Vaccine diplomacy during the Cold War (ii), heads or tails. Tails: Antonina Shubladze and the Soviet vaccine against acute encephalomyelitis and multiple sclerosis

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ABSTRACT

The most remarkable results of the collaboration in the field of medicine between the Soviet Union and Western countries during the Cold War were the oral poliomyelitis vaccine and the near-complete eradication of the disease worldwide, which are addressed in a first article. The counterpoint of the so-called vaccine diplomacy was the controversy that arose in the 1950s around the Soviet vaccine against acute encephalomyelitis and multiple sclerosis, developed on the initiative of Antonina Shubladze after the discovery of a virus associated with those diseases, belonging to the family *Rhabdoviridae*. The vaccine was used for several decades in the Soviet Union and occasionally in other countries. This article analyses its development and the reactions it caused in the Western world, especially in the United States through Albert Sabin. It is interesting to study the story of this treatment for multiple sclerosis, at a time when the current means for diagnosis and treatment of the disease were not available, as well as to analyse the strong discordance between data from its study in the USSR and in the West.

KEYWORDS

Vaccine against acute encephalomyelitis and multiple sclerosis, rabies virus, Antonina Shubladze, Albert Sabin, Cold War, Soviet Union, Western countries

Introduction

A previous article addressed soft diplomacy through medicine during the Cold War, citing the example of Sabin's oral poliomyelitis vaccine, which represented a success of the collaboration between countries, also thanks to the extraordinary outcomes in controlling the disease.[1] In this process, known as vaccine diplomacy,[2] such success was not enjoyed by the Soviet vaccine against acute encephalomyelitis and multiple sclerosis. Although the first mention of the subject was made in a British journal in 1946,[3] it did not attract the attention of Western researchers until the mid-1950s. In this article, we analyse the development of the vaccine in the Soviet Union under the leadership of Antonina Shubladze (1909-1993) and how it came to light and was studied in the Western world, a process that occurred at the same time as the development of the oral poliomyelitis vaccine. Albert Sabin (1906-1993) played a significant role in both processes.

Over the years, the aetiopathogenesis of multiple sclerosis had been associated with different viruses. This is the story of the Soviet Union's attempt to associate the disease with one virus, which was finally discovered to belong to the *Rhabdoviridae* family. This virus was used to manufacture a therapeutic vaccine, whose effectiveness and safety was questioned by some Soviet and many

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Figure 1. Mikhail Margulis.[5]

Western scientists. Despite this, it was used for several decades in patients with multiple sclerosis and acute encephalomyelitis in the USSR and post-Soviet states.

Material and methods

An exhaustive literature search was performed in different languages on the development of the Margulis-Shubladze vaccine and its impact in the Soviet Union and the Western world. The related correspondence stored in Albert Sabin's personal archive at the University of Cincinnati, which is freely accessible online, was also analysed. The review particularly focused on the terms acute encephalomyelitis, acute disseminated encephalomyelitis, multiple sclerosis, diffuse sclerosis, and disseminated sclerosis (the translation of the term frequently used in the Russian and Ukrainian languages to refer to this condition). We have also reviewed the lives of the main protagonists of this story, particularly that of Antonina Shubladze.

Results

The initial study

When the expedition of the Soviet virologists Mikhail Chumakov (1909-1993), Anatoly Smorodintsev (1901-1986), Marina Voroshilova (1922-1986), and Lev Lukin arrived in February 1956 at Albert Sabin's laboratory in Cincinnati, the latter was intrigued by the information they gave him on the development of a vaccine against multiple sclerosis by some of their colleagues.[4]

In 1946, the neurologist Mikhail Margulis (1879-1951) and virologists Valentin Soloviev (1907-1986) and Antonina Shubladze reported in the *Journal of Neurology, Neuropathology and Psychiatry* that they had isolated two identical virus strains in two patients diagnosed with acute disseminated encephalomyelitis at the Botkin Hospital in Moscow during the Second World War (Figure 1, 2 and 3).[5,6] The first was a 32-year-old man who was admitted in November 1942 due to headache, fever, paraparesis, and other acute neurological deficits; he recovered at four months but experienced relapses in June 1944 and March 1945. The second patient was a 38-year-old woman who was admitted in February 1943 due to signs of confusion and generalised weakness, who died after nine days of progression. The autopsy study performed by Margulis revealed disseminated foci of demyelination and miliary necrosis in the brain and brainstem. An aetiological study discovered the presence of two strains of the same filterable virus, one in the blood of albino mice inoculated with blood from the first patient after a second pass (Sv. strain) and the other after a first pass in the brain tissue of a mouse injected with brain tissue from the second patient (Ef. strain). These strains were identical, and different from the neurotropic viruses known to that date. Inoculation of the virus in the rodent brain caused similar central nervous system lesions to those of the second patient; subsequently, they developed a vaccine using rat brain tissue inactivated with formaldehyde. This vaccine was used to treat the first patient during his third hospitalisation in March 1945, after which he experienced a clinical remission that led to his discharge three months later, and continued receiving it on an outpatient basis. The patient may have presented multiple sclerosis rather than acute encephalomyelitis.[3]

This article, published in 1946, included the first mention in the international medical literature of the expression

acute disseminated encephalomyelitis.[7] Nevertheless, the majority of texts from the time continued using the term acute encephalomyelitis.

