Trypanosoma cruzi, cancer and the Cold War

Trypanosoma cruzi, *câncer e a Guerra Fria*

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Abstract

In the summer of 1946, the international community of cancer researchers was inspired by the announcement that two Soviet scientists, Nina Kliueva and Grigorii Roskin, had discovered anticancer properties in culture extracts made from the South American protozoan, *Trypanosoma cruzi*, and had produced a preparation – named after its discoverers KR – which showed clear therapeutic effects on cancer patients. Research teams from various countries enthusiastically pursued the promising new line of investigation. The story of the rise and fall of interest in the anticancer properties of *T. cruzi* in different countries suggests that during the second half of the twentieth century, the Cold War competition between the superpowers played an important role in shaping the research agendas of cancer studies.

Keywords: Nina Kliueva; Grigorii Roskin; cancer research; Trypanosoma cruzi; Cold War.

Resumo

No verão de 1946, a comunidade internacional que desenvolve pesquisas sobre o câncer, inspirou-se no anúncio de que dois cientistas soviéticos, Nina Kliueva e Grigorii Roskin, descobriram propriedades anticancerígenas em cultura extraída do protozoário existente na América Latina, o Trypanosoma cruzi *e produziram um preparado que foi denominado com as iniciais KR – em sua homenagem. Grupos de pesquisadores de diversos países buscaram com entusiasmo as promessas dessa nova linha de investigação. A história da ascensão e queda do interesse nas propriedades anticâncer do* T. cruzi *em diferentes países sugere que durante a segunda metade do século 20, a Guerra Fria teve um papel importante na definição das agendas de pesquisas sobre o câncer.*

Palavras-chave: Nina Kliueva; Grigorii Roskin; pesquisa em câncer; Trypanosoma cruzi; Guerra Fria.

In the summer of 1950, the *Annals of the Brazilian Academy of Sciences* carried an unusual article. Submitted jointly by Carlos Chagas Filho, director of the Instituto de Biofísica (Institute of Biophysics) at the Universidade do Brasil (University of Brazil) in Rio de Janeiro, and Hertha Meyer, head of the institute's histological laboratory, the article described (in English, not Portuguese) their experiments growing several strains of *Trypanosoma cruzi* in the tissue cultures of normal chicken cells and spindle cell sarcoma (Meyer, Chagas, 1950).[1] Carlos Chagas Filho, the younger son of the discoverer of *T. cruzi*, had, unlike his brother Evandro, shown little interest in his father's favorite protozoan, not to mention cancer: his own and his institute's main subject of investigation was the electrogenesis of an electric eel endemic to the Amazon, the poraque (*Electrophorus electricus*) (Chagas, Carvalho, 1961). Although Hertha Meyer had conducted research on the lifecycle of various parasitic protozoa, including *T. cruzi*, in the tissue cultures of chick embryo cells, she had never before studied cancer (Meyer, Oliveira, 1948). Why would these researchers spend their time and energy and the institute's resources on a subject so remote from their personal interests? And how did they come up with the idea that *T. cruzi* might have any relation to cancer?

In an ideal world, scientists would set their research agendas according to their intellectual interest in uncovering the 'secrets' of nature. In the real world, research agendas are shaped by a variety of contexts (social, political, economic, etc.) in which science and scientists exist at particular times and places. In the second half of the twentieth century, the overriding context for scientific development around the world was the Cold War. When considering Cold War science, what immediately springs to mind is the superpowers, the arms and space races, nuclear secrets, national security, and 'atomic' spies. Historians have studied in detail the so-called 'academic-military-industrial complex', focusing in particular on the three disciplines of physics, mathematics and chemistry that were needed for the development of nuclear weapons, rockets and space exploration.[2] At the same time, for the most part they have assumed that those scientific disciplines that had no immediate military or security application were 'untouched' by the Cold War. For instance, a recent collection on Cancer in the Twentieth Century contains not one reference to the Cold War (Cantor, 2007). Even those few works that deal with the Cold War history of social and biomedical sciences focus almost exclusively on their possible military and national security applications (Rasmussen, 1997, 2002; Creager, 2006[3]). Similarly, although some historians of science have argued forcefully for the expansion of the geographical 'boundaries' in studies of Cold War science, the majority of historical work on the subject still examines, almost exclusively, events and developments within and between the two superpowers – the USSR and the USA – and their European satellites.[4]

In this article, I suggest that Cold War influences can be detected in the research agendas of even such obviously 'non-military' sciences as parasitology and oncology, and that such influences extended beyond the 'usual suspects' in the stories about Cold War science, reaching many other settings. Even though the story presented below touches only tangentially on certain events in such countries as Brazil, Uruguay and Chile, I believe there is a bigger story to be uncovered behind these events, a story that could illuminate the Cold War context of the history of oncology and of science in general in

South America. Far from attempting to provide definitive answers to the variety of questions it raises, this article aims at stimulating further explorations of Cold War biomedical sciences, particularly in South American settings.[5]

Trypanosoma cruzi and cancer in the Soviet Union

The idea that *T. cruzi* might affect malignant tumors originated in the late 1920s in Soviet Russia.[6] In 1931, an article entitled "Protozoan infection and experimental cancer" appeared on the pages of the most prominent periodical devoted to cancer studies, *Zeitschrift fur Krebsforschung* (Roskin, Exempliarskaia, 1931). Authored by a professor of cytology at Moscow University, Grigorii Roskin, and one of his numerous students, the article described an interesting phenomenon – the mutual inhibition of implanted malignant tumors and trypanosome infection in mice – and suggested that trypanosome infection might be used as a cancer cure.

This discovery did not stem from an unexpected, accidental observation, as is often the case with similar discoveries[7]; it was the result of extensive research and carefully planned experiments. At that time, physicians employed three major methods of cancer treatment: surgical excision, radio- or X-ray-irradiation and chemotherapy, the use of chemical substances derived from inorganic poisons, such as lead and arsenic. Roskin decided to take a different approach, which he named biotherapy. His extensive cytological studies convinced him that malignant cells might differ from normal ones in a number of biological characteristics, including their immunological specificity, sensitivity to poisons and toxins, and the penetrability of their membranes (Roskin, 1930). These differences, he theorized, could provide an entry-point for finding a biological agent that could selectively destroy cancerous cells without also damaging normal ones.

