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Le infezioni nella Storia della Medicina

Infections in the History of medicine

The history of the Greek Anti-Malaria League and the influence of the Italian School of Malariology

La storia della Lega anti-malaria greca e l'influenza della Scuola italiana di malariologia

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INTRODUCTION

Following the liberation of Greece from the Ottoman Empire in 1832 and until the eve of the 20th century, the small new country remained under the siege of malaria [1-4], the deadly disease at times becoming out of control. The nascent Greek state was fragile and always at risk of a new war with the Ottoman Empire. From 1882 to 1887, the Greek Army suffered enormous losses due to malaria; approximately 42,000 soldiers were treated in the Military Hospital of Athens [5]. At the population level, from 1899 until 1906, 2,147 individuals, especially neonates and young children, died of malaria [5].

The sanitary campaigns against malaria in Greece started in the beginning of the 20th century and can be divided into three periods. The first period, from 1900-1930 comprises the initial control efforts of the pioneers of the Greek Anti-Malaria League. The second period covers the years 1930-1940, with the anti-malaria campaign organized by the Malaria Department of the Athens School of Hygiene. The final period from 1945-1960 comprises the successful joint efforts of the Malaria Department of the National School of Hygiene of Athens, UNRRA and Rockefeller Foundation in the first years after the end of World War II.

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Malaria in Greece and Italy: a parallel history

Malaria is a disease probably as old as humanity itself. The palaeo-pathological study of prehistoric human skeletal remains suggests that malaria was present during the Neolithic Age [6-8]. In the ancient world, malaria was endemic in the Mediterranean region. Malaria was endemic in Greece as depicted in the case reports in Hippocrates' first book of "*Epidemics*" and "*Airs, Waters, Places*" [9-11].

Conditions were similar in the Italian peninsula as early as the Etruscan era [6, 7]. The Greek physicians who came to Rome like Galen, Heraclides and Agathinus also described the disease and focused on the fevers in their treatises [12]. An interesting fact is detected from the epigraphic data of the Christian cemeteries of Rome from 3rd-7th century AD, many centuries later. The epigraphic inscriptions as documented in the editions of *Inscriptiones Christianae Urbis Romae* and *Rivista di Archeologia Cristiana*, included the day, week and month of burials, revealing a high mortality rate for all age groups in September [13].

Using this data, the biological cycle of *Anopheles* during the summer months in the swamps around Rome can be easily correlated with the onset of malaria in September. Similar data on fever mortality can be found in other Christian cemeteries in Italy.

The records of the Deliberations of the Consiglio Comunale depict malaria as a new Hannibal, *ante portas* of Rome, until the eve of the 20th century [14].

In the Middle Ages, many eminent Byzantine physicians, such as Oribasius and Paul of Aegi-

na, provide information on fevers in the Eastern Roman Empire (Byzantium) while at the same time in Italy the Monastic Orders of the Benedictines and Cistercians, were further developing the nursing of patients [12, 15]. Moreover, these Orders, although they did not possess scientific knowledge of the interaction between the environment and the disease but acting in compliance with their motto *Ora et labora*, cultivated the land, changing the topography of lakes and rivers and controlling the annual floods [15].

Until the middle of the 19th century, the only accurate epidemiological data regarding the Greek territory was derived from British records for the Ionian Islands (1815-1864), during the period of the British Protectorate following the Treaty of Paris in 1815 [16-18]. British physicians studied malaria while assessing the mortality and morbidity from local infectious diseases in their new colonies. According to this data, the most prevalent endemic infectious disease in the region was malaria, which in the British studies was described as t*ertian fever*, *quartan fever*, *benign or malignant fever*. In studies carried out by Greek physicians of the Ionian Islands who had studied medicine in Italian universities, fevers were described as *therma continua* or *amphimerina paludosa* [16, 19]. Beginning in 1815, the British Army recorded numerous casualties due to malaria and during the period 1822-1829, fevers were the leading cause of death in the British garrisons of the Ionian Islands [20].

The military physician of the Allied Regiment of Sicily, Dr. Benza, later Protomedico and member of the Magistrato di Sanita di Corfu (1831), investigated the morbidity of the "malignant fevers" among the soldiers of the local regiments in the fortress of Corfu [21]. Dr. Benza proposed that the cause of this morbidity was: " *that the temperature of the Veccia Fortezza di Corfu was 10 degrees higher than in any of the barrack-rooms at Corfu*", but he did not connect the mortality with the swamps present around the town and of course the mosquitoes that bred there [21]. However, as the Inspector of the British Military Hospitals in the Mediterranean, John Davy, explains: "*It is more easy to say what malaria is not, that what it is…*". Dr. Davy's research also provides us with interesting data on malaria mortality as well as a comparison of the disease's prevalence in Greece and Malta. Similar conditions were found in other Greek regions under the rule of Ottoman Empire and it seems that the disease was consistently endemic there [22].

Actually, malaria in Greece did not attract much attention before the liberation from the Ottoman Empire. Brief references to reports about malaria in Greece, can be found in Roux's edition of "*Histoire médicale de l'Armée française en Morée*" (1829), in Faure's "*Des Fièvres intermittents et continues*" (1833) and Thomann's "*Ueber die Wechselfieber in Griechenland*" (1839). Also, a geographical-climatological study carried out by Gittard in 1834, "*Considérations generals sur la Constitution physique de Péloponèse et son influence sur le caractère et les maladies de ses habitants*", provides us useful information on the Greek climate and the connection with malaria [12].

Some Greek physicians practising in the Greek State collected epidemiologic data locally. Several publications on malaria, mostly case reports and reviews, rather than original research studies, can be found in the Proceedings of the Medical Society of Athens from 1835-1900. According to the records of the Medical Society of Athens found in the Microbiology-Epidemiology-Hygiene section, there are four studies on the nature of malaria (1849, 1855, 1859 and 1894), two on malaria epidemics in Athens (1868, 1886), and only one epidemiological study (1861). In 1881, Hirsch published his study on the historical and geographical distribution of Greece, containing remarkable data on malaria prevalence [12]. During 1884, Stéphanos published his monumental work "*La Grèce au point de vue naturel, ethnologique, anthropologique, démographique et médical*", in which he provides us information about the topography of the disease in Greece. According to Stéphanos, malaria incidence in modern Greece fluctuated from year to year. The proportion patients with malaria in the total number of admissions in the City Hospital of Athens "Αστυ κλινική Αθηνών" ranged from 56.3% in 1865 to just 19.9% in 1867. After 1890, the proportion ranged from 25.4% to 8.8% [12].

In 1895 the Medical Newspaper of the Army inaugurated a section entitled "Epidemic diseases of Athens", where the physicians recorded disease morbidity and the mortality in the capital monthly [3, 4]. In the Greek studies, physicians differentiated clinical forms of malaria into: intermittent fevers, remittent fevers, pernicious fevers, blackwater fever, chronic malaria and malarial cachexia. The pernicious fevers (which had either quotidian or tertian periodicity)

were further subdivided into: comatose fever, gastric fever, hyperpyrexial fever and convulsive fever [12].

