Army Malaria Institute: its Evolution and Achievements. First Decade: 1965-1975

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Abstract

This article describes the resumption of malaria research activities by the Australian Army during the mid-1960s - about 20 years after they were discontinued at the end of World War II . At the start of the decade, some malaria infections were no longer being suppressed adequately by proguanil or chloroquine, whereas the addition of dapsone to the prophylactic regimen was effective in preventing falciparum malaria during military operations in Vietnam. However, severe toxicity observed in a few individuals following the use of this drug combination emphasized the need to develop alternative prophylactic regimens. The small malaria research unit was able to demonstrate potentiation of antimalarial activity between proguanil and dapsone in a rodent malaria model, raising the possibility that a drug combination using lower (and non-toxic) doses of dapsone might be effective in protecting soldiers against drug-resistant malaria. This synergistic drug activity was only able to be determined in mice inoculated with blood from other infected mice because routine malaria transmission via infected mosquitoes reared in the insectary proved difficult. Although anopheline mosquito colonies could not be used successfully to determine the causal prophylactic activity of drugs against sporozoite-induced infections, they were becoming useful for investigating the biological properties of a novel fungus discovered to attack mosquito larvae in the insectary. Initial plans to evaluate the effectiveness of new antimalarial drugs in soldier volunteers were shelved in favour of taking appropriate measures to procure Aotus monkeys in which drug activity against human malarial parasites could be assessed.

Background

Malaria has been recognized for a very long time to be a major threat during combat operations in malarious areas. During the First World War, personal protection and mosquito reduction, mainly by drainage and oiling of mosquito breeding sites, were the main measures used to prevent malaria. The only antimalarial drug available was quinine and, although it was partially effective in treating patients with malaria, toxicity precluded the prolonged use of this drug for malaria prevention. Later on, in the 1920s and 30s, German scientists discovered the first two synthetic antimalarials - pamaquine and atebrine. Chloroquine, which came to be the most widely used antimalarial in the latter half of the 20th century, was not synthesized by them until the early 1940s. At about the same time, British scientists discovered proguanil (Paludrine). During the Pacific War in the 1940s, malaria became a serious problem for Australian and other troops during combat operations. This prompted General Douglas MacArthur to comment that "this will be a long war, if for every Division I have facing the enemy, I must count on another Division in hospital with malaria, and a third Division convalescing from this debilitating disease". Because of the gravity of the situation, the US Army embarked on an intensive program to evaluate various drug regimens for their effectiveness in the prevention and treatment of malaria.

Australian Army contribution to malaria prevention. There was an alarmingly high rate of malaria cases among Australian troops during the first year of the campaigns in Milne Bay and Kokoda. In February 1943 analysis of sickness casualties from the disease showed that if malarial infections continued at these levels there would be insufficient available manpower in Australia to maintain the required force in New Guinea.[1] This was a key stimulus to the formation of the Land Headquarters Malaria Research Unit (LHQ-MRU) which was established at Cairns, North Queensland by Brigadier N.H. Fairley in June 1943. Early investigations carried out by this Unit revealed that malaria could be controlled by taking one tablet of atebrine (100 mg) every day.[2] Enforcement of this drug regimen by Unit Commanders ensured that thousands of soldiers in New Guinea were protected against malaria. In fact, strict discipline reduced malaria in the Australian Army to a level previously unknown in a force operating in a highly malarious area. Nevertheless, despite its efficacy, the drug did have some disagreeable side-effects, such as a yellowish discolouration of the skin, and it was not widely used after the war. Treatment of established vivax infections with pamaquine was

useful in preventing malaria relapses, whereas administration of the drug to a small number of volunteers during the pre-erythrocytic incubation period did not prevent subsequent primary attacks of vivax malaria but did prevent relapses.[3] Proguanil was not useful for treatment, but this well-tolerated drug was very effective in preventing falciparum malaria when administered during the incubation period.[4] Although parasite resistance to proguanil started to appear in a few places as early as 1948, it remained effective in protecting most Australian soldiers for another two decades.

