SUPPRESSION OF MALARIA BY MEPACRINE.

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ALTHOUGH the use of mepacrine in the prophylaxis of malaria was by no means new, the credit for demonstrating conclusively the military value of the drug belongs to the Australian group of workers under Brigadier Hamilton Fairley and his account will be regarded, no doubt, as one of the classic papers of Military Hygiene (Hamilton Fairley, 1945).

Mepacrine was used in the recent war by the Allied Forces wherever troops were exposed to the risk of malaria. Largely as a result of this treatment troops were able to fight in areas where otherwise the casualty rates would have precluded active operations on any scale. It is no exaggeration to say that mepacrine was one of the factors which made possible the defeat of the Japanese. Although the future may witness the evolution of more radical methods of malaria control, mepacrine nevertheless loomed large in the medical history of the war just concluded. It is for this reason that it was considered of value to place on record certain field observations made in Burma on the results obtained by suppression of malaria with mepacrine.

INCIDENCE OF MALARIA.

Most of Burma is highly malarious. Before the Japanese Invasion the mortality among the civil population due to this disease exceeded that from any other cause (Simmonds *et al.*, 1944). In the vicinity of the larger towns such as Rangoon, there is little or no active transmission. The incidence of the disease is also low in the central dry zone about Meiktila. With these exceptions the disease is everywhere endemic and in " foothill " country the intensity of infection is extremely high. The results of a small sample of the many surveys made during the war are set out in Table I and serve to illustrate these features.

TABLE I.

Area	*Date*	*Spleen rate*	*Parasite rate*	*Remarks*
Rangoon ..	Jan.–Aug. 1946	2·76%	—	Combined result of several surveys
Tann ..	Sept. 1944	73%	6%	Two-thirds of parasite were M.T.
Kalaw Road ..	July–Aug. 1945	60–100%	—	—
Silchar ..	Nov. 1944	95%	—	—
Kabaw Valley	—	75%	—	Average of many surveys in 1944
Tennassarin (Ye Road) ..	Dec. 1945	79%	—	*A. minimus* larval breeding noted
Near Prome ..	Dec. 1945	72%	—	—
Mawchi Road	Jan. 1946	78%	—	Near Tanngoo
Anisakan ..	Nov. 1945	66%	—	Near Maymyo

Such high endemicity is naturally reflected in the experience of non-immune troops operating in the country. In the first Burma War of 1825-26

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the troops who invaded the Arakan suffered relatively enormous casualties from malaria. It is said that in a few weeks everyone who was not dead was sick in hospital. One regiment had a 25 per cent mortality within a month of landing on this coast (Christian, 1945). In the first years of the last campaign, say from 1942 to mid 1944, malaria again took a heavy toll. Several examples can be given. Thus a certain division fighting in the Kabaw Valley in May and June 1943 was suffering a crude rate of 5 per 1,000 per day, equivalent to nearly 200 per cent per annum.

The term "crude rate" in this paper is reserved for the incidence of "malaria and NYD fever" calculated on a return of such cases diagnosed for the most part on clinical grounds. The diagnosis might require revision after investigation of the cases in hospital or C.C.S. and only a proportion of the cases would then be recorded as "confirmed" malaria. The crude rate has therefore obvious drawbacks. However, administrative considerations precluded the compilation of any more accurate statistics within any reasonable space of time and in practice it was found that the crude rate proved of value not only as an index of trends but also in the negative sense that a low crude rate was not compatible with any very high incidence of actual malaria.

On the Arakan coast in June 1944, the crude rate reached 3·24 per 1,000 per day. As late as November 1944 a formation advancing along the Ledo Road recorded a crude rate of 4·3 per 1,000 per day. According to Marriott (1945) malaria was *the* greatest medical problem in South East Asia Command. During the transmission season up to 80 per cent of all admissions to medical units could be expected to rise from this cause. The crude rate for the Army in this theatre is shown in histogram form in fig. 1.

The Effect of Suppressive Mepacrine.