For Roskin, such a biological agent was right at hand. In the 1920s, concurrently with his research on cancer, Roskin had conducted a broad study of various parasitic protozoa, particularly trypanosomes.[8] This group includes such dangerous parasites as *T. gambiense*, which causes sleeping sickness in Africa; *T. pecaudi*, *T. equiperdum*, and *T. suauri*, which cause fatal diseases in cattle, horses and camels in different parts of the world; and *T. cruzi*, which causes Chagas' disease in South America. All trypanosomes are extremely aggressive to their hosts, and Roskin thought that if they affected healthy organisms so profoundly, their effect on tumors could perhaps be even greater.

The idea of employing one disease to cure another has a very long history, and reports of attempts to use acute infections to cure malignant tumors date back to as early as the 1880s. But a more immediate influence on Roskin was probably the discovery of malariotherapy. In 1927, Austrian psychiatrist Julius Wagner-Jauregg received a Nobel Prize "for his discovery of the therapeutic importance of malaria vaccination in cases of dementia paralytica" (Julius Wagner-Jauregg, 1938). It was believed that malariotherapy stimulated the organism's immune system so effectively that it began combating not only malaria, but also tertiary syphilis that caused paralysis. This kind of stimulation of the immune system was apparently non-specific and was tried against a variety of diseases, including cancer.[9] Malaria is a protozoan infection caused by the parasite, *Plasmodium*,

which invades red blood cells. It was probably malariotherapy that inspired Roskin to search among other protozoa – trypanosomes – for a biological weapon against cancer.

Roskin chose one particular species for his experiments, *T. cruzi*, a choice that may also have been prompted by malariotherapy. *T. cruzi* has a very peculiar lifecycle, bearing certain similarities to that of the malaria plasmodium. Unlike its relatives, which live and reproduce in the host's blood stream, *T. cruzi* migrates into various organs, such as the heart, liver and spleen, where the parasite invades the cells (as does the malaria plasmodium) and reproduces. This attraction to particular organs is what led Roskin to hypothesize that, due to certain biological specificity, tumors could be particularly attractive for the parasite.

Roskin's experiments seemed to confirm the idea. He implanted mice with the Ehrlich carcinoma and simultaneously infected them with the trypanosome. At first, in experimental animals, both the infection (the number of trypanosomes seen under the microscope) and the implant grew. But it also appeared that they inhibited each other: tumors in control animals (not infected with the trypanosome) grew faster than tumors in experimental ones, and trypanosome-infected mice with tumors lived longer than infected mice without implants. Later, the infection continued to grow and eventually killed the mice, while the tumors diminished and disappeared. In controls, the growth of the implants continued and eventually killed the mice. Out of the 45 mice used in the experiment, the implants completely disappeared in 30 of them, while in the rest (15), the implants showed a clear reduction in size; all 45 control mice died of tumors. "Trypanosome infection – Roskin concluded in 1931 – had a biotherapeutic effect on the growth of carcinomas in mice" (Roskin, Ekzempliarskaia, 1931, p.344).

But was this effect caused by the trypanosome, or was it just a by-product of serious illness and fever, as was the case with malariotherapy? Roskin addressed this question in two series of experiments, using a spirochete that causes relapsing fever (*Spirohaeta duttoni*) and another species of trypanosome (*T. equiperdum*). The results were negative: relapsing fever had no noticeable effect on mice tumors and *T. equiperdum* showed only a slight inhibition of the first stages of tumor development. Clearly, the influence of *T. cruzi* on malignant tumors essentially differed from that of the spirochete and of *T. equiperdum*. But how did *T. cruzi* affect tumors? Roskin found an answer to this question by viewing microscopic cytological preparations of the tumors from infected mice. What he saw was peculiar: the tumors appeared to have 'melted' and there were many trypanosomes gathered in their blood vessels. Furthermore, trypanosomes had often impregnated the tumorous cells themselves and the nuclei of these cells had clear signs of degeneration. This picture led Roskin to suggest that "here, the complex process of struggle between cancerous cells and trypanosomes unfolds before our eyes" (Roskin, Ekzempliarskaia, 1931, p.346).

Roskin set forth four hypotheses for the possible mechanism by which the trypanosome inhibited malignant growth. First, trypanosomes might disorganize the metabolism of the infected organism, and thus inhibit the development of tumors, which, according to a belief common at that time, required a large and possibly specific supply of materials from the host organism. Second, like malariotherapy, trypanosome infection might stimulate a non-specific immunological reaction, which could in turn affect implanted tumors. Third, trypanosomes might invade tumorous cells and directly destroy them.

Fourth, either trypanosomes excreted certain toxins that had a directly destructive effect on tumorous cells, or the host organism produced antibodies against trypanosomes (or their toxins), which simultaneously appear co-active against tumorous cells. Roskin stated that one or any combination of the four hypothetical factors might play a role in the inhibition of tumor transplants by trypanosome infection.

During the following years, with the help of his students, Roskin further developed the idea of cancer biotherapy and conducted numerous experiments to test his hypotheses. He showed that not only live trypanosomes, but also their extracts exhibited antitumor activity, supporting his hypothesis about the existence of trypanosome toxins. He tested a number of other protozoa and confirmed that only *T. cruzi* had a clearly inhibiting effect on various implanted tumors in mice. He also discovered that this effect was absent if the mouse's immune system was suppressed, which indicated the importance of the role of the immune system in trypanosome antitumor activity (Roskin, Romanova, 1935, 1936a, 1936b, 1937, 1938a, 1938b). In the mid-1930s, Roskin perfected the technique for extracting the toxin and, together with a doctor at a Moscow clinic, conducted preliminary trials of the toxin in patients with inoperable cancer. They chose three patients with cancer of the larynx and one with cancer of the esophagus, because changes in these tumors could easily be observed. In each case, the diagnosis had been confirmed by a biopsy. The toxin was injected directly into the tumors in increasing doses on every other day for a period of one to two months. In all the patients, a pain-relieving effect, a reduction of the tumors, and a subsiding of inflammation and bleeding were noticed. Roskin came to the conclusion that the trypanosome toxin indeed had a curative effect on malignant tumors in human patients. He published his findings at the end of 1939 (Bongard, Roskin, 1939). The same year, Roskin's wife, Nina Kliueva, a microbiologist, immunologist and specialist in the production of vaccines, joined her husband's quest to convert his laboratory techniques into an industrial process that would allow the manufacture of a stable, effective and cheap preparation from *T. cruzi*.