At the end of the 19th century, the calculation made from the entries to the Athenian public, private or university's hospitals show the various kinds of malaria in Athens: intermittent fevers (91.52%), remittent fevers (3.44%), pernicious fevers (0.3%), blackwater fever (0.06%) and malarial cachexia (4.66%) [12]. For the entire country the proportions were: intermittent fevers (91.67%), remittent fevers (6%), pernicious fevers (0.27%), blackwater fever (0.09%) and malarial cachexia (1.95%) [12].

In Italy, after the unification of the country in 1860, there were intensive efforts for the eradication of malaria and a series of laws were voted in 1878 to ensure the protection of public health [23, 24].

The circumstances in the Kingdom of Italy in 1866 were dramatic. Unification added malarial regions to the country, resulting in almost 2 million cases and 20,000 deaths [23]. Immigration to the regions of north-eastern Italy, with the Veneto region as a typical example, was another cause of malaria's expansion [25]. Until the eve of the 20th century, Italian legislation, the draining of swamps and the distribution of quinine resulted in significant improvements in many regions [23].

The establishment of the Rome Institute of Experimental Hygiene by Professor Corrado Tommasi in 1885 substantially advanced malaria research [26].

The investigations f Golgi, Celli and Marchiafava expanded our knowledge on the plasmodium, that Laveran discovered [27-29]. Following Manson and Ross's proposal regarding the role of mosquitoes in malaria transmission, the Italian anti-malarial school was in the forefront of anti-malarial research and eminent scientists such as Grassi, Bignami and Bastianelli demonstrated that species of Anophelines present in Italy can transmit the plasmodium to humans [30]. Italian malariology (represented by Bastianelli, Bignami, Celli, Fermi, Golgi, Grassi, Marchiafava, Missiroli, Rafaele) already had significant scientific precedents, which explains the success of the Italian antimalarial campaigns as opposed to the first Greek attempts at malaria eradication [28].

Foundation of the Greek Anti-Malaria League

In 1901 a group of physicians made a proposal to the Government for an anti-malaria campaign. However, due to political instability, the defeat in the Greek-Turkish War of 1897 and the destroyed postwar economy, the State was unable to organize even a small anti-malaria project for the country's capital, let alone a nation-wide anti-malaria campaign. Malaria could be found even in the heart of Athens. From 1860 to 1905, there were 14 major malaria epidemics in the Athens area [31]. The area surrounding the Panathenian Stadium, where the first modern Olympic Games were held in 1896, was full of swamps created by the River Ilissos, with a subsequent morbidity rate of 95% in the area. At around the same time, 1896-1905 the morbidity percentage of the Greek armed forces ranged from 37.1%-44.8% [31].

During the Greek Medical Congress of 1905 scientists exerted great pressure on the Greek Government to draw up an anti-malaria plan. Following the refusal of the Greek Government to organize the ambitious project, the Professor of Hygiene and Microbiology in the Athens Medical School and General Head of the Military Sanitary Service, Constantinos Savvas, and the pediatrician Dr. Ioannis Kardamatis, who later served as Professor of Parasitology and

Figure 1 - Professor Constantinos Savvas.

Tropical Diseases from 1909-1915, decided to take matters into their own hands (Figures 1 and 2) [31].

Following the Greek Medical Congress of 1905, on February 18, they decided to found an institution, that they announced would be known as the "Greek Anti-Malaria League" [32]. A few days later, the King of Greece, George I, declared the League under his patronage. Inspiration for the League's insignia came from the labours of Hercules described in ancient Greek mythology, specifically his fight against the Lernean Hydra, a terrifying mythical monster with multiple regenerating heads that lived in the swamps of Lake Lerna.

The year 1905 was a particularly difficult one. Savvas and Kardamatis estimated that there were 250,000 new cases of malaria in Greece that year [32].

Heavy rainfall in 1904 had increased stagnant water bodies, causing a consequent increase in the incidence of malaria. The first call for help came from the village of Oropos, 30 km northeast of Athens, an area with a malaria prevalence greater than 95%. The League dispatched its first two "heroes", Dr. Kardamatis and Dr. Diamesis to fight against the malarial Hydra. The two physicians, armed with a microscope and 1000 g of quinine encountered 1,370 patients in the villages around Oropos [31]. In response to their emergency telegram to Athens for more quinine, the Greek Government immediately ordered the Greek Army to contribute its quinine stock.

Figure 2 - Dr. Ioannis Kardamatis.

The two physicians distributed quinine to all patients door-to-door and, as a result, they succeeded in eliminating the epidemic. During the epidemic the two physicians had the opportunity to conduct small-scale experiments concerning the effective dose of quinine in order to develop therapeutic plans [33]. A few weeks later, a second epidemic broke out in the village of Avlida.

This time Kardamatis and Diamesis had only 500 g of quinine for 400 patients and despite the emergency telegrams, they received no additional quinine and the mission failed completely [31]. Professor Savvas realized that besides malaria, he had two more enemies, the lack of quinine and the lack of collaboration from the Government. At that time quinine was being imported, its market price was extremely high and some unscrupulous people were tampering with the drug.

Establishing State monopoly for the sale of quinine became one more goal in the League's agenda. According to the League's declaration, every Greek citizen should have the right to buy cheap quinine or receive it at no cost. However, according to Savvas and Kardamatis before proposing a new law on quinine's State monopoly, the League needed organization.

The first visit to Italy and the League's priorities

Collaboration between Greek and Italian malariologists began in 1904. Professor Savvas, a personal friend of Professor Angelo Celli, had witnessed the effectiveness of the Italian anti-malaria campaign during his journey in Rome in 1904, a year before founding the Greek League. Shortly before founding the Greek League Professor Savvas sent representatives to Italy, Algeria, and Corsica to collect data about their system and organization.

During the first visit of the Greek physicians to Italy, the League's members were impressed by the organization of the Italian anti-malarial fight. They learned for first time about the relation of ichthyology, like the use of the larva-eating fish *Gambusia affinis* to minimise the proliferation of the Anopheles mosquito and conse-

quently reduce its abundance in lakes [33]. Inspired by Professor Celli, Professor Savvas decided that only the Italian experience would be useful and requested organizational assistance. In 1903, he printed a pamphlet based on the findings of Professor Celli, entitled "Instructions for the eradication of fevers", in which he described the mechanism of malaria transmission, the Italian laws on quinine trade (*Laws and Declarations: Law 505 on 23 December 1900, Royal Declaration 82 on 3 March 1901, Law 460 on 2 November 1901, Declaration of the Ministry of Internal Affairs 12 June 1902*), and the therapeutic dosage of quinine (Figure 3).

