Malaria epidemics in Europe after the First World War: the early stages of an international approach to the control of the disease

Malária epidêmica na Europa após a Primeira Guerra Mundial: estágios iniciais de uma abordagem internacional de controle da doença

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Abstract

The severity and endemicity of malaria declined gradually in Europe until WWI. During and after the war, the number of malaria cases increased substantially and peaked in 1922-1924. This prompted the Hygiene Commission of the League of Nations to establish a Malaria Commission in 1923 to define the most efficient anti-malaria procedures. Additionally, between 1924 and 1930 there were several international meetings and collaborations concerning malaria, which involved the main institutes of parasitology and the Rockefeller Foundation. The Commission reports, the guidelines for anti-malaria campaigns and the scientific programs which came out of these meetings and collaborations are analyzed in the present paper.

Keywords: malaria; League of Nations; Malaria Commission; Bonifica Program; Rockefeller Foundation.

Resumo

Antes da Segunda Guerra Mundial, a severidade e endemicidade da malária diminuíram gradualmente na Europa. Durante e após a guerra, o número de casos cresceu substancialmente, chegando ao máximo entre 1922 e 1924. Isso fez com que a Comissão de Higiene da Liga das Nações estabelecesse, em 1923, a Comissão de Malária, para definir procedimentos mais eficazes contra a doença. Entre 1924 e 1930 encontros e colaborações internacionais, nos quais estiveram envolvidos os principais intitutos de parasitologia e a Fundação Rockefeller, discutiram a enfermidade. Os relatórios da Comissão, as diretrizes para campanhas antimaláricas e os programas científicos decorrentes desses encontros e colaborações são analisados no artigo.

Palavras-chave: malária; Liga das Nações; Comissão de Malária; Programa Bonifica; Fundação Rockefeller.

Malaria was endemic in Europe until it was almost completely eradicated in the 1950's. The frequency and severity of outbreaks of malaria in Europe declined gradually over the 50 years preceding WWI, despite the persistence of highly infected areas in southern Europe, Corsica, Italy, Spain, the Balkans and the Ottoman Empire (Hackett, 1937). This steady decrease in the prevalence of malaria was the consequence of a complex combination of factors, including policies to drain marshes, reclaim land from bodies of water, and distribute quinine. These resulted in changes in the conditions required for the proliferation of mosquito vectors, and more generally in improved living and working conditions for the people (Packard, 2007).

At the turn of the 20th century, it was discovered that malaria was an arthropod-borne parasitic disease. This provided the rationale for a medical approach to its prophylaxis, with health systems being adapted to deliver different strategies aimed at interrupting the circulation of the *Plasmodium* parasite between the vector, *Anopheles*, and man. Textbooks on parasitology from this period reflect the prevailing optimism about the feasibility of malaria being controlled or even eradicated (Brumpt, 1913).

The First World War and the political and sanitary chaos which followed in its wake in Eastern Europe and the Balkans resulted in a new state of affairs. The medical strategies designed before the war, which were based primarily on the widespread use of quinine, had certainly proven effective in controlling malaria outbreaks locally, such as the one which devastated the Armée d'Orient in 1916 (Sergent, Sergent, 1921). However, despite this knowledge and experience, the number of malaria cases still rose after the war, reaching a peak in 1922-1924. Malaria had re-emerged in areas where it had ceased to be endemic, and appeared with greater frequency and severity everywhere else, including in Italy, where the death toll climbed from 1 per 10,000 inhabitants in 1910 to 3.2 at the end of WWI (Celli, 1933). This trend was also associated with attacks of malignant (pernicious) malaria in areas where it had rarely been seen before. In Eastern Europe, the 1922-1923 'epidemics' in Soviet Russia and the Ukraine are often seen as examples of the dramatic changes in the distribution and features of malaria.[1] In 1913, malaria was occurring at a rate of 500 cases per 10,000 people, but by 1923 it had reached about 5,000 cases per 10,000 in the German Republic of the Volga, with an estimated death rate of at least 3% (Anigstein, Pittaluga, 1925).[2] Gustavo Pittaluga (1876-1956) estimated that in 1923, 18 million people suffered from malaria in Russia, and that sixty thousand deaths occurred out of a total population of about 110 million (Anigstein, Pittaluga, 1925). Similar observations were made throughout the whole of eastern and south-eastern Europe and the former Ottoman Empire. The situation was well summarized in a 1931 report by Émile Marchoux (1862-1943) on the activity of the Malaria Commission of the League of Nations between 1924 and 1930 (Marchoux, 1931). The war had introduced new, large-scale changes to mosquito and *Plasmodium* distribution which had all contributed to the 'success' of the fight against malaria. They included the forced migration of large numbers of people from infected areas[3], the sudden exposure of populations to *Plasmodium* sp. that were new to them, the collapse of health systems due to war, the unavailability of quinine in most countries, and all in the context of the worst poverty seen in years. The 'sanitary landscape' of Eastern

Europe was rendered even less palatable by epidemics of typhus cholera and relapsing fever, on top of hunger and even famine in European Russia and the Ukraine.

The catastrophic medical and social conditions which followed WWI could clearly not be dealt with by countries acting alone, particularly the newly independent states and countries ravaged by civil war. As a consequence, an international, interventionist sanitary policy[4] was initiated by the League of Nations at its second session, in February 1920 (L'Épidémie..., 1920), and independently by the Rockefeller Foundation (Fosdick, 1989). Indeed, the Epidemics Commission of the League of Nations, an *ad hoc* commission of physicians and epidemiologists created in March 1920, organized supranational assistance for local health authorities in Poland, Russia and the Baltic states aimed primarily at protecting uninfected populations from the typhus and cholera epidemics. The supranational dimension of the campaign against typhus was emphasized by the European Health Conference held in Warsaw in March 1922, which gathered epidemiologists and physicians from all European countries, including Germany and the Soviet Union (Rapports..., 1922).

For political and social reasons (Balinska, 1995), the control of typhus was given priority by the League of Nations.[5] However, the attempts to control it triggered a cascade of decisions which resulted in the creation of specialized sub-commissions, one of which was devoted to malaria. On the basis of consistent information confirming the renewed severity of malaria in 1922-1923, and after the typhus epidemics had been controlled, the League of Nations launched its initiative against malaria. The Malaria Sub-Commission of the Health Organization was created in May 1923 and transformed into a full Commission in March 1924. In contrast to typhus, which could spread rapidly anywhere, thus needing emergency sanitary decisions, malaria, despite its recent spread, remained a chronic but localized disease. The creation of the Malaria Commission was thus more likely to have been genuinely aimed at the control of a parasitic disease in the long term, rather than a short-term response to a medical emergency. The first analytical report of the Malaria Commission was published in March 1925 (Report..., 1925a).

The League of Nations was not the only organization concerned with malaria in Europe. Malaria studies had been resumed in all the important European laboratories which had engaged in studies of this nature before the Great War. In addition, numerous attempts to control malaria under various climatic and geographic conditions were being tested in Europe, particularly in Spain and Italy, as well as in French, English and Belgian colonies. Moreover, in 1924, a newcomer to Europe, the International Hygiene Board of the Rockefeller Foundation, had started anti-malaria campaigns in Italy, following the successful field trials of its original campaigns using anti-larval procedures in the US and Central and South America (Vieira, 1998).

The ten years following the end of WWI had been marked by very active scientific exchanges among scientists from nearly all European countries, including former warring parties. The First International Congress of Malariology, held in Rome in October 1925, brought together all the leading malariologists of the day, many of whom were members of the Malaria Commission or its expert advisers. The congress was a striking example of the diversity of approaches to the malaria problem. Not only were scientific results discussed,

as expected for a scientific meeting, but techniques for controlling the disease were also presented, compared and critically reviewed.

By consulting the Malaria Commission reports, the proceedings of the First International Congress of Malariology, Émile Brumpt's archives[6], and the Rockefeller Foundation archives[7], we were able to investigate the diversity of scientific opinions among malariologists as well as the political context in which they were expressed. In the debates, there was a clear opposition between "malariologists who favored anti-mosquito measures and those who advocated treating patients and implementing social reforms" (Evans, 1989). The latter included those advocating the Italian Bonifica, a set of procedures originally designed in Italy in the late 1800's for the sanitation of regions with endemic malaria, largely based on land reclamation practices. The aim of the present paper is to discuss a reality that was far more complex than a choice between two well-defined approaches. The field practices for fighting malaria that were proposed by the commission revealed a less dogmatic approach to the disease, combining direct and indirect measures designed to significantly reduce transmission of *Plasmodium* in a given geographic, social and economic context. In fact, after 1927 and the second report of the Malaria Commission (James, 1927), priority was certainly given to improving the living conditions of the people in infected areas. However, this priority was not given because of any local failure of anti-mosquito procedures; rather, it was because long-term scientific programs needed to be completed before efficient anti-mosquito procedures could be introduced on a large scale. Research programs which had emerged from the discussions in 1924 and 1925 had resulted in remarkable progress in insect biology and genetics by the end of the 1930's, but with no or few benefits in terms of malaria control. The eradication of malaria in Europe after WWII through the use of DDT resulted from an altogether different line of research in chemistry[8], which was merged after 1943 with earlier strategies to fight mosquitoes and insects in general.

Common knowledge on malaria in 1924-1925

A 1913 reference treatise on parasitology (Brumpt, 1913) shows that after the discovery of the blood parasite, *Plasmodium*, in 1880, research had initially focused on characterizing the different parasites of man and their association with the diverse forms of malaria. Climatic and microbial theories of malaria were progressively abandoned. By the end of the 19th century, three human parasites had been identified morphologically: *Plasmodium falciparum, P. vivax* and *P. malariae*. They were associated, respectively, with severe irregular and malignant fevers, serious tertian fevers, and chronic, milder, quartan fevers. The geographical distribution of the different types of fever and different *Plasmodia* was more or less superimposable and the maps tended to be stable: *P. falciparum* dominated in tropical regions, along with malignant malaria; *P. vivax* and *P. malariae* were found in more temperate climes, with differences in geographical distribution associated with local conditions.[9] After the recognition in 1900 that dipters from the genus *Anopheles* were responsible for the transmission of malaria parasites, research turned towards the description of the cycle of the *Plasmodia* in the insect and in man, and, in the context of emerging medical entomology, towards the precise taxonomy of the specific insect vectors (Coluzzi et al,

2008). Indeed, not all *Anopheles* species were vectors of *Plasmodium*, and not every vector species supported the transmission of all parasites in the same way. Each species of *Plasmodium* had its most efficient cycle in a given species of *Anopheles*. Epidemiologists were cautiously optimistic that malaria could be eradicated, provided the 'bad' *Anopheles* (i.e. those supporting the proliferation and transmission of the *Plasmodium* in a given geographical location) were destroyed (or people taken away or protected from them), and the proportion of *Plasmodium*-bearing humans was diminished through of the use of quinine.

