

The Rockefeller Foundation's anti-typhus project in Spain: a lesson in failure

O projeto anti-tifo da Fundação Rockefeller em Espanha: uma lição de insucesso

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Abstract

Among the major diseases of interest to the Rockefeller Foundation in the 1920s and 1930s was typhus. The Foundation's anti-typhus focus was sharpened at the end of the 1930s by the expectation of another European war: its public health staff anticipated that enormous numbers of refugees and the repetition of World War I's trench warfare would lead to typhus epidemics. The Foundation increased its investment in *Rickettsia* research, decided to test existing anti-typhus vaccines, and studied the insect transmission of typhus.

An outbreak of typhus in Spain right after the Spanish Civil War caught the interest of the Foundation as an opportunity to both study the vaccines and to study the transmission of the disease. The Foundation sent a young researcher there to study the disease and also shipped several guinea pigs to Spain to be infected with the typhus-carrying lice. American newspapers covered the story of the transport of the Guinea pigs via Pan-American's flights to Lisbon (and delivery to Spain), and their return to the United States to study the strain of typhus that was rampant in Spain.

The work in Spain gave the foundation clear evidence that the existing anti-typhus vaccines were not very effective and provided impetus for the Foundation's future focus on insecticidal approaches to typhus control. It was an important step toward the Foundation's collaboration with the United States' military's plans for the invasion of North Africa and led directly into the Foundation's later acceptance of DDT as an effective anti-typhus strategy. Ultimately the Foundation turned its experience with DDT into a global attack on malaria – one of the most important stories in 20th century tropical medicine.

Key Words:

Rockefeller Foundation, typhus epidemics, Spain, vaccines and DDT, World War II.

Resumo

O tifo situava-se entre as principais doenças de interesse para a Fundação Rockefeller entre 1920 e 1930, aguçado no final da década de 1930 pela expectativa de uma outra guerra na Europa: o seu *staff* previa que a difusão de epidemias de tifo como resultado de um número elevado de refugiados e da repetição da guerra de trincheiras da Iª Guerra Mundial. A Fundação aumentou o seu investimento na investigação em *Rickettsia*, decidiu testar vacinas anti-tifo existentes e estudou a transmissão da doença pelo piolho.

Logo após a Guerra Civil Espanhola, um surto de tifo em Espanha, despertou o interesse da Fundação como uma oportunidade para estudar as vacinas e a transmissão da doença. A Fundação enviou para Espanha um jovem investigador e várias cobaias para serem infetadas com os piolhos, transportadores de tifo. Os jornais americanos cobriram a história do transporte das cobaias através de voos Pan-americanos para Lisboa (para entrega em Espanha), e o seu retorno aos Estados Unidos, para estudar a epidemia de tifo, que era galopante na Espanha.

Os resultados obtidos em Espanha deram à Fundação clara evidência de que as vacinas anti-tifo existentes não eram muito eficazes e impulsionou o uso de inseticidas para o controlo do tifo. Foi um passo importante para a colaboração da Fundação com os planos militares dos Estados Unidos para a invasão do Norte da África e conduziu diretamente à aceitação do DDT (pela Fundação), como estratégia anti-tifo. Em última análise, a Fundação utilizou a sua experiência com o DDT num ataque global à malária - uma das histórias mais importantes da medicina tropical do século XX.

Palavras Chave:

Fundação Rockefeller, epidemia de tifo, Espanha, vacinas anti-tifo e DDT, Iª Guerra Mundial.

Introduction

Failure is not the usual focus of historical inquiry. As U.S. President John F. Kennedy remarked in a military context, “Victory has a hundred fathers and defeat is an orphan” [1]. To paraphrase that: histories of success generate a hundred historical inquiries, but histories of failure, such as is presented here, are rare. However, histories of failure clarify choices and opportunities, and demonstrate how the inadequacies of routine and accepted ways of doing things move us toward creativity and innovation. The history of failure in this case involves the ancient disease of typhus, the Rockefeller Foundation and Spain in 1940 and 1941.