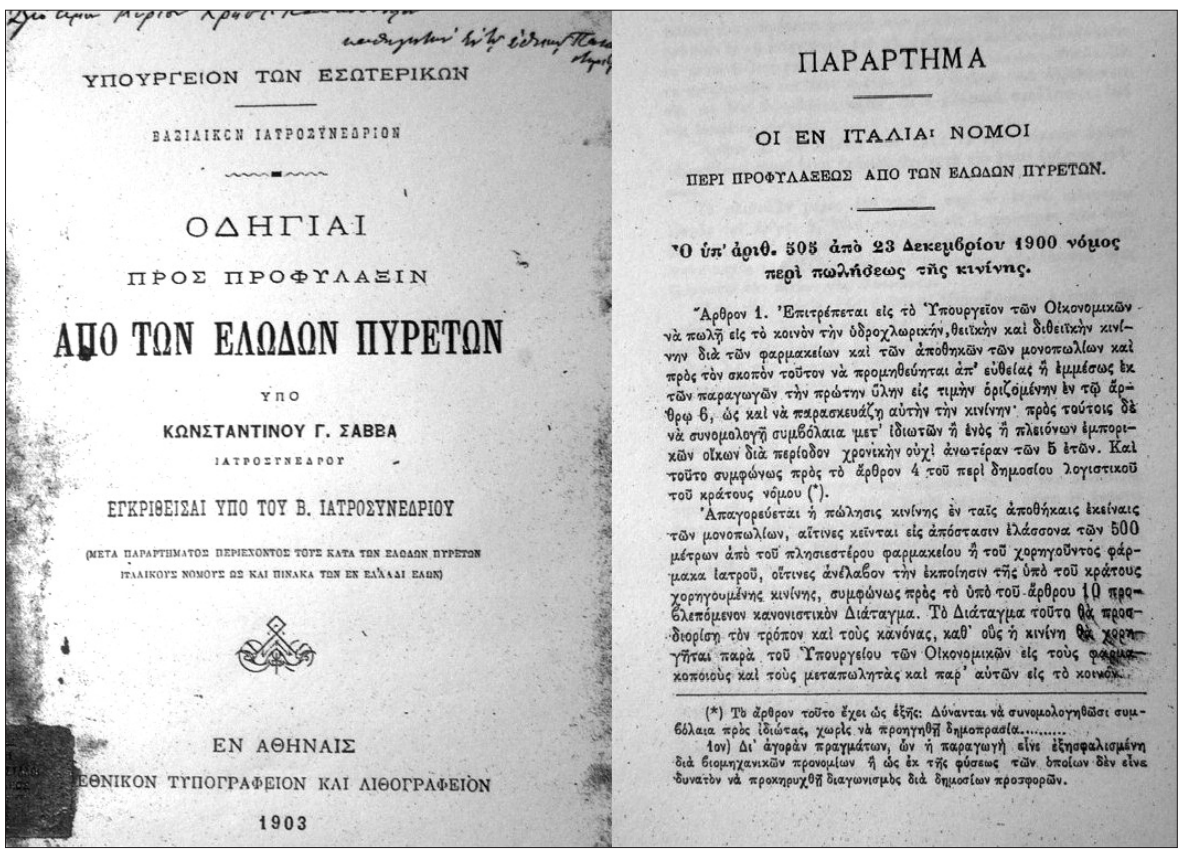
He also included a few maps with epidemiological data on malaria's prevalence in certain Greek regions.

A thousand copies of this pamphlet were printed and sent to all physicians in urban and rural centres, to all Greek Mayors and municipal civil engineers. Having collected the latest Italian data in 1905, the League decided to organize their plan in four directions according to the principles of the Italian malariologists' concept:

a) popularization of knowledge on malaria transmission and symptoms;
b) increase in awareness on the preventability of the disease;
c) the draining of swamps;
d) exerting pressure on the Greek State for a law on State monopoly over the sale of quinine and of course the availability of cheap quinine for all Greek citizens, like in Italy [34].

The members added another objective, the collection of accurate epidemiological data and a basis for "follow-up" surveillance.

Professor Savvas described the Greek League as the twin brother of the Italian League. As he states in 1928, the secret of the Greek League's success was the fact that: "*The Greek anti-malaria League was based on the Italian League of my good friend, Professor of Hygiene in Rome, Angelo Celli. I saw the actions and the efficacy of Celli during my journey in Rome in 1904*" [34]. Unfortunately, without financial help from the Govern-



ΥΠΟΥΡΓΕΙΟΝ ΤΩΝ ΕΣΩΤΕΡΙΚΩΝ

ΒΑΣΙΛΙΚΟΝ ΙΑΤΡΟΣΥΝΕΔΡΙΟΝ

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ΕΝ ΑΘΗΝΑΙΣ

ΕΘΝΙΚΟΝ ΤΥΠΟΓΡΑΦΕΙΟΝ ΚΑΙ ΛΙΘΟΓΡΑΦΕΙΟΝ

1903

ΠΑΡΑΡΤΗΜΑ

ΟΙ ΕΝ ΙΤΑΛΙΑ: ΝΟΜΟΙ

ΠΕΡΙ ΠΡΟΦΥΛΑΞΕΩΣ ΑΠΟ ΤΩΝ ΕΛΩΔΩΝ ΠΥΡΕΤΩΝ.

Ὁ ὑπ' ἀριθ. 505 ἀπὸ 23 Δεκεμβρίου 1900 νόμος περὶ πωλήσεως τῆς κινίνης.

Ἄρθρον 1. Ἐπιτρέπεται εἰς τὸ Ὑπουργεῖον τῶν Οἰκονομικῶν νὰ πωλῇ εἰς τὸ κοινὸν τὴν ὑδροχλωρικήν, θειϊκὴν καὶ διθειϊκὴν κινίνην διὰ τῶν φαρμακείων καὶ τῶν ἀποθηκῶν τῶν μονοπωλίων καὶ πρὸς τὸν σκοπὸν τοῦτον νὰ προμηθεύηται ἀπ' εὐθείας ἢ ἐμμέσως ἐκ τῶν παραγωγῶν τὴν πρώτην ὕλην εἰς τιμὴν ὁριζομένην ἐν τῷ ἄρθρῳ 6, ὡς καὶ νὰ παρασκευάζῃ αὐτὴν τὴν κινίνην· πρὸς τούτοις δὲ νὰ συνομολογῇ συμβόλαια μετ' ἰδιωτῶν ἢ ἑνὸς ἢ πλειόνων ἐμπορικῶν οἴκων διὰ περίοδον χρονικὴν οὐχὶ ἀνωτέραν τῶν 5 ἐτῶν. Καὶ τοῦτο συμφώνως πρὸς τὸ ἄρθρον 4 τοῦ περὶ δημοσίου λογιστικοῦ τοῦ κράτους νόμου (*).

Ἀπαγορεύεται ἡ πώλησις κινίνης ἐν ταῖς ἀποθήκαις ἐκείναις τῶν μονοπωλίων, αἵτινες κεῖνται εἰς ἀπόστασιν ἐλάσσονα τῶν 500 μέτρων ἀπὸ τοῦ πλησιεστέρου φαρμακείου ἢ τοῦ χορηγοῦντος φάρμακα ἰατροῦ, οἵτινες ἀνέλαβον τὴν ἐκποίησιν τῆς ὑπὸ τοῦ κράτους χορηγουμένης κινίνης, συμφώνως πρὸς τὸ ὑπὸ τοῦ ἄρθρου 10 προβλεπόμενον κανονιστικὸν Διάταγμα. Τὸ Διάταγμα τοῦτο θὰ προσδιορίσῃ τὸν τρόπον καὶ τοὺς κανόνας, καθ' οὓς ἡ κινίνη θὰ χορηγῆται παρὰ τοῦ Ὑπουργείου τῶν Οἰκονομικῶν εἰς τοὺς φαρμακοποιοὺς καὶ τοὺς μεταπωλητὰς καὶ παρ' αὐτῶν εἰς τὸ κοινόν.