Subsequently, the authors confirmed that serum from 70% of patients with acute encephalomyelitis and from 50% of those with multiple sclerosis neutralised preparations containing the Sv. and Ef. variants of the virus, whereas only one patient out of 27 with other neurological diseases showed positive results. They classified this pathogen as the causal agent of acute encephalomyelitis and, given its serological specificity in patients with multiple sclerosis, assumed an aetiological equivalence between both neurological conditions. The authors believed that negative cases were caused by other unidentified viruses. Given the clinical and anatomopathological heterogeneity of these neurological disorders, positivity for the virus contributed to the diagnosis of doubtful cases.[3,8] These viruses were administered to mice, rats, guinea pigs, rabbits, dogs, monkeys, and chicken embryos. Demyelination was more marked in dogs and rabbits than in rodents, in which necrosis was the predominant feature. No inclusion bodies were identified in any model.[3,9]

Up to 1946, the vaccine had been used to treat 19 patients with multiple sclerosis and a few with acute encephalomyelitis. Diagnosis was essentially based on clinical signs and supported by tests of blood and cerebrospinal fluid (CSF), which were also used for virological studies. Autopsy studies were also performed in deceased patients. In the group of patients with multiple sclerosis, there was a significant clinical improvement in 11 cases, which was more pronounced in six of them. Among the eight cases not showing a positive response, two presented advanced clinical forms, one showed a rapidly progressive course, and five displayed moderately severe impairment. The treatment of the handful of patients with acute encephalomyelitis was successful. Clinical improvements were accompanied by a considerable increase in titres of antibodies against the virus in the plasma.[3]

These authors also published a monograph in 1947 summarising the research conducted to date on the subject.[10] Mikhail Margulis died in 1951, but his surname continued to be used in the titles of subsequent publications and in the name of the vaccine, known as the Margulis-Shubladze vaccine.

Figure 2. Antonina Shubladze in the 1930s.[6]

The virus and the vaccine

Shubladze's group isolated four identical strains of the virus (Sv., Ef., Vo., and Bul.), which were pathogenic in several experimental animals, in the blood and CSF of patients with acute encephalomyelitis. For the aetiological diagnosis of acute encephalomyelitis and multiple sclerosis, they continued using antibody neutralisation tests; for treatment, they used the vaccine manufactured from the formaldehyde-inactivated Sv. strain. The vaccine was also used to develop an intradermal allergy test as a complementary diagnostic technique.[8,11] In 1959, Shubladze isolated a fifth strain (the Reznik strain), which was more immunogenic.[12]

The virus was named OEMch (ОЭМч, ostrogo entsefalomiyelita cheloveka) in Russian,[12,13] EHA (encéphalomyélite humaine aiguë) in French,[14,15] HAE (human acute encephalomyelitis) in English,[12] and EHA

Figure 3. Valentin Soloviev on the expedition to the Far East, 1937. Source: ©Grodekov Museum.

(encefalomielitis humana aguda) in Spanish. In 1950, it was named *Demyelinisator hominis* and *Myelinophagus hominis*, but these names fell into disuse.[16,17]

The vaccine was made up of a 15% suspension of the brains of mice and rats infected with the Ef. and Sv. strains of HAE and euthanised in the acute stage of the disease; the virus was inactivated with a 0.2% formaldehyde solution. This product could be desiccated and stored for up to three years. It was created by Otar Andzhaparidze (1920-1996), a collaborator of Antonina Shubladze at the Ivanovsky Institute of Virology of the USSR Academy of Medical Sciences in Moscow. It was manufactured for several decades at the Mechnikov Institute of Microbiology and Immunology of the USSR Ministry of Health in Kharkiv.[8] It was subsequently manufactured using the Reznik strain.[12]

The characteristics of the virus were described by Antonina Shubladze and Sophia Gaidamovich (1921-2003), who showed that the virus was immunologically similar to the rabies virus, but was different in some aspects. Thus, they did not observe Negri bodies in the nervous cells of vertebrates infected with the virus, and the epidemiology, clinical symptoms, and vital prognosis were different than those of rabies in humans. In May 1956, they presented their experiences with the virus and the vaccine outside the Soviet Union during the First International Congress on Infectious Diseases, held in Lyon.[8,14,15]

The HAE virus showed a close association in terms of antigenic properties with the fixed and street rabies viruses, fox encephalitis (Tobolsk strain), and equine encephalomyelitis (strain no. 17). The latter two are extremely similar to the rabies virus, especially the fixed rabies virus, but are not pathogenic in humans. The histological symptoms of fox encephalitis included micronecrosis and demyelination, as is also the case with HAE. Margulis found demyelination foci in the spinal cord of rabbits infected with equine and fox encephalitis virus, and with the rabies virus.[8]

Association of the virus with multiple sclerosis

After the first serological findings, Shubladze's group additionally analysed 432 serum samples of patients with multiple sclerosis of different ages and with different disease duration and severity. At that time, the diagnostic criteria were essentially clinical. They observed a positive neutralisation reaction against the HAE virus in 142 patients (32%). Rutshevi et al.,[8] of Kharkiv, reported positivity in 26 out of 69 patients (38%).

Antibodies were present in all groups with multiple sclerosis, but predominated in those with moderate severity; titres increased with clinical improvement. Titres were higher in patients with progression times between one and five years, and more discrete in those patients whose disease had manifested less than a year prior.[8]

Shubladze's group reported positivity in 28% of cases in subsequent series. In patients seropositive for the HAE virus, they found an activation of specific cell immune reactions against the virus during relapses.[12,18]

Antonina Shubladze and Igor Barinsky (1937-2021) observed that the disease caused by the HAE virus in experimental animals, especially mice and birds, may present a chronic relapsing-remitting course for several months, sharing clinical similarities with multiple sclerosis.[12,18,19]

Barinsky et al.[12] reported in 2015 that they had isolated nine identical strains of the HAE virus, some in the blood and CSF of patients with multiple sclerosis.