The malaria studies by Brigadier Fairley's group at the LHQ Malaria Research Unit at Cairns not only carried out meticulous studies to evaluate the effectiveness of antimalarial drugs, but they also obtained considerable new information about the life cycle of the human malaria parasite and the pharmacokinetics of various drugs. All these accomplishments over a period of just 3 years (1943-1946) could not have been possible without the participation of hundreds of soldiers and a very dedicated group of investigators. The remarkable saga of this effort to control malaria and its outstanding achievements have been documented in considerable detail in Tony Sweeney's book - Frontline Malaria.[5]

Antimalarial drugs in the 1950s. In the years after WWII chloroquine became the main drug used for the treatment and prevention of malaria, although the Australian Army continued to use proguanil for prevention where parasite resistance to this drug had not yet developed. Two other drugs were also introduced – pyrimethamine, an antifolate similar to proguanil, and amodiaquine, a 4-aminoquinoline similar to chloroquine.[6] In the meantime, an intensive program had been initiated in the USA to synthesize 8-aminoquinoline compounds that might be less toxic and more effective than plasmoquine which had its origin in the 1920s. Primaquine emerged as the best and least toxic of these new 8-aminoquinolines for eradicating the residual liver stages of *Plasmodium vivax*[6] and was first used very effectively against vivax malaria during the Korean conflict in the 1950s. However, some vivax infections, especially from the southwest Pacific area, had a reduced susceptibility to this drug.[7]

Global malaria eradication program. Anti-mosquito measures are of course an extremely important component of any antimalarial control activities. Following the discovery of DDT, 6-monthly indoor residual spraying (IRS) to control adult anopheline mosquitoes was introduced as a supplementary measure to ground control of larval breeding sites. In 1955 the WHO launched a global malaria eradication program based on IRS combined with active and passive surveillance to detect and treat malaria infections. Although a few countries achieved malaria eradication, most countries struggled to interrupt malaria transmission.[6] Certainly, in unstable environments with a breakdown in public health activities, such as military conflicts, protection of troops continued to rely heavily on ground control measures and rigorous adherence to personal protection against mosquito bites, in addition to chemoprophylaxis.

Proguanil resistance. During the early 1960s, daily proguanil prophylaxis, coupled with anti-mosquito measures, seemed to control malaria quite well during limited deployments overseas. However, in 1962, there was a major malaria outbreak among Australian and New Zealand troops serving with the 28 COMWEL Brigade in northern Malaya. Although antimalarial discipline may not have been as good as it should have been, limited investigations by the malaria research unit in Kuala Lumpur indicated that some strains of malaria in the area had developed resistance to proguanil.

Chloroquine resistance. By the early 1960's, there was also evidence of emerging chloroquine resistance in Southeast Asia and South America. It was soon observed that chloroquine could no longer provide adequate protection against falciparum malaria for American troops in Vietnam. Most of these infections were also resistant to pyrimethamine and, to a lesser extent, proguanil. This prompted the US Army to embark on a major malaria research program which included the synthesis of thousands of chemical compounds and screening them for their antimalarial activity using the *Plasmodium berghei* malaria mouse model.[8] The most promising compounds were then screened for their activity against chloroquine- and antifolate-resistant isolates of *Plasmodium falciparum* using a newly-developed in vitro test.[9] Some of them then underwent further evaluation in *Aotus* monkeys and human volunteers.[10] Based on some early findings, American troops were treated with various combinations of quinine, pyrimethamine, dapsone, and various sulphonamides. In some US units, daily dapsone was added to the weekly chloroquine-primaquine prophylactic regimen.