(*) Τὸ ἄρθρον τοῦτο ἔχει ὡς ἑξῆς: Δύνανται νὰ συνομολογηθῶσι συμβόλαια πρὸς ἰδιώτας, χωρὶς νὰ προηγηθῇ δημοπρασία.....

1ον) Δι' ἀγορὰν πραγμάτων, ὧν ἡ παραγωγὴ εἶνε ἐξησφαλισμένη διὰ βιομηχανικῶν προνομίων ἢ ὡς ἐκ τῆς φύσεως τῶν ὁποίων δὲν εἶνε δυνατὸν νὰ προκηρυχθῇ διαγωνισμὸς διὰ δημοσίων προσφορῶν.

Figure 3 - The Greek translation of the Italian laws on anti-malaria protection by C. Savvas ("Instructions for the eradication of the fevers", Athens 1903, 53-74).

ment they were unable to introduce the Italian model in Greece. In 1906, they managed to import from Italy a large population of *Gambusia* fish for the Greek lakes.

Furthermore, the League requested the nomination of Dr. Kardamatis as Hygiene Assistant in the Ministry of Transport and later as Sanitary Inspector of the Ministry of Health, and the request was accepted by the government. In order to improve data accuracy, the League organized the collection of information on the number of patients and deaths registered in hospitals and treated by private physicians.

Using the data collected from 1908-1914, haematological studies and splenomegaly measurements, the League obtained a clear picture of malaria prevalence in the country and had the opportunity to assess the effect of quinine on the epidemiology of the disease [34].

Based on the Italian experience, the League organized local committees in 30 major Greek cities with the help of the Greek Red Cross and the League's members started an educational programme with presentations in numerous villages [31, 34]. For the first time the ignorant audience became informed on the nature, the first symptoms, and protection from malaria.

According to the personal memoirs of the League's physicians, the speeches in the villages were a great and very emotional event. The poor villagers felt enormous gratitude and in return offered their hospitality and food to the visiting physicians. In the following years, with the help of the Ministry of the Economy, the League distributed 150,000 manuals to teachers and students, and an extra 300,000 copies of Professor Savvas's pamphlet "Ten Simple Instructions against Malaria" [31, 34].

In 1906, the Scottish epidemiologist Sir Ronald Ross visited Greece following the invitation of the British Company of Lake Copais, which had taken on the task of draining the lake.

His presence in Greece was seen as an opportunity for the League and immediately Savvas and Kardamatis joined forces with him. Ross discovered an extremely high prevalence of malaria among the workers of Lake Copais Company as well as in the surrounding area, where 65% of the children suffered from excessive splenomegaly [35].

Ross proposed to the League the drainage of all swamps in the area and the treatment of all the citizens living around the lake with quinine. He also instructed the use of petrol as an insecticide against mosquito larvae [35].

The League translated and distributed 3,000 copies of Ross's paper concerning protection from fevers and mosquito eradication. The greatest success of the League however, came near the end of that decade, namely the passing of the "Law for State quinine" voted in the Greek Parliament on the Assembly of February 18, 1908, coincidentally on the League's third "birthday" [34, 36].

The League's epidemiological studies

The epidemiological study of malaria following the massive use of quinine was a crucial point in the League's actions. Starting in 1907, Dr. Kardamatis conducted a pilot study with quinine distribution in the villages around Marathon, where the famous ancient battle took place. Malaria prevalence in the area dropped from 100% to 47% in 1907, to 13% in1908 and eventually to 2% in 1909 [37, 38]. Dr. Kardamatis also studied child morbidity in Athens, which decreased from 93% in 1901 to nearly 0%, after the use of quinine in 1910 [39].

In 1909, the League published the manual "Malaria in Greece and Crete" with the presentation of the first epidemiologic map of the country (Figure 4).

On a national scale, the League managed to limit malaria prevalence to 30% in 1915. By 1920, of the country's 476 municipalities only 29 were declared free from the disease. Of the remaining 445, 76 had morbidity rates between 51-100%, 254 between 11-50%, and the remaing 115 below 10%. Areas with morbidity rates of 50-60%, 40-50%, and 30-39% in 1907 showed a corresponding decrease to 10-20%, 3-17% and 3-13% respectively [37, 38]. The most important problem, however, was the completion of draining works that progressed slowly, due to little motivation on behalf of the State. According to the League's data there were 639 swamps extending over 88,000 hectares of Greek territory, which increased to 1769 swamps (400,000 hectares), following the annexation of the new territories after the Balkan Wars and the First World War [34].

In 1924, Dr. Kardamatis published the study "Statistical maps of swamps and frequency of malaria in Greece" and in 1925 the League and the Greek Red Cross published the study "Actions in Macedonia and Thrace". The League divided the Greek territory into two parts, Old Greece (the country before the two victorious Balkan Wars against Turkey and Bulgaria) and New Greece (the liberated Greek territories). In

1924 the mean frequency of malaria in Greece was 23% (Old Greece 26%, New Greece 20%) [34]. Seventeen municipalities and 617 villages in both Old and New Greece were free of the disease corresponding to 348,722 persons, i.e. 1/16 of the total population [34]. Infected municipalities and villages of Old and New Greece totalled 836 (prevalence 10-49%) and 403 (prevalence 50-100%) [34].

1924-1930: new malaria geography

The Greek-Turkish War in 1921-1922 began with major victories for the Greek Army in Asia Minor. However, further inland and devoid of supplies the Greek Army suffered defeat during its retreat from the Turkish Army, led by Kemal Ataturk. Defeat in the war led to a new Treaty, followed by changes in the borders and an influx of 1,200,000 Greek refugees from Asia Minor, altering the demography of Greece. The refugee camps set up by the Greek State were unable to provide housing to the refugees forcing them to settle in the marshy areas surrounding urban and rural regions. Cholera, typhus, dysentery and malaria followed in the new primitive settlements. A characteristic example is that of a camp in Thrace, where all the members of 35 families, of the 75 housed there, died of malaria. According to the reports of the Directory of Health (League of Nations), the annual mortality from malaria in Greece increased from 7.94 (per 10,000 inhabitants) in 1925 to 10.24 in 1930 [34, 40]. In contrast, malaria mortality in Europe, at around the same time was less than 1.8 per 10,000 inhabitants [40]. During this period malaria mortality increased annually in urban areas with a total of 5,847 deaths reported. The situation was even worse in rural areas, with 25,554 deaths in 5 years (Figures 5 and 6) [40]. Officially, 152,642 patients were admitted to public hospitals, Teaching hospitals of the Medical School of the University of Athens or charitable institutions. The number was actually greater, given that thousands of the poor villagers never had access to country hospitals.

