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## Landmarks in Malaria Research\*

(a Review)

MEIR YOELI

The battlefields of yesterday's campaigns and struggles are the ploughed fields of today. The wheat ripens there, the corn grows tall and the ubiquitous grass covers all the routes and tracks of armies. An historian eager to retrace past battles must take to the hills, and there from a promontory overlooking the plains scan the wide horizon for landmarks of the past.

There is, I believe, no better stage from which to view the long and arduous trail of malaria research and malaria control than from this ancient, still young and beautiful soil of Greece. For it was in Greece that the flail of the swamp fevers struck most cruelly, persistently, and devastatingly, for centuries, leaving harvests of death and untold suffering. It was again in Greece, a quarter of a century ago, that the strategy of scientific knowledge and dedication, fortified by stamina and preparedness, broke the age-old bondage, and triumphed. And by this splendid example and success, Greek malariologists brought a message of hope to other countries, still struggling hard to control malaria in their own lands.

The presence of malaria in Greece in ancient times has been well documented (5). Its prevalence, epidemiology and effect since the early years of this century have carefully been studied both by Greek and foreign physicians (1, 3, 5). The vastness of the problem, its somber magnitude, still echo in the words of Sir Ronald Ross after his visit to the Kopais region in 1906: "I have not seen anything worse in the marshy areas of India, nor have I seen anything similar in Africa."

Literary quotations, however, can hardly match the impact of statistical evidence. In the years 1925–1937, out of a total national population of 7 million, 1½ million to 2 million malaria cases occurred annually in Greece (15–30 % of the total population). The average yearly mortality from the disease reached 5,200. Malaria ranked second in the list of the childhood diseases; second only to pneumonia. The average

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Professor Gregori Livadas, whose malaria control efforts through many years were crowned by the eradication of the malaria fevers from Greece.

consumption of quinine in the country amounted to 30 tons per year (6).

The ominous threat which the malaria fevers posed to Greece, to its people, to its economy, to the very heart and life of the nation, did not remain unchallenged. Throughout her long and heroic history great challenges have brought out new leaders. In the beginning of this century and up to the nineteen twenties, it was Dr. K. Savvas and Dr. J. Kardamitis who carried the banner. They were the early apostles of malaria control. Quinisation was their slogan. It was an old, hazardous, often unreliable weapon. It was the only armament available to them at the time. It lessened suffering, but it did not stem the tide. In the

years 1930–1937, with the establishment of a special national anti-malaria service in Greece, directed by Professor Gregory Livadas and in collaboration with the members of the Rockefeller Foundation – M. C. BALFOUR, M. Barber, R. C. Shannon and I. B. Rice – a scientific program of malaria control was implemented, based on the elucidation of the bionomics and biological characters of the anopheline vector species and their geographical distribution. Results were evaluated and measured by exact epidemiological and malariometric methods (spleen rate, parasite rate and sporozoite index) (1). Control measures consisted of larvicides, a far from easy task, often exhausting the patience of the field workers, considering the difficult, often inaccessible breeding places. Success was slow in coming, yet clearly visible. Among the lasting contributions which this era of malaria control had produced was the training and molding of a highly disciplined and dedicated cadre of field workers, teams that covered the entire country. They got their baptism of fire in Paris-green sprayed swamps; and they dreamed of more powerful, longer lasting protective weapons. World War II and the invasion of Greece broke up their work. Systematic malaria control ceased in occupied Greece and the country reverted to its old endemo-epidemic state.

I came to Greece and to Macedonia with the British forces at the end of World War II and I had ample opportunity in my surveys to observe the malarial fevers burning in the eyes of many thousands of Greek school and village children; the pallor, the cachexia, the splenomegalies; the overgrown swamps full of *Anopheles sacharovi* and the hill streams teeming with *Anopheles superpictus*. It was in the fall of 1945, on the eve of the great DDT campaign.

Much has been written on the eradication of malaria from Greece. The subject has now become a near classic in the annals of modern Public Health. As the years recede and the mists of time envelope the past, this achievement will appear to future generations as a saga, a modern legend of the redemption of the land. But Greece's example is not unique. Other countries on the European, Asiatic and American continents succeeded with aid and guidance from the World Health Organization to eliminate malaria from their lands. What is unique and of particular interest about Greece is that it stood at the crossroads of ideas, it served as a testing ground, where the old, well entrenched beliefs swayed and collapsed and novel conceptions born of setbacks and doubts emerged into the light. It was on the battlefields of Macedonia (1916–1917) in World War I that Charles Morely WENYON, Edmond and Etienne Sargent and their colleagues watched, powerless, while the great malaria epidemics raged among the Allied troops, and quinine failed to act as a prophylactic drug (12). It was there on those battlefields that Schaudin's seemingly invulnerable postulate of the