The 1922 edition of Brumpt's treatise (Brumpt, 1922) was contemporary to the creation of the Health Commission. The chapter devoted to malaria was slightly longer than in the 2nd edition of the book: fifty pages vs. 43. New topics were introduced, reflecting a more complex approach to the natural history of malaria. They included the design of techniques for physicians to rapidly quantify the incidence of the disease (the splenic index), a microscopic description of the parasites, the potential for zooprophylaxis (whereby the biting of cattle was supposed to lower the frequency of biting of humans), and the recourse to new pharmaceutical reagents (Atoxyl) to kill parasites, or physical treatments (X-rays) to attenuate spleen pain. Although still relying on the same dual approach as before, preventive measures now also took several new factors into account. The biology of the insect, particularly its preference for houses (indoors and outdoors), as well as its feeding and reproductive behavior, was perceived as an important issue in the persistence and transmission of the disease, as were the organization of human habitats (vicinity of cattle, temperature of rooms, working habits, protection of houses and water from insects, etc.) and the respective stability of insect and human populations. Malaria studies by scientists and physicians were already branching out from Grassi's simple model (the *Plasmodium-Anopheles*-man triangle; Fantini, 1994) to delve into the complex 'biological associations' of multiple ecological factors (Drouin, 1993). It is interesting to note that Brumpt mentioned drainage of stagnant water as being an effective procedure, but did not discuss land reclamation or the Italian Bonifica policy. This suggests that such policies were not recognized as falling within the medical paradigm for malaria, a point which will be discussed later at length.

The apparent victory over malaria achieved by the medical services of the Armée d'Orient, organized by Edmond and Étienne Sergent in 1916, was taken by Brumpt as proof that malaria could be controlled, particularly through the widespread use of quinine. However, he did mention that prevention procedures were often ineffective since they were rarely applied properly because of the cost of treatment and the provision of physical protection, and because people were generally ignorant about the subject and undisciplined (Brumpt, 1922, p.177-178). This caveat indicates that 'classic' prevention methods would fail if applied to 'undisciplined', migrant and poor communities.

A Europe-oriented malaria commission

This was indeed the very situation the Malaria Commission faced in Eastern Europe: it had to find efficient solutions for a multifaceted problem, delineated only in part by the

medical and scientific knowledge of the time, and rendered more complex by the social and political chaos that had followed the war.

The initial purpose of the 1923 Sub-Commission was to collect information concerning the development of malaria epidemics in every European country; to describe the measures taken in each country to combat the disease; and to address the questions raised by quinine use for preventive purposes. Information was to be gathered 'administratively' through questionnaires sent to each country. With the unabated spread of malaria throughout 1923, the fully-fledged Malaria Commission, created in 1924, must have decided that information gathered from questionnaires alone would be inadequate and unreliable. It therefore initiated a new approach that relied primarily on field studies carried out by Commission members themselves.

Upon its creation, the Malaria Commission comprised six members of the Health Commission (A. Lutrario, Rome; B. Nocht, Hamburg; G. Pittaluga, Madrid; D. Ottolenghi, Bologna; L. Raynaud, Algiers; L. Bernard, Paris), two experts (Colonel S. P. James, London and E. Marchoux, Paris) and seven correspondents (N. H. Swellengrebel, Amsterdam; L. Anigstein, Warsaw; M. Ciuca, Jassy; E. Marcinovski, Moscow; K. Markoff, Sofia; C. Moutoussis, Athens and H. Labranca, Rome). The list of members reflects the Commission's primary interest in European problems, although some members were better known for their work outside Europe (Marchoux in Brazil and Senegal, James in India and South-East Asia). The presence of Lutrario, the powerful Italian Director of Health, reflected the importance granted to Italy in the Malaria Commission. It is also of interest to note that two members, Nocht and Marcinovski, belonged to nations which had not yet been admitted to the League of Nations. Experts and correspondents, such as Émile Brumpt, who joined the Commission in 1926, were added to the list or replaced others, bringing the final number of members to about fifty. Written contributions were also solicited from scientists in non-European countries, including Carlos Chagas (Brazil; Chagas, 1925). Descriptions submitted by local experts were also published or used in the members' reports. Thus the combined efforts of the official members of the Malaria Commission, the corresponding members and the final reporting process reflected a genuinely international approach to malaria, despite the fact that the disease had mostly been studied in the European context, at least during the first years of the Commission's existence.

Separate reports addressed the need for an increased supply of quinine, the rationale for its distribution, the quest for substitutes, including vaccinations, and zooprophylaxis. For instance, the supply of quinine was considered adequate to cover all needs in 1923 (450 tons vis-à-vis a maximum production of 750 tons), but a shortage was foreseen if it started to be used properly (Perrot, 1924). Thus, the cultivation and isolation of strains of *Cinchona officinalis* that gave a higher yield were studied throughout the inter-war period, as were improvements to extraction techniques.

Printed reports were published by the publications department of the Health Organization of the League of Nations, in Geneva. The reports produced between 1924 and 1930 concerning malaria in different countries fell into two main categories. Most were individual reports, which the Commission summarized periodically to produce genuinely international overviews. These reports included studies by national experts from

northern Europe – Britain, the Netherlands, Germany and Scandinavia – where malaria had declined rapidly since the war. Enquiries on malaria in Greece and Albania were made by Commission members at the request of their governments. Meanwhile, Italy, deemed a special case in the fight against malaria, was also given special treatment in several reports, including that of a mission to Sicily in 1926. By contrast, the descriptions of malaria in Eastern Europe and in most of the Balkan states, areas where the severity of the epidemics had originally triggered the creation of the Commission, were genuinely collaborative and international, as were the visits to Spain, Egypt and Palestine in 1925. One or two members of the Commission, associated with local experts, traveled through the countries concerned, examined the epidemiological situation in various places, particularly in agricultural areas, visited health institutions, and talked at length with local health professionals about their needs and practices. Immediately after these visits, all the members of the Commission gathered in Italy and reported on their results. A preliminary report was drafted by Nocht, Pittaluga, James and Lothian[10] and approved by the Malaria Commission on March 26, 1925 (Report…, 1925b). The final report was approved in 1927 (James, 1927), but although it was based on the same observations as those reported in 1924, it drew strikingly different conclusions.

The 1924 mission to Eastern Europe

The itinerary

The tour included Russia, Romania, the Kingdom of the Serbs, Croats and Slovenes, Greece and Bulgaria. They left Zagreb on May 28th, 1924 and ended the tour in Rome for a final meeting on August 27-28th, 1924. Figure 1 depicts the route taken by the Malaria Commission. It seems that the study tour of the Ukraine (Don Area) made by Swellengrebel and that of the Volga and Caucasus areas made by Anigstein must have been rather superficial and limited to a handful of large cities. The reports on the Ukraine (Annex 8) and the Volga area (Annex 9) confirm the extreme difficulty the investigators faced in reaching solid conclusions, not only because of the paucity of direct observations that could be made in the field, but also because of the absence of reliable statistical data and the prevalence of other pathologies within a broader context of famine, particularly in the Ukraine (Report…, 1925a). As a result, the considerations retained in the report were only of a general nature.[11] The skepticism about the Russian data was justified *a posteriori* by the clichés used by E. Marcinowsky[12] in his communication to the First International Congress of Malariology in October 1925 (Congrès..., 1926). In contrast, the tours to the other countries were less open to criticism. Each individual report was very detailed. They contained descriptions of numerous visits to malaria-infected sites in the countryside, as well as to hospitals and teaching institutions. There do not seem to have been any restrictions on access to any of the sites. Detailed, reliable statistical data were obtained. The local practices used to combat malaria were reported, as were the local characteristics of anopheline breeding grounds. Information on administration and budgets was obtained. The reports were drawn up and then discussed. Sections of the final reports indicated that some members disagreed with some of the conclusions reached by the majority of the members.

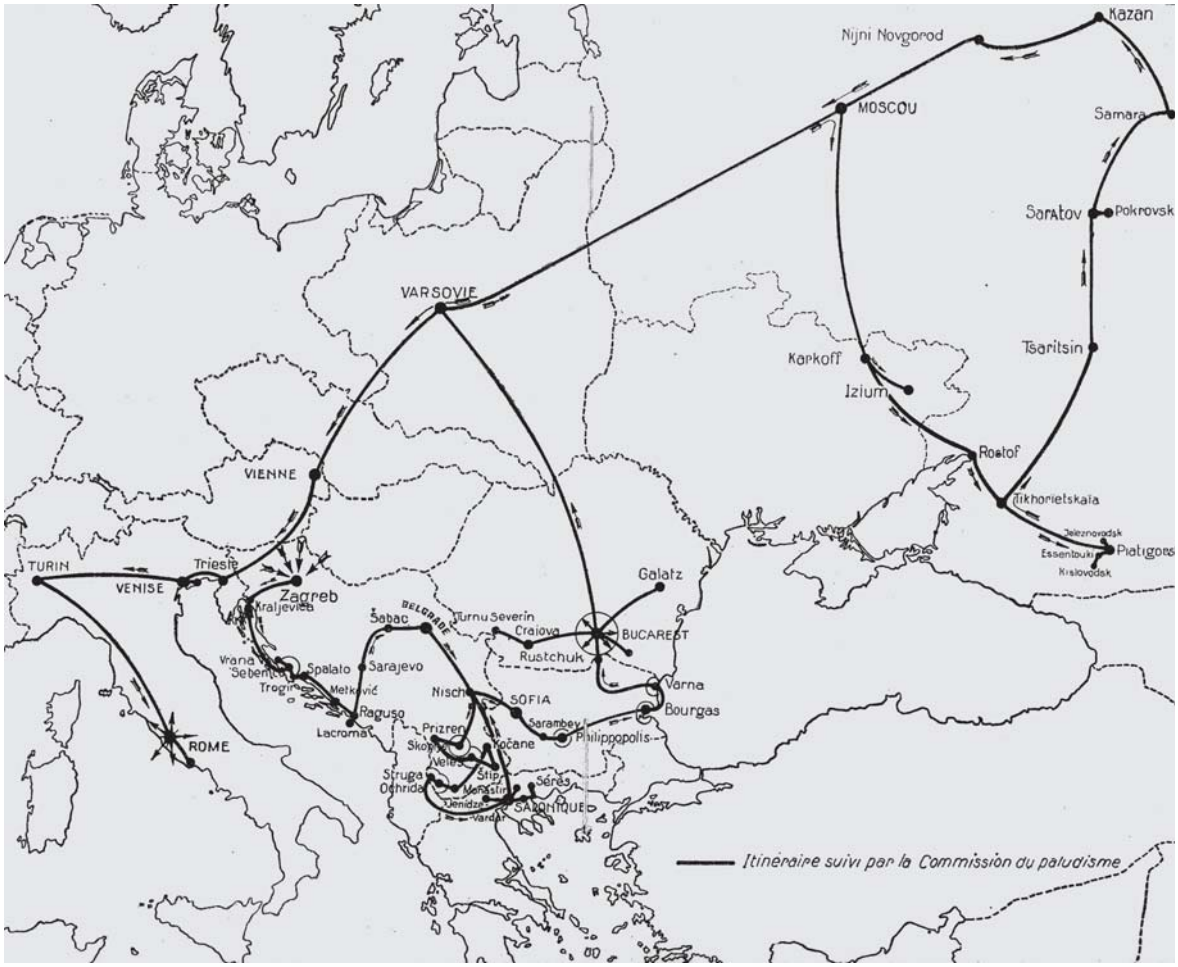

Figure 1: Itinerary of the Malaria Commission's 1924 study tour of Eastern Europe. They traveled on board a ship from Nijni-Novgorod to Tsaritsin on the Volga river (League..., 1925)

The conclusions reached by the Commission: The report published in March 1925 can be divided into two main parts (Report…, 1925a). The first part, entitled "Summarised impressions of the tour", is followed by thirteen detailed sectional reports, each written by a different Commission member. The sectional reports provided precise descriptions of the various aspects of the malaria problem in each country visited. In addition, they pointed out particular conditions that helped to explain the devastating epidemics of 1922-1923 (refugees from Anatolia to Greek Macedonia and Bulgaria, refugees from malaria-infested Russian Turkistan to the Upper Volga area, famine in the Ukraine, etc). They also reported on the unexpected occurrence of tropical malaria, presumably carried by refugees, and malignant forms of otherwise rather benign infections by *Plasmodium vivax* and/or *P. malariae*. Interestingly, the sectional reports all contained paragraphs describing the fauna, flora, temperature, water salinity, etc., of the mosquito breeding grounds in a bid to define the local conditions that supported the proliferation of the vectors. In other words, there was some concern on the part of the investigators to take account of the 'biological complexity' approach to malaria.