Clinical assessment of the vaccine

The vaccine was initially used in 1945-1946 in 66 patients with multiple sclerosis and 12 with acute encephalomyelitis at Botkin Hospital and the Central Research Institute in Moscow; this sample included 19 cases already published in the first article.[3] Among patients with multiple sclerosis, there was a significant improvement in 30% of cases and a moderate improvement in 35%. The significant clinical improvement was accompanied by a marked increase in neutralising antibodies against the virus. A significant improvement was observed in 75% of patients with acute encephalomyelitis. A follow-up study was also performed of ten patients with multiple sclerosis treated with brain preparations from healthy animals and preserved in formaldehyde, who presented no improvement. The treatment schedules applied involved courses of three cycles of 4-5 subcutaneous injections twice per week with increasing doses of up to 5 mL, with 2-3 weeks between cycles.[8]

After these results, the use of the vaccine was recommended and the Order of the USSR Ministry of Health No. 141 of 19 April 1947 dictated the performance of a therapeutic trial in 13 nervous diseases clinics in several cities in the country. In June 1948, a special conference on the vaccine analysed results from the treatment of 145 patients with multiple sclerosis, who showed a significant improvement in 23% of cases, moderate improvement in 43%, and no improvement in 34%. Contrary to the recommendations issued on the use of the vaccine during the first years of progression and in less advanced cases of the disease, many patients with chronic symptoms and significant disability were treated; this was attributed to a lower percentage of positive responses. The conference concluded by underscoring the effectiveness of the vaccine and the need to use it both in hospital and in outpatient settings. Results improved with greater numbers of injections. Side effects included hyperaemia around the administration site on the forearm, with tumefaction of the regional lymph nodes, which was accompanied by general symptoms including mild fever, weakness, headache, increased erythrocyte sedimentation rate, and leukocytosis. The absence of these effects was frequently associated with a decreased therapeutic response.[8,16,20]

By late 1955, the Soviet literature already included reports of around 500 treated patients with multiple sclerosis, 30% of whom presented significant improvements with decreased severity of motor, sensory, and vegetative disorders. Shubladze and Gaidamovich justified the relatively low effectiveness of the vaccine, mentioning existing irreversible changes in the central nervous system, and misdiagnoses. They also considered that a 30% response rate in such a severe and treatment-resistant disease meant that this vaccine was at least the best available option.[16,21]

In 1959, more than ten years after the introduction of the vaccine, the recommended treatment schedule was two or three initial courses followed by an annual course. The authors also recommended intradermal administration, which reduced costs and made the vaccine more accessible for outpatient administration, although, as each dose included a lower amount of antigen, the number of doses had to be increased.[8]

The vaccine was named after Margulis and Shubladze,[13,16] Margoulis and Choubladze in the French literature,[15,22] or simply Shubladze.[4,19] Its purpose was not prophylactic but therapeutic, and it was thought to act by stimulating the body's immunity against the infection.[19,20] Unlike prophylactic immunisations, which aimed to prevent acute infections, therapeutic immunisations are used to slow the development of chronic conditions.[23]

Diagnostic intradermal reaction

In 1954, Shubladze and Gaidamovich reported observing a specific skin reaction after the intradermal administration of 0.2 cm^3 of the vaccine, with a hyperaemic infiltrate measuring 2 × 3 cm forming after 24-48 hours if the reaction was positive. In 1958, Heinz Müller-Dietz (1923-1998) reviewed data from four Soviet studies on this test, published between 1954 and 1957. The rate of positivity in 70 cases of acute encephalomyelitis was 100%. In the 132 patients with multiple sclerosis from the first three studies, 91.5% tested positive, whereas in the fourth, by Anna Rogover, a collaborator of Nikolai Grashchenkov (1898-1965), positivity was observed in 62.5% of 32 patients. In 797 control subjects with other neurological diseases, positivity was reported in 2% in the first three studies, whereas in Rogover's study, 20.5% of 160 patients tested positive. In another study published in 1956, Shubladze and Gaidamovich reported a positive reaction in 96.7% of patients with multiple sclerosis and 1.5% of controls.[16,21] G.F. Kolesnikov observed positivity in 95.5% of his patients with multiple sclerosis and acute encephalomyelitis, compared to 1% in the control group. L.P. Popova found positive results in 98.5% of her patients. These tests provided a more accurate diagnosis than serological studies, and were even used on an outpatient basis, without complications.[8,24]

The Margulis-Shubladze vaccine in the Soviet Union

Some Soviet researchers were sceptical of the Margulis-Shubladze vaccine, although they did not publicly disclose this opinion.[4,19] This was noticed by the members of a mission of American microbiologists and epidemiologists that travelled to the USSR in 1956. They visited Dr Shubladze at her laboratory at the Ivanovsky Institute, where they were informed in detail on the progress of her research on the HAE virus in multiple sclerosis. One diverging opinion was that of the neurologist Nikolai Grashchenkov of Botkin Hospital in Moscow, who told them that he was convinced that multiple sclerosis was different from acute encephalomyelitis and also considered the skin reaction to the vaccine to be non-specific. However, M.I. Levi, head of the Virology Department of the Mechnikov Institute of Microbiology and Immunology in Kharkiv, informed them that he had vaccinated patients with multiple sclerosis and agreed with the observations made by Shubladze regarding the clinical response and the associated increase in antibodies. Allergic reactions were rare, although half of the patients presented mild systemic reactions. Regarding the viral aetiology, he noted that whereas the serum of a patient with multiple sclerosis neutralised the HAE virus at a dilution of 1:10 000, this only occurred at 1:100 with the rabies and fox encephalitis viruses. He also informed them that exportation of the vaccine had begun with the help of the administration in Moscow.[19]

The Leningrad neurologist Aleksandr Panov (1905-1978), who had been using the vaccine since 1948, observed significant improvements in 25%-30% of the first 100 patients with multiple sclerosis whom he treated, 65 of whom presented severe symptoms.[8] By 1957, he had treated more than 150 cases. He believed that 0.2 mL intradermal injections caused the same immune response as subcutaneous injections, and combined both forms. He administered subcutaneous injections in the subscapular area, with courses of 12 injections divided into two cycles of six injections, 12-14 days apart, with doses of 2-3 mL in the first cycle and 5 mL in the second, followed by repeated monthly administration of 0.2 mL intradermal injections and 4.8 mL subcutaneous injections. He spaced out injections if pronounced side effects were observed.[20]

Data from other researchers who used the vaccine to treat multiple sclerosis are heterogeneous. E.G. Breus obtained a significant improvement in 39% of 67 patients. M.M. Korin and E.M. Gaidamovich reported significant improvements in 51% of their 157 patients. However, I.I. Blazhko and S.I. Gritorash were less optimistic. Although they observed an initial improvement in 63% of their 54 patients, this did not persist in severe and moderate cases; however, effectiveness increased with repeated treatment courses.[8,16,22]