direct penetration of the sporozoite of human plasmodia into red cells received its first fateful blow. From the Wellcome Laboratory in Salonika, in the early post-war years, Neil Hamilton Fairley studied black-water fever and elucidated the nature of the hemozoin pigment. Observing malaria in the field in those «Meisters Lehrjahre» he prepared for tasks ahead. Finally, it was in Greece, during the final stages of the DDT campaign that the tenuous line separating success from failure in the application of modern insecticides was first clearly revealed, with the appearance of DDT resistance in *A. sacharovi*, as demonstrated by LIVADAS and GEORGOPOULOS (7).

I have thus far focused on malaria in a single country. Through this prism we can now view the global aspects of the disease, its control and research; the promises, expectations and future advances. Through it we can scan the past and trace the waves of discoveries which carried malariology to its present shores.

To start with, one must look back into the archaic past and begin with the remote Hippocratic era, when the early foundations of clinical medicine and diagnosis were first laid. The recognition of the rhythm of the fevers and their specific patterns, accompanied by enlargement of the spleen must be considered the first and earliest landmark on the long road of malaria research. The introduction, in the early years of the seventeenth century, of cinchona febrifuga, the «Jesuit powder», as a curative substance against the swamp fevers, represents an historical landmark. For it was not only the invaluable healing power of the bark and its saving of innumerable lives, but also its selective therapeutic action, and ability to separate malaria from other agues, that launched a new era in the differential diagnosis of fevers, as outlined in the treatise of Francesco TORTI (10).

The isolation, by Joseph Pelletier and Joseph B. Caventou of France, of quinine and the other cinchona alkaloids, marks a most important advance in control of the disease. It gave physicians a therapeutic agent, for the first time, pure in substance and reproducible in its effect. This discovery instantaneously shifted malaria therapy from the domain of unpredictable folk medication to the sphere of precise therapeutics.

It is with a sense of deep respect and gratitude that we recall the memory of Pelletier and Caventou. Through their discovery they sought no personal gain, and in their generosity they bequeathed it to the welfare of mankind.

A full century has passed in which quinine occupied the sole and supreme position in therapy. Its mode of action, however, was not understood, and awaited further elucidation. It was not until 1927, with the introduction, by Werner SCHULEMANN, of the synthetic quinoline Plasmochin (8), followed shortly by the discovery, by Walter KIKUTH and his group at I.G. Farbenindustrie, of the antimalarial action of



Atebrin, an acridine derivative (4), that a new era in chemotherapy and prophylaxis in malaria began.

In bringing before you first the early advances in treatment, I have merely followed an historical perspective. Treatment of the fevers, the acute attack, the relapse and the chronic illness, was long considered the preferred method of control – long before the causative agents of malaria were discovered. If such an assumption seems to us nowadays to be naive and somewhat illusionary in the light of past experience, this concept must nevertheless be considered logical and valid when judged in the light of the limited knowledge available in those days.

The elucidation of the life cycles of the malaria parasites and their growth has been the central axis around which malaria research has revolved in the past. Originating from the classical discovery of Laveran in 1880, a powerful scientific tide swept the twentieth century, extending to wide horizons. Amid the vast expanse of research the crests of the big waves still stand out, rolling on from different directions, each wave followed by another, merging together and contributing strength and continuity – from Alphonse Laveran to Ronald Ross, from Camilo Golgi to Ettore Marchiafava and Battista Grassi. Converging toward them were other waves from the East, contributions of B. Danilewsky and D. L. Romanowsky and those from the New World – the work of W. G. MacCallum and E. L. Opie. The outcome of this great tide was a clear understanding of the cycles of development of the parasite and its effect upon the host – elucidation of a complex metamorphosis involving a sporogonic, schizogonic and gametogonic cycle within the life of a haemosporidian parasite.

At the time, and until the end of the World War I, it appeared that the picture drawn was clear and final, that nothing could be added or removed. But the probing mind is not satisfied with outwardly harmonious structures, it searches for the invisible cracks in the walls. A number of unexplained phenomena in the course of malaria infections, discrepancies between sporozoite and blood induced infections, and the puzzling, unexplained action of drugs, led to the belief that a vital link was missing in the cycle. Where do sporozoites migrate after their inoculation into the body? Where is the site, the organ, the cell, in which this development takes place during the silent incubation period? Without a clear understanding of this problem, malaria therapy and prophylaxis would remain in the dark, lacking clear direction.

