John Hull Grundy Lecture

Mosquitoes, Malaria and War; Then and Now
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CMG, OBE, MD, FRCP

All whom war, dearth, age, agues, tyrannies
Despair, law, chance, had slain . . .
John Donne (Holy Sonnets VII)

In his foreword to the final volume of the Official Medical History of the Second World War Sir Austin Bradford-Hill, quoted the well known truth, that throughout history, victory or defeat in war has often been swayed by disease. He also stressed that during the fateful years 1940-1945, the prevention of illness had been one of the characteristics of the military medical services.

There is little doubt that but for the prevention and control of malaria the decisive campaigns in the Far East would have been lost, with incalculable consequences.

Many authors have described the role of malaria during the military operations of the past 50 years. The present paper attempts to collect and consolidate some facts and statistical data which have now become available from British, Australian and American sources. The second aim is to compare the past malaria situation with the new problems and potential dangers that may become acute in case of any major conflict in tropical areas.

The latest volume of the History of the Second World War as seen mainly from the United Kingdom, deals with Casualties and Medical Statistics. It brings together the details of specific causes of disease in various Services or Commands and indicates the enormous wastage of manpower due to illness. It also shows how essential is a good system of recording sickness or injury, and how important this knowledge is for epidemiology and preventive medicine. Naturally, no statistics can be complete under war conditions, but the lessons that those data teach are of enormous value.

Malaria emerges as having been one of the main causes of illness of troops during the Second World War in tropical areas; even in some Mediterranean zones with more equable climate, outbreaks of malaria during the transmission season jeopardized several military campaigns.

1. Malaria in the Second World War

A table based on data gleaned from Franklin Mellor's latest series of statistics covering the period 1940-1945 reveals the impact of malaria on the British and Commonwealth Forces (Table I). However, these overall figures do not specify that in some British units on the Indo-Burma Front the malaria incidence in 1943 was as high as 1746 per 1000. In the Middle East some rates of admission for malaria ranged from a peak of 677 in 1940 to 380 per 1000 in 1945. In West Africa the rates were as follows: 762 in 1942, 442 in 1943, 278 in 1944 and 92 per 1000 in 1945.

Some comments on this table may be of interest: In North-West Europe malaria was reported at an equivalent annual rate of 13.8 per 1000 in July-September 1944, but this figure fell to 1.9 per 1000 in October-December 1944. Statistics were broken down into indigenous malaria, viz. contracted in north-west Europe, and non-indigenous malaria occurring in men who have been exposed to it in other war areas. Obviously there was a great difference between them. While the former had in 1945 an estimated (or equivalent) annual rate of 1.3 per 1000, the latter was 9.7 per 1000. Most of the cases were due to "benign tertian" infections and falciparum malaria was rarely reported.

The North African and Central Mediterranean zone showed much higher incidence, though overall statistical data should be accepted here with caution because of the varying ethnic composition of troops and uneven degree of their exposure during the seasonal transmission of the infection. The dramatic story of the impact of malaria on the Italian campaign has been admirably told by Thompson. The British Eighth Army faced an exceptionally severe challenge of malaria in Sicily, just before the invasion of the Italian mainland in the summer of 1943. In 1944 before the battle for Cassino about 8000 men were laid down with malaria contracted when passing through the Roman Campagna near Monte San Biagio. It is likely that the increase of malaria in that area was due to the deliberate destruction by the enemy of pumping installations which were part of the remarkably successful Italian drainage scheme of this formerly highly malarious area. The third mass infection of the British troops was in 1945 on the rice-growing plains of Lombardy near Ravenna. In the Middle East force a similar trend of malaria incidence with a peak level in 1944 was observed. Here once again the complex ethnic composition of troops (British, American, and Australian) and the effect of their exposure to the indigenous or non-indigenous infections in other areas must be considered.

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Indian, Canadian, South African, African, New Zealand) and some differences of reporting call for caution in accepting official figures. The high (10-15 per 1000) rate of PUO (pyrexia of unknown origin) as a diagnosis of convenience supports the suspicion that the true incidence of malaria was at least 25% greater. The great differences of the incidence of malaria in different parts of the Middle East are shown in Table 2.

Generally speaking the malaria incidence in this area was not unduly high; annual rates between 22-34 per 1000 were not alarming. Nevertheless, considering the fact that broadly speaking the Middle East had only a moderate malaria endemicity, these rates were disappointing. True enough there were some more malarious zones such as the Jordan Valley and coastal plains in Africa, former malaria endemicity, these rates were disappointing. True enough, malaria was at least 25% greater. The great differences of the incidence of malaria in different parts of the Middle East are shown in Table 2.

The comprehensive malaria control organisation was designed to maintain constant observation on the ecology of the various anopheline vectors, develop new methods of control, undertake general anti-larval measures through special malaria control units, and train or supervise units in anti-mosquito and personal protection measures. Advisers at each Command Headquarters, local hygiene officers and sections, two malaria field laboratories and nearly thirty special malaria control units, employing large gangs of labourers, composed the special Middle East control organisation.

In India, where a tremendous amount of knowledge on malaria and a great experience of its control existed, thanks to the decades of work of the Indian Medical Service, and of research institutes in Calcutta, Delhi and elsewhere, the organisation of control activity in wartime was rapid.

Anti-malaria units (AMU) were formed and trained, their main task consisted of rapid reconnaissance of the epidemiological situation and advice on control measures. These units were to work in conjunction with field hygiene sections, whose resources were insufficient. The number of anti-malaria units was based not on the strength of
the fighting forces but on the type of area into which the troops were likely to move. The usual allotment to an Army Corps was six AMUs, of which three remained as corps units and one was attached to each division. Another type of unit formed in India during the War was the Malaria Forward Treatment Unit (MFTU) which made it possible to treat severe cases as near the forward area as possible, so that evacuation of patients to a base hospital would not be carried for and the men could soon return to their fighting units. The MFTUs were in fact small and lightly equipped 200 bed hospitals, where the time required in 1945 for successful treatment of a case of malaria was 8-9 days on the average.