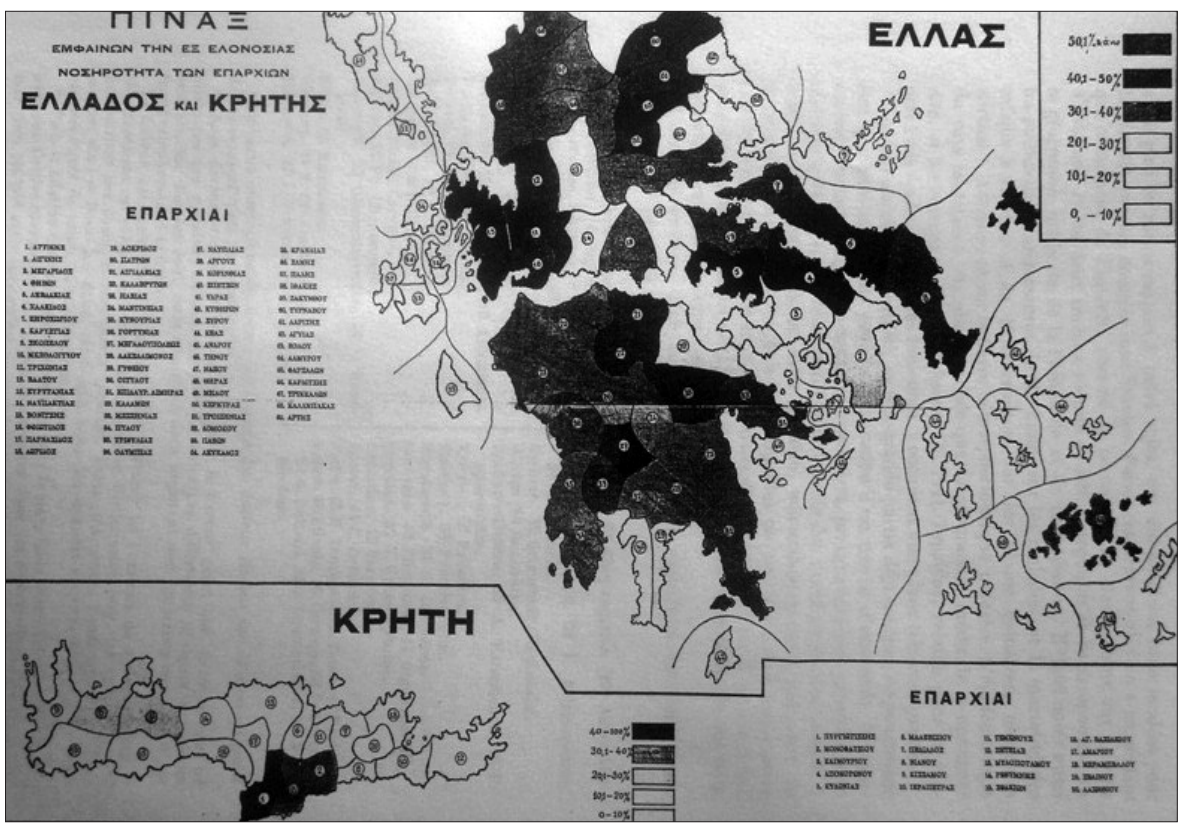

Figure 4 - The first epidemiologic map of the splenic index in Greece and Crete* (1909) (**Crete depicted in a separate sector for political reasons. The island had nominal independence under the protection of Greece, the Ottoman Empire, Great Britain, France, Italy and the Austro-Hungarian Empire*).

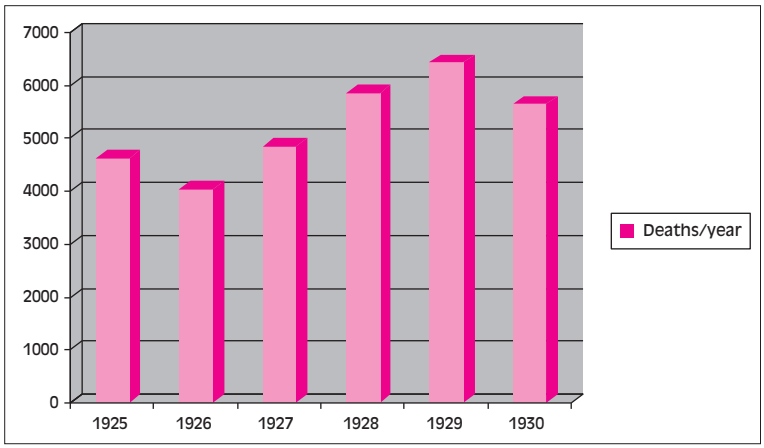

Figure 5 - Deaths from malaria in Greece (1925-1930). Source "*Public Health in Greece*", Proceedings of the Directorate of Health, Ministry of Health, Athens 1933.

Morbidity was higher in northern Greece, where most refugee camps were located (Tables 1and 2) An international relief initiative was undertaken by the American and the British Red Cross, the Near East Relief by the Greek immigrants in USA, the Quakers and the Society of the American Ladies [40].

Although the country's economy was almost destroyed, the League introduced an ambitious plan for draining works in Greece in 1924-1928. The task was undertaken by numerous engineers-members of the League, worked in the provinces constructing or re-constructing cisterns, roads and swamp drainage, supported by private funding or aided by the Greek Ministry of Economics. There was also an effort to eliminate the malaria mosquito from the lakes, using petrol and Paris Green powder with the help of the physicians and the personnel of the Greek Red Cross [34]. In 1927, the League inaugurated a programme with viewing of a Greek production film entitled "Malaria" in all the regions. Fifty-seven viewings of the film in 18 cities, mainly in northern Greece in the refugee camps, were organized in 1927, during which a total of 66,700 citizens, 4,200 pupils and 9,500 soldiers had the opportunity to experience cinema for the first time in their lives, watching a movie about the deadly disease [34].

Following the Greek defeat of 1922 and the arrival of the refugees, the League needed a new plan for mass quinine treatment and a modification of the existing malaria epidemiological maps. After years of investigations, the Department of Malariology and the League concluded that the parasitic index was 25% in some regions, and as for the separate plasmodia, *Plasmodium vivax* had increased by 60% and *Plasmodium falciparum* by 80% [34]. The splenic index had also increased in the rural regions (50-100%) and in the urban areas (10-30%) [34]. During this period the Greek Authorities imported 9,795,000 kg of quinine from the American Red Cross, 1,608,178 kg from Germany, 154,600 kg from the British Red Cross and 5,000,000 kg from other sources for the Com-

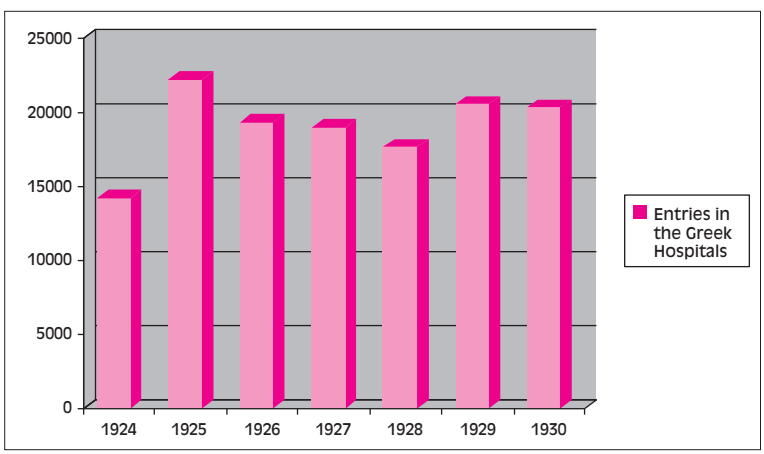

Figure 6 - Admission from malaria to public hospitals. The Hospitals of the Athens Medical School and the Charity Institutions (1924-1930) (Source "*Public Health in Greece*", Proceedings of the Directorate of Health, Ministry of Health, Athens 1933).