Establishment of Malaria Research Laboratory

The emergence of chloroquine resistance in the early 1960s, coupled with the demonstration that some Australian soldiers in Malaya were not being adequately protected by daily proguanil prophylaxis, prompted Professor Robert Black, Army Consultant in Tropical Medicine, to recommend the establishment of a Malaria Research Laboratory (MRL). As an Army Captain serving at the LHQ Malaria Research

Unit at Cairns, Professor Black had experienced first hand the devastating impact of malaria on combat operations in the 1940s. With the growing commitment of Australian troops to conflicts in Southeast Asia, Professor Black proposed, in 1965, that the MRL be established under his supervision at the University of Sydney's School of Public Health and Tropical Medicine (SPHTM). In June 1966, approval was given for the MRL to be established, staffed initially by a Major Medical Officer, two Captain Scientific Officers and three non-commissioned (NCO) Laboratory Technicians. Professor Black hoped that human malaria studies, similar to those at Cairns, could be conducted in Army volunteers to counter the growing drug resistance problem.

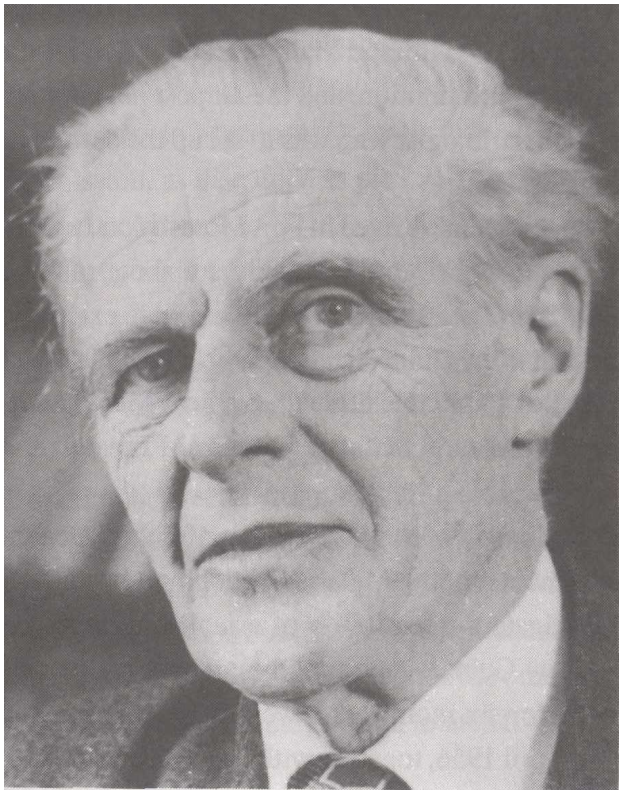

Figure 1. Professor Robert Hughes Black, Army Consultant in Tropical Medicine

In the meantime, the importance of identifying effective drug regimens for malaria prophylaxis was highlighted by Australian troops deployed to Vietnam. Towards the end of 1966 and 1967 (after the wet season), Australian troops experienced peak monthly malaria rates of 140 and 190 per thousand per year. Despite very intensive efforts that all personnel took 200mg proguanil daily (double the normal dose) and took every precaution to avoid mosquito bites, the rate rose to 455 in October 1968. In November, a study was initiated to assess the value of adding 25mg dapsone to the daily suppressive dose of 200mg proguanil. The suspicion that parasites had developed a marked degree of resistance to proguanil was confirmed when dapsone/proguanil prophylaxis resulted in a dramatic reduction in the incidence of falciparum malaria. Furthermore, this synergistic drug combination provided better protection than alternative regimens used by other forces in the area.[11] Unfortunately, a number of soldiers – mainly in US units taking daily dapsone and weekly chloroquine/primaquine developed agranulocytosis following daily administration of 25mg dapsone.[12,13] Consequently, the use of a daily dose of dapsone was no longer included in malaria prophylactic regimens.

Facilities and Staff

Following the establishment of the MRL in 1966, a biochemist/parasitologist (Captain George Michael Galvin), an entomologist (Lieutenant Elizabeth Kalucy), and some technicians commenced their work in small quarters located at the SPHTM. Although some basic malaria research procedures were established, laboratory studies were hampered by inadequate accommodation and the lack of qualified staff. Michael Galvin was transferred in 1968 and Elizabeth Kalucy resigned the following year for family reasons, with the result that the mosquito colony which was set up to transmit rodent malaria could no longer be maintained.