Typhus was at the time a disease that had been studied extensively in both its cause and effect. A recent article has noted that the “two milestone discoveries” regarding typhus occurred in 1909, when Stanislaus von Prowazek discovered “the causative agent of epidemic typhus fever,” later named *Rickettsia prowazekii* by S. Burt Wolbach; and when Charles Nicolle identified of the human body louse as the means of transmitting typhus from person to person. [2] It also was known by that time that the human body louse had adapted not only to human bodies as environments, but also to the comforts of human clothing.

As a matter of history, typhus was understood to flourish in dense urban environments, during warfare, and in prison and refugee situations – any time that people were in prolonged close contact and especially when their normal defenses were reduced by other diseases and poor nutrition. World War I had produced those situations, and typhus had been rampant. At the onset of World War II public health officials and military planners anticipated major typhus outbreaks, yet in the ensuing twenty years there had been little progress in understanding how to control typhus. The fundamental anti-typhus strategy by the outbreak of World War II remained sanitation: making the human body louse’s human environment less hospitable by encouraging physical cleanliness with soap and hot water; by fumigating infested clothing and bedding with steam or hot air; and by using insecticides not toxic to humans, such as rotenone. Although strategies based on sanitation were effective if consistently enforced, they were primarily responses to epidemics, and did not prevent them.

This was the background for the Rockefeller Foundation’s interest in typhus as it geared up to work in concert with the United States government to prepare for a global explosion of typhus after the beginning of World War II. The Foundation was in many respects better prepared to engage the disease than the U.S. government or any other international organization, such as the Red Cross. Only the Institutes Pasteur had a similar global reach. Created in 1913, the Foundation had from the beginning focused on public health and epidemic disease. It had established or funded public health research institutes in North America, Europe, South Ameri-

ca and East Asia, and had conducted disease-control demonstrations throughout the world. [3] While most of its control work had focused on hookworm (ankylostomiasis), yellow fever, malaria, and tuberculosis, the Foundation recognized typhus as a major problem. At the beginning of World War II it established the Rockefeller Foundation Health Commission as an agency “to render services in the public health field to regions afflicted with public health problems related to the war... A study of nutritional problems and control of possible epidemics are among its chief concerns” [4: 116] At that time the Foundation revealed that it had “an active interest in typhus,” and that it was testing “seven different types of typhus vaccine” [4: 116]. The Foundation also stated that:

In spite of the fact that it is an age-old problem, our basic knowledge regarding [typhus] is far from adequate. We know in a general way that it is spread from person to person by means of the body louse and that it develops rapidly with devastating results when people are crowded together under unsanitary conditions and when there is a heavy louse infestation... But we do not know how best to control or eradicate louse breeding under war conditions [5:21].

The typhus program of the Rockefeller Foundation

It is useful to begin the story of the Rockefeller Foundation’s typhus program with observations and recommendations made by John H. Janney in December 1941, just after the United States entered the war. Janney brought to his observations the perspective of a Rockefeller public health officer for more than two decades. After remarking that “it is important that typhus is increasing rapidly in Europe,” Janney summarized the situation facing the Allies: “the control of typhus is a responsibility which Great Britain and The United States will have to face in winning the war. Neither of these countries has, at the moment, personnel trained in anti-typhus work with experience more recent than 1921. Little has been added to the knowledge of the part played by lice in transmitting the disease and delousing methods are not improved over those used twenty years ago”. Faced with this situation, Janney called for an “immediate and serious improvement in our epidemiological, entomological, and technical control knowledge of typhus.” [6]¹

The Rockefeller Foundation had established a modest anti-typhus program in 1940 by connecting with the Harvard University laboratory of Hans Zinsser, who had for many years been investigating the family of *Rickettsia* microbes and had already published his classic historical work, *Rats, Lice and History* [7]. In that book Zinsser argued that much of human history has been shaped by epidemic disease, and that typhus in warfare had killed more soldiers than were killed by enemy action [5:20-21]. Zinsser had worked out a meth-