Table 1 - Comparison of morbidity (%) between the local inhabitants and refugees in the geographic regions of "Old" Greece, 1923-1924.

Geographic regions	*"Old" Greece (Peloponnese, Thessaly, Ionian Islands, Aegean Islands, mainland)*			
	1923		*1924*	
	Local Inhabitants	*Refugees*	*Local Inhabitants*	*Refugees*
Mainland (& Athens)	33.3	51.5	22.8	36.8
Peloponnesus	27.3	37.2	25.7	39.8
Thessaly	52.7	56.7	13.6	27.3
Ionian Islands	24.1	35.6	12.6	43.3
Aegean Islands	7.3	45.2	21.1	11.1

Source "Public Health in Greece", Proceedings of the Directorate of Health, Ministry of Health, Athens 1933.

mittee of the Refugees [34]. The League had to choose between six different prophylactic dosages, i.e. the German, Italian, English, French, Austrian and Greek. The latter was a result of the League's investigations during the annual follow-up of quinine administration in Greece. The League preferred the Greek dosage of two pills/day (1 for children younger than 10 years old) from June 1st to November 1st, whereas in some cases the League adopted the Italian schema with the same dosage from June 1st until December 1st [34]. After its successful introduction by Ziemann in Cameroon and Lemanski in Tunis, intramuscular injection of quinine was adopted by the League [34]. The physicians visiting refugee camps discovered that sanitary conditions were primitive and a significant number of patients, specifically 10% of those infected with Plasmodium *vivax* appeared to self-healing without quinine. Conversely, the percentage reported by Janeso (*Atti della Società per gli studi della malaria. Vol. VIII, 1905, p.195*) for self-healing without quinine in patients with Plasmodium *vivax* malaria was 23% [34].

Table 2 - Morbidity (%) of the total population of the refugees in "New" Greece (Epirus and Northern Greece) according to the entries at the Refugees' Hospitals, 1923-1924.

Cities	*1923*	*1924*
Thessaloniki	49.3	52.4
Seres	46.7	62.8
Kilkis	61.8	36.2
Lagada	59.4	54.1
Florina		25.2
Veria		84.5

Source "Public Health in Greece", Proceedings of the Directorate of Health, Ministry of Health, Athens 1933.

The problem of quinine quality

One of the League's main problems was the quality of the quinine supply. Indeed, the circulation of poor quality quinine during periods of political and military unrest was the main cause of the increase in malaria prevalence in Greece (Table 3). Even after the law on the State's quinine monopoly had been passed, in 1908, the State continued to silently accept imports from private companies after 1915. Until 1924, the "monopoly" of importation was in the hands of private pharmaceutical manufacturers exclusively from Holland [34]. With the State's motivation, the Ministry of Health employed an alternative source from Japan and as a result the price of quinine decreased significantly [34]. After 1924 the State no longer had any control over quinine importation and the circulating "new quinine" that replaced the State drug contained only 0.1 g of quinine per pill (even though the label indicated that it contained 0.2 g) [34]. The new "drug" cost 0.50 drachmas per box compared to 0.65 drachmas for the State drug. The League and a team of "untouchable" employees of the Ministry of Health organised the struggle against unscrupulous traders held responsible, along five fronts, as proposed by Professor Savvas:

1) enforcement of the 1908 law on quinine;
2) implementation of total control over quinine imports by the State;
3) adjustment of the quinine quantity imported to the size of the Greek population and the number of patients according to official epidemiologic data;

4) enforcement of control over the amounts of quinine sent to hospitals, pharmacies and private physicians by the Ministry of Health and
5) the institution for the production of quinine, supported by the State like that existing in Italy [34].

The League's second journey to Italy: the Italian administrative and scientific model

The new Government under Eleftherios Venizelos as Prime Minister (1928-1932) decided to reform the Greek Health Services. The Dengue epidemic of 1927-1928, with one million cases (including the Prime Minister Venizelos himself) and 3,000 deaths, increased the need for health reforms but also altered the mentality of many Greek politicians. Public health was not high priority in governmental policy in the first two decades of the 20th century [41]. Greek politicians - even those belonging to progressive political parties - endorsed the conservative European political concept of the 19th century that health services were humanitarian institutions rather than an organized medical system [31]. Incredible though it may sound, Prime Minister Venizelos was accused by his political opposition in 1930 of spending money on Public Health. The first step of the health reformation in 1925 was the relocation of the Public Health Department from the Ministry of Transport to the Ministry of Health (Table 4) [40].

Ever since its establishment, the League, a private institution, had dealt with public health issues in Greece. However, their economic resources now depleted, the members of the League decided that the Greek State needed to assume a leading role in the fight against malaria. This decision was proclaimed by Professor Savvas and is documented in the League's official Proceedings, entitled "On the State's Responsibility" [34].

In 1927 the Minister of Health asked Professor Savvas to organize a standard operating procedure for the malariologists' missions in the provinces. Professor Savvas answered the Minister in three words: monopoly, autonomy, education, implying that Greece needed enforcement of the law on the quinine monopoly, an autonomous institution dealing with malaria and a Malariology School. Thirteen years after the Greek League's foundation, Professor Savvas decided once again to ask Italy for help. He organised a training trip to the High School of Malaria in Rome and the School of Malaria in Nettuno [34]. A physician was also sent to the School of Tropical Diseases in Hamburg, Germany, but once again he ultimately preferred the Italian way [34]. The Italian specialized anti-malaria institutes and the administrative model gave Professor Savvas the idea for a similar proposal to the Greek Government [34]. According to the Proceedings of the League on record, the Greek representative, Dr. Dimissas, returned to the League with a detailed report of his experiences in Italy [34].

Table 3 - Influence of the tampered quinine trade in malaria morbidity (%).

Period	*Morbidity (%)*	*Major events*
1880-1907	28.8	• Political instability • Greek-Turkish War • Non-existence of State's Monopoly • Tampered quinine
1908-1913	9.8	• Balkan Wars • Law on State's Quinine Monopoly • Control of the imports • Original quinine
1914-1918	32.4	• First World War • Tampered quinine
1919-1920	34.8	• Political instability • Tampered quinine
1921-1922	17.9	• Greek-Turkish War • The new borders between Greece and Turkey (Treaty of Lausanne, 1922) • Decision on the exchange of the Greek and the Turkish populations between the two countries • Refugees • State control on quinine • Original quinine
1923-1924	34.2	• Anarchy of imports • High price of quinine • Epidemics of malaria • Tampered quinine

According to the report, he arrived in Rome on 23rd May 1928 and on the same day had a meeting with Dr. Basile from the Directorate of Public Health and Dr. Labranca from the Department of Malaria Defence, arranged by the Greek ambassador. Dr. Labranca organised a detailed schedule for Dr. Dimissas' visit. Aided by Professor Moggiora, director of the State Microbiological Laboratory, Dr. Russo, the Head of the Rockefeller Foundation in Rome, Professor Missiroli, Dr. Haeckett and the malariologists of the Italian Red Cross Dr. Ilvento and Dr. Falleroni, Dr. Dimissas began his tour of the malaria laboratories and stations.