The need for enhanced malaria research activities was stressed following a statement by the Adjutant-General in 1969 that "events in Vietnam had shown the Australian Army to be extremely vulnerable to the ravages of Malaria". He also commented on the "meagre, ineffective and totally inadequate research effort".[14] In the same year, a medical officer (Major Ian Saint-Yves) and an entomologist (Captain Anthony Sweeney) were recruited, both having been involved previously in malaria control/eradication activities in PNG. An Army Malaria Research Advisory Board (AMRAB) was also established to serve as an expert committee and to give professional guidance and authority to the subject of malaria research within the Australian Army. The first meeting of the Board, convened under the auspices of the Adjutant-General, was held on 9 Dec 69 under the chairmanship of the Director General of Medical Services, Major General C.M. Gurner. Subsequent meetings during 1970 considered various ways of meeting the challenges posed by the growing malaria problem, including the possible use of Army volunteers to develop effective antimalarial drug regimens.

Figure 2. Unit staff January 1970. From L to R: CAPT A.W. Sweeney, MAJ I. Saint-Yves, CPL N. Tinney, CPL R. Green and CPL C. Gulley

In July 1970, the MRL was re-designated as the 1st Malaria Research Unit (1MRU) (Raising/ Reorganization Instruction 31/70 dated 17 Jun 70). The staff was increased from 6 to 8, comprising a Colonel Director, three Major Scientific Officers, three NCO Laboratory Technicians and one Clerk. It was hoped that a full-time Director would provide the necessary leadership and expertise to tackle the growing malaria problem. It was also planned to move AMRU from the University to be co-located in more appropriate facilities at 2 Military Hospital, Ingleburn, located southwest of Sydney. Unfortunately, adequate staffing of the unit remained a problem, with many technical staff being at the unit for less than a year. An exception to this was Corporal David Cowdrey who was assigned to the Unit in 1971 and remained actively involved in malaria research activities (including 14 overseas deployments) until his retirement in 1989. In an effort to fill the vacant Director's position, the option of civilianising the position was accepted in June 1972. Following the resignation of Major Saint-Yves in June 1973, 4 staff members remained, with Captain Sweeney being the only one of the original 1MRU group.

In July 1973 Dr AP Ray was appointed as the first director of the unit and work proceeded to accommodate the Unit on the grounds of 2 Military Hospital at Ingleburn. When AMRAB was convened during the opening ceremonies in April 1974, Dr Ray and Professor Black envisaged that the scope of work at the unit could now be expanded with a view to progressive assessment of drugs in infected rodents, then in *P. falciparum*-infected *Aotus* monkeys and, finally, in infected Army volunteers at the adjacent Field Hospital. As 8 of the 9 establishment positions were being filled, there was a feeling of optimism that, with some additional staff, these proposed research activities could be carried out over the ensuing years.

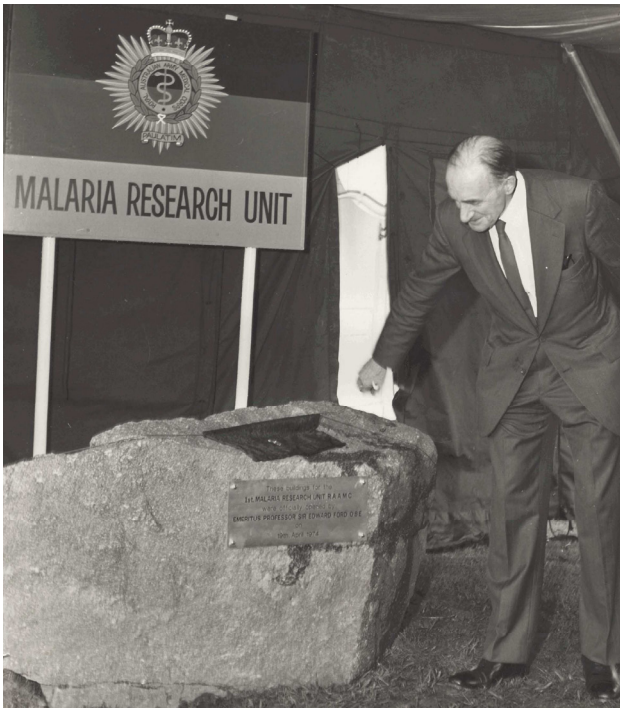

Figure 3. Emeritus Professor Sir Edward Ford opening Unit at Ingleburn on 19 April 1974. He played a dominant role in the New Guinea Force (1942-1943) "in defeating malaria before it defeated us".