Other units that came into existence in India during the War were the Malaria Field Laboratories. Those staffed by competent entomologists were particularly important and their work on mosquito bionomics was of great value. Thus in Assam it was found that A. leucosphyrus was an additional carrier during the monsoon period. In Arakan, A. jeyporiensis candidiensis and A. philippinensis began transmission early, thus enabling A. minimus to start more intensive transmission later. In the Kabaw valley the behaviour of A. minimus was such that ordinary protective clothing was insufficient.

And yet, in spite of all this, the incidence of malaria in the India Command was high throughout the period 1941-1945. Table 1 indicates that the average ratio of malaria incidence between British Officers, Indian Officers, British Other Ranks and Indian Other Ranks was 100:68:160:159. The difference between the first two groups may have been due to better malaria awareness among Indian officers, and their greater discipline, while the difference between the two groups of officers and the two groups of Other Ranks may be ascribed to the same factor in addition to greater exposure of the latter.

South-East Asia Command (SEAC)

Data on malaria incidence in the South-East Asia Command have been divided into two groups: the Indo-Burma Front and Ceylon (Sri Lanka) because of the difference of their epidemiological characteristics. In 1942 several units of the Eastern Command in India became operational as the Fourteenth Army and the statistical data of the Indo-Burma front comprise a mixed bag of records.

Following the Japanese advance in South-East Asia and the withdrawal of the British and Indian troops along with some 500,000 civilians from Burma, the situation became grave as the 1943 annual sickness rate of the troops on the Indo-Burma Front rose to 1200 per 1000. The medical services were strained to their utmost capacity, as the daily number of malaria cases in 1943-1944 was 5560 and 3606 respectively during several weeks.

The incidence of malaria in British and Indian troops was between 100 and 250 per 1000 per year. The death rate ascribed to this disease varied between 0.11 and 0.59 per 1000, the latter being a peak figure in 1942; the average malaria fatality rate was generally lower in Indian troops (0.21 per 1000) than in the British (0.23 per 1000).

The high relapse rate of vivax malaria gave rise to many problems; about 50 per cent of these cases relapsed either within the first three months or between the sixth and the ninth months of the primary attack. It was difficult to decide whether a particular relapse was a true relapse or a fresh infection. Altogether malaria and PUO were responsible for one half of all hospital admissions during the period 1941-1944.

On the Indo-Burma Front fighting took place in areas notorious for a high incidence of various infectious diseases with a high annual rainfall and difficult conditions of supplies and medical services. Various illnesses accounted in 1942 for 70% of all hospital admissions. In 1943 this figure decreased to 66%, in 1944 to 59% and in 1945 to 48%; the most important single cause of illness was malaria.

One of the interesting features of Table 1 is the great difference between the low incidence of malaria in African troops of the 81st Division in comparison with other troops in this Command. The Africans had between eight and thirteen times less malaria than the non-Africans; on the other hand the difference between the British and Indian troops was much less pronounced, the latter being only 10% less than in the former.

### Table 2
Middle East Forces. Admissions to hospitals for malaria and PUO in 1942 by various Commands

<table>
<thead>
<tr>
<th></th>
<th>Egypt &amp; 8th Army</th>
<th>Palestine</th>
<th>Syria 9th Army</th>
<th>Cyprus 9th Army</th>
<th>Sudan</th>
<th>Eritrea</th>
<th>Malta</th>
<th>Aden</th>
<th>Persia &amp; Iraq 10th Army</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria Pyrexia of unknown origin (PUO)</td>
<td>22.7</td>
<td>20.5</td>
<td>27.7</td>
<td>43.5</td>
<td>47.3</td>
<td>107.9</td>
<td>0.14</td>
<td>50.0</td>
<td>44.6</td>
</tr>
<tr>
<td></td>
<td>9.7</td>
<td>14.8</td>
<td>7.5</td>
<td>7.9</td>
<td>13.5</td>
<td>3.8</td>
<td>0.8</td>
<td>1.9</td>
<td>0.6</td>
</tr>
</tbody>
</table>
West and East Africa Commands

Data on malaria in the West African Command are not shown in the volume edited by Franklin Mellor, but they are of considerable interest as in this Command a relatively small contingent of British officers and other ranks was merged with a much larger group of African soldiers to form eventually the 81st and 82nd Divisions, which in 1944-45 took part in fighting on the Indo-Burma Front. During the years 1941-45 malaria took a heavy toll of the European contingent of the British Army in West Africa, as can be seen in Table 3. The extremely high rates of P. falciparum malaria in 1941-1943 were due to the fact that the British troops did much night training, were housed in hastily prepared camps and their personal protection measures were not well followed. Much improvement in 1944 was caused by better anti-malaria discipline and by a change from quinine prophylaxis to mepacrine. It was this change of anti-malaria prophylaxis that was responsible for the disappearance of blackwater fever from the Command.

Statistical data for malaria in the East African Command are sketchy in spite of a valuable report by Wilson and Melville. It appears that in 1943 the incidence among the troops composed of contingents from Britain, Kenya, Tanganyika, Nyasaland, Somalia, Rhodesia, Madagascar, Mauritius and Seychelles, was 91 per 1000; in 1944 the rate was 101 per 1000, and in 1945 - 53 per 1000. The fatality rate (probably also due to blackwater fever) was 0.24 per 1000.

The Royal Navy and Air Force

In the Royal Navy malaria was not a serious problem for evident reasons. The highest rate of admissions was in 1943 when the figure was close to 11 per 1000 for all ranks, out of a total average force of 600,000 (Table 4). Admissions for malaria to the RN Hospital at Haslar were only 3.3% as compared with nearly 10% in World War I.