His wife's support notwithstanding, Roskin's findings attracted little if any attention from clinicians and researchers involved with cancer studies either in Russia or abroad. At that time the oncological community was concerned with other issues: X-ray- and radiotherapy, studies of carcinogens and the perfection of surgical techniques. In addition, the beginning of World War II interrupted Kliueva and Roskin's work, turning their attention to the more pressing problems of combating infectious diseases and producing urgently needed vaccines against such intestinal infections as typhoid and dysentery for the Soviet army. As a result, the culture of *T. cruzi* kept at Roskin's lab at Moscow University since the early 1930s was lost. For a time, it seemed as if the idea of cancer biotherapy was lost, too.

"U.S., Soviet to share research in cancer"

Curiously, it was the war that prompted the revival of Kliueva and Roskin's research, and this time it attracted unprecedented attention in Russia and abroad, particularly in the United States. The wartime alliance between the Big Three – the United Kingdom, the

United States, and the USSR – revived contact between Soviet and Western science, particularly in the field of biomedicine, which had been curtailed during the 1930s. In late 1943, the Western Allies sent a joint medical mission to the Soviet Union (Hastings, Shimkin, 1946). It included two US scientists: A. Baird Hastings, professor of physiological chemistry at Harvard University and a member of the medical committee of the US Office of Scientific Research and Development, and Michael B. Shimkin, an oncologist from the National Cancer Institute (NCI) and the personal envoy of the US Surgeon General. Representing the British were Howard Florey, the 'father' of penicillin, and his assistant, A.G. Sanders. The group arrived in Moscow in February 1944 and spent a month there establishing contact with various Soviet medical institutions and scientists. One result of the mission was an exchange of materials and publications relating to antibiotics.[10]

This allied mission also played a key role in the revival of Kliueva and Roskin's research: it proved instrumental in arranging for a delivery to Moscow of fresh *T. cruzi* cultures from the Wellcome Laboratories of Tropical Medicine in London, which allowed the couple to resume their work in early 1945. It also alerted Western scientists to their progress in developing a cancer cure by encouraging an exchange of publications between Soviet and Western scientists. In the spring of 1944, Soviet medical officials asked Roskin to present some of his work for publication in the United States. Roskin prepared an article on "The toxin therapy of experimental cancer," which summarized his prewar experiments with *T. cruzi*, and later that year forwarded it to the United States.[11] In the summer of 1946, Roskin's article appeared in the leading US cancer journal, *Cancer Research* (Roskin, 1946, 1946-1947).

However, even before the publication of the article, Roskin's research attracted the close attention of American oncologists. Studies into the effects of various bacterial products on malignant tumors had a long tradition in the United States. Begun in the 1890s by William B. Coley, who had described the positive effects of bacterial toxins (obtained from *Streptococcus erysipelas* and *Serratia marcescens*) on human tumors, this line of research was carried on in the late 1930s and early 1940s by Murray J. Shear, head of the chemotherapy department at the National Cancer Institute (NCI).[12] Shear conducted a large series of investigations on the effects of a toxin obtained from *S. marcescens* on human and animal cancer, demonstrating that the culture filtrates containing the toxin produced hemorrhages and the subsequent necrosis of tumors. Shear identified an active fraction of the toxin as a large polysaccharide molecule and conducted a thorough study of its composition. Unfortunately, the clinical trials of the polysaccharide showed severe side effects, which prevented any therapeutic use of the toxin as a cancer cure.[13]

In 1944, Shear was organizing a large interdisciplinary and cross-institutional research program in cancer chemotherapy (Shear, 1947). In surveying the available literature, he came across a reference to one of Roskin's articles describing the effects of the trypanosome toxin on experimental tumors. Shear became very interested in Roskin's findings, which resonated so well with his own work, and soon learned much more about the Russian research. It seems likely that the manuscript sent by Roskin to the United States in 1944 reached Shear, and he might even have reviewed it for *Cancer Research*. The news of the Russian developments certainly affected Shear's thinking about the chemotherapy program he was creating at that time. He invited a protozoologist, Theodore S. Hauschka, from

Philadelphia's Lankenau Hospital, to join the program in order to duplicate Roskin's research and, if successful, to expand it.[14] Based on Roskin's article, Hauschka conceived a plan for extensive investigation and on March 22nd, 1945, submitted it to Shear for approval. Shear incorporated his proposal into the joint chemotherapy program. Hauschka quickly organized a small research group in Philadelphia, which enthusiastically launched a project on Protozoa and Cancer. They soon began preliminary experiments in collaboration with several NCI researchers.[15]

Hauschka immediately tried to contact Roskin. On May 22nd, 1945, he sent Roskin a long letter, telling his Soviet colleague about Shear's program on tumor chemotherapy and his own role in the program.[16] Hauschka mentioned that he had collected six different strains of *T. cruzi* and would like to reproduce Roskin's technique as closely as possible. He requested additional information on the strain used in Roskin's experiments and asked whether it "would be possible to obtain a culture" for his investigations. Apparently, Shear sent Roskin a similar letter, for later that year he received several reprints of Roskin's earlier publications from Moscow.[17] In January 1946, Roskin informed the American oncologists about the ongoing clinical tests of the new preparation, named KR after its authors, which Kliueva had developed from the trypanosome. Roskin also notified them that he was writing a book with his wife about "the biotherapy of malignant tumors," and promised to send them a copy as soon as it was published. Roskin kept his US colleagues informed of the progress of his research and regularly sent Shear reprints of his latest publications.[18] Shear, in turn, had them immediately translated into English and recommended for publication in the United States.[19]

In the spring of 1946, Kliueva and Roskin's research on "preparation KR" made headlines in the Soviet press and found its way into the Western media: in late March, several American radio stations broadcast stories about a "miracle cure" discovered by the Soviet scientists. Furthermore, reports on KR disseminated through the USSR's diplomatic network reached as far afield as Uruguay. As Roskin wrote to Shear on April 28th, "it is not our fault, but now our experiments have gotten into the newspapers, and Professor Kliueva and I greatly fear that we will be perceived as charlatans who promise 'miracle cures' by mysterious preparations to the terminally ill".[20] This publicity indeed resulted in a flood of letters from American doctors, patients and their relatives to the US Embassy in Moscow with appeals for information and, if possible, the preparation itself.

