor.

Like many a contemporary academic,



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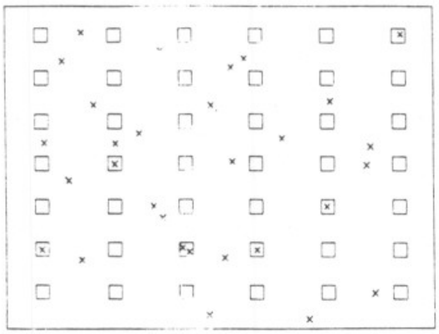

Mutation research by Timoféeff and others revealed a linear relation between X-ray dose and number of mutations (h). The target theory (i), published in 1937 by Timoféeff along with **Zimmer** and **Delbrück** (j), held that X rays cause mutations much the way randomly thrown bombs hit targets. This work enabled Timoféeff to make a crude but influential estimate of the size of a gene.

Timoféeff used the American offer to negotiate an improvement in his position at the Institute for Brain Research. The institute granted his department virtual autonomy, in everything except material requests. Timoféeff's independence later was further enhanced by his collaborations with scientists at the Auer Society, a huge chemical concern that was directly involved in war work and, in particular, with the production of uranium for the German atomic project. When Germany declared war on the U.S.S.R. in 1941, the possibility of returning home vanished.

At the end of World War II, the staff of the brain research institute was evacuated to Göttingen. Again, Timoféeff could have fled but instead chose to remain in Berlin, where he and a handful of his co-workers awaited the arrival of the Red Army. Some friends believe that Timoféeff expected to be acknowledged as an anti-Nazi. Furthermore, many German scientists, including Timoféeff, had speculated that it was better to collaborate with the Russians, who needed scientists, than with the Americans, who needed no one. He was in any case extremely reluctant to move to the West. Delbrück believed that Timoféeff knew he would be arrested but preferred serving a sentence in the U.S.S.R. to becoming a refugee. On the night before the Red Army arrived, Timoféeff told Peyrou that he realized his decision to stay in Berlin might prove fatal.

When the Soviet troops arrived, Timoféeff was arrested, but Avrami P. Zavenyagin, the deputy commissar of internal affairs, soon ordered him released. Zavenyagin recognized that Timoféeff's research in radiobiology and radiation genetics could be important for the Soviet atomic project. Timoféeff's situation changed yet again when a delegation from the Moscow Academy of Sciences arrived and ordered him rearrested.

This time Timoféeff was imprisoned. At one point, he was incarcerated in the same prison as Alexander Solzhenitsyn, who described in *The Gulag Archipelago* the scientific seminars that Timoféeff organized there. After a few months, Timoféeff was transferred to a labor camp in North Kazakhstan. For two years, his friends and family were unable to learn where he was or even whether he was alive.

Fortunately, Zavenyagin still had plans of his own. After a prolonged search, he finally located Timoféeff, who by then was close to death from starvation and nearly blind from vitamin A deficiency (he never fully regained his sight). In 1947 Timoféeff was transferred to a secret military research center near Sverdlovsk, in the Ural Mountains, where he organized a radiation biology laboratory. His wife and second son, along with some former co-workers, received word to join him.

During the next decade, Timoféeff developed the new field of radiation biogeocenology, the analysis of the distribution, accumulation and migration of radioactive isotopes in experimental and natural biological systems. Because of the secret nature of his work, he was one of the few Soviet scientists allowed to continue genetic research while Lysenko was in power.

In 1955, two years after Stalin's death, Timoféeff received amnesty. He moved to Sverdlovsk, where he organized a biophysics laboratory at the Ural Division of the Academy of Sciences; he also founded an experimental station and summer school at nearby Lake Miassovo. This school played a crucial role in keeping the tradition of classical genetics alive during Lysenko's reign. In 1964 Timoféeff moved to Obninsk (50 miles southwest of Moscow) to organize a department of genetics and radiobiology at the new Institute of Medical Radiology.

Although he received awards from several foreign scientific societies, Timoféeff was never allowed to travel abroad; he was also largely prohibited from publishing in popular scientific journals. At home, Timoféeff became something of a cult figure, but his con-

Timoféeff was able to have several prisoners and drafted workers reassigned to his genetics department on the basis of grossly inflated claims about their qualifications and potential contribution to the war effort. For some workers, it was also necessary to forge identity papers and other documents.

It is difficult to know what to make of Timoféeff's decision to continue his research in Nazi Germany. With the advantage of hindsight, it is obvious that he should have accepted the invitation to go to Cold Spring Harbor or that he should have tried to find a position elsewhere in Europe. But in the mid-1930s even some Jewish scientists were reluctant to leave Germany; for example, the geneticist Richard Goldschmidt left only after he was forcibly retired from his directorial position at the Kaiser Wilhelm Institute.