In contradistinction, the Royal Air Force suffered heavily from malaria and the total number of cases was nearly 75,000. For the RAF (overseas) as a whole, the worst years were 1943 (76 per 1000) and 1944 (75 per 1000). There was a considerable fall in 1945 to 31 per 1000. In India and South-East Asia the peak was in 1944 with 157 per 1000, in the Middle East in 1940 and 1941 with 60 cases per 1000 and in Iraq in 1944 with 83 per 1000. In West Africa in 1942 there was an incidence of 844 cases per 1000 in a force just over 5,000 strong.

In the United Kingdom 5,077 cases of malaria were recorded in members of the RAf who contracted their infections, primary or relapsing, when serving abroad.

In the Far East vivax malaria was consistently more common than falciparum malaria whereas in the Middle East in 1940 and 1941 the latter was the commoner of the two; in 1942-45 in the Middle East vivax malaria showed a higher incidence. In West Africa the infections were predominantly due to P. falciparum. Quartan malaria was rare in all Commands.

Much of this wastage in the early stage of the War was due to the failure of the executive to realise that malaria...
discipline required the active co-operation of all ranks. It was often difficult for the RAF to select camp sites of low malarial risk because the primary consideration was to find a level stretch of ground for a landing strip and the best of such sites were often in low lying, marshy districts. In many instances dress discipline was poor, officers and men bathed after dusk and failed to carry out other precautions such as the use of repellents and mosquito nets. Prophylactic mepacrine was not taken consistently. The work of malaria control squads was not effective without the full support of all unit commanders.

As in the Army so in the RAF it was the introduction of mepacrine in 1943 instead of quinine, and a better discipline of the Force that changed the situation. It also created a few problems apart from occasional adverse effects. There were widespread rumours that the new drug caused sterility and impotence. The second possibility was particularly worrying but the fears were soon dispelled. Some concern was expressed about the effect of mepacrine on flying personnel and to them this compound was not given until July 1944.

In two countries of West Africa where the RAF had important bases the RAMC carried out extensive reclamation schemes to improve the malarious conditions existing close to the RAF camps and airports. One was in Accra, Ghana, where a combined British-American base was operating. The other, more interesting, was near Lagos in Nigeria; it was initiated by Lt Col Gilroy, in charge of No 7 Field Malaria Laboratory. The Lagos-Apapa swamp drainage project began in 1942, when Lagos became one of the nodal points of the little known but vital Transcontinental ATA Ferry Service of the RAF. This was organized to keep up the steady supply of front line aircraft for the Middle East when the Mediterranean sea-route was blocked by the Italians.

Fighter planes, Hurricanes mainly, were shipped in crates from Britain to West Africa. Takoradi in Ghana and Lagos in Nigeria served as main bases for the assembly and test flights of these single engine, one-man planes. From Lagos these planes were flown by civilian pilots (Canadian, French, Polish, Yugoslav; men well over 40 and several women) across Africa in small hops, with refuelling every 400-500 miles at primitive landing strips. They flew in air-caravans consisting of 6-8 planes, following the leader, a light bomber with navigational facilities. The air-route was across Nigeria, French Equatorial Africa, Sudan and then up the Nile valley to Luxor or Cairo. Several thousand planes were delivered in this way in 1943-44 with very few losses.

As early as 1941 it became evident that the Lagos airbase was situated in the immediate vicinity of a coastal mangrove swamp breeding high numbers of A. gambiae and A. melas. Up to 500 blood-fed Anopheles were collected daily in tents of an anti-aircraft battery and the weekly incidence of malaria was about 100 per 1000. In mid-1942 it was decided to drain the main swamp and as this was successful the work was soon extended to all swampy lands within 1 mile perimeter of the airbase. The results of this work, consisting of the exclusion of high tides from the low-lying area by a sea wall provided with a tide gate, and draining the shallow swamp by a system of converging channels were excellent. Details of it will be found in Gilroy's excellent monograph 20 and in a preliminary paper by Gilroy and Bruce-Chwatt 21. This work, planned by an RAMC unit, carried out by a Nigerian labour force, supervised by joint RAMC and RAF staff, is a rare example of a semi-permanent malaria control project completed successfully during the War 22.

### Australian Forces

Throughout the War malaria was an ever present problem in the Australian Forces. Cases of malaria in Palestine and in Greece in 1940-41 were not unduly alarming but the Syrian campaign in 1941 showed the impact of this disease in mobile operations. From August to October 1941, about 1400 cases occurred out of a total of 2331 for that whole year in the Middle East 12,23.

With the change of the main theatre of operations for the Australians from the Middle East to the South West Pacific in early 1942, the problem of malaria had greatly increased, not only for the military but also for the civilian authorities in Australia. In North Queensland and in the Northern Territories scattered endemic foci were present before, and the main danger lay in the massive introduction of malaria into this part of the Australian continent by troops returning from New Guinea and elsewhere. This danger became evident when in March 1942 an outbreak of malaria affected 7% of the civilian population at Cairns 24,25.

In the meantime the situation in New Guinea was grim both militarily and otherwise. The areas of endemic malaria round Port Moresby were increasing, as the previous control measures became slack; preventive measures among the troops were unsatisfactory, as shown by a sharp epidemic of malaria with 3000 cases in the Forces at Milne Bay in the south-east of the island 23.

Another intense epidemic of falciparum and vivax malaria with 12000 cases occurred in early 1943 in Central Papua during the action against the Japanese. In March 1943 atebrin (mepacrine) was adopted and enforced as a daily preventive drug; when better curative methods were introduced the situation improved. This was largely due to the formation of special Malaria Control Units attached to forward fighting troops. Moreover, Mobile Entomological Sections were formed to provide special information on appropriate control methods.

A new policy made unit commanders personally responsible for regular chemoprophylaxis of their troops. DDT spraying was introduced at ground level and from the air. Consequently the alarming earlier malaria incidence of 740 per 1000 among the troops in base and forward areas fell in November 1944 to 26 per 1000.