Activities

The role of the MRL was to carry out malaria research activities to protect soldiers adequately and safely against drug-resistant malaria spreading southward from its original focus along the Thai-Cambodian border. By the late 1960s, there were rumours that chloroquine-resistant malaria may even have reached PNG, although this could not be confirmed when Major Saint-Yves investigated this possibility in the Milne Bay area following a request from PNG authorities.[15] In addition to the malaria research efforts by the US Army and some other overseas organizations, the Australian Army's participation was considered important because malaria and malaria vectors have certain characteristics unique to the Pacific region. Although investigations with human malaria parasites cannot be initiated, the following studies were performed following the establishment of a rodent malaria model and an insectary.

Antimalarial activity against rodent parasites

Rodent malaria models have been used since the 1950s to obtain preliminary information about the potential antimalarial activity of various drugs and drug combinations.[16] Such studies usually constituted the first step in developing new drug regimens for the prophylaxis and treatment of

malaria. Studies with rodent malaria were initiated at the Unit before the move to Ingleburn. Although attempts to do this were not entirely successful in the beginning, it was soon possible to routinely transmit rodent malaria parasites from mouse to mouse through intra-peritoneal inoculation of P. *berghei*-infected red cells. This provided the means for assessing the efficacy of various drugs and drug combinations in mice infected with chloroquine-resistant strains of *P. berghei.*

Proguanil and dapsone were among the first drugs to be evaluated in the rodent model, including the assessment of urinary drug concentrations by spectrofluorimetry. Results showed potentiation of antimalarial activity between various combinations of dapsone and proguanil. Early observations of synergistic activity, even at low doses of dapsone, suggested that the drug combinations might retain their efficacy at dapsone doses lower than those used by Australian soldiers during the Vietnam conflict. If further studies were to confirm these preliminary findings, lowering the dose of dapsone might avoid the rare case of agranulocytosis observed during proguanil/dapsone prophylaxis in Vietnam.

Transmission of rodent malaria via anopheline mosquitoes

The rearing of anopheline mosquitoes in an insectary commenced soon after the establishment of MRL. Its primary purpose was to transmit *P. berghei* from one rodent to another via susceptible anopheline mosquitoes, thereby enabling the causal prophylactic activity to be determined against pre-erythrocytic liver stages. As far as malaria protection was concerned, the ability of a drug (e.g. proguanil) to exert its activity against the liver stages (before release of parasites into the blood circulation) had distinct advantages over a drug that acted only against the blood stages.

The first mosquito colony of *Anopheles annulipes* was established by Elizabeth Kalucy in 1968 from specimens collected at Castle Hill in Sydney. The colony was maintained by a labour-intensive, induced mating technique because natural mating in cages was not possible. During May 1969 cyclical transmission of rodent malaria was achieved by feeding mosquitoes from this colony on mice infected with a gametocyte producing NK65 strain of *P. berghei*[17]. Dissections of mosquitoes two or more weeks after feeding showed oocysts in about half the stomachs and heavy sporozoite infections in the salivary glands of a few mosquitoes. Parasitaemia developed in five albino rats bitten by mosquitoes which had previously taken infective blood meals from mice. These encouraging results suggested that this mosquito/parasite combination might lead to the establishment of an experimental transmission model of rodent malaria. Unfortunately further experiments with this strain of *An. annulipes* were not possible because of the lack of technical staff to maintain the mosquito colony after Kalucy's departure in 1969.