This pressure from home led the US Ambassador to the Soviet Union, Walter B. Smith, to investigate the matter personally. In early June, in an attempt to secure access to the KR preparation for American patients, he paid visits to several high-ranking officials at the USSR Academy of Medical Sciences and the Ministry of Public Health (Minzdrav). Smith even met the authors of the reported discovery, Kliueva and Roskin, who told him that the preparation was being produced in very small quantities and was not available for the general public.[21] Obviously impressed by what he had learned, Smith approached the Minzdrav with a formal proposal to organize a collaborative US-Soviet project to study KR, saying that the US would provide the funding for the project and all the necessary equipment and materials. In mid-July, Smith sent a package of materials labeled A Soviet Cancer Remedy to the US Secretary of State.[22]

During the summer, KR research became the focus of close attention by the US medical and popular press.[23] KR became a showpiece of Soviet medical science and was demonstrated to all visiting scientific delegations from the United States. The 'father' of streptomycin, Selman A. Waksman, who visited Moscow in early August 1946, learned about Kliueva and Roskin's research and noted it in his account of his Russian visit (Waksman, 1947). Later that month, the president of the American-Soviet Medical Society, microbiologist Stuart Mudd, came to the USSR and visited Kliueva and Roskin's laboratory.[24] Upon his return home, Mudd described this visit as "a high point scientifically" of his entire tour through the Soviet Union (Mudd, Mudd, 1946, p.210).

In the fall, the publicity of the KR research received a new boost, spurred by a visit by several Soviet medical specialists to the United States. In early May 1946, the US Surgeon General had invited the academician-secretary (the CEO) of the USSR Academy of Medical Sciences, Vasilii Parin, to come to the United States as a special consultant for the US Public Health Service. The Minzdrav seized the opportunity, sending along its own delegation: three prominent oncologists were to accompany Parin on his tour. Ambassador Smith took personal charge of arranging visas for the Soviet oncologists as a way to promote similar visits by American scientists. In his letter to the Minzdrav, Smith expressed the hope that the visit would be "of great mutual benefit" and that it would also be possible "for American cancer research workers to visit the Soviet Union in the near future to study Soviet research and development in this field".[25]

In early October, Parin left Moscow for the United States. On the eve of his arrival, the *New York Times* published a lengthy article on the KR research by its Moscow correspondent (Middleton, Oct. 11 1946). It was supplemented with another article, reporting that the NCI had undertaken "to carry out the Soviet experiments [with KR] in this country and check on their claims" (Laurence, Oct. 11 1946).[26] During the next few days, KR figured prominently on the pages of the American press.[27] To present the Soviet achievements to his American peers, Parin brought with him a copy of Kliueva and Roskin's book manuscript "The biotherapy of malignant tumors" and samples of the KR preparation, which he forwarded to the NCI. Together with the three Soviet oncologists, Parin spent nearly three months visiting medical schools and clinics around the US. Wherever he went, he was repeatedly asked about the present status of KR research and its prospects.[28] He usually gave a brief outline of Kliueva and Roskin's work and stressed that it was only "at the experimental stage", noting that "publicity about KR has been exaggerated". According to reports in the American press, he asserted, "you would have thought that the problem was already solved. ... That is not the case. ... We can decide whether KR is good for treatment only after some years [of] work with it".

The Soviet physicians greatly enjoyed their American trip, and it seemed that Ambassador Smith's hope of promoting mutual visits by Soviet and American oncologists would come true. In an interview before his departure for home, published by the *New York Times* under the evocative title, "U.S., Soviet to share research in cancer", Parin announced that "an exchange of cancer research specialists between Russia and the United States probably will take place in the near future" (U.S., Soviet to share…, Jan. 18 1947). Indeed, the US oncologists invited a large group of their Soviet colleagues, including, of course, Kliueva

and Roskin, to attend the fourth International Cancer Research Congress scheduled to meet in September 1947 in St. Louis, Missouri. In their turn, as another article in the *New York Times* reported, the Soviet oncologists arranged for reciprocal visits of Soviet and American scientists. The newspaper stated that three delegates from the NCI were scheduled to leave for Russia in two weeks (Russian physicians…, Dec. 24 1946).

The three delegates were Theodore Hauschka, Murray Shear and Michael Shimkin. They had applied for visas to come to the Soviet Union and meet Kliueva and Roskin "for the purpose of discussing our experimental results and of exchanging data".[29] Shimkin informed the Soviet embassy that "the National Cancer Institute would like to send a committee of experts to Moscow to consult with Professors Kliueva and Roskin regarding their announced treatment of cancer with extracts of trypanosomes".[30] By the time the Soviet physicians had ended their US tour in January 1947, it seemed that the US scientists would finally get the chance to see Kliueva and Roskin's experiments, as it were, *in vivo*. They were ready to fly to Moscow: they had taken inoculations against possible infections and had even bought sheepskin coats and fur caps in anticipation of the "terrible Russian winter".[31] The US Embassy in Moscow also continually pressured the Soviet side regarding the visit of the American oncologists.[32] But the 'negotiations' among various Soviet agencies over the visit dragged on. On February 4th, 1947, Ambassador Smith submitted a long letter to the Soviet authorities on the "cultural exchanges" between the two countries, which again raised the issue of the proposed visit by the three American oncologists to Kliueva and Roskin's laboratory.[33] Noting that "the achievements of Doctors Kliueva and Roskin in the field of cancer arouse the greatest interest in the United States", Smith stressed that "my conversations with Doctors Kliueva and Roskin, as well as other members of the Soviet Academy of Medical Sciences, created an impression that their recent contribution to the struggle against cancer may have very important consequences". He concluded that if the request of American scientists to visit Kliueva's laboratory could be granted, "the people and the government of the United States will be most grateful".[34] But the events of the next months shattered any hope of US and Soviet oncologists actually sharing their research.