The existence of an exo-erythrocytic cycle in avian malaria was first demonstrated by G. Rafaelle in 1934. His findings were confirmed and extended by the discovery, by S. P. James, and Tate, of a tissue phase in *Plasmodium gallinaceum*, in cells of the reticuloendothelial system. Clay G. Huff, in detailed experimental studies, described the sequence of events from the moment of sporozoite penetration to the invasion of

the blood. But it was not until 1948 that the primary tissue phase of primate and human plasmodia was discovered through the splendid work of H. E. SHORTT (9) and P. C. C. GARNHAM. Avian malaria first pointed the way to the existence of the cycle, but it failed to lead to the target. N. Hamilton FAIRLEY's studies (2) on human volunteers narrowed the gap by demonstrating a negative, noninfective phase of the blood during the incubation period of sporozoite induced malaria. However, it remained for the two savants from the London School of Tropical Medicine, through brilliant experimental planning, intuition and execution, to demonstrate the stages of the primary cycle in the parenchyma cells of the liver. Coming half a century after the work of Laveran, Ross and Grassi, this new discovery ranks with its predecessors among the greatest landmarks of malaria research.

During the whole period in which morphology and development of the malaria parasites were studied, endeavors were made to clarify host reactions to plasmodial infections. Field observations in many parts of the globe revealed the existence of an acquired immunity in populations of endemic regions. The degree of resistance paralleled the frequency of sporozoite «bombardment». Acquired immunity was a slow process, requiring time and continued exposure; it was expressed in the early years of life by a stage of acute infestation, accompanied by fever, high parasitemia and splenomegaly. Not infrequently the infection overpowered its host, resulting in fatal outcome.

Resistance in naturally exposed populations depended on age and exposure, and the immunity was species specific. Malaria could assume epidemic proportions in such communities with the introduction of new plasmodial strains. Among the first to carry out observations on populations in highly endemic areas was Sir Richard Christophers in India. Later studies extended to many other regions, notably to the holo-endemic areas of Africa, culminating in the important immunity studies of J. A. McGregor and his group in Gambia.

Avian and primate malaria served as early models for immunity studies. One must remember the pioneer work of Edmond Sergent in Algiers, J. A. Sinton in India, and William H. Taliaferro at the University of Chicago. The introduction of malaria therapy for neurosyphilis permitted direct immunological experimental observations on man. The investigations of M. Ciuca of Bucharest are notable in this respect. Malaria research, and especially immunological work, was greatly strengthened and expanded with the discovery of *Plasmodium berghei* in 1948 by Ignaz VINCKE (11) in the forest galleries of Katanga. Rodent malaria became the most important tool for large-scale experimentation; its value, moreover, was greatly enhanced by the demonstration that its pre-erythrocytic cycle was similar in its pattern and location to the primate and human plasmodia (14, 15).

It is impossible to review all the vast literature and studies on immunity in rodent plasmodia. It is my privilege today to mention some of the authors who have made lasting contributions to the subject: Augusto Corradetti of Rome, Saul Adler and Avivah Zuckerman from Jerusalem, Fabiani of France, N. K. Brown in London, and Ruth Nussenzweig in New York. Modern immunological research in malaria, buoyed by the availability of rodent plasmodial models, reaches presently toward more distant goals. It brings to its tasks principles and techniques which have long been successfully employed in solving some of the problems of viral and bacterial diseases.

Lastly, let me mention the adaptation of human plasmodia to susceptible primate hosts, an important landmark in malaria research, the results of the studies of Martin YOUNG (16) and his group at the Gorgas Laboratories in Panama.

The success achieved in the past quarter century in the eradication of malaria from many highly endemic regions of the globe is directly related to the scientific planning and application of residual insecticides. DDT has been the primary weapon in all the campaigns won, and the Malaria Division of the World Health Organization, the stimulating and guiding power behind all campaigns. When one contemplates that the discovery of DDT did not originate in the camp of malarialogy, one comprehends the great blessing in the cross-fertilization and interdependence of science.

Whatever the outcome of future antimalaria campaigns, whatever the planning or the methods of execution, the era of DDT will long remain a turning point in the history of malaria control, and the work of Paul Müller, its discoverer, a lasting contribution to global Public Health (13).

From the vista of this Congress in Athens, we look today on a century of malaria research. It is a long, winding, uphill road, studded with great landmarks. The view compels admiration for past achievements. The view inspires confidence in future exploits. The distant goal and vision of global elimination of the malaria fevers still stands. The promise will be kept. Fresh ideas, new knowledge, young minds, and dedication, will be required for the realization of this goal, and scientific élan and total commitment from governments.

In this unfinished, greatest of all Public Health epics, there are pages still to be written, and new discoveries, new landmarks to grace the road ahead.

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