Although the sectional reports provide a wealth of interesting information, we will focus in the present paper on the "Summarised Impressions of the Tour", since this part of

the report was designed to draw up common guidelines that could be applied to all infected European countries (Report…, 1925a).

In order to be able to compare the data from the different countries, the Commission extracted data on specific parameters from each report (for example "social factors in malaria epidemics"), then grouped the individual observations to identify any common or distinctive traits. The analysis below follows the general scheme of the report and uses its subheadings.

Epidemiology

Orography: Under this term used mostly by geographers came descriptions of streamflows and the distribution of water in a given landscape. In all the countries, malaria was associated with the presence of marshes and stagnant water. In most of them the Commission associated a high risk of malaria with 'domestic' water: wells, fountains, aqueducts, cisterns and ponds, when located close to housing or work environments.

Anophelism: The main vector found in the summer months was nearly always *Anopheles maculipennis*. It was prevalent around domestic waters and inside houses and stables. The problem of "anophelism without malaria" (Hackett, 1937; Fantini, 1994; Evans, 1987; Opinel, 2008; Gachelin and Opinel, 2008) was not mentioned in this part of the report.[13]

Social factors: "The commission has been astonished by the importance of housing and food conditions in the different places studied: firstly, these factors influence resistance to malaria, and secondly they affect mortality rates." (Report…1925a, p.25).[14] Towns were not greatly affected, but rural housing was designed in such a way that it often favored the proliferation of *Anopheles* in houses and their immediate vicinity. Housing should therefore be completely redesigned, meaning that houses should actually be rebuilt so as to keep mosquitoes out of the living quarters, or built in mosquito-free areas. The effectiveness of using physical barriers to prevent insects from entering houses was deemed illusory given the economic state of nearly all the countries. The Commission drew attention to famine in the Ukraine and Russia and among refugees, and concluded that "Malaria is in short a social disease and equally with tuberculosis, is liable to be influenced and even partly eliminated to an appreciable extent by proved measures of social hygiene – notably those conditions of housing and feeding to which reference has been made" (Report…, 1925a, p.27). Mass migration was one of the social factors covered in the report. In particular, this had led to the introduction of parasites to areas where the people were not used to them (i.e. they were not 'immunized'). The Commission noted the significance of infections by more than one *Plasmodium* species in the Balkans, and outbreaks of pernicious malaria everywhere, but particularly in Russia (*P. falciparum* carried from Turkistan) and even in Italy. The latter parasite was brought to the north of Italy by soldiers from the south in a process that was akin to the traditional seasonal flows of agricultural workers, but more intense. At the time of the survey, however, populations, including displaced peoples, were becoming 'immune' to the new parasites, and the frequency of pernicious cases was in rapid decline.

Incidence and forms of malaria: The Commission confirmed the increase in the frequency and severity of malaria in all the countries visited. Its views were based on

morbidity and mortality records when these were available, although in some countries the numbers were no more than estimates. The Commission was clearly skeptical about the figures provided by the local authorities in the Ukraine and Russia. They also concluded that malaria in traditionally endemic areas had basically retained the same features it had had before the war, or was in the process of returning to them.

Parasitology and research: All the countries had trained physicians and technicians. A systematic survey to identify the parasites through blood tests should thus have been feasible. However, this was not common practice. The Commission believed a consensus could be reached about the extent of the disease by first palpating the spleen of all children, and then looking for parasites in the blood smears of patients with an enlarged spleen.

Organization of campaigns

Administrative: The anti-malaria campaigns were conducted in each country in such different ways that it was hard to compare them. However, the Commission noted that Italy and Romania had set up particularly efficient administrative structures. The reforms introduced in Greece and Russia appeared judicious, but were too recent for their results to be assessed.

Personnel and equipment: The availability of personnel and equipment also varied considerably from country to country. With the exception of Italy, there were not enough resources of either kind for campaigns to be conducted effectively. Russia had almost none of the resources required, and what supplies it did have were spread over such immense areas that they were too thin on the ground to be of any real use. Although good training centers existed in all the countries, too few personnel had been trained. The Italian malaria training station at Nettuno, in Italy, was mentioned as a model to be followed.

Finances: Only in Italy was the financing of malaria campaigns recorded in sufficient detail to be judged satisfactory. In all the other countries only more general budgets were provided with a shortlist of priorities (purchase of quinine, hydraulic works, etc.), making it impossible to accurately gauge how much was actually allocated to malaria campaigns. This lack of precision can be attributed in part to the fact that several different ministries were involved in anti-malaria measures (agriculture, health, internal affairs, armed forces, etc.).

Legislation: Italy was again cited as having model legislation. Its public health laws were judged to be entirely satisfactory, as was the State's monopoly on the purchase, storage and distribution of quinine (Greece had a similar model). The Commission considered the laws passed in Russia in 1923 and 1924 as original and interesting, as they aimed to prevent the creation of new sites at risk of malaria during agricultural and other public works.

Propaganda: Propaganda about malaria was used everywhere, but less in Romania, Bulgaria and Greece than in Serbia and Italy. The Commission was impressed by Russia's anti-malaria propaganda efforts, which included films, mobile hygiene exhibitions on railway wagons and conferences, all of which were targeted particularly at schools, factories and workers' clubs. However, doubts were expressed as to the efficiency of the propaganda directed at the peasantry because of the number, diversity and complexity of ethnological factors that had to be considered.

Systems: By 'system', the Commission meant the way the campaigns were organized. Depending on the country, the efforts were either malaria-oriented and then organized on a national or provincial level (Italy, Kingdom of the Serbs and Croats), or else considered as non-specific and thus included in broader hygiene campaigns designed to prevent infectious diseases in general (Russia).

Measures involving man

Therapeutics: The Commission was reassured that quinine was widely accepted as the basis for treating malaria. However, the supply and distribution of quinine was often deficient or disorganized. Excepting Italy, a country in which everything concerning quinine was strictly controlled, most other countries were deficient in at least one area. Most did not have the resources to buy quinine and depended either on old stocks or on stocks of quinine provided by Germany as part of its war reparations. Its prescription and distribution was usually haphazard. Even when distribution was perfectly organized in theory, as was the case in Russia, there was such a shortage of supplies (25% of Russia's estimated needs), a chronic shortage of personnel, and an undisciplined population (the treatment was interrupted as soon as the symptoms disappeared) that the administration of quinine was all but useless. In addition, there was no defined protocol for its administration. The single injection sometimes given to refugees appeared absurd to members of the Commission, who concluded that quinine supplies were being wasted, and that a major management effort was needed to rectify the situation. The Commission mentioned the use of other alkaloids derived from quinquina in Italy and the use of X-radiation of enlarged spleens to relieve splenic pain[15], but it did not express any opinion on the effects of these treatments.

Quinine prophylaxis: The Commission was rather negative about quinine prophylaxis. "The observations of the Commission do not lead to any favourable conclusion advocating the general prophylactic issues of quinine, the more so the drug can be much more usefully employed in treating actual cases" (Report…, 1925a, p.49). However, it did note that quinine prophylaxis could be efficient for disciplined, stable groups, such as the armed forces or railway workers.

Measures against the mosquito

Anti-larva procedure: The Commission expressed skepticism about most of the techniques being used to destroy larvae. The use of plants harmful to larvae was more frequently taught than put into practice. The employment of larvivorous fishes such as *Gambusia affinis* had started in Spain in 1922 and in Italy in 1924, but the results had not proved convincing, except, perhaps, in irrigation and drainage canals, provided the fish had been properly acclimatized. A similar skepticism prevailed about the use of chemicals like cresol or copper sulfate. Paris Green was being tested in Dalmatia and Italy, but no results had yet been published. Pumping seawater into lagoons to make them more saline had proved efficient in the context of large-scale works, as in the canals of Venice and Ferrara. Regular spraying of petrol on stagnant waters in the vicinity of houses appeared to be a reliable anti-larval technique, particularly when associated with clearing the vegetation on the banks, but this deprived cattle of access to drinking water. Similarly, stopping leaks

from fountains and wells and cementing around ponds could render the areas less suitable for larvae to breed.

Anti-adult mosquito procedures: with the exception of Italy, wire-gauze windows were rarely used due to their cost. The exception was the protection of railway and medical facilities. The quality of the gauze (mesh size) also needed to be defined. Mosquito nets were not routinely used, and the chemical destruction of insects inside houses was uncommon, although some protection was offered by smoke from open fires. The best method was still the manual killing of any mosquitoes that entered houses (often two hundred per room!), which were the most likely to infect their residents. Despite claims made by peasants and shepherds, it was judged that the presence of animals and stables close to housing did not affect the rate of infection of humans.

Improvement measures

Of the soil: In this part of the report, experts were back in familiar territory: "In almost all the countries visited, many marshy areas, shallow lakes and lagoons and similar actual or potential mosquito-breeding areas demand drainage treatment" (Report…, 1925a). The experts distinguished the various means for achieving this (e.g. forestation) from the classic method of drainage, which had to be adapted to each local situation. The procedures in place in Italy were again the reference: "Italy has long led the way with her major bonifications undertaken, from the first, not only for economic and agricultural reasons, but also with a hygienic end in view – a fact distinguishing them from those of other countries where the purpose was purely agricultural." (Report…, 1925a, p.59). The link between economy and hygiene for a malaria campaign to be efficient was certainly a dominant general conclusion of the Commission. They noted the absence of water management projects in countries other than Italy, largely because of insufficient funding, but also because the precise implications of the Italian Bonifica program were not understood.[16]

Of the population: The Commission felt "bound to reiterate the importance of the general social and hygienic condition of a people in relation to the extent and severity with which malaria shows itself. Housing and food should be improved." They believed that "improved economic conditions … will tend to stimulate the inertia of misery into organized activity and allow the extension of health services, and make quinine use more efficient." (Report…, 1925a, p.63).

A preliminary program to fight malaria tinged with humility

The Commission distinguished the endemicity of malaria from epidemic outbreaks of the disease, which were mostly due to human migration. They noted that the ordinary methods of fighting the endemic disease were ineffective in epidemics. Moreover, some of the European countries in question had been so occupied with post-war epidemics that they were only just starting to establish a health policy that would include major campaigns against malaria. The Commission noted repeatedly that greater attention should be paid to general sanitation and public health, and thus that states should prepare for malaria in the long term rather than focusing on responding to epidemics. In addition, a novel

type of malarial endemicity was observed to develop after an outbreak. In view of this, in defining the steps to be taken, the Commission first admitted that no single, definitive, practical solution could be proposed to eradicate malaria across the board. Instead, it introduced a series of indispensable primary measures which could be introduced at a low cost everywhere:

– Thorough treatment and after treatment of all cases of malaria (which depended on the set-up of the health services per se);
– The discovery and treatment of all cases diagnosed after careful inspections of schools, factories and houses;
– The instruction of the inhabitants as to how malaria is spread, how to catch and kill mosquitoes daily, the importance of using mosquito nets, and the importance of clearing stagnant domestic water around houses.