od of cultivating the main European strain of typhus causation, *Rickettsia prowazekii*, with a view toward developing an anti-typhus vaccine. Before his untimely death in September 1940 he was developing a consortium of typhus researchers in France, Poland, Romania and the United States, including Charles Nicolle of the Institut Pasteur, and at one point had the intention of testing a vaccination in Spain [8]. After Zinsser's death one of the Foundation's officers, Wilbur Sawyer, spent some time assessing the state of typhus research and public health work in Europe. He found that the British were concerned about typhus epidemics, but had little anti-typhus vaccine on hand. [9]² He also found that the London School of Tropical Medicine and Hygiene had developed an insecticide that appeared promising, but found the British had done little toward an anti-typhus strategy [10]. The Rockefeller Foundation believed it had the field of anti-typhus work virtually to itself, and took on the challenge of developing an anti-typhus strategy.

At this point, early in 1941, the Rockefeller Foundation had twenty-five years of experience investigating serious diseases, yet its officers still found nothing more interesting than new epidemics where new strategies and techniques could be tested. But the Foundation did not engage in a full-fledged campaigns against disease, preferring demonstration projects and trials where innovations could be tried and brought into practice. Among the countries where the Foundation had conducted such demonstrations and trials was Spain, where it also had made some contributions to the development of modern science [11]. It had malaria control projects at Campo Lugar beginning in 1930 and later in Madrigaleho, and three other municipalities; then it opened a health demonstration project at Vallecas, outside of Madrid, in 1936 [12,13,14]. In conformity with Rockefeller practices in public health, both initiatives were intended to have Rockefeller support for several years in order to convince the Spanish government to copy their methodologies and extend them throughout the nation [15].

Prior to the demonstration projects the Foundation had made more than thirty grants to public health officials and laboratory scientists with the aim of modernizing what the Foundation perceived to be a backward public health system in Spain [16]. The influence of the Foundation in public health was so pervasive that in 1933, Oo-keh Khaw, a parasitologist from the Peking Union Medical College in China who visited Spain on a Rockefeller grant stated that he was everywhere encountering Rockefeller-trained workers [17,18]. A section of his report describes his experience:

The first two weeks in May were spent in Spain... It was a great opportunity to see anti-malaria work alone in a country which has achieved some success. The Programme was drawn up by the Malaria Division of the Public Health Department of the Ministry of the Interior. One of the Divisional Inspectors – a Rockefeller Foundation Fellow of

Johns Hopkins – came with me, so that besides being received with kindness – hospitality everywhere – I saw not only anti-malaria work but other public health activities as well. The latter are receiving feverish attention and are carried out in approved American style as most of the heads [of public health units] are Rockefeller Foundation fellows [19].

It was this heritage of pervasive influence in the Spanish public health establishment that the Foundation drew on to set up a trial of several existing typhus vaccines produced in the United States, Canada, Mexico, and Tunisia, in order to establish which one was most effective. In February 1941 the Foundation was told that José Alberto Palanca, director of the public health administration in Spain, would welcome experimental anti-typhus work by the Foundation [20]. With the typhus situation in Spain becoming increasingly serious, John Snyder went to Spain early in 1941 and established a laboratory at the Instituto de Sanidad [21]. *The Times* of London reported in April 1941 from Madrid that “typhus fever has become epidemic,” and that:

Of the various epidemics from which Madrid has suffered since the opening of the century this is the most important, not because of the number of cases or the mortality which has resulted but because of the circumstances in which it has arisen. The Civil War and its aftermath, which have brought restrictions and malnutrition, and a scarcity of certain articles, including washing soap. So far some 300 cases have been registered, with 27 deaths, including those of two doctors. It is said that about 20 to 30 new cases are coming in daily... The disease is also reported from Murcia, Granada, Seville and Almeria (...) [22].

Snyder worked under the general authority of John H. Janney, mentioned earlier, to test several anti-typhus vaccines. Spanish public health officials had been manufacturing and administering the Laigret vaccine, developed at the Institut Pasteur in Tunis, which had demonstrated efficacy against murine typhus (*Rickettsia typhi*). Apparently the vaccine had come to the attention of the Spanish authorities when Jean Liagret, its developer, had come to Spain in 1936 under the auspices of the League of Nations to examine infectious diseases emerging during the Civil War [23]. Reportedly the Liagret vaccine was “used with apparent success in terminating ... prison epidemics” in Spain [21]. However, the Rockefeller Foundation quickly assessed the Laigret vaccine as difficult to produce in large quantity, because it was based on *Rickettsia* cultivated in live rat brains, and not useful in

1 - Although J.H. Janney is the author of this document, recommendations in the latter part of it were made jointly with Dr. John C. Snyder.