Trypanosoma cruzi and cancer in the United States

The exchange of research materials between Soviet and US oncologists, exemplified by the transfer of Kliueva and Roskin's book manuscript on cancer biotherapy, precipitated a major shift in US-Soviet relations from World War II cooperation to Cold War confrontation.[35] A few days after his return from the United States, Parin was accused of "divulging a state secret" and in mid-February 1947 he was arrested as an "American spy". Meanwhile, in early June 1947, Kliueva and Roskin, though not arrested, were put on a show trial – "the honor court" – for their "anti-patriotic behavior". The main accusation at the trial was that they had shared the results of their research on KR with American oncologists.[36] Yet, despite the trial and the massive campaign that ensued against 'anti-patriots', which radically curtailed all contact between Soviet and Western scientists, Kliueva and Roskin were allowed to continue their research on *T. cruzi*. Indeed, the Soviet authorities built

a large institute for KR research and even orchestrated a delivery of fresh trypanosome cultures, this time directly from the source, Brazil. In the spring of 1947, the USSR Academy of Sciences mounted a scientific expedition aboard a special ship to observe a total solar eclipse that could be seen from Brazil. But the ship's doctor was given a special assignment: to catch several armadillos and collect their parasites in order to obtain new strains of *T. cruzi*. As it happened, the expedition landed in the very province, Minas Gerais, where Carlos Chagas had first found the trypanosomes.[37] Soviet KR research moved forward apace, albeit now in total secrecy. As I have detailed elsewhere, the main reason the Soviet authorities classified KR research 'top secret' in 1947 was its perceived symbolic value as a counterweight to America's atomic monopoly in the Cold War confrontation.[38]

Although news of Parin's arrest and the honor court did reach US diplomats stationed in Moscow, the US scientific community seem to have been unaware of the Iron Curtain that now separated them from their Soviet colleagues. The publicity accorded to the KR experiments in the US media during Parin's visit clearly enticed US researchers to take seriously both the idea of cancer biotherapy and the possibility that *T. cruzi* might have antitumor properties. In late 1946 and early 1947, in a search for anticancer substances, a group of biochemists from the William G. Kerckhoff Laboratories of the Biological Sciences at the California Institute of Technology tested several dozen microorganisms, including three species of trypanosomes (*T. brasiliensis*, *T. lewisi* and *T. cruzi*), in the tissue cultures of spontaneous and transplantable mammalian tumors. Although they did find several bacteria that retarded the growth of the tissue cultures, none of the trypanosomes exhibited any specific antitumor effect (Cohen, Borsook, Dubnoff, 1947).

As one might expect, Shear's chemotherapy program became a major locus of research on *T. cruzi*. Although frustrated in his attempts to personally visit Kliueva and Roskin in Moscow, Hauschka was encouraged by his early results that fell "in line with Roskin's data",[39] and actively pursued his research. In May 1947, at the annual meeting of the American Association for Cancer Research (AACR) in Chicago, Hauschka presented the results of his two-year study into the effects of six different strains of the trypanosome upon four varieties of tumors in mice (Hauschka, 1947b). Almost simultaneously, the NCI journal published a long article by Hauschka and his collaborators detailing the results of the investigations presented at the conference.[40] According to their findings, "infections of *Trypanosoma cruzi* significantly retarded the growth of three transplantable tumors," while "spontaneous breast adenocarcinoma … was slightly retarded in growth". Hauschka also reported that lysates of the heat-killed cultures of one strain showed no effect against the tumors, yet lysates prepared from another strain (obtained from the same source as Roskin's) "contained a tumor-necrotizing 'endotoxin'". This endotoxin, however, also produced "degenerative symptoms in liver, spleen and kidney", and test mice treated with this lysate died earlier than the controls.

In the summer of 1947, the *American Review of Soviet Medicine* carried the English translation of Kliueva's report delivered in early 1946 to the USSR Academy of Medical Sciences, describing the positive results of KR clinical tests on 18 patients with inoperable tumors.[41] Waldemar Kaempfert, the head of the *New York Times* science section, immediately published a lengthy summary of the article, along with his own commentary. Unlike

Hauschka and Shear, he was highly skeptical about the whole idea of cancer biotherapy, not to mention the results of the treatment of cancer patients with extracts of *T. cruzi*. "Not until KR has been made and tested here and the reports from Russia are confirmed – Kaempfert asserted – will physicians depart from the current surgical and radiological practice in dealing with malignant tumors" (Kaempfert, July 6 1947).

Kaempfert did not have to wait too long for news of US tests with KR. In early September the Fourth International Cancer Congress convened in St. Louis, Missouri. Although, of course, no Soviet scientists attended the congress, KR figured prominently in both the discussions at the event and their coverage in the popular press.[42] At a session on chemotherapy chaired by Shear, Hauschka delivered a long report on the endotoxin of *T. cruzi*.[43] He had little of substance to add to the report he had presented in May and the article published in the NCI journal that summer, but the tone of his presentation was much less optimistic. He reiterated that infection with live trypanosomes had 'retarded' the growth of tumors in experimental mice, but when the mice were treated with an anti-trypanosome drug to alleviate the symptoms of Chagas disease, "the previously inhibited tumors grew again". His appraisal of experiments with the endotoxin was even less hopeful. To produce his endotoxin Hauschka used mice infected with the trypanosome and had "to sacrifice 40-50 mice" for "each [of the] tumor-bearing mice under the treatment". Obviously, he could produce only enough endotoxin for experiments with mice on a very limited scale, and, as he put it himself, "clinical tests with *T. cruzi* material are neither indicated, nor in sight at the present".