For centuries, hydrological works, drainage and land reclamation had been seen as the basis for any long-term policy designed to eradicate endemic fevers, then malaria. The Commission concluded that engineering techniques for channeling and draining water were of unquestionable value. However, water management was left to government agencies and to the initiatives of trained personnel (which meant many more technical personnel needed to be trained). The Commission advocated simple, local procedures that were well known and easy to introduce on the small scale, even by unskilled workers, such as draining stagnant water or spraying petroleum.

Considering that the Commission's conclusions were the outcome of a lengthy, difficult and methodical study of malaria in Eastern and Mediterranean Europe, they may appear rather thin on the ground. It is difficult to detect the schism between the two 'schools' of malariology in the report, although social factors and the need for economic improvement are repeatedly pointed out. We would prefer to say that the conclusions reached by the Commission were tinged with humility and realism, and genuinely reflected what could actually be done in the context of the prevailing technical, educational and financial situation after years of war and epidemics of influenza and typhus. The proposals could also be seen as a way of introducing easily understandable procedures into daily and routine activities in the home and in farm work, and thus an attempt to create a kind of 'anti-malaria culture' in the population, who would then avoid hazardous practices. Propaganda, particularly in Russia, was clearly designed with this in mind. However, even with such apparently limited ambitions, the suggested primary measures required the training of medical staff, the establishment of a medical network for quinine distribution, an adequate supply of quinine, and a continuous policy of teaching people about simple rules for anti-malaria hygiene, particularly in schools.

Comparing anti-malaria strategies: the First International Congress of Malariology in Rome, 1925

The First International Congress of Malariology was held in Rome on October 4th to 6th, 1925: just a few months after the discussion of the Malaria Commission report. The

event provides a precise introduction to the techniques and strategies for malaria control used at that time by a group of recognized experts (about 230 participants from around the world) that was larger than the Malaria Commission, and also represented different epidemiological situations. It is worth emphasizing that the meeting constituted one of the very first opportunities for most of the participants to meet each other and to engage in serious scientific discussions about several aspects of malariology, especially the pathophysiology of malaria and its different forms, and the strategies designed in different countries to fight the disease. Speakers offered syntheses of their own, so the Congress constituted a kind of complement to the Commission's March 1925 report, extended to the entire world.

The congress was organized by the Italian Society of Malariology. In addition to many Italian participants and a large official Italian delegation headed by Marchiafava[17], Lutrario and Messea, all directors of health services, the invited participants were French (such as Brumpt, Faculté de Médecine de Paris; Tanon, Société de Médecine et d'Hygiène Tropicale, Paris; Marchoux, Public Health Director; Edmond and Étienne Sergent, Institut Pasteur of Algiers), Brazilian (Chagas, Instituto Oswaldo Cruz, Rio), American (Gunn and Hackett, Rockefeller Foundation head office and representative in Italy), Spanish (Pittaluga, Directorate of Public Health), and Dutch (Swellengrebel). The League of Nations was represented by James, Lutrario, Nocht and Pittaluga. The London School of Hygiene and Tropical Medicine and the Liverpool School of Tropical Medicine were represented by Thompson and Stephens, respectively. Thus, all the major figures and institutions dealing specifically in malaria and more generally in parasitology were at the congress.

The congress proceedings give a precise idea of the theories and methods in use or under development at the time. The community agreed on the causes of malaria, but different delegates favored different methods for attacking the *Plasmodium* cycle, based on their own experience. As a result, the therapeutic and prophylactic techniques they defended were not exactly the same. Their choices depended upon the hierarchy given to the different factors that contributed towards epidemics in a given geographic location. Nearly all the prevention techniques reported were already known: the mass preventive administration of quinine; protection from adult mosquitoes; environmental improvements (drainage, mowing of river banks, drainage of ponds or any still water reservoir); and larvicide methods (spraying of oil or Paris Green, although the latter was still experimental and quite a new material which, because of its low cost, superseded the use of trioxymethylene powder). The discussions thus revolved around the relative effectiveness and importance of each of these approaches.

About half of the written contributions to the congress presented procedures used in different countries, and therefore defended specific national or local approaches to the issue. Nevertheless, some brought interesting general notions to the debate. De Sousa (Brazil) insisted on the usefulness of first identifying the areas where the sub-species of *Anopheles* identified as the vector (*Anopheles argyritasis*) lived, then treating only these areas. He argued that this saved a lot of money. The influence of the Rockefeller Foundation is obvious in this particular case. Also, individual doses of quinine were centrally prepared at Instituto Oswaldo Cruz in Rio de Janeiro, and a school of malariology had been

established in the same city with the help of the Rockefeller Foundation. Edmond Sergent (1878-1948) and Étienne Sergent (1876-1969) described a kind of colonial approach to the malaria problem in Algeria, by focusing their report on the type of persons to be protected (whether individuals or groups, whether staying for a long or short time in an infected area) but mainly considered colonial settlements and garrisons. The methods were largely the same as described before WWI, and included the alternation of water irrigation flows every 14 days so that larvae could not complete their development, since these sites were repeatedly dried up. The method had been tried with some success in a small area in the Mitidja, near Algiers (Sergent, 1910). The communication by J. Kliger (Haifa, Palestine) described the almost total eradication of malaria in the Jordan Valley (Huleh area, north of Tiberias lake) by using combinations of all the anti-larval (fish) and drainage techniques available, where appropriate. This resulted in such an improvement to the quality of the land with respect to malaria and marshes that agriculture could be introduced safely (Report…, 1925b).

More personal views on how to solve the malaria problem were also expressed. These are particularly interesting since they reveal diverse approaches to the fight against malaria. Some were biased towards chemistry, searching for the best way to kill the *Plasmodium*. Marchoux delivered a kind of synthesis in which he discussed the disease as associated to a unique species or to several species of parasites (privileging the latter, like most malariologists). Marchoux was mostly interested in the medical approach to the problem, and was concerned with the type of chemotherapy to be used when prophylaxis had not been used or had proven ineffective. Chemotherapy was then the only way to cure patients and interrupt the parasitic cycle. In addition to quinine and some other alkaloids, he favored the use of arsenobenzenes such as Stovarsol, a new drug synthesized by a colleague at Institut Pasteur, Ernest Fourneau (Debue-Barazer, 2007). Indeed, a paper was given by Feletti, an Italian malariologist from Catane, who confirmed the positive therapeutic effects of Stovarsol on malaria.[18] Other treatments, such as irradiation of the spleen or the use of mercury derivatives, were also proposed.[19] For Marchoux, despite all the epidemiological factors that were usually considered in anti-malaria campaigns, the ultimate objective of prophylaxis was achieved by treating human reservoirs of the parasite, by curing all previously infected individuals. Thus, he argued, systematic administration of quinine was the only direct method, the other methods being indirect (including Bonifica and anti-larval measures) and known to be less effective.

In contrast to Marchoux's proposal, an intriguing and potentially useful aspect of the biology of *Anopheles* was discussed by another outstanding figure in parasitology, Carlos Chagas (1879-1934). His idea was to interrupt the cycle of transmission of *Plasmodium* by killing the most infectious insects: those present in houses. Chagas developed a rather audacious yet intriguing theory known as the household hypothesis. For him "malaria is primarily a domiciliary infection" (Chagas, 1925, p.67*)*. As he saw it, the notion that houses were the focus of malaria infection was essential, and constituted an undeniable principle. The house was an important element in the longevity of the *Anopheles*, and contributed "to the completion of hematozoon cycle in the body" (Chagas, 1925, p.67). Chagas believed that the mosquito died when it laid its eggs on water. In the absence of

water (as in houses), egg laying was delayed by up to twenty days and the insects were able to infect humans since the parasite had completed its cycle (one must keep in mind that the parasite was not infectious if its cycle was not completed in the *Anopheles*). When confined to a closed environment, *Anopheles* can bite humans repeatedly and infect large numbers of people. Moreover, according to Chagas, as the mosquito became heavier because of the weight of its eggs, it would take shorter flights and would tend to remain inside the house or in its vicinity. Chagas considered 'home-bred' mosquitoes to be one of the major causes of infection and re-infection. One thing that seemed to confirm his theory was the fact that the most infected demographic group was infants and young children, who spent longer indoors. Chagas's proposed method of prophylaxis therefore consisted in killing the insects inside houses. A physical barrier (metal screens) could also prevent mosquitoes from entering houses. Once they were inside, they should be killed with sulfur or pyrethrin fumigation, as used to fight yellow fever in Rio de Janeiro in 1903 (Löwy, 2001) and also proposed for use against *Anopheles* in Algiers by the Sergent brothers in 1909. Chagas said he had successfully used the method in areas with very high endemicity and epidemicity; indeed, it was a theory he had already proposed in 1906 in his doctoral thesis (Chagas, 1906-1907). He ultimately accepted the additional practice of systematic administration of quinine, thus joining his voice to Marchoux's after having insisted on in-house killing of mosquitoes. Nonetheless, Chagas' lecture contributed to the propagation of housing-oriented theories on malaria.[20]

Two antilarval procedures that were entirely different from previously known methods certainly constituted the main novelty of the meeting. Indeed, both were examples of inexpensive, local anti-larval measures that complemented or even opposed policies focusing on hydraulic works or the systematic administration of quinine. The idea was to kill the vector before it was able to infect humans. So far, the dispersion of fluid oils or petrol was the only well-tested and efficient anti-larval procedure.

The first idea was that larvae could be eaten by fish.[21] *Gambusia affinis* or *G. holbrooki* are small, larvivorous fish found in the wild in Eastern American rivers. Provided they could be accustomed to the salinity of the waters where they were to be used and there were no predators present, *Gambusia* would proliferate and consume the *Anopheles* larvae at the water/air interface. Their use had been recommended by the American Health Department in 1919, and breeding colonies had first been created in Spain in 1921 and in Italy in 1924. Sella, a distinguished Italian parasitologist, gave a paper describing the procedures used and the results obtained. Our analysis of the Italian national archives (Invio..., 1939) has indirectly confirmed the validity of this method (primarily that used by Brumpt in Corsica; Opinel, Gachelin, 2004) and, above all, its worldwide success. Actually, the *Gambusia* breeding program established by the Istituto Ittiogenico de Roma in ponds near Rome and their sale to different locations in Italy and some foreign countries (France, Cameroon, Greece, etc.) was a source of profit. This trade can be traced up to 1939, and constitutes a hallmark of the widespread use of fish in the control of malaria (Invio..., 1939).