During 1944-45, when further military operations took
place, the incidence of malaria among 130,000 troops was at the acceptable level of 10 cases per 1000. However, in one area of Aitape-Wewak there was in March-April 1945 an outbreak of malaria in spite of all possible preventive and curative methods. This episode remained unexplained until the Medical Research Unit at Cairns solved the mystery by proving the existence of a mepacrine-resistant strain of *P. falciparum*. This was a warning for the future, a warning that was amply confirmed 20 years later.

This brief account of the Australian experience during the campaigns in the Far East provides the best possible evidence of the two main factors in malaria control in war areas. One was the scientific background provided in this case by the Malaria Research Unit at Cairns with a staff of parasitologists, entomologists and epidemiologists, brilliantly organised and led by Brig Hamilton Fairley. The other was that the responsibility for preventive measures rested squarely with the combatant commanders, exercising full disciplinary action when necessary.

**United States Army**

Malaria became a serious problem in the US Army in many parts of the world, as shown in Table 5, simplified from the data given by Mowrey in the volume produced by the Office of the Surgeon General, Department of the Army. Nearly 500,000 cases occurred during the four years and the highest numbers were reported in 1943-44. It has been estimated that altogether about 9 million man-days were lost in the US Forces during that period.

Malaria was a serious problem in North Africa (Fig 1); it was prevalent in some zones of Morocco, the Constantine area of Algeria, in Tunisia and in Corsica, and especially in Sicily, Sardinia, Salerno and the Pontine Marshes. There were 69,000 cases during 1943-44 with 944,000 man-days lost. During the Sicilian campaign, the US Seventh and British Eighth Armies lost, from malaria alone, the equivalent of the fighting effectiveness of two infantry divisions. In fact there were more losses due to malaria than there were battle casualties; the US Seventh Army reported 9,892 cases of malaria and 8,375 battle casualties and the British Eighth Army reported 11,590 and approximately 9,000 respectively.

Nearly 33,000 malaria cases in the European area were reported. Protected by copyright.  

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**Table 5**

**Malaria incidence in the US Army in 1942-45, by area and year (Rate shown per 1000 average strength)**

<table>
<thead>
<tr>
<th>Area of admission to treatment</th>
<th>1942-45</th>
<th>1942</th>
<th>1943</th>
<th>1944</th>
<th>1945</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>Rate</td>
<td>Cases</td>
<td>Rate</td>
<td>Cases</td>
<td>Rate</td>
<td>Cases</td>
</tr>
<tr>
<td>Continental USA</td>
<td>81,772</td>
<td>5.5</td>
<td>6,235</td>
<td>1.2</td>
<td>29,525</td>
<td>7.4</td>
</tr>
<tr>
<td>Europe</td>
<td>32,790</td>
<td>7.8</td>
<td>662</td>
<td>2.5</td>
<td>17,585</td>
<td>10.5</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>80,532</td>
<td>52.6</td>
<td>33,232</td>
<td>72.8</td>
<td>38,830</td>
<td>59.8</td>
</tr>
<tr>
<td>Middle East</td>
<td>10,715</td>
<td>80.5</td>
<td>6,669</td>
<td>125.7</td>
<td>2,900</td>
<td>62.8</td>
</tr>
<tr>
<td>India, Burma, China</td>
<td>44,052</td>
<td>98.5</td>
<td>9,160</td>
<td>231.2</td>
<td>26,265</td>
<td>155.7</td>
</tr>
<tr>
<td>South-West Pacific</td>
<td>124,109</td>
<td>78.3</td>
<td>47,663</td>
<td>251.0</td>
<td>33,475</td>
<td>62.1</td>
</tr>
<tr>
<td>Latin America</td>
<td>17,891</td>
<td>47.1</td>
<td>4,874</td>
<td>40.3</td>
<td>1,245</td>
<td>14.5</td>
</tr>
<tr>
<td>Total Overseas</td>
<td>410,727</td>
<td>39.0</td>
<td>168,632</td>
<td>99.9</td>
<td>138,630</td>
<td>36.3</td>
</tr>
<tr>
<td>Total Army</td>
<td>492,299</td>
<td>19.4</td>
<td>23,267</td>
<td>7.2</td>
<td>174,867</td>
<td>25.5</td>
</tr>
</tbody>
</table>
imported by troops who had originally served in North Africa. There were 4,806 cases of malaria among US troops stationed in England before D-day 1944 (Fig. 2).

The highest incidence was seen in India-Burma-China (Fig 3), and in the South Pacific. Although the overall annual malaria incidence, even in these two areas, has never exceeded 250 per 1000 per year, the respective rates in some large units were much higher. The First Marine Division on Guadalcanal ceased to be an effective combat unit in 1943, as 80% of its strength were admitted to hospitals for malaria. The 25th Infantry Division, also in Guadalcanal, had by April 1943 a malaria incidence of 2385 per 1000; it was transferred to New Zealand for rehabilitation and then to New Caledonia for reorganization. The 32nd Infantry Division had 67% of its troops ill with malaria after their withdrawal from New Guinea.

On the India-Burma-China theatre of war there were in 1943 over 9,000 cases of malaria and the 20th General Hospital, near Ledo in Assam, had 73% of its patients ill with malaria. The Air Force Base unit in Karachi, Pakistan had in October 1944 a malaria incidence of 1202 cases per 1000 strength.

Of the 411,000 cases of malaria contracted overseas by the US Army during the War, 65% were due to \textit{P. vivax}, 12% were caused by \textit{P. falciparum}, 0.3% by \textit{P. malariae} and about 22% were either mixed infections or unidentified. Malaria caused by \textit{P. vivax} had the highest incidence in the Indochina-Burma-China theatre of war.

Incidence in the Indian-Burma-China theatre, the Southwest Pacific and the Central and South Pacific areas. The highest incidence due to \textit{P. falciparum} occurred in Liberia, in the Middle East and the India-Burma-China theatre. \textit{P. malariae} was found chiefly in the Mediterranean, the South West Pacific, India-Burma-China, and the Central and South Pacific areas.$^5$

Relapses of vivax malaria were particularly troublesome in the Mediterranean area, where they occurred in about 50% of all cases; in the India-Burma-China area the relapse rate was 25% and some patients had up to 10 relapses of their first attack.