In contrast to Hauschka's cautiously pessimistic assessment, William Malisoff, a former associate professor of biochemistry at the University of Pennsylvania and the director of the Longevity Research Foundation in New York City, presented a highly optimistic account of his own research on *T. cruzi* extracts. Apparently prompted by the publication of Kliueva and Roskin's articles in the *American Review of Soviet Medicine*, as well as Hauschka's article in the NCI journal, Malisoff had begun his experiments in the summer and his report had not been scheduled to be made at the congress. But, as a clear testimony to the widespread interest in KR among US oncologists, he was given a spot to present his studies at the congress. Malisoff's experiments with two strains of the trypanosome on two different types of mouse tumors completely confirmed the findings of the Soviet researchers.[44] He had carefully followed Kliueva and Roskin's technique in preparing the extracts and in treating the experimental animals, reporting that "within three days, following daily injections, the tumors soften and shrink and show signs of healing". He claimed that "ten injections suffice to ensure the regression or complete disappearance of the tumor". Furthermore, Malisoff's results seemed to contradict Hauschka's finding that the 'endotoxin' damaged the mice's internal organs. According to his data, in mice with tumors injected with the trypanosome extracts "all organs, especially the liver and kidneys, were found to be normal". He even performed special tests on mice without tumors, which received "four times the therapeutic dose without showing any damage to their organs". According to reports in the popular press, "next month Malisoff and colleagues will begin the first U.S. human tests of KR".[45] But just two months later, in November, Malisoff died suddenly

of a heart attack.[46] A few weeks later, *Science* published an article written on the basis of the report he gave at the St. Louis Congress.[47]

The popular press had received Malisoff's report enthusiastically, but the reaction of the professional community was much more cautious. Hauschka was clearly annoyed by the obvious contradiction of Malisoff's results to his own painstaking, two-year-long research. He asked Malisoff for samples of his strains of both *T. cruzi* and mice tumors. Malisoff obliged, and Hauschka immediately began experimenting with the new materials. He shared the samples with Shear's group at the NCI, which also launched its own investigation. In March 1948, at the AACR annual meeting, Shear presented the results of tests with the extracts of six different strains of *T. cruzi* (including the one used by Malisoff) on implanted sarcomas. According to Shear, "no gross evidence was observed of any effect on the tumors by the lysed trypanosome preparations. Histologic[al] studies revealed no significant difference between trypanosome-treated tumors and controls" (Belkin et al., 1949). The same month, investigators at the Research Laboratories of the pharmaceutical firm Parke, Davis and Co. reported their failure to inhibit the growth of carcinoma in rabbits treated with *T. cruzi* lysates (Gruhzit, Fisken, 1948). A few months later, Hauschka published the results of his experiments, which also disproved Malisoff's optimistic assessment (Hauschka, Goodwin, 1948).[48] In Hauschka's studies, the strain of spontaneous adenocarcinoma used by Malisoff "showed more than 50% tumor regressions in the untreated mice." Hauschka thus dismissed all of the results obtained by Malisoff with this tumor as "spontaneous regressions". The lysates of *T. cruzi* produced from Malisoff's strain "gave no sign of cancerolytic effect and did not prolong survival. On the contrary, deaths among the treated mice were more frequent than among the controls". Almost simultaneously, a group of New York-based researchers reported that they had observed no inhibition of tumor growth in mice with spontaneous mammary carcinoma (obtained from Shear) treated with whole culture lysate of *T. cruzi*. Yet in experiments with transplanted carcinoma (obtained from Hauschka), they noted "a greater degree of inhibition in the treated groups as compared with the control groups". Furthermore, the researchers found only "occasional damage" to the internal organs of mice treated with the lysate, thus undermining Hauschka's assertion regarding the toxic effects of the *T. cruzi* 'endotoxin'.[49] Despite all these contradictory results, practically every survey of chemotherapy published in the late 1940s mentioned the possible anti-tumor activity of the trypanosome extracts.[50] But in 1950, the NCI did not renew its grant for Hauschka's work with *T. cruzi*. Hauschka and his group moved on to study the immunology and genetics of cancer.[51] Other US researchers also seem to have lost interest in the protozoan: after 1950 no publication on *T. cruzi* and cancer appeared in the United States.

Trypanosoma cruzi, cancer and the Cold War

The Cold War profoundly affected all facets of life around the world. It spurred intense competition between the two superpowers – the Soviet Union and the United States – and the two great blocs – East and West – that they created, leaving some countries not directly involved in either bloc free to pursue their own interests by "playing both sides against

the middle". This competition played out in a variety of fields, ranging from sports to space exploration, weaponry to education, architecture to medicine. However, it is arguable that in no other field was this competition as fierce as it was in science. The Cold War not only enhanced the strategic importance of science as a source of new (particularly, military) technologies, but also gave it unprecedented symbolic value as a propaganda tool. It transformed scientists into strategic state assets – as an indispensable sources of new kinds of weaponry – and, at the same time, into potential state liabilities, as possible security risks able to divulge state military secrets to the enemy. It induced the state patrons of science all over the world both to considerably boost the funding and prestige of science and to impose much stricter controls over national scientific communities, particularly their international relations, than the world community had ever before experienced.[52] By enveloping scientific research with the impenetrable cover of secrecy, communication between scientists operating in the two blocs was disrupted, which had a major influence on their choice of research topics, subjects and methods in a variety of fields.

Cancer studies were obviously no exception. Even though research into the possible antitumor properties of *T. cruzi* continued in such disparate places as Chile, France and Uruguay, by the beginning of the 1950s US scientists had completely abandoned their studies of its once promising 'endotoxin'. The ambiguity of the results obtained by various investigators regarding its efficacy against experimental tumors played a major role in the discontinuation of this line of investigation in the United States, without it ever having reached the stage of clinical tests on human patients. The US studies had been conducted using different strains of the trypanosome on a variety of experimental tumors in different animals and tissue cultures, which greatly diminished the possibility of reaching a definitive conclusion. Certainly, the technical difficulties in cultivating the protozoan and producing its 'endotoxin' contributed greatly to the disillusionment about its possible clinical value.