That said, Timoféeff's decision to stay was ipso facto a decision to cooperate with the Nazis. At minimum, it meant lending his scientific prestige to the regime in exchange for the considerable support the Nazis accorded to scientific research, especially experimental mutation research.

Overall, the political pressures on scientists in Nazi Germany were remarkably slight. Scientists did not have to become party members to obtain grants for biological research; Ute Deichmann and Müller-Hill have shown that party membership did not even necessarily confer an advantage. Timoféeff had acquired tremendous independence for his laboratory. And the Institute for Brain Research was located in the suburbs of Berlin, where the Nazi presence was somewhat less overbearing.

Even so, German politics necessarily intruded into life within the institute. In May 1933 the Nazi civil service law was extended to the Kaiser Wilhelm Society. All Jews were immediately dismissed except for institute directors, who were allowed to continue through 1935. Vogt, the director of Timoféeff's own institute, was forced from his position in 1936 because of his anti-Nazi sympathies.

The Nazis' presence is also revealed in various compromises that Timoféeff made with the regime. He participated in a course of lectures for S. S. doctors, although he apparently only gave technical lectures on mutation research. He signed official correspondence "Heil Hitler." Timoféeff occasionally published in Nazi medical journals such as *Zeil und Weg* (*Ends and Means*) and *Der Erbarzt* (*The Genetic Doctor*), in which he wrote of the need to identify the heterozygous carriers of genetic diseases, those having one mutant set of genes. Because most deleterious genes are hidden in apparently normal individuals, he explained, an effective program to reduce the incidence of genetic disease requires a method to detect such carriers.

Timoféeff never specified what measures should have been taken if these carriers were identified. Even so, such research seemed to lend support to Nazi racial hygiene theories, which pronounced the importance of purifying the German genetic stock. The Nazis used that doctrine as a rationale for exterminating "impure" people, particularly the Jews. Timoféeff's research on radiation biology was also seen as relevant to understanding the possible effects of atomic weapons on a human population.

Timoféeff's relation with the Auer Society and with researchers at the Kaiser Wilhelm Institute for Physics has inspired charges that he was involved with the German atomic project. Timoféeff's group at the Institute for Brain Research did pursue studies of radiologic protection and neutron-dosimetry that were financed by Walter Gerlach, the director of Germany's program of atomic research. But the atomic project was not simply an effort to build a bomb; rather, it was a broad enterprise that included many civilian applications, such as the generation of nuclear energy. Timoféeff seems never to have been directly involved in weapons development, although he worked with people who were.

Timoféeff was closely associated with a number of scientists, including Nikolas Riehl (the Russian-born chief chemist of the Auer Society) and the physicist Pascual Jordan, who worked on weapons-related research. Riehl insists that their work connections arose from the fact that many physicists were interested in biophysical problems and that Timoféeff had "no relationship whatsoever" to weapons development.

Perhaps the most serious charge against Timoféeff originated with a remark in Müller-Hill's review of *The Bison*. Müller-Hill noted that some of Timoféeff's collaborators injected human subjects with radioactive thorium X (now known as radium 222) to find out how long it would remain in the body. These experiments were conducted at Timoféeff's institute and with his knowledge. The researchers did not identify their subjects or say how large a dose they injected.

The idea that the dosage was kept secret has gained wide currency even though at least two published articles explicitly state that the experiments involved a dose of about 30 microcuries of thorium X. One Soviet author recently calculated that the administered dose of thorium X would have been lethal. He based this shocking claim on a set of radiation standards published by R. D. Evans, a leading authority on radiation therapy. But Evans examined the effects of exposure to radium 226, which has a half-life of 1,600 years; the half-life of thorium X, in comparison, is 3.64 days. Because of its long half-life, radium 226 releases a vastly greater total amount of radiation during the time it resides in the body. In fact, Evans reports that a dose of 30 microcuries of thorium X should produce no significant health effects.

The controversy over Timoféeff's actions continues to the present. In 1988 the Soviet government denied an application for his rehabilitation on the grounds that Timoféeff had conducted research that enhanced Fascist military power and that he therefore had "betrayed the motherland by going over to the side of the enemy." But on October 16, 1991, the procurator general of the U.S.S.R. asserted that there had been no legal basis for the original charge of treason issued in 1946.

Whatever the ultimate legal and moral judgment on Timoféeff, his scientific achievements are undeniable. He made noteworthy contributions to the understanding of the nature of the gene, genetic variability and the biological effects of exposure to radiation, work whose value has not been adequately acknowledged in the West.

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