There were 302 deaths due to malaria during the period 1942-45; 292 of these deaths occurred among overseas admissions of this total. 157 deaths occurred in Pacific areas (113 deaths for the South West Pacific and 44 deaths for the Central and South Pacific areas). The fatality rate of malaria (chiefly due to \textit{P. falciparum}) was of the order of 0.25%, the highest occurring in the India-Burma-China theatre of war.

\textbf{Malaria in the Japan Imperial Army and in POW Camps}

Malaria had not spared the Japanese Forces themselves; in the Japanese 14th Army between 10-12,000 soldiers were ill in 1942 after the attack on Bataan; in New Guinea about 37% of their average strength of 80,000 were incapacitated by malaria in 1943, with an estimated rate of 1440 per 1000 per year.$^8$ No-one will ever know to what extent malaria alone had contributed to the appalling morbidity and mortality rate of British and Australian prisoners-of-war in the Far East. The official statistics of 1946 report that the total number of British and Australian Army personnel taken prisoner by the Japanese was around 43,000, of whom 11,000 died or were killed in captivity.$^7,18$
Much more could be said about the infamous POW camps of Changi and Krantji in Malaya where some 30,000 British and Australian Army prisoners were kept for 3 years, in dreadful conditions. It is estimated that not less than 6950 of them had malaria and some 700 died of its direct or indirect effects*. The same situation was reported in Filipino-American prisoners of war held in various camps after the loss of Bataan; of 30,000 deaths that occurred in 1942 in two main camps about one quarter were due to malaria18.

II Malaria during the Korean and Vietnam Wars

The military operations in Korea and South-East Asia opened a new chapter in the modern history of malaria in war. Few reports on these campaigns are available and only sketchy data prove that once again tropical diseases generally and malaria in particular could inflict enormous losses on troops, even if some attempts are made at their protection.

Between 1945 and 1954 the French had in Indochina an annual average strength of 100,000 for the Metropolitan forces and 78,000 for their allied indigenous troops. There were 294,000 malarial cases during the 9 year campaign though only 70,400 required hospitalization. Quinine and mepacrine were used as a prophylactic during the early period but gave way to proguanil and in 1952 to chloroquine at 300 mg base once a week. The malaria incidence in the French Forces in Indochina was as follows, at per 1000 p. year: 1946 = 478, 1947 = 325, 1948 = 314, 1949 = 235, 1950 = 177, 1951 = 138, 1952 = 121, 1953 = 112, 1954 = 10429.

It has been said that the prevalence of malaria among the Viet Cong units was between 50-75 per cent; in some groups of prisoners the incidence of malaria was so high that raids on plantations and dispensaries were made to obtain supplies of drugs.

Apparenty, in 1965 about 1% of USA military personnel in Vietnam were acquiring malaria for every day they spent in the war area30. Already at the end of that year the monthly number of cases of malaria in the US Forces reached nearly 800 and equalled the number of evacuated battle casualties. In 1966 some infantry units had a malaria incidence of 30% of the strength per month. Tigger31 also pointed out that the exposure of large numbers of American forces to falciparum malaria endemic in South Vietnam coincided with the evidence gathered in 1962-63 of resistance of this malaria parasite to 4-aminoquinolines in four countries of South-East Asia (Malaya, Cambodia, Thailand and South Vietnam). The incidence of malaria in the US Forces in Vietnam fell from 50 per 1000 in 1965 to 17 per 1000 in 1971. Between 1965 and 1971 nearly 82,000 cases of malaria occurred there, two thirds of this figure in the Army and one third in the Marines. Because of the time required for convalescence, this disease became the main drain on the effective fighting strength39,32. The fatality rate of P. falciparum malaria (0.3%) was low because of the excellence of treatment. However, clinical problems encountered with resistance of the parasite to chloroquine were serious. Moreover, during the years 1966 and 1970 not less than 14,120 cases of imported malaria occurred in the USA, mainly in military personnel returning from Vietnam; over 80% of them were due to P. vivax and 12% to P. falciparum. Obviously the majority of cases of vivax malaria were relapses of infections acquired in Vietnam33. The diagnosis of malaria was difficult since irregular taking of prophylactic drugs made a single blood examination unreliable and it had become a practice to take 4-6 blood films during the first one or two days after hospital admission, before the diagnosis of malaria infection could be confirmed. Thus the true incidence of this infection was probably higher than indicated in official records (Fig 4)34,35.

The major (over 85%) proportion of malaria cases occurring in Vietnam was due to P. falciparum and resistance of some Vietnam strains of this species to chloroquine was probably one of the factors responsible for the high incidence of malaria. However the taking of antimalarial prophylactic drugs in the US Forces was unsatisfactory and, whenever the supervision improved, the incidence of malaria decreased36.

An interesting observation made in Vietnam during the study of resistant falciparum malaria in the US Army was the difference of the course of infection between white and black American troops37. Thus the initial attack rate in the black (Negro) ethnic group was 7.9% instead of the expected 11.7% although the exposure to malaria infection was about equal. Moreover, only 4.4% of them had a recrudescence after treatment (while the expected rate was 11.7%) and none had a severely resistant infection. The duration of fever after the start of treatment was less in black soldiers than in white.