After Tony Sweeney's arrival at the unit in 1970, a new colony of *An. annulipes* was established from larvae collected at Nattai River near Mittagong. In January 1971 *An. hilli* larvae collected during a field survey at Gove in the Northern Territory were transported back to the insectary.[18] This species adapted very well to the laboratory as it could mate in the confined space of small laboratory cages and could mature the first egg batch without the need for a blood meal.

Figure 4. CAPT A.W. Sweeney feeding Anopheles mosquitoes.

A second series of *P. berghei* transmission experiments using the two new colonies of anopheline mosquitoes were made with the NK65 strain and also with the ANKA strain.[19] Both species were almost completely refractory to the NK65 strain as only around 1% of mosquitoes fed on infected mice developed oocysts and sporozoites. Results with the ANKA strain were not much better - *An. annulipes* could not be infected and *An. hilli*, despite its ease of maintenance, experienced a 90% mortality during the 2-3 week holding period necessary for the completion of the mosquito cycle of the parasite. Although a few mice were able to be infected by inoculation of sporozoites from surviving mosquitoes, it became obvious that a local mosquito/rodent malaria model for causal prophylactic studies was not a feasible proposition with the available mosquito colonies

Antimalarial activity against human parasites.

Although the rodent malaria model, even without mosquito transmission, was useful for obtaining

preliminary information about the activity of potential antimalarial drugs, it could not reliably predict the efficacy of such drugs against human malaria. An animal model that can be infected with human malaria parasites would obviously be a very important asset as an intermediary step in assessing the potential value of drugs before their administration to human volunteers. After the discovery in the early 1960s that human malaria infections could be experimentally induced in *Aotus* monkeys (Owl monkeys) from South America, it became possible to assess the potential value of drugs against human malaria parasites before their evaluation in human volunteers.[10] With the extension of chloroquine-resistant malaria in Southeast Asia and a greater urgency to identify effective alternative drugs, AMRAB agreed in 1974 that steps be taken to acquire this monkey model for research activities at the Unit. Importation restrictions, construction of climate-controlled primate accommodation, and training of animal handlers delayed the arrival of the first shipment of 12 monkeys until 1982.

Since inception of the Unit in the mid-1960s, human studies with Army volunteers at the Military Hospital, modelled on those carried out at the LHQ unit during the mid-1940s, were considered to be an important component of the project. During 1973 and 1974 the feasibility of such studies received considerable attention by various members of AMRAB. After careful consideration, it was decided that such studies could not be instituted then for a variety of different reasons. Instead, efforts were made to approach military and public health authorities in the Asia-Pacific region to explore the possibility of carrying out collaborative field studies to evaluate new drug regimens in malarious areas of their country. Early attempts to do so were not particularly successful. The prime example was the demise of attempts to develop collaborative field studies in assessing the prophylactic effectiveness of a proguanil/dapsone combination in a highly malarious area of India. Despite progressive approval by relevant health authorities in the Indian and Australian armies over a period of 2 years, this potentially very important project never got off the ground.

Discovery and laboratory evaluation of the fungus Culicinomyces as a biological control agent of mosquitoes.

During February 1972, a dramatic larval mortality was noted in the *An. hilli* colony. Within a period of three days more than 90% of larvae were dead or moribund and the extinction of the colony seemed imminent. The suspicion that a fungus was responsible was confirmed after inoculating trays of healthy larvae with dead specimens, isolating the fungus on a nutrient agar medium, and killing larvae by exposing them to spores (conidia) produced in artificial culture.[20] The taxonomic status of the fungus was clarified in 1973 after the same organism was discovered infecting mosquito larvae in North Carolina, USA. It was subsequently described as a new taxon, *Culicinomyces clavisporus*.[21]

Initial studies indicated that *Culicinomyes* was a very efficient larval pathogen that might have potential as a biological control agent of mosquitoes. Accordingly, it was subjected to systematic laboratory investigation to evaluate this possibility. The mode of infection was via the alimentary tract. The conidia were ingested during feeding and adhere to the cuticle lining the mosquito foregut and hindgut, where they germinated and penetrated into the body cavity. This subsequently became filled with a dense interior mycelium. After death, a sporulating layer formed on the exterior cuticle which produced conidia that were infectious to other larvae.[22] It implied that the fungus could be able to recycle in the aquatic environment after its original application and infect successive generations of mosquito larvae. The additional finding that infective conidia was readily obtained in aerated broth cultures of peptone and yeast extract heightened the possibility of industrial mass production.