Larvae could also be killed by some chemicals. Indeed, the second novelty presented at the congress was considered a breakthrough in the field of anti-larval procedures. Two American scientists reported on the use of a specific larvicidal chemical agent called Paris

Green. It is a chemical made by combining arsenic oxide and copper sulfate to produce a deep green compound previously used as the basis for anti-algae paint for wooden ships and as a pesticide against the potato beetle. The powder was mixed with road dust at a 1:100 ratio and spread on the water surface. The larvae would ingest the particles and eventually die. M. A. Barber reported large-scale experiments in the USA on the various ways of spreading the drug and showed a 99% decline in larvae following aerial spraying. L. W. Hackett (1884-1962) reported on the efficacy of Paris Green under Italian climatic conditions in geographical areas untouched by the Bonifica program (Congrès..., 1926, p.158), having first mentioned the positive results of earlier experiments carried out in other countries by Hayne (USA, 1922), King (USA, 1923), Kliger and Shapiro (Palestine, 1923-1924), Boyd and Davis (Brazil, 1923), and Tiedeman (Philippines, 1924). He then reported on the results of his experiments with Alberto Missiroli (1883-1951) during the 1924-1925 campaigns against malaria. Missiroli and Hackett noted that all the larvae in the treated areas died overnight. After repeated spraying campaigns in April, May and June, the population of adult *Anopheles* was greatly reduced. The trials, presented as the result of collaborative work between the International Board of Hygiene of the Rockefeller Foundation and the Italian Health Department, were undertaken in Porto-Torres (Sardinia) along six kilometers of the Turitano river (a total of 243,000m^2 were sprayed; see Figures 2 and 3) and in Bianconovo (Calabria). In addition to the report on the effectiveness of

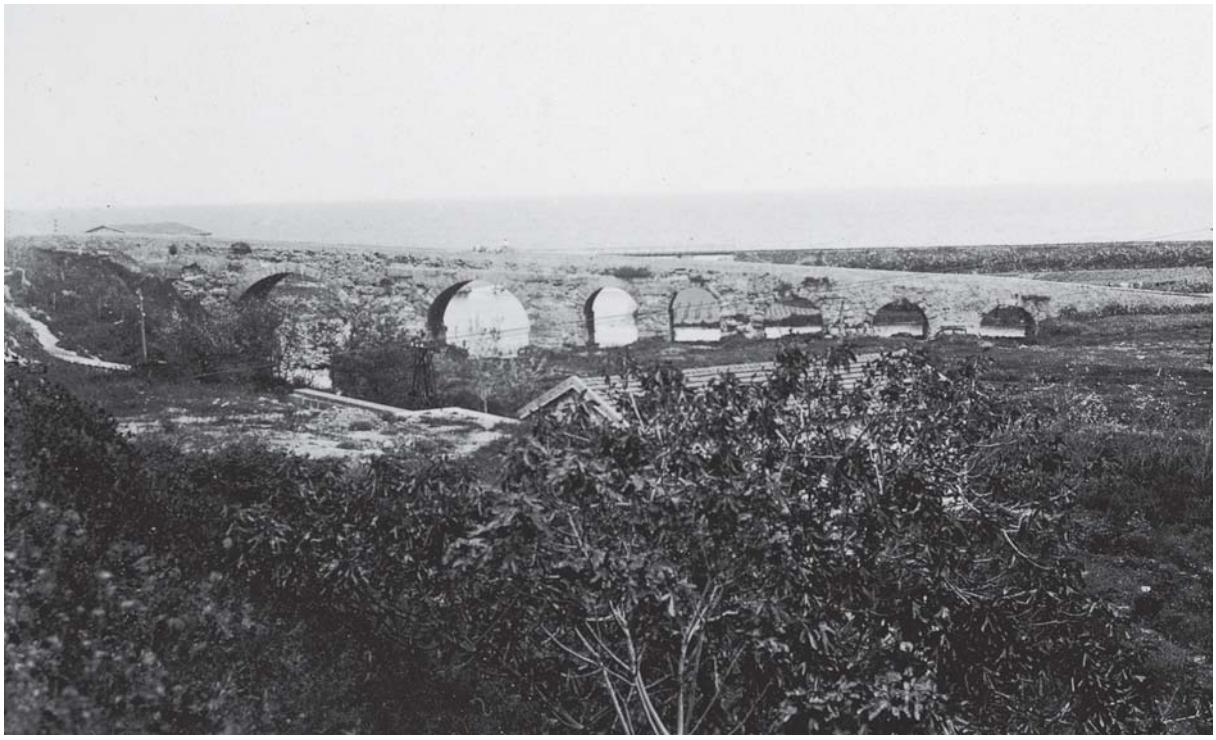

Figure 2: Porto Torres, Sardinia: malaria-infested area in the vicinity of Ponte Romano at the mouth of Turitano river. The roof visible in the photograph is that of the building used by the Rockefeller Foundation workers to prepare Paris Green (Mayor of Porto Torres, personal communication; Archives..., 1926)

Figure 3: Porto Torres, Sardinia: main stream of the Turitano river. The entire area had been cleared of *Anopheles* by the Rockefeller Foundation in conjunction with the Department of Health in a seven-year mission following the initial 1925 trials (M. Coluzzi, personal communication; Archives..., 1926)

Paris Green, Hackett reported on some other properties of the chemical. The drug did not kill eggs and pupae and did not affect other animal species.[22] Two days after treatment, the arsenic had disappeared and the water was drinkable. The overall costs were low, mainly due to reduced manpower requirements: something in the region of 10 Lires/1000 square meters, or 2.55 Lires/inhabitant in Porto-Torres and 1.75 Lires/inhabitant in Calabria. Skilled labor was not required. Treatment with Paris Green was supplemented by seeding of *Gambusia* wherever necessary. However, Hackett admitted that hydrological works were still needed for treating large areas of water.[23] (Figure 4)

Efficient, cheap, portable, and unattractive for thieves: all these features made Paris Green a very appealing procedure from amongst the diversity of anti-malaria methods. Hackett had previously regularly reported to the New York headquarters (Hackett, 19th May 1925, 7th Aug. 1925). He mentioned that their results had been applauded at the Rome meeting.[24] One month later he told the New York offices that he had distributed thousand copies of the paper he had delivered at the Rome congress (Hackett, 20th Nov.

Figure 4: Porto Torres, Sardinia: Offices for the distribution of quinine (Archives..., 1926)

1925). Members of the Malaria Commission of the League of Nations, notably Swellengrebel, added the testing of Paris Green to their commissioned field trials of anti-larvae agents (Swellengrebel, Rodenwaldt, 21st Jan. 1927).

The Rockefeller Foundation's approach to malaria: a scientifically and economically sound anti-larval strategy.

Hackett's field trials were the first in Europe that made use of the Rockefeller Foundation's strategy to combat malaria. They can also be seen as part of a broader implementation of the foundation's hygiene initiatives in Europe. The Italian government may have recognized the successes of the Rockefeller Foundation's campaigns against hookworm, yellow fever and malaria in the Americas, and may have requested its help for malaria control. However, we have recently shown that at that very time, the foundation was actively looking for places and means for establishing institutes of hygiene in Europe (Opinel, Gachelin, 2004).

Italy was on its list. Whatever the motives for his presence in Italy, Hackett was there in 1923. He won over Mussolini, who was keen to draw closer ties with American institutions, and soon started working on malaria in several locations, all highly infested areas that were outside the domains covered by the Grande Bonifica authorities (Hackett, 1937).

Actually, since 1913, the Rockefeller Foundation had had a scientifically and economically sound anti-larval approach to malaria that was largely inspired by Darling's studies in Panama at the beginning of the 20th century (Vieira, 1998). The procedures changed according to the geographical conditions. We previously described the economic and scientific rationales behind the foundation's anti-malaria strategy in the Mediterranean area in a study on Brumpt's work in Corsica (Opinel, Gachelin, 2004). Basically, the Rockefeller Foundation would contribute to any campaign if certain, precise conditions were met: agreement of the local and political authorities and partial financing of the campaign by local authorities. Much of the initial budget for the first three years would be provided by the Rockefeller Foundation, renewable for a further three years if steps were taken by the local authorities to take over the foundation's initiatives. By the end of the six-year contract, the local health administration should have the means to keep the campaigns going by themselves. This strategy implied investments in training local people, and relied on local action funded by local administrations. As such, it excluded large-scale hydrological and public works.

The preliminary work included an extensive epidemiological study of the population, associated with an extensive, meticulous search for potentially infectious *Anopheles*, and finally a very detailed assessment of their breeding grounds. Modern laboratory equipment was used. For every location, the results of the work were depicted on a map which showed the species of *Anopheles*, the type of *Plasmodium* in the patients, the stages of larval development, and detailed orographic/hydrological information on the location (Figure 5). By this procedure, the places to be treated were identified and the different, inexpensive methods to be used in each case were selected.[25] In some cases, a description was even made on the level of individual farms and their immediate surroundings, as shown for example in Brumpt's report to the *Commission d'hygiène* written in 1926 following the first field school of the School of Malariology of Paris in Camargue (Brumpt, 1926). Quinine was only administered to patients via a network of dispensaries. The idea was to interrupt the cycle of *Plasmodium* transmission by killing *Anopheles* larvae before they had developed into adults and could become infected. It was an approach that was efficient and inexpensive, mostly involving unskilled labor. This obviously made the Rockefeller Foundation's program attractive to politicians, and it also explains why the foundation actively researched new anti-larval agents (such as Paris Green and *Gambusia*) and also carried out extensive studies on insect biology and genetics.[26] Medical entomologists, such as Brumpt in France and Missiroli and others in Italy, were very interested in these original approaches, largely because they directly linked scientific research with field applications. Also, in contrast to large hydraulic works, which depended on State authorization and compliance, the Rockefeller Foundation's strategy placed individual responsibility at the very heart of anti-malaria campaigns.

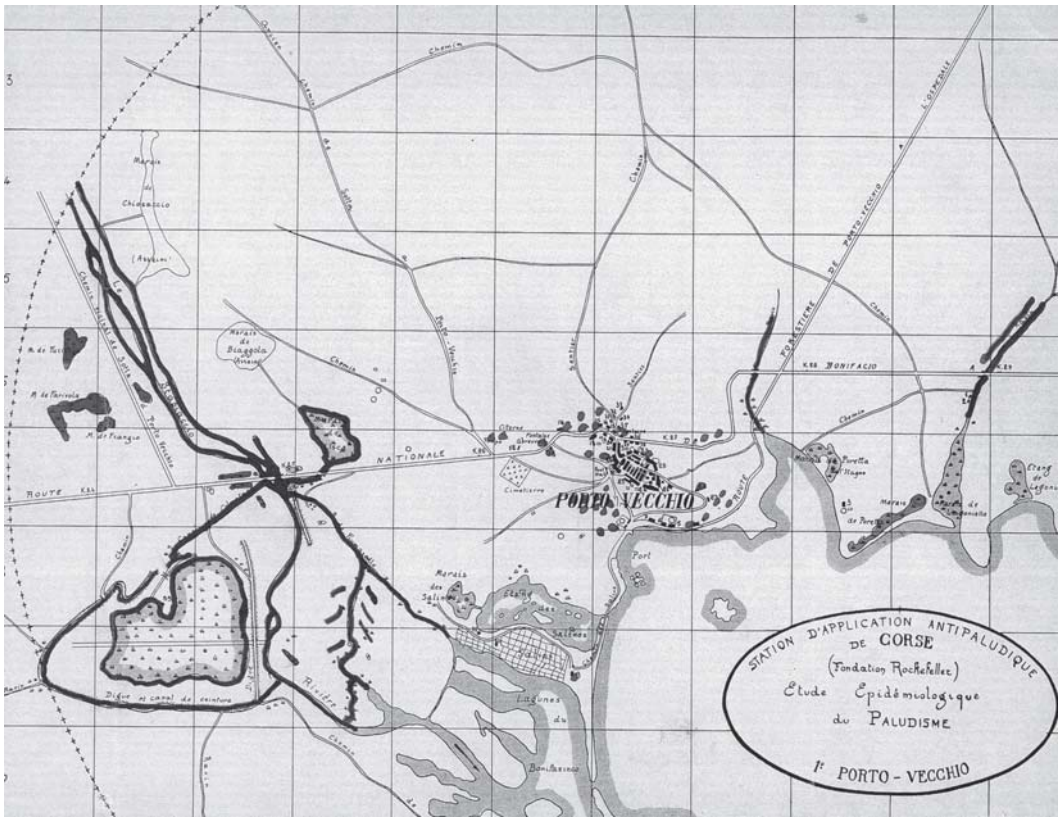

Figure 5: Sanitation map of Porto-Vecchio, Corsica. The places where petrol and Paris Green should be spread to kill *Anopheles* larvae are indicated in brown and purple, respectively (Archives..., 1926)

Was the Italian Grande Bonifica primarily aimed at combating malaria?