Although malaria in the British Commonwealth forces that were operating in the war area of South-East Asia has been lower than that estimated for the US Army, the direct comparison is injudicious because of different strengths of units, different areas of operations and different degrees of exposure. Contingents of the Australian
Army were present in Vietnam in significant numbers from 1965 until the end of 1971; their peak strength in 1969 was about 7,000 and most of them operated in the Phuoc Tuy Province to the east of Saigon. The Australians had during the period 1965-1968 a low average malaria incidence of about 30 per 1000 per year, but with sharp seasonal peaks at the end of each year, of the order of 140-180 per 1000. The peak at the end of 1968 of over 300 per 1000 was particularly worrying and a new antimalarial regimen (proguanil and dapsone) was instituted with very satisfactory results, since in 1969 the malaria incidence dropped sharply to much lower figures.38,39

The incidence of malaria in the British Forces operating in the Far East between 1960 and 1970 was not unduly high; the total number of cases was just under 1,000 and the annual incidence varied between 3 and 12 per 1000 per year with peaks of over 10 per 1000 in 1961 and 1969. These figures are based on the total numbers of personnel, including those stationed at the base headquarters and in non-malarious areas. If the incidence of malaria is calculated only for troops exposed to risk the relevant figures will be higher.40,41,44

In comparison with the data from the Far East, the incidence of malaria in the British Forces serving during the same period in the Persian Gulf area was very much lower, averaging about 3 per 1000 per year with peaks of 5-7 per 1000 in 1962 and 1964 (Maj Gen Smart quoted by Bruce-Chwatt).45

III Present problems of malaria prevention

The lessons of malaria in the Second World War have been quoted succinctly by Dr Paul F Russell, the great American malariologist responsible for much of the successful prevention of illness in the US Forces in several parts of the world: "The directives, organization, cooperation, integration, training and skill, supply and transport have as much meaning in malarial control as in any other phase of warfare. These factors and above all a malaria-consciousness of the high command and of the troops themselves are essential".42

In more or less static base-units the degree of potential exposure to malaria depends on local epidemiological conditions; this means on the camp-site, closeness to large mosquito-breeding areas and on the type of military habitations. An appraisal of the situation demands a modicum of knowledge of the amount of malaria in the

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Fig. 4. World malaria situation in 1982, according to the World Health Organisation.

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local population, as well as of the type and behaviour characteristics of the *Anopheles* vector. Much of this information may have to be collected *ad hoc* through rapid reconnaissance surveys, which are part of the tactical intelligence, not less important than the awareness of the disposition of enemy units.

In such base camps the use of collective means of prevention by environmental manipulation, larvicides or residual spraying may have some effect, providing that these measures are carried out to perfection and supported by the authority of the local commander. However, no single method, whether collective or individual, such as insecticide spraying, screening of tents and huts, use of bed-nets, repellents, chemoprophylaxis etc. will give complete protection. Only the application of all these measures may provide a relative freedom from infection.

Although at present, malaria has virtually disappeared from Europe, Australia, much of the Mediterranean, North America, most of South Africa, the Caribbean and from some parts of South America, yet the situation in south and south-east Asia, Indonesia, the West Pacific, New Guinea, Central America and the whole of tropical Africa is probably worse than during the Second World War (Fig. 5). This is due to the fact that our previous technical methods of attack on the malaria parasite and on its vector have lost their cutting edge.

Resistance of *Anopheles*, first to DDT and then to other insecticides, has assumed a world-wide dimension. The Fifth Report of the WHO Expert Committee on Vector Biology and Control (1980) noted that 51 species of *Anopheles* are now resistant to one or more insecticides: 34 species are resistant to DDT, 47 to dieldrin and 30 to both these compounds. Ten species are resistant to organophosphates, such as malathion and 4 to carbamates. Moreover, some strains of *Anopheles sacharovi* and *A. gambiae* are resistant to pyrethroids, the newest products of modern synthetic chemistry. The development of DDT and dieldrin-resistance in the major vector species has created "problem areas", where malaria control and eradication are severely handicapped, in the following parts of the world:

**Western Asia:** DDT- and dieldrin-resistance in *A. stephensi* in Afghanistan, Iraq, southern Iran and Saudi Arabia. DDT- and dieldrin-resistance in *A.sacharovi* in Greece, Iran, Iraq, Pakistan, Azerbaijan, USSR, Syria and Southern Turkey.

**South-East Asia:** DDT- and dieldrin-resistance in *A.stephensi* and *A. culicifacies* in India and Pakistan. DDT-resistance in *A.fluvitattis* in India and Saudi Arabia; DDT- and dieldrin-resistance in *A.aconitus* and *A.sundaicus* in Indonesia.

**Africa:** DDT- and dieldrin-resistance in *A.gambiae* (sensu lato) in vast areas of tropical Africa and Sudan.

**Middle America:** DDT- and dieldrin-resistance in *A.albimanus* in El Salvador, Nicaragua, Honduras, Guatemala and southern Mexico, followed by malathion-

and propoxur-resistance in El Salvador and Nicaragua.

Notable new records which have contributed to the deterioration of the situation are as follows:

The development of resistance to malathion by field populations of *A.stephensi* in Iran, Iraq and Pakistan, *A.arabiensis* in Sudan and *A.culicifacies* in India. The dramatic resurgence of malaria in Turkey and Syria during 1976-1977 may have been due to the multi-resistance of *A.sacharovi* to organophosphates, carbamates and chlorinated hydrocarbon insecticides. Resistance has also spread to DDT and dieldrin in *A.amnularis* in India, Nepal, Bangladesh, *A.maculatus* in Malaysia, and is strongly suspected in *A.minimus* in Indonesia and in Thailand. *A.balabacensis* (A. dirus) is also suspected strongly to have developed resistance to DDT in Thailand. New reports of resistance to DDT, dieldrin/HCH and malathion in *A.sinensis* have come from China, and DDT from Vietnam. *A.vagus* from Vietnam has also shown resistance to DDT and dieldrin/HCH and *A.subpictus* from the same country to DDT.

Multiple resistance in the vectors of malaria, particularly in areas where intense use of pesticides is made in agriculture, has been of great concern in recent years. Several species of mosquitoes are often found breeding in agricultural areas and are liable to be exposed to insecticides employed in crop spraying. However, this results in suppression of the natural enemies of mosquitoes and exerts a high selection pressure for frequent development of mosquito resistance to insecticides.

The increasingly complex genetic and biochemical factors of the resistance phenomenon make it difficult to forecast the response of a given mosquito population in any area at a given time; at best only a partial effect can be hoped for. The relevance of this to the logistics of supplies is evident.