Mepacrine for the suppression of malaria came to be used on a larger scale in the latter half of 1944 and supplies were adequate for a general issue to XIV Army by November of that year. Orders governing the issue of the drug provided for the daily exhibition of one tablet (0·1 gramme) per man. The method usually adopted was to issue the tablet at the evening roll call parade. Each unit was required to maintain a register of issues made and to carry its own reserve. The Australian workers were satisfied that "break-throughs" of clinically recognizable sickness could always be ascribed to faulty administration of the drug. By and large this was also the experience with the Burman strains of plasmodium. Where the crude rate for a formation or unit remained high it was invariably found on investigation that compliance with orders left much to be desired. Visits would be paid to the unit in question by anti-malaria officers followed if necessary by representations by the appropriate formation Commander. A vigilant watch on crude rates was always maintained and where necessary attention directed to any slackness in "mepacrine discipline." As the results, in terms of man-power saved, became in due course obvious, Commanders at all levels were, with few exceptions, only too ready to accept advice. A fluoroscopic method of estimating the urinary mepacrine

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excretion of groups of men was adopted for use in the field. The results, interpreted statistically, afforded a fair estimate of the regularity and adequacy of the mepacrine intake of the group. Where the method was applied to a unit or formation with an unduly high sick wastage, a salutary effect on the sick rate was soon perceptible.

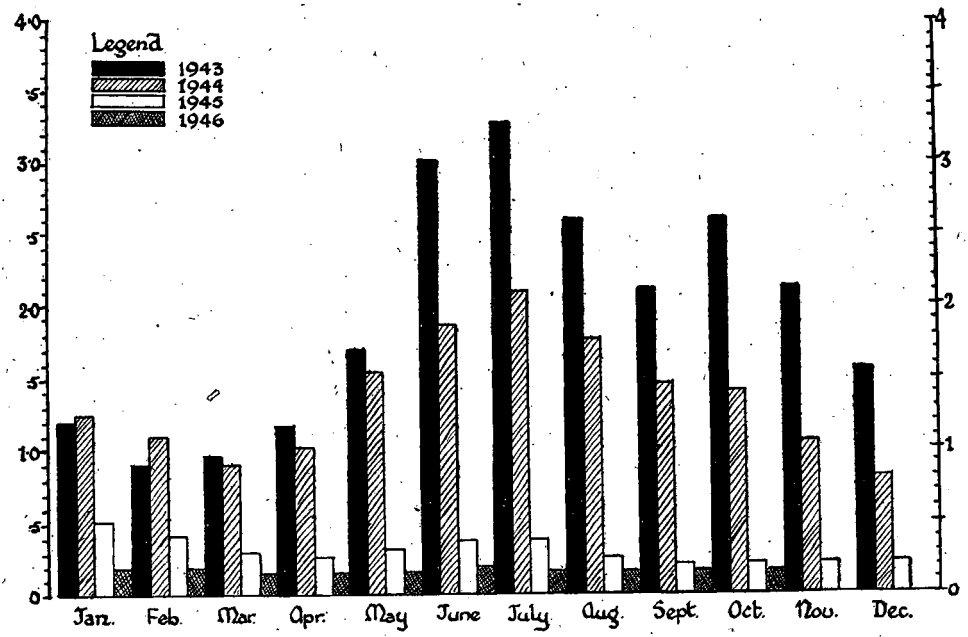

FIG. 1.—Mean mortality crude rates per 1,000 per day of the Army in Burma.

As will be seen from fig. 1, the crude rate for the Army in Burma fell substantially early in 1945 and the rise expected in May and June failed to materialize, although the troops were still exposed to infection in such places as the Arakan, the Kabaw Valley, the fringes of the Pegu-Yoma and the Kalaw and Mawchi Roads. The crude rates for one of the Corps are shown in Table II. During the material times this Corps was fighting on the highly

TABLE II.

	1944	1945
April	1·29	0·15
May	3·24	0·20
June	2·96	0·15

Crude rates per 1,000 per day for a Corps in the Arakan.

malarious Arakan coast. In 1944 no mepacrine was being used but by 1945 mepacrine had been in use for some time. The experience of Brigade "A"

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is shown graphically in fig. 2. When a survey of urinary mepacrine excretion was made in April 1945 there was evidence of grossly irregular and inadequate consumption. Towards the end of May the Brigade fought up the Meiktila-Kalaw axis in very difficult foothill country at a period of active transmission (Point A). A very high crude rate soon resulted. The formation was largely supplied by " air-drop " and the loss of consignments of mepacrine did not help matters. Early in June a " booster " course of mepacrine was given to each man (0·3 gramme daily for five days) (Point B). There was an immediate fall in the crude rate (Point C) followed by a temporary rise and then a drop to a low level which was maintained despite the fact that the brigade continued to be exposed to a high degree of infection.