The rabies vaccine in the treatment of multiple sclerosis

After the antigenic relationship between the HAE and the rabies virus had been established, Kolesnikov observed a significant improvement in 30 patients with multiple

sclerosis whom he treated with the rabies vaccine from 1954, most of whom were in the initial stages of the disease. This improvement was accompanied by an increase in serum titres of antibodies against the virus.[24] O.V. Markov, S.D. Varshavskaya, and N.S. Matusova also used the rabies vaccine for multiple sclerosis, with the aim of stimulating defence mechanisms against the infection.[8]

The Margulis-Shubladze vaccine outside the Soviet Union

In 1952, James Innes (1903-1974) and Leonard Kurland (1921-2001) mentioned the HAE virus in their article on the possible viral aetiology of multiple sclerosis, in which they mentioned that researchers outside the Soviet Union could not obtain the Sv. and Ef. strains of the virus isolated by Margulis, Soloviev, and Shubladze, and requested access to them and to the vaccine to perform additional studies on the association of the virus with the disease.[9]

Research was not conducted in Western countries until 1957-1958. As mentioned above, in February 1956 a mission of American microbiologists and epidemiologists visited Moscow to meet Professor Shubladze, who informed them about her research on the virus and the vaccine, as well as in other fields of virology.[19] By late May of the same year, Antonina Shubladze and Sophia Gaidamovich presented the results of their research on the HAE virus at the First International Congress on Infectious Diseases, held in Lyon.[14,15] Furthermore, Albert Sabin also visited Shubladze's laboratory in Moscow in June of the same year and in May 1957, when she handed him several strains of the HAE virus. In the month of August, she also sent the strains to Heinrich (1887-1964) and Edith Pette (1898-1972) in Hamburg, and George Dick (1898-1972) received them in the autumn in Belfast; Dick was the first to publish his research on the virus.[15,25]

George Dick's research in Belfast

After news of the "Russian vaccine" against multiple sclerosis reached Great Britain in spring 1957, healthcare experts requested information from Moscow. The Soviet authorities agreed to share it with them in exchange for information on diphtheria and whooping cough, and so they did. British physicians had been consulted by patients with multiple sclerosis and their family members on the vaccine and how to obtain it. As the results of the Soviet research had been presented in Lyon, the French designation of the HAE virus prevailed (encéphalomyélite humaine aiguë), as well as the French adaptation of the authors' names (Choubladze and Gaidamovitch). In their communication, they reported that the HAE virus was immunologically associated with the rabies virus, but was different in terms of epidemiology and the symptoms it caused. Furthermore, Negri bodies were not found in the nervous cells of animals infected with the Sv. strain.[14,15] The vaccine had already been used in Northern Ireland and Scotland for clinical purposes. More needed to be known about the virus, so the British authorities sent a sample to the virologist George Dick of Queen's University in Belfast for analysis.[15,26] Dick, McKeown, and Wilson published an article in January 1958 mentioning that they had not identified neutralising antibodies against the HAE virus in the serum of 50 patients from Northern Ireland with multiple sclerosis and ten control subjects with other neurological diseases, although they did not know what method the Soviet virologists had used. They received lyophilised virus inside a vial containing the Sv. strain, desiccated in May 1956. They inoculated the virus intracerebrally in mice, and used this tissue to perform their experiments. In the histological study of the mouse brain, they observed hyperaemia, inflammatory reaction, and Negri bodies in nervous cells, which led them to show that the virus was identical to the rabies virus. They observed no demyelination and, as they also found no neutralising bodies, identified no association with multiple sclerosis; therefore, they concluded that it was not reasonable to use the vaccine, whose administration was also dangerous. Furthermore, it was difficult to judge the clinical effects of treatment in a disease with an erratic course including spontaneous remissions.[15] In 1947, George Dick had discovered the Zika virus in Uganda (Figure 4).[27]

In February 1958, questions were put by two members of parliament to the British Minister of Health, Derek Walker-Smith (1910-1992), about the Margulis-Shubladze vaccine; he answered that it was not being used due to the lack of sufficient evidence with regard to its effectiveness and safety.[28]

In April 1958, the virologist Christopher Andrewes (1896-1988) published an editorial in the *British Medical Journal* based on the data published by Dick and on those provided privately by Albert Sabin. He asserted that there were no randomised controlled clinical trials with the vaccine and that the rational basis for its use was questionable, as evidence of the virus' causal role in multiple sclerosis was lacking. In addition, the vaccine was

Figure 4. George Dick.[27]

associated with potential risks and high costs, as it was not covered by the national insurance system and had to be paid for in dollars, with each course of treatment costing the equivalent of 20 pounds.[26,29]

George Dick wrote to Albert Sabin in July 1958 after returning from a trip to the USSR, where he had spoken with Prof Shubladze. They felt forced to publish something to counteract the political pressures: "Imperialist fascists in Belfast blocked the import of good medicine for the proletariat of the United Kingdom." He was surprised by his negative results in the neutralisation tests as compared to those of Sabin, which were the result of differences in the techniques used and serum storage conditions.[30] In late July 1958, readers of the *British Medical Journal* witnessed the unusual spectacle of a public retraction by a Soviet scientist. In a short text signed by Dick and Shubladze, the authors stated that there was a clear need for new research into the characteristics of the virus, as it was similar to the rabies virus. Regarding treatment, it was not possible to offer recommendations until its characteristics were better known.[31]