By the end of 1975 the initial promise of *Culicinomyces* as a mosquito larvicide was reinforced by further favourable laboratory results. The host range was expanded to include *Anopheles, Culex* and *Aedes*, three medically important genera of mosquitoes, as well as larvae of *Chironomidae* (midges) and biting midges of the family *Ceratapogonidae*.[23] Additional investigations revealed that *Psychodidae* (moth flies), other aquatic insect larvae, freshwater shrimps, and the mosquito fish *Gambusia* were not affected by long term exposure to infective conidia, indicating that this fungus only acted against certain families of the Order Diptera.

Conclusion

The small malaria research unit, established in the mid-1960s in response to the growing threat of drug-resistant malaria to Australian troops, was hampered in the scope and extent of its activities by limited or inadequate staff and facilities during the first decade of its operation. Although significant studies with human malaria parasites could not be carried out, useful information was obtained during investigations involving mice and mosquitoes. The main achievements of the unit were : 1) establishment of a rodent malaria model and an insectary to rear various species of anopheline mosquitoes; 2) preliminary data indicating that low doses of dapsone could act synergistically with proguanil to potentiate

the activity against rodent malaria parasites; 3) discovery that the fungus *Culicinomyces clavisporus* attacked mosquito larvae and might eventually be used as a biological control agent.

Acknowledgement

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Highlights

Early 1960's Chloroquine resistance develops in Southeast Asia and proguanil resistance is observed among Australian soldiers in Malaya.

1965 Professor Robert Black, Army Consultant in Tropical Medicine, recommends establishment of a Malaria Research Laboratory (MRL), with a view to future assessment of the effectiveness of new drug regimens in Army volunteers.

1966 High prevalence of malaria among Australian troops in Vietnam is controlled when dapsone is added to proguanil prophylaxis, although a few soldiers develop agranulocytosis while taking dapsone.

MRL is established at the University of Sydney, but establishment of basic malaria research procedures are hampered by limited staff and inadequate laboratory facilities.

1969/1970 Adjutant-General stresses importance of enhancing malaria research activities and establishes the Army Malaria Research Advisory Board (AMRAB).

MRL re-designated 1st Malaria Research Unit (1MRU).

Research activities strengthened, leading to routine blood transmission of rodent malaria parasites in mice and occasional transmission of rodent malaria by anopheline mosquitoes reared in the insectary.

1972 Discovery of a new fungus, *Culicinomyces clavisporus*, killing larvae in mosquito colony.

1973 With only 4 staff members still at the unit, adequate staffing remains a problem.

1974 Following appointment of Dr A P Ray as director, 1MRU is re-located from University of Sydney to grounds of 2 Military Hospital at Ingleburn, southwest of Sydney.

Eight of the 9 establishment positions are filled.

AMRAB recommends that Aotus monkeys be procured to assess the potential value of new drugs against human malaria parasites.

Earlier plans to evaluate the efficacy of new antimalarial drugs in Army volunteers at the military hospital are shelved in favour of collaborative field studies in malarious countries.

1975 Transmission of rodent malaria parasites via blood inoculation is well established.

Although various species of anopheline mosquitoes have been colonised by now, routine malaria transmission via mosquitoes remains problematical, thereby preventing assessment of drug activity against parasite liver stages and gametocytes.

Preliminary findings indicate potentiation of activity between low doses of proguanil and dapsone against rodent malaria parasites, suggesting that dapsone dosage may be able to be reduced to prevent possible agranulocytosis during proguanil/dapsone prophylaxis.

Progressive studies with *Culicinomyces* continue to produce favourable laboratory results and encourage further investigations to determine its potential value as a biological control agent for mosquitoes.

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