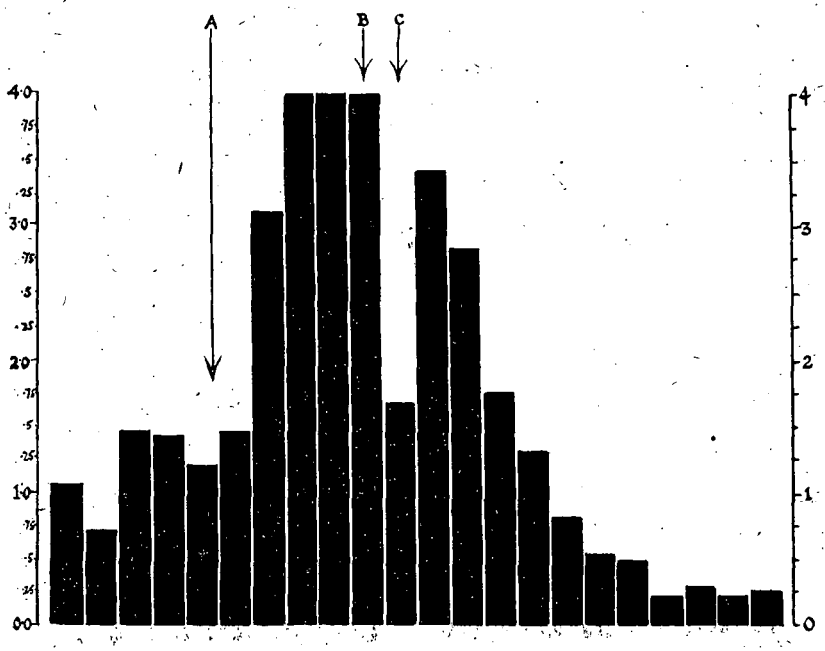

FIG. 2.—Brigade " A." Weekly crude rates per 1,000 per day.

Other instances might be quoted. There was, for example, a certain medical unit stationed in Silchar in November 1944, when the spleen rate in the area was 95 per cent. At that time 40 per cent of the unit personnel were sick with malaria but within two weeks of commencing suppressive treatment the ineffectives had been reduced to just 1 per cent of the unit strength.

It is conceded that the evidence advanced so far in favour of the value of suppressive mepacrine is open to objection as being largely circumstantial. There was undoubtedly a marked reduction in the incidence of " malaria and NYD fever " following on the introduction of suppressive treatment on a large scale. The diagnoses on which the rates were based were rough and ready clinical decisions and as such are not as valuable as would have been the

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ultimate diagnosis on discharge from the medical unit treating the case. There is also another consideration which might detract from the value of the evidence. Mepacrine was but one of several weapons used in the battle of malaria. The fact that DDT came to be used increasingly during the very period when the suppressive regime was being enforced extensively in itself complicates the issue. In addition there were the personal measures designed to minimize the risk of mosquito bites; nets, repellent ointments (and later, Skat), regulations as to dress, etc. All these measures were employed with varying degrees of application at different times and in different places. Undoubtedly they all contributed their quota in greater and lesser degree to the shape of the histogram in fig. 1. Such personal measures (with the possible exception of skat) were never really practicable for forward troops, and DDT was rarely used effectively under conditions of active warfare in the jungle forward of, say, Divisional Headquarters. The Brigade fighting up the foothills to Kalaw (fig. 2), for example, was not able to rely on DDT for any protection against mosquitoes. In the case, too, of the Corps "island-hopping" on the Arakan Coast (Table II) any effect on the sick rate due to DDT must be considered negligible.

The Withdrawal of Suppressive Mepacrine.

Once active warfare had been completed it was obviously desirable to desist from using suppressive treatment. In an attempt to obtain some guide as to the effect of a general withdrawal of suppressive treatment two specially selected units were ordered to cease taking mepacrine in February 1946. The units selected had been stationed in non-malarious areas (Rangoon and Maymyo) for between three and six months prior to February and during this time had observed strict mepacrine discipline. Before moving to the malaria-free station, however, both units had been exposed to severe risks of infection. Between them the two units mustered 400 men. During the nine weeks following withdrawal, together they produced six proved cases of B.T. relapses all occurring in the fifth to sixth week of the withdrawal period. One of the units was then unfortunately disbanded and further observation of its personnel was impossible. The other unit (180 strong) was observed for a further twenty-two weeks. During this time one B.T. relapse and one M.T. attack occurred as well as three cases of clinical malaria (i.e. which could not be confirmed microscopically). A third unit of 200 men which had not at any time been subjected to any very high malaria risks also ceased suppressive treatment in February 1946, and was under observation for a total of thirty weeks. The only case of malaria which occurred was a B.T. relapse twelve weeks after ceasing to take mepacrine. These observations seemed to indicate that a general withdrawal of suppressive treatment was not likely to be followed by any great increase in malaria casualties, even among troops exposed in the past to severe malaria risks. As active transmission was not occurring in Rangoon a general withdrawal of suppressive treatment was ordered for troops in the city area at the end of May 1946. Numbers of malaria cases admitted thereafter to hospital were available but the "popula-