The exact opposite of the anti-larval approach taken by the Rockefeller Foundation was the long-term Italian project named Grande Bonifica. The Malaria Commission had noted several times that Italy, although faced with a similar increase in the number and severity of malaria cases during and after WWI, managed the crisis rapidly by itself. For most of the Commission members, the efficient management of the Italian malaria crisis underlined the importance of a good health system coupled with a long-term policy of land management, the Grande Bonifica. Was this the model to follow? It may come as some surprise, then, that Grande Bonifica was neither presented scientifically nor discussed at the Congress. How can this be explained?

It was obviously not from ignorance of the scheme. Nearly all the members of the Malaria Commission met in Venice on August 15th, 1924, for a study tour of the Italian campaigns against malaria. Only areas included in the program were visited: the initial tour itinerary was shortened and restricted to the places where the government had invested the most and where Grande Bonifica and large hydrological works could be considered to have been beneficial (Po valley, Agro Romano and the Pontine marshes). Sardinia, Sicily and Campania – all heavily infected – were excluded from the itinerary, although a tour to Sicily was organized later. Two main reports were written at the end of the survey. The report on the tour was written by L. Raynaud, Inspector-General of the Health Services of Algeria. It was followed by cautionary comments by Swellengrebel entitled, "Some aspects

of the malaria problem in Italy" (Swellengrebel, 1925a, p.168). The existence of two different reports drawing very different conclusions illustrates the debate over the impact Bonifica had on malaria and whether it should be coordinated with anti-malaria campaigns. It also indicates the confusion about issues which appear to have been deliberately organized by the Italians, probably because of the existing divergence on malaria between Italian scientists, the Directorate of Health, and the powerful Ministry of Public Works. The report written by Raynaud reflects the official nature of the visit: it contains few observations by the Commission proper and is mostly limited to information provided by Italian officials. Its conclusion thus summarizes well what the Italian government deemed to be efficient. The initial 1883 Bonifica law had been made necessary by the need to reclaim land for agriculture by draining marshes. Italy had lived with fevers for ages, and campaigns against malaria had always run in parallel with agricultural development. Raynaud considered the coherent development of Bonifica laws to be of critical importance[27], while adjusting the fight against malaria to take new scientific discoveries into account (he points out the importance of Italian research and scientific organizations). The notion of four distinct Bonifica strategies was introduced. First, considerable funds had been invested in land reclamation, extensive drainage and the construction of a hydraulic system (see Figure 6 for the network of canals in Campagna Romana and Figure 7 for plans of hydraulic plants): Grande Bonifica, as it was called after 1923 (Raynaud prefers to speak of "telluric prophylaxis of malaria"), was placed under the control of the Ministry of Public Works or of local consortiums. According to Lutrario, more than five hundred million Lires had been allocated to the

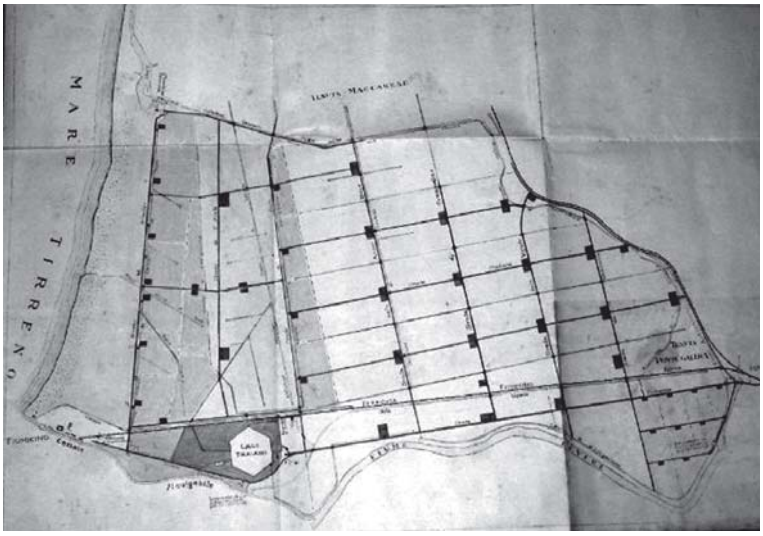

Figure 6: Network of drainage channels in Agro Romano, north of the mouth of the Tibre river (Progetto..., 1925)

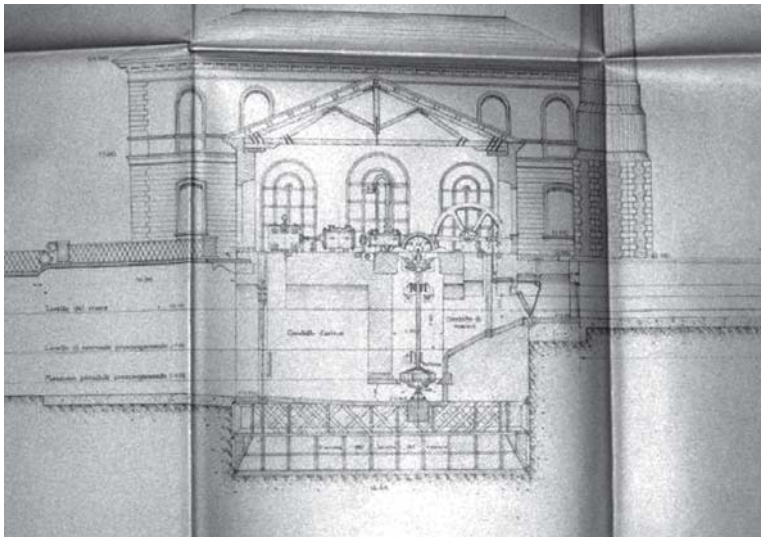

Figure 7: Scheme of an electricity driven hydraulic pump plant in Agro Romano (Scheme..., ca. 1924)

Bonifica program since 1883, which also made it an important economic driver because of the contracts won by the many firms involved in the hydraulic and public works. Actually, this dominant situation stood in stark contrast with the comparative weakness of the health department in charge of the distribution of quinine. The second critical measure taken in the previous years concerned the law on the state monopoly of quinine. The Torino quinine factory, placed under the control of the Ministry of Finance, produced sixty tons of quinine a year (which was supplemented by 27 tons of imported quinine). It was sold at a fixed price and distributed either in municipal dispensaries or through numerous charitable institutions. About ten thousand specialized physicians (*Condotti medici*) were in charge of malaria surveys and treatment, and the Directorate of Public Health was in charge of malaria sanatoriums, and mobile and fixed dispensaries. The quinine monopoly facilitated the cure of patients and prophylaxis; indeed, the use of quinine for prevention was considered very effective: this well-defined organization of quinine production and distribution led to the second program: human *bonifica*. Third, local anti-larval measures, named small *bonifica*, were considered helpful but of limited value, despite the strong support they enjoyed from Grassi and co-workers in their laboratory in Fiumicino, near Ostia. The fourth program, land *bonifica*, consisted of the agricultural development of reclaimed land. Finally, the importance of the training of specialized personal was emphasized (the training station at Nettuno was visited). The selection of the places to receive all the *bonifica* measures was motivated by economic and political factors: they were located in the richest parts of the country.

Yet the question remains: Was there any evidence that the Grande Bonifica policy was actually effective against malaria? And if so, should the Commission have recommended that other countries follow suit? This may sound presumptuous, but it was clearly one of Swellengrebel's concerns (Report…, 1925a, p.168). After a lengthy, cautionary introduction, the Dutch malariologist stated that he was not convinced by the official reports: for him, the answer to the two questions was 'no'. In addition, he pointed out that draining land and distributing quinine could not be characterized as recent scientific progress. Malaria had always been associated with marshes, but the presence of marshes was not what made malaria endemic, since few people lived in their vicinity. The roots of the endemicity of the disease were more local than general. He pointed to the lack of evidence that extensive hydrological works and draining had actually resulted in a decrease in malaria. Indeed, these engineering works often increased the number of mosquitoes and then increased the endemicity of malaria because of the marked influx of agricultural workers. However, because the people were less poor, they developed milder forms of the disease and the overall mortality decreased, although endemicity did not. Swellengrebel had seen a similar course of events in Holland. It was thus not correct to define the Grande Bonifica as an anti-malaria strategy. Wherever the sanitary conditions were genuinely improved, the anti-malaria effects observed were due to better housing and diverse hygiene-enhancing procedures such as the creation of small towns in the center of the improved land.[28] In addition, wrote Swellengrebel, it was not true that everyone in Italy agreed with the anti-malaria role the Grande Bonifica procedures were reputed to have: most Italian scientists and physicians had concluded that anti-larval measures (small *bonifica*) were the real

achievements of modern science and the only genuinely helpful interventions for communities living in infested areas, including in areas that had received the program. For Swellengrebel, Grande Bonifica had had no direct effect on malaria endemicity, although he did note: "The exception of course are hydraulic works of such a kind as to prevent all larval growth, in which case its hygienic value may stand quite apart from its economic merit" (Swellengrebel, 1925a, p.169). Swellengrebel concluded that an effective fight against malaria should comprise two phases: first an individual (local) phase aimed at reducing the death rate but not necessarily the sick rate, to be followed by a general sanitation phase, which could be associated with Grande Bonifica as well as other strategies aimed at improving the people's economic circumstances and consequently their overall health and resistance to infection.

The intervention made by Swellengrebel, who clearly disagreed with Raynaud[29], was evidently the basis for the primary guidelines proposed by the Commission, discussed in a previous section of this paper. The lesson to be drawn from Italy was that the Grande Bonifica was not 'the' model for campaigns against malaria, but could be part of a much more complex and lengthy process aimed at coupling economic development with improvements in general sanitary conditions. Grande Bonifica was exported wholesale to Argentina, but failed (Carter, 2007). A second lesson drawn by Raynaud was that the effective administration of quinine had most probably been behind the rapid improvement in malaria after the war.

The Congress of Malariology took place in this very peculiar context. Success in fighting malaria had clearly become a political issue, of which Bonifica was admitted to be the tool. The congress was placed under the patronage of Benito Mussolini, who opened it with an official inaugural speech in the presence of several ministers and political luminaries who attended at least part of the meeting. He underlined the striking example of international collaboration in the fight against malaria, involving Italy, France, England and the USA. For him, the congress program was "a program of prevention primarily envisaging the methods to be used in the fight" (Mussolini, 1926, p.30), and he justified state intervention in the resolution of the malaria problem because of its severity and the monopoly of the manufacture and distribution of quinine. Malaria was one of the most important public health problems the Italian kingdom had dealt with, by a combination of Bonifica programs and quinine administration.

Surprisingly, the progress in the fight against malaria achieved thanks to Bonifica was not discussed at the congress. However, it was made apparent to all the participants that the main project (and effectively the major achievement) of the fascist government was the Bonifica program in the Po valley and the Pontine marshes, and that the Italian officials saw this program and malaria control as inextricably linked. At the end of the congress, Professor Gosio (Director of Health of Rome) asked for a resolution to be passed by the participants: "The International Congress of Malariology, applauding the marvellous work of so many people involved in *bonifica* and that of so many agriculture workers who deserved so much with respect to hygiene and civilization, considering that Grande Bonifica is a very true and very stable step against malaria, expresses the strong wish that Grande Bonifica is further intensified in agreement with modern etiological knowledge"[30]

(Congrès..., 1926). The resolution was not discussed by the participants, but was subsequently adopted by the organizing committee of the congress, with the notable exception of the Director of Health of Campania. A discussion of the principles and benefits of Grande Bonifica was later added to Malaria commission reports by the Italian parasitologist Lutrario (Lutrario, 1928).