More importantly, however, the experiments with *T. cruzi* represented just a tiny subset of the fast-growing chemotherapy program launched by the NCI in the late 1940s to screen tens of thousands of chemical and biological substances for their possible anti-tumor properties.[53] Inspired by and in many respects similar to the screening program for antibiotic-producing microorganisms, the race to find a 'cancer cure' prompted the emergence of a very particular research system. This system placed a premium on the quick testing of numerous substances on a strain of experimental tumor (standard for a particular laboratory) with minimal expenditure of time and resources in order to discard 'ineffective' and identify 'promising' substances for further in-depth investigations. Under this semi-industrial screening program, US oncologists could ill afford to 'waste' the time and resources necessary for cultivating *T. cruzi*, manufacturing its 'endotoxin', conducting detailed investigations of its properties, and comparing the effectiveness of 'endotoxins' produced from different strains of the protozoan on different types of experimental tumors. Besides, by the end of the 1940s, US researchers had identified several classes of substances, ranging from various hormones to folic acid and mustard gas derivatives, which seemed highly promising and thus attracted considerable attention and resources.

This situation might explain the appearance of Chagas and Meyer's article in 1950. It seems that the NCI simply 'outsourced' research on Kliueva and Roskin's claims regarding

the specific affinity of *T. cruzi* to malignant tissues to the Brazilian scientists: the study conducted at Chagas's Instituto de Biofísica was funded (and most likely directly instigated) by the NCI. Obviously, it was much cheaper and faster to conduct the experiments in Rio de Janeiro than in Bethesda or New York City: there was a ready supply of numerous strains of *T. cruzi* and Brazil's foremost histologist, Meyer, had developed a highly effective research system based on cultivating the trypanosome in embryonic tissue cultures. A thorough search of Brazilian archives might yet reveal Carlos Chagas Filho's reasons for agreeing to undertake this study, which clearly fell outside his personal area of interest. Perhaps he felt a family obligation to contribute to research on the protozoan discovered by his father and studied extensively by his older brother. But one cannot exclude the possibility that Chagas might well have seen this 'small favor' to US researchers as a means for building his personal alliance with the US scientific community, securing external funding for his institute and thus enhancing its domestic standing *vis-à-vis* other Brazilian institutions.

The ambiguity of the results and limited resources were certainly not the only factors that led to the curtailment of *T. cruzi* investigations by US oncologists. It would be fair to suggest that equally important was the complete silence on the part of the Soviet scientists, Kliueva and Roskin. The US researchers knew of a number of studies conducted by scientists in Europe (in Belgium, France, the Netherlands and Switzerland), and they even translated and republished some of them in the NCI journal.[54] The results of the European research, however, proved as ambiguous as the American ones. Some investigators reported the complete absence of any retardation of tumorous growth in experimental animals treated with either live *T. cruzi* or its lysates (Lob, 1949, 1950). Others noted some positive effects of the treatments, although such effects were not stable (Coudert, Juttin, 1950; Galliard, Brumpt, Martines, 1950). Yet, amidst all these research activities not a word came from the couple who had started it all. As US investigators pointedly observed in 1948, "at no time did we have detailed information regarding their [Kliueva and Roskin's] methods of *T. cruzi* cultivation and lysate preparation" (Spain, Malomut, Warshaw, 1948, p.136).

As of the end of 1946, all communication between Soviet and US researchers was effectively severed. As Stuart Mudd complained to the Soviet authorities in February 1948, "during 1947 the receipt of manuscripts [for publication in the *American Review of Soviet Medicine*] from the USSR fell off and finally ceased altogether; and the receipt of journals and books in the biological and medical sciences has become infrequent and small in amount".[55] Furthermore, during the time of the most intense investigation of and debates over KR in the West in the late 1940s, Kliueva and Roskin did not publish one single article on their research, even in Soviet periodicals. Unbeknownst to Western scientists, in 1947 the Soviet authorities classified research on KR as 'top secret' and four years later discontinued it altogether. We can only speculate about how exactly the US researchers interpreted the absence of information on KR from the Soviet Union, but it seems logical that one possible reading was that this once highly publicized preparation failed to live up to its initial promise; a situation not too infrequent in cancer research and, in this particular case, not too far from the truth. US researchers perhaps expected (not unreasonably) that if Kliueva and Roskin had proven the effectiveness of their preparation, the Soviet authorities would

not miss the propaganda opportunity presented by the announcement of such a development. This is certainly how Ambassador Smith read the situation. As he explained in a letter to the US Secretary of State in the spring of 1947, "Soviet Government and Soviet Academy of Medical Sciences feel that they may be on eve of an important discovery, for which they do not wish to share credit with any foreigners, although perfectly willing to share benefits".[56] In the spring of 1949, Ambassador Smith returned home from his Moscow assignment, and a few months later the *New York Times* serialized his reminiscences about his "three years in Moscow". Among many other events, he described his involvement with KR research and its authors (Smith, Nov. 25 1949). For the first time, the American public learned of Parin's arrest and Kliueva and Roskin's trial. But although Smith recounted details of his meeting with Kliueva and Roskin, as well as his praise of their investigation at the stage they had reached in the summer of 1946, he uttered not a word on the current state of KR research, which could easily be construed as evidence of its failure.

That Kliueva and Roskin's silence was an important factor in the fate of similar research in the West is clearly demonstrated by the dramatic change in the situation after their reappearance on the international scientific scene in the late 1950s.[57] The 'warming up' of the Cold War atmosphere enabled the scientists to revive and declassify their research in the Soviet Union. In 1957 they were finally able to publish results of their studies on KR conducted during the five years from 1946 to 1951 in a voluminous tome, entitled *The problem of anti-cancer antibiotics*.[58] The volume was reviewed by major international journals and generated a new wave of research. In 1963, the British publishing house, Pergamon Press, launched an English translation of the book. Based on Kliueva and Roskin's data confirmed by French investigators, the French pharmaceutical firm Institut Merieux produced and marketed a preparation from *T. cruzi* under the name *Trypanosa*. Not to be outdone by the French, the Soviet pharmaceutical industry produced and marketed its own preparation named Cruzin. Studies of the antitumor properties of *T. cruzi* again came to command the attention of researchers and clinicians around the world, including Brazil, Venezuela and Chile.