Few new insecticides are being produced, since the chemical industry is reluctant to embark on the costly and chancy process of development, followed by lengthy toxicity trials and the opprobrium of the environmental lobby. Genetic methods of control have been disappointing and biological larvicides such as *B.thuringiensis* or *B.sphaericus* are of limited use.

It is obvious that in any mobile military operation most of the above methods of control cannot be applied and...
chemoprophylaxis of malaria is then the last and best resort. Herein lies one of the main problems involving the human factor. All individual methods of protection depend forcibly on the individual, be it wearing proper clothing, using repellents or taking antimalarial drugs. Training in the use of these methods, supervision of medical authorities and responsibility of the commanding officer may secure success. Unfortunately one of the lessons of the past was that the value of these simple measures is fully recognised only after they have been disregarded.

The cruellest blow of the past 20 years was the appearance of resistance of *P. falciparum* to chloroquine and other 4-aminoquinolines, first reported from northern areas of South America, and soon observed in South-East Asia. This resistance caused much trouble in 1965 when the US Army was using as a malaria prophylactic a combination of chloroquine and primaquine known as the CP tablet. As many as 26,000 cases of malaria occurred among the Americans in Vietnam during the period 1965-68 due to resistance of *P. falciparum*, although deliberate avoidance of chemoprophylaxis, to fall ill and get out, was not uncommon.

In 1966, when it was obvious that this prophylactic regimen was inadequate, a daily dose of 25 mg of DDS (dapsone) was added to the two combined drugs. This halved the malaria attack rates in Army units where the malaria discipline was good but made little difference in units where the taking of prophylactic antimalarials was defective. The taking of DDS created problems of toxicity and particularly the appearance of methemoglobinaemia, especially in individuals with G6PD deficiency.

Men returning to the USA were instructed to take the CP tablet containing 300 mg chloroquine and 45 mg primaquine once a week for eight weeks after their return. The value of this radical treatment for prevention of relapses of vivax malaria has been generally confirmed but there is evidence that a large number of all ranks did not follow the prescribed regimen and the mean relapse rate for *P. vivax* averaged 20%. About 70% of returning troops failed to complete the full 8 weeks course of radical treatment. The rate of failure among officers and other ranks was almost equal and common reasons given were forgetting to take the tablets, losing them or various side-effects. A survey suggested that the official figure of 1 malaria relapse case in 200 soldiers returning from Vietnam was in fact much higher.

The regimen of antimalarial prophylaxis followed in the Australian contingent in Vietnam consisted of daily 200 mg of proguanil with the addition of 25 mg of DDS during the brief period when the peak of malaria incidence

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Fig. 5. Areas where chloroquine-resistant *Plasmodium falciparum* has been reported (WHO, 1982)
is expected. The results of this method have been satisfactory, as the seasonal peaks of malaria at the end of 1969 and 1970 had not materialized. Among British Commonwealth Forces operating in South-East Asia the possibility of chloroquine resistant malaria was first mooted in 1962 in units operating along the Malaya-Thailand border. The incidence of malaria in these units was not unduly high, but the danger of chloroquine resistance was sufficient to stimulate a number of studies, particularly by McKelvey et al. These studies confirmed that strains of *P. falciparum* with a varying degree of resistance to 4-aminoquinolines were present in a number of areas of West Malaysia and in Singapore. Some 50% of patients exhibited a low degree of chloroquine resistance which responded to higher than usual dosage of the drug.

Introduction of a combination of sulfonamides or sulfones with pyrimethamine at the end of the 1960’s was an important step, too late to play any major role in the military history of the Vietnam conflict. Sulfadoxine with pyrimethamine (generally known as Fansidar) and other similar mixed compounds have been very useful for treatment of *P. falciparum* infections resistant to chloroquine: *P. vivax* does not respond very well to this drug. Initially limited to treatment of malaria, the various sulfonamide/pyrimethamine formulations yielded to commercial pressures and became widely used for prophylaxis with expected consequences. Over the past few years Fansidar has been losing its effectiveness for treatment of *P. falciparum* malaria in South-East Asia and in Brazil as also in other countries of South America. The degree and extent of chloroquine resistance in *P. falciparum* in various parts of the world can now be followed up better thanks to the development of in vitro culture of this parasite and to the use of a standardized method for evaluation of the response of various strains to specific drugs. This method has allowed for a reliable monitoring of the global situation (Fig. 6). This resistance of *P. falciparum* to chloroquine and other 4-aminoquinolines extends now from South-East Asia to a large part of the Indian peninsula and eastwards to vast areas of the Western Pacific including the Philippines, parts of Indonesia, New Guinea, the Solomon Islands, Vanuatu; it is also present in southern China. In South America foci of resistance exist in most of the countries north of the 15°S and also in some parts of Central America.

The situation in tropical Africa causes acute concern. There is now evidence of chloroquine resistance in large parts of East Africa; recent reports indicate the presence of foci of chloroquine resistance also in Central Africa. Moreover there are now confirmed reports of Fansidar resistance in parts of East Africa, in Thailand, in Brazil, and Colombia.

By 1984 the following countries of the tropical continents of the world had small foci or large areas with confirmed resistance of *P. falciparum* to chloroquine: America: Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Panama, Surinam, Venezuela. Asia and Oceania: Bangladesh, Burma, China, Cambodia, Cambodia, East Timor, India, Indonesia, Lao Dem. Rep., Malaysia, Papua New Guinea, Philippines, Solomon Islands, Thailand, Vanuatu, Vietnam. Africa: Angola, Comoro Islands, Gabon, Kenya, Madagascar, Malawi, Namibia, Sudan, Uganda, Tanzania, Zambia.