The study of the vaccine at the University Medical Center Hamburg-Eppendorf

In August 1957, Shubladze delivered several strains of the HAE virus to Heinrich and Edith Pette of the University Medical Center Hamburg-Eppendorf for them to study.[25] They inoculated monkeys, rabbits, and mice with the strains, observing no histological changes comparable with the demyelination present in multiple sclerosis, post-vaccine demyelinating encephalomyelitis, or encephalomyelitis induced in experimental animals. In terms of the number of histological alterations and limitation to the grey matter of the brain, their findings coincided with those seen in encephalomyelitis caused by such neurotropic viruses as the poliomyelitis virus or arboviruses. Only the fine topographical distribution of cerebral grey matter alterations enabled them to make a certain differentiation with other pathologies. Unlike Dick, they observed no Negri bodies in the brains of these animals. They believed that the discrepancy may be due to a different number of serial passages of the virus suspension used by researchers.[15,32,33]

They did not observe neutralising or complement-fixing antibodies against the pathogen in the serum of 62 patients with multiple sclerosis and the CSF of another 17. Sophia Gaidamovich had previously identified neutralising antibodies in the CSF at lower titres than in serum. Furthermore, no neutralising antibodies were found in 30 patients with acute meningoencephalitis of unknown origin and another 20 with various non-inflammatory diseases of the nervous system.[33]

Like Shubladze, the authors did confirm that the virus was closely related in serological terms with rabies virus. They concluded that a causal relationship with multiple sclerosis could not be established.[32,33]

The study of the vaccine by Albert Sabin and other American researchers

Between December 1957 and March 1958, Albert Sabin studied the virus that Antonina Shubladze had provided him in Moscow and confirmed, as the Soviet researchers had done but using a different methodology than Dick, that the blood of patients with multiple sclerosis neutralised the virus, but that the blood of healthy controls also did so. He later discovered that in both cases, neutralisation was not caused by antibodies but by a non-specific factor that deteriorated with prolonged storage in the refrigerator at –20°C or after the serum was heated to

56°C for 30 minutes. Serological tests showed no differences between this virus and the rabies virus, and when histological studies showed the presence of Negri bodies in the mouse brain, Sabin concluded that this was due to the rabies virus and had no association with multiple sclerosis.[4,34] By that time, Sabin was working on the oral poliomyelitis vaccine and researching on the relationship between the herpes simplex virus and multiple sclerosis (Figure 5).[35]

During his visits to the Soviet Union in June-July 1956 and May 1957, Sabin came to be well acquainted with Dr Shubladze and her work in the field. They also met in November of that year in Washington, soon before he started his analysis of the virus.[36] Shubladze told him that serological data and the effects of the vaccine differed between patients, depending on the type of multiple sclerosis, and that the virus may be related exclusively with cases of acute onset, which were those that Sabin used in his study.[37]

In the course of his visits to the Soviet neurological clinics, Sabin had the chance to hear the criticisms of Shubladze's vaccine of some Soviet virologists and neurologists, who considered it to have no significant effect on the course of multiple sclerosis. However, he was not aware of any published study reflecting this scepticism. Specifically, he spent some time with Professor Grashchenkov, head of the neurology and physiology departments of the Botkin Hospital in Moscow and a high-level official of the Ministry of Health, who had been working abroad in the 1930s.[37] He expressed his scepticism regarding the vaccine, which according to Sabin was used by the USSR government as a propaganda tool. The American virologist could not understand the hesitation of some Soviet researchers to publish criticism of the vaccine, at least at that time, when Stalin had already died.[29]

Sabin was in contact with the United States Army Medical Department, and sent them a letter on 13 February 1956 reporting the conversations he was having with Mikhail Chumakov and Anatoli Smorodintsev in Cincinnati. An official answered him two weeks later saying that several army divisions, including intelligence, were interested in the content of those conversations, especially regarding the references to the "Russian vaccine" used in multiple sclerosis, as they had previous information on the subject. This vaccine was being tested not only in the Soviet Union, but also in Sweden and Belgium. Some time before, Joseph Smadel (1907-1963), from the Walter Reed

Figure 5. Centenary of the birth of Albert Sabin (United States Postal Service, 2006).

Institute of Research of the Army, had spoken about the vaccine with the CIA, and more recently, the science attaché of the American embassy in Stockholm had obtained 200 cm^3 of the vaccine, which was sent refrigerated. Smadel aimed to immunise experimental animals with the vaccine to perform serological tests to determine the type of viruses it contained.[38]

Since Sabin's return to the United States in May 1957, he performed successive passages of the Shubladze virus in mice and sent an aliquot to the Biological Control Division of the National Institutes of Health, requesting that it not be distributed to other research centres and that no articles be published until he could perform the studies he had promised to Dr Shubladze.[37] The CIA was also closely monitoring the scientific activity of Antonina Shubladze, both her studies on multiple sclerosis and her research with other viruses.[39]

At that time, Sabin maintained regular correspondence with Thomas Willmon, medical and research director of the National Multiple Sclerosis Society (NMSS), on the Shubladze virus. In November 1957, Willmon told Sabin

that DeFalco, of Rutgers University, had already studied the properties of the Shubladze vaccine, and had received reports from European colleagues who had confirmed its clinical ineffectiveness.[40] Sabin told Willmon that he was receiving letters and calls from physicians and patients with multiple sclerosis asking about the Soviet vaccine.[41] This was because of the fact that, days earlier, a radio station had disclosed that Sabin was researching the vaccine. As a consequence, the NMSS published a press release stating that they had been aware of the existence of the vaccine since late 1955. It also explained that the Food and Drug Administration had not authorised the vaccine, but that it had been tested in other countries without promising results, with clinical improvements being observed in 30%-40% of patients, similar to the spontaneous evolution of the disease.[25] Also as a result of this report, the pharmaceutical industry questioned Sabin on the characteristics of the Shubladze virus.[42]

The Margulis-Shubladze vaccine in other countries

Between May and August 1956, Georges Boudin (1906-1983) and colleagues,[22] in Paris, treated nine patients who presented acute exacerbation of multiple sclerosis, observing no visible benefits, although clinical follow-up lasted only a few weeks. According to documents in the National Archives of France, actions were taken in 1955-1958 to import the Margulis and Shubladze serum, also known as the *Knioss* vaccine, from the USSR.[43]