The Cold War not only involved science in the fierce competition between the superpowers, it also enveloped much of scientific research in a dark cloak of secrecy and made scientists objects and instruments of their respective national intelligence services. Historians are just beginning to explore the impact of secrecy on the development of science, nationally and globally. I hope that this article will stimulate further inquiries into how exactly Cold War competition and secrecy affected the choice of research priorities, the criteria for their adjudication, and society's control of their funding around the world. On a more specific level, I hope that this article will also encourage investigations into the effects of the Cold War on science in South American settings.

NOTES

[1] At that time this species was called *Shyzotrypanum cruzi*, see Hoare, 1972, p.332-380.

[2] The literature on the transformations of the three disciplines brought about during the Cold War and the role of military applications in this process is quite voluminous. See, for example, Mendelsohn, Smith, Weingart, 1988; Leslie, 1993; Lowen, 1997, and many others.

[3] See also a special issue of the *Social Studies of Science* on "Science in the Cold War", particularly the editor's introduction (Solovey, 2001).

[4] See, for instance, Krige, Barth, 2006.

[5] The Cold War history of South American science remains a grossly understudied area. To give but one example, in his examination of the development of the scientific community in Brazil during the twentieth century, Simon Schwartzman (1991) does not even mention the Cold War.

[6] For a detailed analysis of this story, see Krementsov, 2002.

[7] This was the case with the early use of bacteriotoxins, nitrogen mustard and folic acid antagonists as anticancer substances; see Zubrod, 1979.

[8] Roskin had been trained as a protozoologist and in the 1920s he headed the Protozoology Department in the Institute of Microbiology, Moscow.

[9] See Braunstein, 1929.

[10] See Ward, 1980.

[11] See the State Archive of the Russian Federation (hereafter—GARF), f. r5283, op. 14, d. 344, ll. 61-61 reverse, 64, 75.

[12] See Zubrod, 1984 and Löwy, 1994.

[13] See Hartwell, Shear, Adams, 1943, Shear, 1944, and many others.

[14] See Shear's correspondence with Hauschka in Murray J. Shear Papers, Box 21, held at the US National Library of Medicine (hereafter NLM).

[15] See Hauschka, 1947a and Rees, 1947.

[16] The original manuscript of this letter is preserved among Kliueva's papers held at the Archive of the Russian Academy of Medical Sciences.

[17] Shear Papers, Box 21, NLM.

[18] Shear Papers, Box 21, NLM.

[19] See Klyueva, 1946-1947 and Klyueva, Roskin, 1946-1947.

[20] G. Roskin to M. Shear, April 28, 1946. Shear Papers, Box 21, KR, NML.

[21] For the records of these meetings, see the US National Archives (hereafter USNA), 812, 1 Cancer.

[22] See USNA, 812, 1 Cancer.

[23] See KR for cancer, July 8 1946.

[24] See the Archive of Foreign Policy of the Russian Federation (hereafter AVP), f. 0129, op. 30, papka 189, d. 89, ll. 38, 44-48, 50-55. A large collection of various materials related to Mudd's trip to Russia is preserved in Stuart Mudd Papers held at the Archives of the University of Pennsylvania (hereafter UPA), Medical Microbiology, UPC 2, 9MM. For a historical account of the society's activities, see Lear, 1997.

[25] See USNA, 812. 1 Cancer.

[26] Similar article "from a correspondent in Moscow" dated October 12, 1946, appeared in JAMA (see The cancerolytic substance..., 1947).

[27] See Can cancer..., Oct. 12 1946, KR for cancer, Oct. 13 1946 and KR experiments, Oct. 20 1946.

[28] See Vaccine held cure..., Oct. 24 1946. The following quotations are from the report on Parin's speech in San Francisco (see Medical sciences..., Dec. 31 1946).

[29] AVP, f. 192, op. 13, papka 99, d. 47, ll. 106, 126-139.

[30] AVP, f. 192, op. 13, papka 99, d. 47, l. 126.

[31] See correspondence between Shear and Hauschka in Shear's papers, Box 21, NML.

[32] AVP, f. 0129, op. 30, papka 189, d. 89, ll. 27, 61, 68, 74-75; see also USNA, 812. 1 Cancer.

[33] For a Russian translation of the letter, see AVP, f. 0129, op. 31, papka 201, d. 96, ll. 9-12.

[34] Excerpts from the letter were soon published in the American press. See Middleton, Feb. 19 1947.

[35] For details, see Krementsov, 2007.

[36] For details, see Krementsov, 2002.

[37] This fact is described in the memoirs of a member of the expedition, astronomer Iosif Shklovskii (1991, p.44-67).

[38] For the subsequent development of Soviet research on KR, see Krementsov, 2002.

[39] See Hauschka, 1947a.

[40] See Hauschka, Saxe Jr., Blair, 1947.

[41] See Klyueva, 1946-1947.

[42] See, for instance, a special feature on the congress in In 10 or 15 years..., Sept. 15 1947.

[43] See Hauschka, 1947c.

[44] See Laurence, Sept. 6 1947. All the following quotations are from this source.

[45] See In 10 or 15 years..., Sept. 15 1947.

[46] See his obituary in *New York Times*, November 17 1947, p.21.

[47] See Malisoff, 1947.

[48] All the following quotations are from this source.

[49] See Spain, Malomut, Warshaw, 1948.

[50] See Gellhorn, Jones, Feb. 1949.

[51] See Hauschka, 1952 and Hauschka, Goodwin, Brown, 1951.

[52] See Doel et al., 2005.

[53] For details, see Bud, 1978, Zubrod, 1984 and Goodman, Walsh, 2001.

[54] See Jederloo et al., 1950.

[55] S. Mudd to A. Gromyko, February 12, 1948. Stuart Mudd Papers. Box 6. UPA.

[56] See NA, 812. 1 Cancer.

[57] For details, see Krementsov, 2002.

[58] For an explanation of the change in depicting their preparation from 'endotoxin' to 'antibiotic', see Krementsov, 2000.

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