He immediately noted that the Department of Malaria had considerable authority, as a part of

Table 4 - Major sanitary reforms and laws during the turbulent and dramatic political period 1923-1930.

Year	*Major political events*	*Major Sanitary reforms and laws*
1923	• The Greek-Italian conflict (assassination of the Italian General Tellini in Albania) and the Corfu Incident • Coup d'état by the Greek Army • Dethronement of King George II of the Greeks • Referendum • Republic of Greece • Elections	• Central Service of Hygiene
1924	• Unsuccessful coup d'état by Greek Army Units • Political instability • Four governments in one year	
1925	• New *coup d'état* by the Greek Army	• Law on control of public and private health institutions • Coast and Harbour Sanitary Services • School of Hygiene Physicians • Organization of the Ministry of Health
1926	• Elections • Invasion of the Greek Army in Bulgaria	• The Sanitary Services of the Ministry of Health included to the Ministry of the Interior
1927	• Two governments in one year	• New Ministry of Health
1928	• Elections • Venizelos's Government • "The quinine scandal"	• International Treatise of Paris on the prophylaxis and eradication of acute and chronic diseases (signed by Greece) • Measures on prophylaxis and eradication of epidemic diseases • Central Service of Ministry of Health with 8 Departments • The responsibility of epidemic prophylaxis and eradication under the Minister of Health.
1929	• Venizelos's Government	• New Law on State Monopoly of quinine
1930	• Venizelos's Government	• Foundation of the Hygiene Centre of Athens with 6 Departments (The third Department was the Malaria Department) 12-member Committee in the Malaria Department

the Directorate of Public Health. The Department of Malaria supervised the anti-malaria campaign in endemic regions, oversaw all the sanitary-engineering works, managed quinine distribution and liaised between the Ministries of Internal Affairs and Agriculture as well as with private Italian anti-malarial societies. The need for a supreme authority with direct control over malaria affairs was a valuable realization for the League that constantly faced a multitude of bureaucratic problems and conflicts of interest between the various Departments of the Ministry of Health. In Italy, there were four institutions coordinated by the Department of Malaria, each with the right for flexible action:

a) the Public Health Microbiological Laboratory;
b) the Rockefeller Foundation;
c) the anti-malaria department of the Italian Red Cross;
d) private anti-malaria societies [34].

According to the Italian hierarchy, the Greek League was a private company but in the Greek reality, the League was head of the anti-malaria fight.

Another interesting fact for Dr. Dimissas was the authority of the Public Health Microbiology Laboratory. The Microbiology Laboratory supervised the School for anti-malaria training, the educational campaign for Italian schools and pupils, the teams of specialized malariologists in endemic and non-endemic regions, the diagnostic centres, the centres for patient treatment and the quinine supply centres. Dr. Dimissas also became familiar with the organization and function of the schools for malaria training in Rome, Nettuno, Caltanissetta, Sicily, Venice and Cagliari. He visited the Anti-malaria School of Nettuno and reported his impressions regarding its organisation and methodology. His most significant realization was that these schools provided education regarding malaria, not only to trained physicians, but also to the general public regardless of their educational status. Even simple citizens were offered elementary knowledge of the malaria epidemiology in their regions and were instructed to collect local malaria statistics and formulate plans for the construction of engineering works in their villages. Dr. Dimissas' next destination was the Military Anti-raid Training Centre in Poligono, 3 km south of Nettuno, where an Anti-malaria School had been constructed. He was impressed by the culture of the plant *Lemna*, a free-floating aquatic plant, that grows on or just beneath the water surface, thus impeding mosquito larva respiration, and the new technology for Paris Green spraying [34].

The Rockefeller Foundation in Rome was the experimental institution where intensive research was carried out into the eradication of malaria [42-44]. Dr. Dimissas was impressed with the organization of the foundation and the research results presented to him by its representative in Italy, Dr. Haecket. He also visited and collected data from other research institutions of the Rockefeller Foundation in Fiumicino, Sermoneta, Ferrara, Rovigno, Porto Torres, Verkita, Sassari, Ostia, Catania and Bianconuovo in Calabria. The Greek League was also interested in the activities of the Italian Red Cross that supervised Diagnostic Centres, the Anti-Malaria Hospitals and mobile teams of malariologists. Dr. Dimissas visited the Diagnostic Centre of the Italian Red Cross in Casalta and characterized it as an example for a similar effort in Greece. The Diagnostic Centre of Casalta, a marshy region, was divided into six zones: Casalta la Palude, Torre del Pavillon, Zarella, Fossa Nuova, Forum Appii and Porta Maggiore, each with a microbiology laboratory and a small room with 3-4 beds for short-term treatment.

Dr. Dimissas also studied the organisation of other Italian institutions such as the Syndicate of Sicily, the Anti-malaria Society of Venice, and the National Institute of Pontin, as well as the collaboration between them, and took special interest in the Italian Railways Society. Following the annexation of the new Greek territories, more than 500 kilometres of railway were added in regions where malaria was very prevalent, resulting in a significant increase in malaria morbidity amongst the railway workers. [34].

The League's proposal for the reformation of the Greek Anti-malaria institutions

Now well acquainted with the knowledge of the Italian Administration scheme, Professor Savvas described his new plan for reformation, in which he attempted to modify the Italian model to fit Greek requirements and above all the Greek economic situation. It was the ideal time to propose change, given Greek anger over the famous quinine scandal, in which a Director from the Ministry of Hygiene was found involved in the embezzlement of 7,000 kg of State quinine. First of all, Greece needed an autonomous Department of Hygiene within the

Ministry of Hygiene, an institution that would remain uninfluenced by political changes. This Hygiene Department would control the urban and provincial anti-malaria national centres, each staffed with a malariologist, an engineer specializing in water resources, an agriculturist and an accountant.

Inspired by the organization of the Italian Red Cross, he divided the country into five geographical zones headed by five inspectors [34]. In each zone, the inspector would be head in the local Microbiology Laboratory and a local anti-malaria Committee, with the assistance of the Greek Red Cross [34]. Professor Savvas also proposed the foundation of a School of Malariology, a Central Microbiology Laboratory and an urban Anti-malaria centre [34]. According to his plan, the Ministry of Economics had to set up two autonomous funds, the Central Fund for Malaria and the Fund for Water Resources for drainage works and water supply networks [34].

Professor Savvas also promoted closer collaboration with the Rockefeller Foundation in order to modernise the fight against malaria. The Rockefeller Foundation arrived in Greece in 1925, with Drs. Balfour, Wright, Shanon, and Barber, with the mission of training of the Greek malariologists and the observation of malaria's seasonality [34, 40]. However, the Rockefeller Foundation played merely an advisory role to the Greek State and had no authority for autonomous activity. Complementary proposals, inspired by the School of Nettuno in Italy, were the education of the committees of railway workers and the Greek refugees. Professor Savvas also proposed a law for the community services of prisoners in drainage works, with the incentive of reduced sentences [34]. Also, the League made educational proposals such as the founding of a School of Malaria and a Military School of Malaria.