2 - Researchers should note that Rockefeller Foundation officers' diaries are available digitally in: www.rockfound.org.

suppressing the strain of typhus then active in Spain.

The Foundation then turned to its widespread network of sources, and the vaccines subsequently tested by the Foundation in Spain are an illustration of its international connectivity. One vaccine had been developed by Herald Cox of the Rocky Mountain Laboratory of the United States Public Health Service. Cox had spent four years in the Olitsky laboratory at the Rockefeller Institute for Medical Research in New York City learning about viruses, and was well-known to the Rockefeller network. Apparently the Cox vaccine, which was manufactured by the Lederle pharmaceutical company, was the only commercially-available vaccine in the United States. After obtaining a supply of that vaccine, Snyder and his support staff in Spain inoculated themselves with it. Each got a mild case of typhus but recovered. They then inoculated 20,000 Spanish citizens with the Cox vaccine [4: 80].

Other vaccines tested by Snyder in Spain included one developed by Ruiz Casteñeda at the Departamento de Investigaciones Médicas, of the Hospital General in Mexico City: Casteñeda had been in Zinsser's Harvard laboratory on a Rockefeller fellowship before he returned to Mexico to develop a vaccine based on the strains of murine typhus endemic to coastal regions of Mexico. The Foundation also drew on a typhus vaccine developed by James Craigie of the Connaught Laboratories in Toronto, Canada.

The project in Spain had all the attributes of what should have been a successful field test. The host nation's public health authorities were cooperative. There was a significant outbreak of epidemic typhus. The Foundation's field officer had up-to-date training, and had several vaccines to test. However, after several months in Spain, Snyder returned to the United States convinced that the project was a failure. He found no convincing evidence that any of the vaccines could be effective in preventing a typhus epidemic. Among those tested none had conferred immunity, and the Cox vaccine appeared only likely to reduce fatalities. The Rockefeller Foundation stated publicly that the tests in Spain were "inconclusive" [5:75].

Perhaps the most important result of the Spanish project was Snyder's success in responding to requests from the United States to bring back strains of the typhus infections he had encountered so that vaccines might be developed to cope with those specifically European varieties. In an episode reported in American newspapers, Snyder was able to infect several guinea pigs with the Spanish strains and ship the guinea pigs to the United States via the Pan American Clipper flight out of Lisbon.

In spite of the inconclusiveness of the work in Spain, the continuing warfare in Europe, and the increased likelihood of United States's entry into the war, made typhus research an on-going element of the Rockefeller Foundation's public health program. The Foundation searched for other outlets for its program, and developed promising connections in Chile, Mexico, and China. Through the Lederle laboratories it also learned about continu-

ing typhus studies in Hungary and Romania.

It is appropriate to examine the Lederle studies to better understand the range and significance of the Rockefeller Foundation's network of researchers and administrators. The head of the Lederle Laboratories, Ralph Wykoff, was well-known to the Rockefeller public health officers because he had collaborated with foundation staff on the construction and operation of centrifuges, among other projects, while he was a member of the Rockefeller Institute staff. Wykoff shared with the Foundation a report by a Lederle operative who recently had been to Hungary and Romania – even though those nations were becoming increasingly aligned with Germany and increasingly hostile to the United States. The report focused on anti-typhus projects undertaken at the institutes of public health in Hungary and Romania – institutes that had been created with Rockefeller funding, and with staff trained through Rockefeller fellowships. Moreover, the report identified former Rockefeller fellows as the leaders of typhus work in Hungary [24].³