All this brought to the fore the use of quinine with tetracycline or clindamycine for treatment of severe *falciparum* malaria, although both chloroquine and Fansidar are still of value in many parts of the tropics. The same applies to chemoprophylaxis, where the two latter drugs are still indicated although much confusion about their use exists even among the experts. It seems that even quinine is now less effective for treatment of *falciparum* malaria in South-East Asia. Thus we are in urgent need of an active blood schizontocidal drug which would maintain its effect for at least one month after a single dose. We also need a well tolerated radical-cure compound, free of side-effects, for prevention of relapses and *P. vivax* and *P. ovale* infections, when given at a single dose or at most, for three days.

Fortunately there is no evidence that resistance to chloroquine or quinine of *Plasmodia* other than *P. falciparum* has developed anywhere.

The dark cloud that now covers the horizon of treatment and prevention of *falciparum* malaria has however a silver lining. It has increased the amount of fundamental and applied research to a remarkable degree. A stupendous effort has been made in the U.S. by the Walter Reed Army Institute of Research which over the past 10 years has screened well over 250,000 various compounds as possible antimalarial drugs. Of these only a handful of promising new compounds have emerged, but some of them are of real value. Outstanding among these is a quinoline-methanol (WA 142490) now known as mefloquine. One of the reasons for the small yield of candidate antimalarials, revealed after a decade of this remarkable effort of the Walter Reed Institute, is the amount and complexity of preclinical information now required for potential human trials. Large numbers of compounds can be screened on rodent malaria models, but then must be also evaluated on *P. falciparum-Aotus* monkey models. Other drug-testing systems such as the in vitro screening against various strains of *P. falciparum* have now improved the predictive ability of experimental research.

Mefloquine underwent a number of clinical and field trials; it proved to be an excellent schizontocidal compound, very similar to quinine although with a slower action. However, because of its chemical closeness to chloroquine there is a likelihood of development of cross-resistance by *P. falciparum*. In fact some cases of such resistance have already been observed in South-East Asia.
Because of this, the present policy is to restrict the use of mefloquine alone and to release it for prophylaxis and treatment only as a combination with sulphadoxine and pyrimethamine, to prevent or delay the appearance of resistance.

Another potentially useful compound selected by the US Army research group is a 9-phenanthrenemethanol (WA 122, 455) known as halofantrine which is undergoing a series of trials. At least four other compounds also merit further studies.

Animal models and especially those based on the use of Aotus monkeys for various strains of *P. falciparum* and *P. vivax* and also those based on sporozoite infections of rhesus monkeys (*Macaca mulata*) with *P. cynomolgi* have been most useful for the discovery of a series of: a) blood schizontocidal drugs more active than chloroquine and b) tissue schizontocidal compounds better than primaquine.

This allowed for evaluation of radical curative activity against *P. vivax* of some 200 compounds of which 19 were as active as primaquine and 15 two to four times more active. This suggests that much progress has been made towards a three-day cure of relapsing infections.

Intensive efforts aiming at the discovery of new and better anti-malarial drugs continue in many parts of the world. Stimulation and remarkable co-ordination of this activity is carried out by the WHO Special Programme for Research and Training in Tropical Diseases. Much information on the recent progress and future possibilities of chemotherapy of malaria will be found in the latest WHO Report, the main points of which can be summarised as follows: 1) The current methods of assessing the trends of resistance of malaria parasites to drugs should be simplified and much more widely used; 2) The drugs and drug combinations, especially those that have an effective range of activity, must not be used haphazardly for prevention or treatment of malaria, but subjected to some limitations to prevent the spread of resistant strains of *Plasmodia*. 3) The research on new compounds and their clinical trials should be speeded up, with a view to developing drugs for the radical cure of multiple resistant *P. falciparum*, for the radical cure of relapsing *P. vivax* and for causal prophylaxis of all species of human *Plasmodia*.

One of the new major advances has been made by Chinese scientists who described recently a number of derivatives of Qinghaosu, a plant known as *Artemisia annua*, used for centuries in traditional Chinese medicine. A compound artemisinine, actually a sesquiterpene lactone, synthesized by Chinese chemists is an effective anti-malarial. A better tolerated artemunate, a soluble ester of the main principle seems to be quite promising. Larger field trials on these two compounds are now in progress.

No doubt, prospects of developing new and better drugs for treatment and prevention of malaria are now brighter than five years ago.

When it comes to prevention, no-one can predict whether the best hopes for the future lie with chemotherapeutic or immunological methods. Much has been said, written and expected from a prospective malaria vaccine and recent progress of immunology justifies many hopes. Three types of antigens are being investigated: attenuated sporozoites, purified erythrocytic merozoites or their products and gametocytes, the latter to develop the development of parasites in the insect vector. Modern immunological methods such as monoclonal antibodies or radioisotope labelling of specific peptides enable us to identify the protective antigen suitable for preparation of vaccines. Moreover, recombinant DNA techniques make it possible to clone the antigen-producing genes into bacteria so that sufficient amounts of vaccines could be produced. An ideal vaccine should be polyvalent for at least two species of *Plasmodia*, fully protective for at least a year, simple in application, free of side effects and economical in use. Although the present prospects for it are optimistic, many years of trials will be needed. It seems that in this contest between new drugs and vaccination the former have an historical advantage, while the latter may yet spring a surprise or two. Prediction is a risky business, especially as the future is not what it used to be. One thing is more predictable, however, namely that any military operation involving troops in tropical parts of the world will face almost the same dangers that armies confronted during the past two major wars. Tropical diseases are still as prevalent as they were 50 years ago. Although some methods of preventive medicine have improved, others have lost their former use through the evolutionary adaptation of pathogens and vectors. True enough, human intelligence has the same evolutionary quality of adaptation to new problems, but it may also create new stages in its history, including threats and dangers of potentially cataclysmic dimensions. We are at this very stage now and live in fear of future conflicts. Should World War III be fought, as it might, with nuclear weapons, so that its probable outcome will be MAD or mutually assured destruction, the problem of malaria will be finally solved and there will be no need for protection from it. Or from anything else, since humanity as we know it today will perish on the field of Armageddon, the eve of Judgement Day.

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L J Bruce-Chwatt