The newspaper *La Feuille de Neuchâtel* reported in May 1956 that samples of a new vaccine manufactured by Margulis and Shubladze to treat multiple sclerosis, an incurable disease, had been sent by air from the Soviet Union to Switzerland and the Netherlands. "These scholars" believed that they had discovered the virus causing the disease, from which a vaccine had been developed to cure it.[44]

The Prague neurologist Kamil Henner (1895-1967) communicated in 1957 that he had observed contradictory responses in his study of the intradermal test in 80 patients with multiple sclerosis and 300 controls. He had also treated some patients with the vaccine.[45]

The neurologists Hans Schwarz (1898-1977) and W. Trucht, of Greifswald in the German Democratic Republic, reported in 1958 on the treatment of 11 patients with multiple sclerosis who received the Margulis-Shubladze vaccine, obtaining no significant results. They had learned of the existence of the vaccine in 1955 thanks to the husband of a patient, who asked them if they were considering using it. With the help of their country's diplomatic service, they were able to access translations of Soviet publications on the vaccine, which were sent from the Kharkiv laboratory.[46]

In Scandinavian countries, where patients were treated with the vaccine, Tore Broman (1908-2000) and colleagues,[47] in Gothenburg, reported in 1960 their experience with the intradermal test, in which they initially identified a higher rate of positive reactions in patients with multiple sclerosis (40%-45%) than in healthy controls or patients with other neurological diseases (20%-25%), although they did not confirm this in subsequent studies. They also showed that reactions were not specific to the pathogen, as they also occurred with formaldehyde-treated brain extracts of uninfected mice, at a similar rate to that observed with the vaccine, indicating that it may be due to allergic factors not associated with the presence of the virus. Broman considered that the result of the skin test was uncertain due to the difficulty of standardising the technique. Furthermore, they found no neutralising antibodies against the virus in any of the three groups studied.[45,47]

A British patient wrote to Albert Sabin in April 1960, stating that the vaccine continued to be used in the United Kingdom after Dick's negative report, with an organised system for its importation and administration. He had the import licence, and the whole process cost 20 pounds, equivalent to 60 dollars. He even corresponded with Dr Shubladze, who one month earlier had informed him that the data had been reviewed, confirming the safety of the vaccine, which had been shown to be effective in one-third of patients with multiple sclerosis; if they improved in the first year, she recommended one or two more courses of treatment in the following years. She was not personally involved in its manufacturing at the Mechnikov Institute in Kharkiv.[48] Sabin answered that the vaccine was identical to the rabies vaccine, which was easily accessible in England, but warned her about the risks of its administration and that its beneficial effects were questionable.[49]

The British journal *The Chemist and Druggist* included in its October 1961 issue an advertisement for the Soviet company V/O Medexport, which exported the Margulis-Shubladze vaccine to the rest of the world (Figure 6).[50]

In November 1963, an Australian patient with multiple sclerosis requested some information from Sabin on

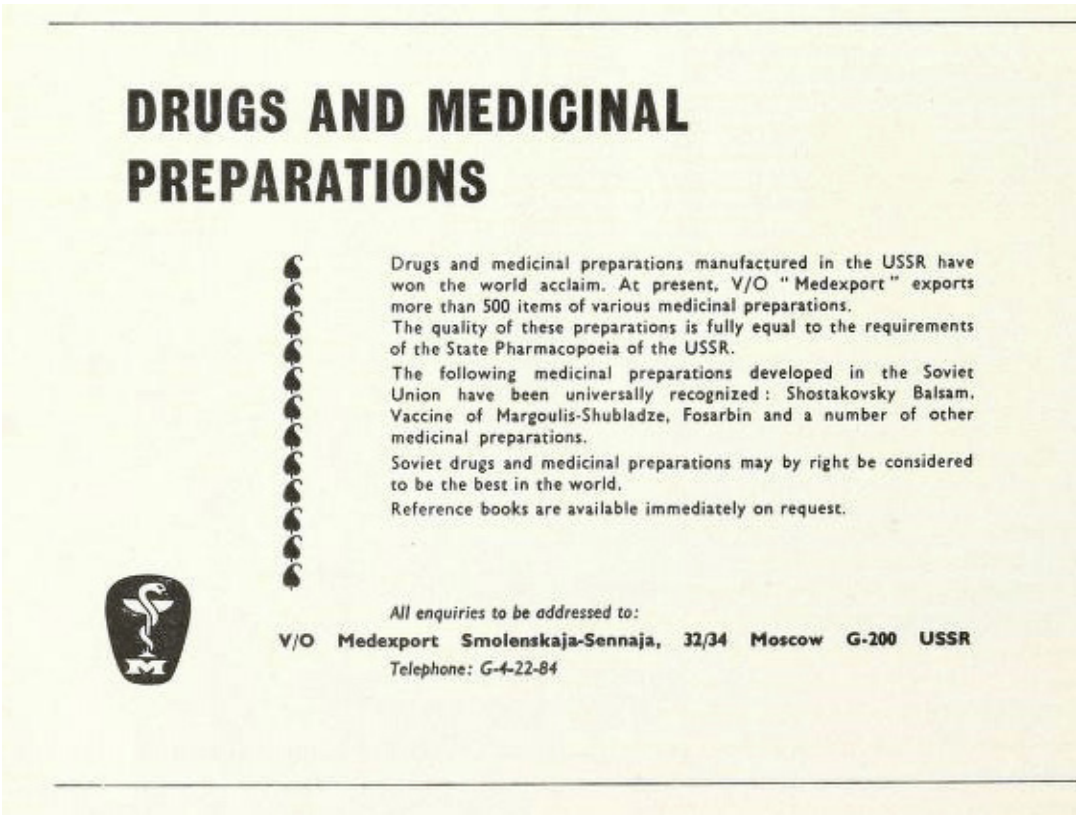

Figure 6. Advertisement for V/O Medexport and the Margulis-Shubladze vaccine, 1961.[50]

the Margulis-Shubladze vaccine. Its import was permitted in Australia, but the only information she possessed was a leaflet from the importer, dated 1957. She only personally knew one or two cases in which the vaccine had been used.[51]