The end of the Greek Anti-malaria League and the age of the Sanitary Reformation

One year after the proposal for the anti-malaria campaign reformation, the League lost its guiding light. Professor Savvas died in 1929 and was greatly mourned by the scientific community. He was a true hero for the Greek people and the news of his demise shrouded the entire country with sorrow. After a 25-year-long struggle against the malarial "Hydra", the League put its members and their priceless experience at the State's disposal, for the long awaited organisation of a national anti-malarial campaign. Malaria eradication became a vital objective for the State that welcomed collaboration with foreign institutions. Although the Italian model, modified by Savvas and Kardamatis, was a high quality plan for Greece, the State eventually opted for American technical help. The next year, enormous mobilization followed, with implementations of changes decided many years before. In 1929, Venizelos lay the legislative foundations for the establishment of Public Health in Greece, including the foundation of anti-malaria institutions. Many of Professor Savvas' proposals were adopted by the State and incorporated in its strategy. The Parliament voted the law (4233/29) on the foundation of the "Hygienic Centrr of Athens", comprising six departments, including the Department of Malaria [40]. The same year the "School of Hygiene" was founded in Athens (Law 4069/29) as well as the department of Hygiene in the Athens Medical School, both responsible for the education of Greek physicians regarding malaria [40]. The School of Hygiene was nominated as the base of the Rockefeller Foundation in Greece and consisted of two departments, the Department of Malaria and the Department of Hygienic Engineering [40]. In 1930, the State founded the Directorate of Malaria (Law 4555/30) of the Department of Malaria, a permanent 12-member committee within the Department of Malaria of the Hygienic Centre of Athens, ultimately in charge of anti-malarial campaigns [40]. It included the League's veterans and had supreme authority over all scientific and administrative matters of the anti-malaria campaign. For economic reasons, the establishment of a Military School of Malaria was not possible. Hence, the Directorate also coordinated with the Health Services of the Greek Army and the Navy, aided by the League of Nations Directorate of Health [40]. The same year the Rockefeller Foundation nominated Dr. Balfour as director of the Malaria Department and Dr. Wright as director of the Department of Sanitary Engineering and established three experimental stations in northern Greece [40].

In 1930, the Directorate re-evaluated the League's epidemiologic data and expanded research into other fields. They concluded that the main causes of malaria in Greece included the specific climatic conditions of the region, the primitive water supply network and acts of human "barbarism" such as changing the

course of rivers [40]. During the 1930s Greece was ready for the second round against malaria. The League's experience served as the starting point while the Rockefeller Foundation provided the necessary technical support. Until Greece entered World War II, key positions in anti-malarial services were held by the Rockefeller Foundation's Greek trainees. In 1942, Dr. Kardamatis died in Athens and once again there was great mourning in the scientific community and the general public alike. During World War II and the chaotic years of a new national Greek tragedy that followed it, the Civil War, the prevalence of malaria increased rapidly once again. After 1945, the third and final successful attempt was begun by the Greek authorities at malaria eradication (the School of Hygiene) and UNRRA with the ambitious plan of DDT air-spraying [45]. The Greek Civil War, followed by the invasion of British troops in Athens, was a time of political and social turmoil, during which a number of eminent and experienced malariologists were fired and prosecuted for their political ideas, or abandoned their positions in order to join the communist army in the mountains. Soon a serious conflict broke out between the Greek State and the representatives of UNRRA based on accusations of espionage and rumours that the Americans attempted to influence Greek political life in return for the sanitary programme of DDT spraying, and thus began a new chapter in the history of malaria eradication in Greece.

CONCLUSION

For 25 years, from 1905 to 1930, the anti-malarial campaign in Greece was conducted by the Greek Anti-Malaria League, a private organisation founded by a few eminent Greek physicians, namely Professor of Hygiene and Microbiology C. Savvas and Dr. I. Kardamatis.

This private initiative aimed to reduce malaria prevalence in the region, using mass quinine treatment and public awareness-raising and education.

Professor Savvas' scientific association with the Italian School of Malariology helped the League in its first steps.

Malaria epidemiology in the country changed significantly in the years following World War I and the national disaster of 1922 that resulted in a massive influx of Greek refugees from Asia Minor.

During this time the League based on the Italian scientific and administrative knowledge, formulated inspired proposals for reforming the Greek anti-malarial institutions, many of which were eventually implanted by the State. The League's experience, accumulated during its 25 years of struggle against malaria, was its legacy to the campaigns that eventually accomplished the eradication of malaria from Greece after World War II.

Keywords: Constantinos Savvas, Ioannis Kardamatis, Italian School of Malariology, malaria.

SUMMARY

In 1905, a group of eminent Greek physicians led by Professor of Hygiene and Microbiology Constantinos Savvas and the pediatrician Dr. Ioannis Kardamatis founded the Greek Anti-Malaria League. The League assumed a role that the State would not, and for the next 25 years organized the country's anti-malaria campaign. During its first steps, the Greek Anti-Malaria League adopted the principles of Professor Angelo Celli's Italian Anti-Malaria League. The League's accomplishments include a decrease in malarial prevalence, due to mass treatment with quinine, new legislation ensuring the provision of quinine, State monopoly and the collection of epidemiologic data. However, defeat in the Greek-Turkish War (1922) and the massive influx of one million Greek refugees that ensued, led to a change in malarial epidemiology. In 1928, following a visit to Italy, the Greek League adopted the organization and knowledge of the Italian Malaria Schools in Rome and in Nettuno, and this experience served as the basis of their proposal to the State for the development of the anti-malaria services infrastructure. The State adopted many of Professor Savvas' proposals and modified his plan according to Greek needs. The League's experience, accumulated during its 25 years of struggle against malaria, was its legacy to the campaigns that eventually accomplished the eradication of malaria from Greece after World War II.

RIASSUNTO

Nel 1905, un gruppo di eminenti medici fondò la Lega Greca Anti-Malaria. I capi della Lega erano Constantinos Savvas, professore di Igiene e Microbiologia, e Ioannis Kardamatis, pediatra. La Lega sostituì lo Stato nell'organizzare, nei successivi 25 anni, una campagna anti-malaria. Nella prima fase, la Lega adottò i principi della Lega Anti-Malaria Italiana del professore Angelo Celli, riuscì a diffondere l'uso massivo del chinino, a creare la nuova legislazione sul monopolio statale del chinino e a raccogliere dati epidemiologici. Gli sforzi della Lega riuscirono a diminuire la prevalenza della malaria. La sconfitta subìta nella guerra greco-turca (1922) e l'onda migratoria di un milione di rifugiati greci modificò la geografia della malaria.

Nel 1928, dopo una visita in Italia, i fondatori della Lega Greca fecero proprie l'organizzazione e le conoscenze delle Scuole di Malaria di Roma e Nettuno. Questa esperienza costituì la base della proposta che la Lega avanzò allo Stato per lo sviluppo di infrastrutture anti-malaria. Lo Stato accolse molte delle proposte del professore Savvas e modificò i propri piani assecondando le necessità del paese. L'esperienza maturata in 25 anni di lotta contro la malaria rappresentò l'eredità della Lega per le campagne successive che si conclusero con l'eradicazione della malattia dalla Grecia dopo la II Guerra Mondiale.

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