The use of the congress to promote Italy's malaria policy was manifest during the Congress tour. The tour took participants to places where Grande Bonifica projects were in progress: the Campagna Romana and the surrounding marshes, the hydraulic plants of Ferrara in the Po valley, and the training school of Nettuno. One of the tour participants, Brumpt, acted as a kind of photo reporter of this tour of the Bonifica and other anti-malaria procedures and their results (Figures 8 to 16).[31] Interestingly enough, this tour was basically the same, albeit shorter, as the one organized for the members of the Malaria Commission a year earlier, which confirms its official design and intent. The result of Grande Bonifica was also a showcase for what Italy had achieved in terms of malaria control and social progress.

Raynaud's support for Bonifica in anti-malaria campaigns and Swellengrebel's skepticism towards its efficacy were thus to be replaced in that very complex context which interlaced political, economic and medical issues. The Italian state's investments in large-scale hydraulic works were impressive and resulted in improved social and health conditions for agricultural workers. Since social improvements were widely assumed to contribute towards a decline in malaria, Bonifica should also contribute to the fight against malaria. However, no evidence was presented with regard to its actual effectiveness against the disease. Moreover, although the improvements in agricultural efficiency were self-evident, the anti-malaria actions shown at the training school of Nettuno were actually applicable to small and human *bonifica* rather than to Grande Bonifica. Swellengrebel's doubts about the precise role of Grande Bonifica in anti-malaria campaigns remained unanswered.

Figure 8: Spraying of Paris Green by individual workers. Agro Romano, 1925 (Archives..., 1925)

Figure 9: Mechanized spraying of Paris Green over a large area of water**.** Agro Romano, 1925 (Archives..., 1925)

Figure 10: A farm on Prince Torlonia's lands in an area included in the Bonifica program. Agro Romano, 1925 (Archives..., 1925)

Figure 11: Malaria training school of Nettuno, Lazio. Examples of drainage systems. (Archives..., 1925)

Figure 12: Malaria training school of Nettuno, Lazio. Display of samples of wire gauze to be fitted in doors and windows (Archives..., 1925)

Figure 13: Malaria training school of Nettuno, Lazio. The tools used for small *bonifica* (Archives..., 1925)

Figure 14: A hut for agricultural workers in Tre Cancelli, in the immediate vicinity of Rome, close to Nettuno. Similar housing was observed in Corsica and Sardinia. The infection rate of the local inhabitants was high (Archives..., 1925)

Figure 15: Surroundings of Ferrara, Po valley: a farm in an area not included in the Bonifica program (Archives..., 1925)

Figure 16: A standard-type farm such as were mass-constructed in *bonified* areas, here in Agro Romano. Note the clear-cut separation between spaces devoted to human housing (top floors) and spaces devoted to animals. Also note the absence of visible 'domestic' water (Archives..., 1925)

Continuations: water management and quinine administration remain the only option until science develops more efficient tools

The years 1924 and 1925 were outstanding in the international scientific community's bid to fight malaria. The Malaria Commission had received a supranational mandate of enquiry and the 1924 mission had required close collaboration between several national health departments and the League of Nations Health Organization. The First International Congress of Malariology offered a platform for a number of experiences from around the world. The involvement of the Rockefeller Foundation was based on American and Italian collaboration. However, the co-authorship of reports by experts and gathering of scientists should not necessarily be seen as implying the development or continuation of collaboration of any sort; nor does it imply that the members of the League of Nations would implement the Commission's recommendations. In addition, the medical context was developing fast. As already noted by the Commission, malaria in Europe had passed its peak and was rapidly moving to endemicity, and thus back to a situation believed to be manageable by each nation. After the emergency, affairs could have shifted back to the national level, especially in the prevailing context of rising nationalism. Even so, several international programs and collaboration initiatives developed, be it from the Congress, from the works of the Malaria Commission, or from the Rockefeller Foundation's trials, or were strongly influenced by them.

First of all, the Commission continued to dispatch missions to collect all kinds of information concerning the disease. About 240 epidemiological and scientific reports were published between 1924 and 1936 and numerous countries were visited. The names of Swellengrebel and James appear most frequently, both as mission delegates and as authors of reports. They were certainly the leading figures in the field in Europe. Although it was not stated explicitly, the activities of the Commission depended on the participation of different nations in the League, and when Italy pulled out in 1937 there were no more publications. Malaria in the Soviet Union was not discussed any further, but the situation in all the other countries visited in 1924-1925 was regularly reported to the Commission, which also monitored the health conditions of refugees in Bulgaria and Greece.

Three remarkable reports were produced on Spain (report CH 55, 1925), Palestine (report CH 51, 1925) and Sicily (report CH 69, 1926). They should have been included in the main 1925 report, but ended up being published independently at a later date; the field research had been conducted there during the 1924 tour. Each report provided specific information. The report on Sicily, where malaria was acutely endemic and pernicious, but not covered by the Grande Bonifica projects, was very explicit about what should be done and what had been undertaken. However, the ensuing efforts were rendered virtually useless by numerous private and illegal initiatives, particularly concerning the management of water flows and retention ponds. This may explain why the report was kept confidential, since it pointed to the inability of local administrations to enforce policies passed in Rome. The report on Palestine, Egypt and Syria showed that a combination of different anti-larval techniques, quinine administration, and well-disciplined water management activities had resulted in great improvements to the health conditions in the upper Jordan Valley (Huleh

marshes) and the creation of new land for agriculture. Its author, Swellengrebel, noted that large amounts of money had been given to well-organized structures to attack the 'roots of the disease', i.e. the populations of *Anopheles*.[32] The report on Spain pointed to quite the opposite scenario (shortage of funding) and a different method (systematic administration of quinine). Swellengrebel remarked on the presence of a very strong administration able to select the areas where treatment had the best chances of success, and then focusing on these.

In 1927, the Commission added the three above-mentioned reports to those published previously, issuing a definitive report in which the systematic administration of quinine and water management (i.e. a kind of Bonifica) were found to be more effective in improving people's welfare than anti-larval methods. The report (James, 1927) even states that modern knowledge about the biology of *Anopheles* was not required for combating malaria effectively. Having been questioned in the 1925 report for its efficacy in anti-malaria campaigns, Bonifica was now re-integrated into the process and deemed highly beneficial and a mainstay of anti-malaria action. Small *bonifica* was not ruled out, but could not be used in isolation. In fact, the report concluded that the different strategies should be tried and adapted to local situations, but it clearly favored water management, quinine administration and the improvement of social conditions. This stood in stark contrast to the dominant anti-larval approach designed and tested by the Rockefeller Foundation. The Commission's members knew that malaria was rapidly declining in the USA and that the Rockefeller Foundation had obtained significant results through its local, low-cost approach. The visit of James and Swellengrebel to the USA in 1927 (CH 86, 1928) set out the reasons behind the discrepancy between Europe and the USA. It was largely due to the unique features of the vector in the USA, which required stagnant water, making the draining of agricultural land and treatment of stagnant water enough to induce a significant reduction in the size of *Anopheles* populations and thus limit parasite transmission. In defining its main guidelines, the Commission's report largely reflected Marchoux's and James's views on malaria control.

Concerning scientific research, in its 1925 report the Malaria Commission had enumerated the list of researches which should be developed to better understand the natural history of malaria. It started with a significant statement about Grassi's laws[33]: that they were inadequate for fully understanding and subsequently controlling malaria. "The discovery of the mosquito-cycle of the disease, of fundamental value though it was, revealed only an important link in the epidemiological chain, and that many auxiliary factors … play an important part in the epidemiology of the disease" (Report…, 1925a, p.184). Thus more and different knowledge had to be acquired on the whole biology and sociology of malaria. The scientific goals were clearly formulated by Swellengrebel (1925a, p.172). The principal obstacle against having a full understanding of the disease was largely the incomplete knowledge of the biology of the vector(s) in its (their) environment. He thus proposed an extensive research program, which we would today define as ecosystemic and ethological in nature. It implied developing a very precise taxonomy of the vectors and other diptera (basically, which species of *Anopheles* in a given area were needed to support the evolution of a *Plasmodium* and transmit it to humans, and what

morphological criteria could be used to identify them); studies on their biology, which should be appreciated *in situ*; studies on their breeding and reproductive behavior; and the characteristics of human habitats that could contribute to the propagation of malaria. With his enduring sensitivity to the biological aspects of malaria, Swellengrebel, in report CH 72, from 1924, and several later ones, insisted on the need to study the biology of *Anopheles in situ*, and discussed the problems raised by anophelism without malaria at length. The Commission had no funds to carry out research on its own, but numerous reports on malaria later included research into these topics by its members or associates.

The most important findings, which answered parts of the questions raised by Swellegrebel, were not however published in the Malaria Commission reports, but in classic scientific journals. A greater understanding of the biology of *Anopheles* was acquired thanks to developments in medical entomology and population genetics in academic establishments (Gachelin, Opinel, 2008). In 1935, Hackett and Missiroli's work on *Anopheles maculipennis* and Swellengrebel's work on *A. labranchiae* solved the problem of anophelism without malaria (Fantini, 1994), defined the notion of stable genetic variants endowed with different breeding and reproductive behaviors (thus eliminating the notion of races), and finally defined *Anopheles* complexes, grouping variants of insects that were morphologically identical but physiologically different. Thus, one important outcome of the Commission concerned the fundamental biology and genetics of *Anopheles*. The paper on races of *A. maculipennis* published in 1935 by Hackett in *Revista de Malariologia* was a reprint of a Malaria Commission report (CH 203, 1933) In addition to laboratory reports, progress in the culture of *Cinchona*, and the extraction, synthesis and different ways of administering quinine were discussed in numerous reports. Some insights into modern medical geography deserve special mention. Several reports dealt with deltas (Danube, Ebro, Rhône, Po), as these were areas that had certain biological features in common but were different in clearly defined ways from other infected localities.

A second successful outcome was the creation of international schools of malariology. Since a shortage of training centers and malaria schools had been noted, the Commission recommended the creation of schools of malariology where physicians of all countries could be trained. Several research and teaching institutions were created, aided by the League of Nations and the Rockefeller Foundation, mostly in the context of medical schools. Three such schools were created in 1926 under the auspices of the former organization, in Hamburg (Institute of Tropical Medicine, B. Nocht), Paris (Faculté de Médecine, E. Brumpt) and London (London School of Hygiene and Tropical Medicine), which trained physicians from a number of countries (Opinel, 2008). The academic and practical curriculum was defined by the Commission each year (for example report CH 56 for the year 1926, CH 74 for the year 1927, etc.). The school of malariology in Rome, which received some funding from the Rockefeller Foundation, was created at the same time but was not under the supervision of the League of Nations although its program was announced by the Commission (Italie..., 1927).

The initiatives of the Rockefeller Foundation had different fates. We have mentioned the outstanding contribution of Hackett and his Italian colleagues in solving an epidemiological enigma and propelling medical entomology into the incipient field of

population genetics and speciation. However, despite his successes, Hackett and Missiroli's field activities in Italy were seriously restricted after 1928, following the largely dominant influence exerted by the Ministry of the Interior in contrast with the weaker Directorate of Public Health, and the increased political weight of the more nationalistic members of the fascist party, who called for the closure of foreign institutions. All these reasons, associated with deep-rooted nationalistic attitudes concerning malaria, accounted in part for the difficulties met by Rockefeller Foundation officials in their dealings with the Italian Ministry of the Interior and Hydraulic Works, which were strongly inclined to promote Bonifica and land reclamation. The Rockefeller Foundation thus paid a high price for collaborating with the relatively weak Italian Department of Public Health. It also paid for the later emphasis the League of Nations put on *bonifica* and quinine administration due to the lack of confidence in the efficacy of anti-larval measures.