The Montreal newspaper *Le Devoir* published a letter in February 1970 addressed to the Canadian Minister of Health, in which a reader informed him of the existence in the Soviet Union of a vaccine for multiple sclerosis and acute encephalomyelitis, which was studied in 1945-1949 and officially approved by that country's Ministry of Health in 1964, after thorough assessment over 15 years. He asked the minister to take an interest in the Margulis-Shubladze vaccine, for the benefit of Canadian patients.[52] In 1971, it was suggested in Canada that the vaccine be imported upon request from the Soviet embassy in Ottawa and the company V/O Medexport in Moscow; however, this was not authorised, as the documentation required by the healthcare authorities was not submitted.[53]

In the Spanish setting, Lluís Barraquer Bordas (1923-2010) reported in 1994 that the article by Margulis, Soloviev, and Shubladze[3] attracted his attention in 1948, as they claimed to have identified the virus that caused multiple sclerosis. This interest dissipated the following year after a conversation he had in Paris with Professor Pierre Mollaret (1898-1987), who assured him that "it was no more than the attenuated rabies virus." Barraquer dated this interview to 1949, which is not possible as the relationship between the HAE virus and the rabies virus was not presented by Shubladze and Gaidamovich until 1954, in the USSR, and 1956, in Lyon. Barraquer would only learn later of the relationship between these two viruses.[54]

Progression of the vaccine and the HAE virus from 1960s

The members of an American medical expedition that visited the USSR in the spring of 1964 were given access to the research of Elena Bychkova, a collaborator of Antonina Shubladze at the Ivanovsky Institute, who observed eosinophilic cytoplasmic inclusions in mice injected with the HAE virus; some of these inclusions lacked an internal structure (Lyssa bodies), whereas others presented the structure of Negri bodies. They observed no demyelinating lesions, but a micrography study performed by other authors showed diffuse demyelination. There was no question that the viruses isolated by Shubladze were rabies virus strains, and the researchers considered it necessary to further study the relationship between this disease and multiple sclerosis.[55,56]

In 1973, Aleksandr Zinchenko suggested that acute encephalomyelitis presented different aetiologies, attributing 25% of cases to the HAE virus and other rabies viruses through serological and intradermal reactions.[11,57]

Antonina Shubladze and her group continued studying the characteristics of the virus in the following years, but the information on the clinical use of the vaccine was diluted; despite this, its manufacture has continued into the 21st century.

By the early 1980s, the *Great Soviet Encyclopedia*, an official outlet for culture and science in the country, did not mention the aetiopathogenic role of the HAE virus in its vast description of multiple sclerosis, or the vaccine as treatment.[58]

In 1993, Sergei Gribencha (1937-2016) reported that the therapeutic regimen for acute encephalomyelitis caused by the HAE virus was based on empirical experience. He proposed treating these patients with a highly immunogenic vaccine of the Vnúkovo-32 strain of the rabies virus, rather than the Reznik strain.[59]

Igor Barinsky et al.[12] published a molecular genetic study of the Reznik strain in 2015. The study showed great genomic similarity of the strain with the fixed rabies virus belonging to the genotype 1 of the *Rhabdoviridae* family, genus *Lyssavirus*.[12]

In 2000, the State Register of Medicines for Russia continued to include the HAE vaccine against acute encephalomyelitis and multiple sclerosis.[60]

In 2005, the Ukrainian company Biolek, based in Kharkiv, was still manufacturing the HAE vaccine, culturing it in the brain of rat pups. It was still indicated for the treatment of acute encephalomyelitis and multiple sclerosis. Its activity was allegedly caused by stimulation of the human body's immunological antiviral resistance mechanisms. It was recommended to start treatment during the first two months of acute encephalomyelitis and at the onset of multiple sclerosis. The administration schedule comprised a course of two cycles of six intramuscular or subcutaneous injections, the first with increasing doses of 2 to 5 mL over 20 days, and the second 10-14 days later, also over 20 days, but with doses of 5 mL. Two or three courses were recommended at the beginning of the treatment course, separated by intervals of two or three months; in the case of multiple sclerosis, it should be repeated annually.[61]

In 2013, Cherednik still attributed 25%-30% of cases of acute disseminated encephalomyelitis to the HAE virus. If the disease was due to this agent the Margulis-Shubladze vaccine was recommended.[13] As late as 2018, this vaccine was still recommended for the treatment of acute disseminated encephalomyelitis if the cause of the disease was confirmed to be the HAE virus.[62]

Acute disseminated encephalomyelitis secondary to anti-rabies vaccination

Acute disseminated encephalomyelitis may be a consequence of anti-rabies and other virus vaccines. Its incidence after anti-rabies vaccination ranges from 1/600 to 1/1500 with the Semple-type vaccine manufactured with bovine brain tissue, 1/7865 with mouse brain, and 1/25 000 with duck embryo.[63,64] From the classical description by Chernyakhivsky and Birkenhof[65,66] in 1934 until today, various cases associated with the vaccine have been described.[64,67,68] Although we have not found any published case related to the vaccine against HAE, we cannot rule out that it may cause this complication, as it was derived from a *Lyssavirus*.