This episode demonstrates that the Foundation's extensive connections allowed it to survey, study, and otherwise learn about typhus virtually throughout the world. Moreover, it could test typhus vaccines in the field with collaboration from local authorities who already knew and trusted the motives of the Foundation. Thus, the field tests of typhus vaccines in Spain permitted Snyder and Janney to assert with confidence that the Foundation's attempt to find an effective typhus vaccination was unlikely to succeed. Certainly, given the historically-demonstrated long development periods required to create a new vaccine, and the pressing needs created when the United States entered the war, the tests in Spain indicated that the Foundation's anti-typhus work had to go in a different direction. Janney and Snyder therefore recommended a turn toward a vector-control strategy – a focus on methods of killing the human body louse with insecticides [25]. Based on Snyder's experience in Spain, the Foundation shifted toward insecticides as an anti-typhus strategy.

In his report to the Rockefeller home office in New York City after the trials in Spain Janney summed up his disappointing experience and the need for a new direction:

Until some better method is developed for typhus control, our efforts will be directed toward reducing the louse index. It appears that the usual methods for delousing by means of steam and hot air may be impractical in Spain. Chemical methods must be studied (...) [26].

Snyder and Janney's recommendation soon was reinforced by a request from the United States' National Research Council Subcommittee on Tropical Diseases that the Rockefeller Foundation investigate "the advisability of undertaking a study of various delousing methods in N[ew] Y[ork]." [27]. The next month the Foundation created a laboratory for the study of louse-borne typhus as a unit of the Foundation's

virus laboratory located on the campus of the Rockefeller Institute for Medical Research in New York City [28].⁴

The Foundation's experience in Spain also gave it the ability to act with authority when in November 1942 the American government created the United States Anti-Typhus Commission, and called on the Foundation for advice. At the first meetings various public health officials focused on further research on the epidemiology of typhus, preventing typhus epidemics by sanitation, and the possibilities of making effective vaccines. But the Rockefeller representatives argued strongly for an insecticidal approach. With the approval of the National Research Council and lukewarm approval from the United States Anti-Typhus Commission, the Foundation established a facility in New York City to test various insecticides.⁵

The Foundation's anti-typhus laboratory, which soon became known as the "Louse Lab," quickly established a collaborative agreement with the United States' Bureau of Entomology and Quarantine in the Department of Agriculture whereby the Bureau would evaluate insecticides, and the Foundation would test them and other louse-control methods on human subjects in field conditions. It quickly became apparent that the Foundation's thirty years of fieldwork in public health and its global network of contacts were advantages that a government agricultural laboratory did not possess. After successfully establishing a colony of lice in New York City, the Foundation was able carry out tests of insecticides at a conscientious objector camp in the United States, and at villages in Mexico, Egypt, and in Algeria – the latter after the successful Allied invasion of North Africa.

Some of the tested insecticides were good at killing lice, but none of them were consistently effective. It was only after a new insecticidal chemical, DDT, became available to the

Foundation in the summer of 1943 that the Foundation's insecticidal strategy was proven to be the right one. Dusting DDT directly onto human skin became the standard method of typhus control, and was used against typhus outbreaks in Naples early in 1944, and in refugee and concentration camps in the concluding months of the war. It also began to be used as a method of killing mosquito larvae for malaria control. DDT quickly became the insecticide of choice throughout the world, in large part because of the global network of public health specialists fostered by the Rockefeller Foundation [28,29,30].

Some concluding remarks

Thus, understanding the failure of the anti-typhus project in Spain provides us with an important preliminary history for the much better-known global history of the World Health Organization's and the Pan-American Health Organization's DDT-based anti-malaria campaigns of the 1950s. Less appreciated is that the failure of the Rockefeller Foundation's typhus project in Spain turned the Foundation and, ultimately, global public health in a direction that no one in 1941-1942 could have anticipated.

3 - A valuable study of anti-typhus operations in Eastern Europe in 1941, contemporary with the events in this paper, was published by J. Lindemann in 2002.

4 - Much of the remainder of this paper is derived from the publication of the author in 2005.

5 - Hechemy KE et al. *A Century of Rickettsiology*, p. 2, notes: "Until the discovery and availability of chloramphenicol and the tetracyclines in the early 1950s, Nicolle's discovery of the vector formed the only basis for measures taken [against typhus]."

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