By contrast, the successes obtained by the Rockefeller Foundation with Paris Green had lasting effects outside Italy. In France, Brumpt used it for several years in his attempts to control malaria in Corsica (Opinel, Gachelin, 2005). He had first met Hackett in June 1925, and worked with him in 1926 in Sardinia and Corsica (Opinel, Gachelin, 2004). Between 1925 and 1931, Brumpt led a malaria control program that was largely inspired and financed by the Rockefeller Foundation. As for Hackett, the spreading of Paris Green and the seeding of *Gambusia* in Corsica in 1926 formed the basis for further preventive initiatives. These trials came to an end after 1931, with a kind of takeover of anti-malaria campaigns by public engineers (Opinel, Gachelin, 2004).

The numerous observations and discussions which occurred in and around the Malaria Commission can certainly not be summarized as a debate between supporters of anti-mosquito measures and supporters of social improvements in the countryside. This would ultimately lead to an opposition between the Rockefeller Foundation (the USA), which developed anti-larval techniques, and Europe, which for centuries had focused on water management. We mentioned that the Commission investigated this very point and concluded that it was the differences in the biology of *Anopheles* strains, rather than the methods per se, that were the issue. Actually, the debate between social improvement and science was a quandary for each and every member of the Commission since, as stated by the Commission itself, no really good or universal solution to fight malaria had come out of the works, missions, enquiries and debates that had been undertaken (Stapleton, 1994).[34] The Commission's primary concern was thus not to set technical, political or scientific issues against one another, but, in the European context, to define the best way to diminish the severity of the disease and hopefully decrease its endemicity, and to prevent expending energy and money on hopeless attempts to eradicate malaria, except at the very local level, as proposed by the Rockefeller Foundation (Stapleton, 1994). Eradication of malaria may have remained the ultimate goal, but under the socio-economic conditions of the time the Commission had set its sights on a more humble objective, largely because of its secondary benefits in terms of the general welfare of the people living in infected areas. Ultimately, Swellengrebel's claim that the Bonifica program reduced the severity but not the endemicity of malaria was implicitly accepted.

Europe-wide collaboration in the fight against malaria had therefore been extremely active over several years. Despite the diverse political and economic reasons which contributed to slowing down anti-malaria activities on the level of transnational entities, numerous reports were issued by the Commission. The main beneficiary appears to have been fundamental research on insect biology and genetics, which advanced greatly between the two world wars, largely along the lines defined by Swellengrebel in 1925. On the other hand, nothing very significant in terms of the prevention or treatment of malaria was discovered during the interwar period; things basically remained as they were in 1925, but, to echo members of the Commission, when these methods were applied carefully, they helped people to coexist with malaria much better than before.

The ultimate anti-insect weapon, DDT, was the novelty everybody was searching for. It first appeared and was tested during WWII after the Malaria Commission and the League of Nations had ceased working in the area. DDT was a product of neither the Commission's research efforts nor the Rockefeller Foundation's approach, but of the Swiss chemical industry. However, it was the Rockefeller Foundation that joined forces with the US Army in the resumption of campaigns against malaria in the Mediterranean area by using DDT in "an area in which the Rockefeller Foundation had extensive pre-war experience" (Stapleton, 1998). Ironically, the Rockefeller Foundation resumed use of the miracle chemical DDT as an anti-mosquito strategy. This was an approach which had been largely neglected during the ten years preceding WWII, although it had been successfully tested at the local level in Italy and Corsica in 1925 in the form of the first miracle-drug, Paris Green, and use of *Gambusia* as a biological weapon.

NOTES

[1] The Arkhangelsk epidemics, often quoted, were part of a larger epidemic in the Volga basin. They caused about six hundred thousand deaths in the basin and were described in Hackett (1937), and Packard (2007).

[2] Concerning mortality, Anigstein notes that malaria is rarely mentioned as the primary cause of death in the records. He estimates the death toll to be much higher.

[3] The main human migrations involved several hundred thousand people who were transferred from Poland and the Baltic area to Siberia and Central Russian Asia in 1914-1915. They came back after the Poland-Russia war ended. At least three million people had fled Russia. About 750,000 refugees fled Turkey in the 1920's to settle in Greece and the Balkans and an opposite flow of Turkish Balkans moved to mainland Turkey, etc.

[4] This is in contrast with the Office International d'Hygiène created in 1907, which, until its demise in 1933, stuck to its policy of only informing governments on the progress of epidemics.

[5] Epidemics of typhus afflicted about thirty million people between 1919 and 1922, claiming at least three million lives in Russia alone (L'épidémie..., 1920; Rapports..., 1922).

[6] Fonds Brumpt, Archives of the Institut Pasteur, Paris (later denominated AIP).

[7] Rockefeller Archives Center, Tarrytown, NY, USA (later denominated RAC).

[8] DDT (or Dichloro-Diphenyl-Trichloroethane) was first synthesized in 1874, but its pesticide properties were only discovered in 1939 by the Swiss chemist P. H. Müller, from Geigy Pharmaceutical, who designed a strategy for its mass production. He was awarded the Nobel Prize in Physiology or Medicine in 1948.

[9] A fourth human parasite, *Plasmodium ovale,* was added to the list in 1922.

[10] Doctor Norman V. Lothian was the secretary of the Commission and accompanied experts in the Balkans, Romania, Russia and Italy.

[11] These reports are of great interest to historians for their descriptions of health and social conditions in the areas in question, as well as the labor conditions, the availability of drugs, access to health care, etc.

[12] Marcinowsky, a prominent Russian parasitologist, had accompanied Anigstein and Swellengrebel on their tour in the Ukraine and the Volga area. He visited Italy in 1925 and the USA in 1927.

[13] It is clear that the problem raised fundamental questions about the genetics of *Anopheles*, which was extensively studied from the end of WWI to its genetic definition in 1938. For a discussion of the role played by different scientists in solving the problem of Anophelism without malaria, see Hackett, 1937; Fantini, 1994; Opinel, 2008; Gachelin and Opinel, 2008.

[14] "La commission a été frappée de l'importance exercée par les conditions d'habitation et de nourriture dans les différents districts: ces facteurs influent en premier lieu sur la résistance au paludisme, en second lieu sur les taux de mortalité." In this and other citations of texts from non-English languages, a free translation has been provided.

[15] Irradiation of the spleen was not designed to kill parasites, but to relieve the abdominal pain suffered by the patients.

[16] In this respect, some members of the commissions were not convinced of the beneficial effects of Bonifica on malaria. They asked for a full description of what 'bonification' precisely meant. A report on the various aspects of *bonifica* was written by Lutrario (1928). He explained that the first law, of 1883, related to the drainage of marshes, and that the law passed in 1923 developed a complete theory of the regimens of water and soil, ultimately leading to the eradication of malaria, provided human *bonifica* (the treatment of all malaria patients with quinine), first introduced in 1908 in the Po valley, was carefully observed.

[17] Ettore Marchiafava (1847-1935), malariologist, chairman of the Congress and also a senator since 1913.

[18] The use of arsenate derivatives to combat parasites had been introduced as early as 1906 in France and Germany to try to combat sleeping sickness. Attempts to extend their usage to malaria were made later. Stovarsol was abandoned a few years later since, as reported by Marchoux himself, it had proven remarkably efficient on *Plasmodium vivax*, but completely ineffective on the most dangerous parasite, *P. falciparum*.

[19] Letter sent to the Italian Ministry of Health on October 16th 1922 concerning a drug produced by Consorzio Neoterapico Nazionale, Rome, *Smalarina cremonese* (mercury and antimony with no quinine): *smalarina* (C8 H13 O7 N4 Hg Sb) 2,5mmg; *ioduro di sodio* 5mmg; *tartrato doppio di K e Na* 10mmg; excipient (Profilassi..., 1939).

[20] Chagas and Brumpt were officially mandated, as part of an international research program launched by the League of Nations on July 2nd 1928, to study the relationship between housing and malaria. This appears to be in line with Chagas's report at the meeting and with Brumpt's work in Corsica and southern France. They never wrote the report, but the case of malaria in households, including the housing maturation and housing instinct of *Anopheles*, was abundantly documented by others in later reports (reports to the League of Nations CH 165, CH 168, CH 194, CH 205). All reports of the malaria commission are available at: http://www.who.int/library/collections/historical/en/index4.html.

[21] The use of larvivorous fish to diminish mosquito populations was already well known at that time. Various fish species had been used, such as carps in the Dombes area in France or in the Huleh area in Palestine (see Report..., 1925b). The difference lies here in the protocols used to define which of the fifty known species of *Gambusia* was best suited to the local conditions.

[22] "Quite safe is properly measured" (Congrès..., 1926, p.164).

[23] Hackett did not mention the use of quinine. However, photographs taken by Brumpt in spring 1926 in Porto-Torres during his stay there with Hackett (Figure 4) indicate that there was a dispensary being used for quinine delivery (jointly operated by the Italians and the Americans; M. Coluzzi, personal communication).

[24] "Many of the delegates have talked to me personally on the subject (of Paris Green), including Nocht, Brumpt, James and Swellengrebel and I suppose that Paris green will now be given a trial at least in various localities on this side of the water" (Hackett, 5th Oct. 1925).

[25] Examples can be found in the annual reports to the Rockefeller Foundation, quoted in Opinel and Gachelin, 2004.

[26] As evidenced by the outstanding contribution of Hackett and Missiroli in elucidating the enigma of *Anophelism* without malaria.

[27] For a summary of Bonifica laws specifically written for the Commission, see Lutrario, 1928.

[28] This can be seen on the map and in the overall organization of cities created during the Mussolini era, such as Latina, 25km south east of Rome, in lands formerly owned by the Vatican.

[29] The caveat written by Swellengrebel clearly conflicts with Raynaud's unquestioning acceptance of Italian proposals. To explain it, it may be of interest to note that Raynaud worked in Algeria, where malaria was highly prevalent in places where agricultural resources had been highly praised from the Roman period. It may be suggested that the policy of land reclamation and organization of new agricultural areas through very large farms and settlement colonies had been very similar in Italy and Algeria.

[30] "Le congrès international de malariologie, tandis qu'il applaudit l'oeuvre merveilleuse de tant de bonificateurs et de tant d'agriculteurs qui ont bien mérité à l'hygiène et à la civilisation, considérant que la Bonification intégrale constitute un pas très vrai et très stable contre le paludisme, émet le voeu qu'elle soit de plus en plus intensifiée en accord avec les connaissances étiologiques modernes."

[31] The photographs taken by Brumpt are organized in an album in a precise order which reflects the intentions of the tour organizers, obviously biased by Brumpt's interests and actions. The organization of Brumpt's albums is under study.

[32] It may seem surprising that the anti-malaria campaign in Palestine, which had been a genuine success, was not proposed as a model of what can be achieved by combining and adapting several approaches.

[33] Grassi's laws, which were actually formulated by Celli, operationally reduced malaria to the mere circulation of the *Plasmodium* between man and *Anopheles*.

[34] "In every country and very largely in every area, there must be preliminary examination to ascertain what method is best suited in the local conditions. At present, it cannot be said that for malaria control there is a method of choice superior to the others" (James, 1927, p.17).

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