Some protagonists

Antonina Konstantinovna Shubladze is one of the emblematic figures of the first generation of Soviet virologists (Figure 7).[69] Born in Tashkent in 1909, she lost her father as a child and her mother remarried with the railroad worker Konstantin Shubladze, of Georgian origin, whose surname she adopted.[70]

After graduating from the First Moscow State Medical Institute in 1932, she joined the Mechnikov Institute of Microbiology and Immunology in Kharkiv, where Lev Zilber (1894-1966), who had created and directed the country's first virology laboratory, became her scientific mentor. Antonina was one of the most active members of the legendary expedition to the Russian Far East in 1937 that discovered tick-borne encephalitis. There, she became Zilber's closest collaborator and coincided with the virologist and epidemiologist Valentin Soloviev, whom she later married. In 1913, the pair shared the Stalin prize with other colleagues who had also participated in the discovery of this type of encephalitis.[71]

In 1938-1939, she directed the viral encephalitis laboratory of the All-Union Institute of Experimental Medicine. In 1939-1946, she led the virology laboratory of the All-Union Institute of Experimental Medicine of the USSR. In 1943, she was awarded the degree of doctor in medical sciences, and from 1967 was a member of the USSR Academy of Medical Sciences. Between 1946 and 1947, she directed the viral encephalitis and compared virology laboratories of the Ivanovsky Institute.[72]

Shubladze showed very broad interests in the field of arboviruses and other neurotropic viruses, and the parotiditis, herpes, and hepatitis viruses, as well as the association between viruses and cancer. In 1960, she created a diagnostic method for viral hepatitis, known as Botkin disease in the Soviet Union. She was a pioneer in the development of diagnostic methods for influenza using the haemagglutination reaction. Shubladze played a remarkable role in the development of vaccines against arbovirus and recurrent herpes viruses, in addition to the vaccine against acute encephalomyelitis and multiple sclerosis. She also discovered the role of red blood cells in the dispersion of viruses through the body.[19,71,72]

She published over 200 articles and several monographs on acute disseminated encephalomyelitis and multiple sclerosis in 1947[10] and 1959,[8] and on herpes virus and hepatitis virus. She also wrote the works *Viraemia and acute and chronic infections* (1974), *Leukocyte culture in virological research* (1980), and *The aetiology of chronic viral infections* (1984), in which she described the association between viral load and the clinical form of the infection. In 1954 she and Sophia Gaidamovich published *A brief course on practical virology*, the first textbook published in the USSR on virology laboratory techniques. She died in 1993.[19,71]

Figure 7. Antonina Shubladze.[69]

Antonina Shubladze, from her position at the Ivanovsky Institute, created a successful school of virologists, including the academician Otar Andzhaparidze (director of the Institute of Virus Preparations), Sophia Gaidamovich (director of the arbovirus department of the Ivanovsky Institute and the Laboratory of Biology and Indication of Arboviruses of the WHO), Elena Bychkova, Sergei Gribencha (head of the immunology laboratory of the Ivanovsky Institute), and Igor Barinsky (Shubladze's successor at the compared virology laboratory of the Ivanovsky Institute, which is now part of the Gamaleya Research Institute of Epidemiology and Microbiology).

Antonina Shubladze's husband Valentin Dmitrievich Soloviev was born in 1907 in Yekaterinburg and graduated in medicine in 1932 in Perm. He was a Navy physician and participated in the first and second medical

expeditions to the Russian Far East (1937-1938), during which he contracted tick-borne encephalitis with optic nerve involvement and loss of vision, which he recovered a few months later. He was one of the recipients of the Stalin prize in 1941 and earned his doctorate in 1942. A virologist and epidemiologist, he held several executive roles throughout his career, including head of the influenza laboratory and deputy director of the Ivanovsky Institute in 1947, deputy director of the virus and *Rickettsia* department of the Mechnikov Institute of Microbiology and Immunology in 1954, and deputy director of the antiviral immunity department of the Gamaleya Institute in 1963. In parallel, from 1951 he led the epidemiology department of the Second Moscow Medical Institute. He was also an academician and Presidium member of the USSR Academy of Sciences, and a WHO expert. He was an important figure in the study of influenza and in the development of different vaccines, being a pioneer in interferon research.[73]

Mikhail Semenovich Margulis was born in Odessa in 1879, into a Jewish family. He graduated from the Imperial Novorossiysk University, first in physics and mathematics (1899), and later in medicine (1902). He worked in the nervous disease department at the Staro-Ekaterininsky hospital in Moscow between 1903 and 1928. From 1918, he was director of the nervous disease department at the Moscow University. In 1922, he also led the nervous disease department at the Moscow Clinical Institute for Advanced Training of Doctors and, from 1931 to his death, led the nervous disease department of the Central Research Institute. Margulis was the first in his country to study demyelinating diseases and to use Thorotrast contrast in radiography studies. He was also interested in encephalitis, syphilis, and amyotrophic lateral sclerosis, which he suggested may be of viral origin. In 1940, he published the first Soviet monograph on infectious diseases of the central nervous system; a year earlier, he had published the first textbook dedicated to nervous system diseases, a classic text he wrote in collaboration with Mikhail Krol (1879-1939) and Nikolai Grashchenkov.[5]

The vaccine from a 21st-century perspective

There is no doubt that Antonina Shubladze was a great medical virologist with an interest in several diseases, including acute encephalomyelitis and multiple sclerosis. She may be considered the leading figure in the discovery of a virus that was associated with these severe neurological diseases, and from which a therapeutic vaccine was created. This happened at a time when no specific diagnostic tools were available and no criteria had been defined to assess treatment response or the follow-up time necessary to confirm effectiveness. The improvement observed in one-third of patients with multiple sclerosis did not surpass the rate expected in this disease with an erratic course. No randomised controlled clinical trials with the vaccine were performed, and we do not know its real effectiveness if we assess it with current criteria. It would make no sense to do this now, given the dangers inherent to using rabies viruses and the availability of effective treatments for the disease.

However, it is surprising that these findings from the USSR were not confirmed abroad, despite the presence of some discordant voices within the country. We may not attribute this contradiction exclusively to incompetence of the Soviet researchers or to political efforts to use the vaccine for propaganda purposes. It may also be due to methodological differences, as pointed out by some Western scientists, as well as other unknown factors that are difficult to identify after all these years.

However, we may point out the fact that, while it was known since 1954 that the vaccine was manufactured with a rabies virus, it continued to be used for many years despite the risks it entailed. Although hardly any mention is made of the vaccine in the majority of Russian and Ukrainian neurological texts, in the early 21st century it continued to be manufactured and was included in the pharmacopoeia of both countries.

Conflicts of interest

The author has no conflicts of interest to declare. The author has received no public or private funding for this study.

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