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tion at risk " is only known approximately. The general sick rate in the area was fairly constant at that time and the relative importance of malaria as a cause of hospital admission has therefore been chosen as the best index available of the trend of events. Malaria admissions are shown as a percentage of all admissions in fig. 3. (All cases diagnosed in hospital as malaria have been included. Although a number of these would be clinical cases without microscopical confirmation there is of course a radical difference between such cases and those which generate a " crude rate." The former are diagnosed as malaria *after* all relevant investigations have been completed.) There were

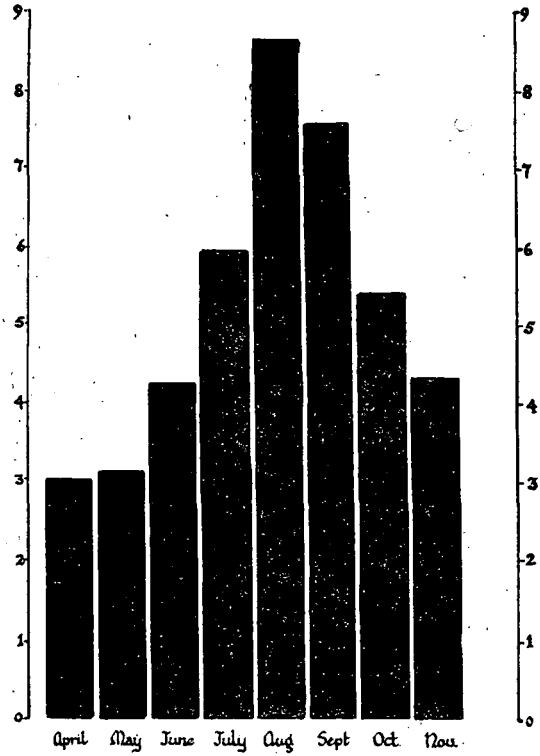

FIG. 3.—Percentages of all hospital admissions recorded as being due to malaria. (Rangoon Troops, 1946.)

approximately 30,000 to 40,000 troops at risk and over five months a total of 798 cases were recorded. This gives a rate per day of between 0·13 and 0·17 per 1,000. It is estimated that approximately 2 per cent of those involved developed malaria in the five months following the withdrawal. The peak incidence occurred about ten weeks after mepacrine treatment was stopped.

Hamilton Fairley had found that 100 per cent of his experimental subjects infected with *Plasmodium vivax* relapsed when mepacrine was withdrawn. The relapses occurred within seven weeks of ceasing to take mepacrine. There are certain important differences between the two series which have to be

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borne in mind. In the Australian experiments every man was infected *ab initio* whereas in the Rangoon population there would be a proportion who had never been infected. Again, the dose of infection in the experimental groups was much more massive than that likely to be acquired under natural conditions. Most of the Rangoon troops had taken mepacrine for many months since their last—presumed—exposure to infection, whereas in the experimental groups mepacrine administration continued for a shorter period after the last infection had been contracted. Compared to the Australian experience, the peak in the curve of relapses in Rangoon is somewhat delayed. This may be due to a difference in the strain of organism as James (1945) referred to a similar delay in infections with Mediterranean strains.

Malaria in Japanese Troops.

The Japanese Army did not use mepacrine for suppressive purposes. Quinine was used in this way although administration appears to have been very lax and uneven. Casualties from malaria were undoubtedly extremely high. One, at least, of the reasons for the halting of the Japanese advance at the very gate of India was the severe malaria casualties suffered by the Japanese Armies.

When the surrender came large numbers of Japanese had wandered for weeks in the jungle of the Pegu Yoma at the height of the malaria season. Other bodies of troops had retreated up to the Mawchi and Kalaw Roads exposed to an equally high intensity of infection. As an example of the prevalence of malaria among such troops it may be mentioned that in July 1945 a group of 89 Japanese persons captured in the Southern Shan States were medically examined. 18 were found to be sick with malaria. Of the total, 81 had parasitæmia and of the other 8 all but one gave a history suggestive of chronic malaria.

Towards the end of 1945 large numbers of the Japanese were being congregated in camps in Tennassarin. The amount of sickness due to malaria among these men was enormous. At one camp of 4,500 men the malaria sick rate for December was equivalent to 206 per cent per annum. (These were all cases confirmed microscopically.) At another camp of 2,000 men 16 per cent had enlarged spleens and parasitæmia. At a third camp of 2,000 strong 12 per cent were ineffective early in January 1946 because of this disease.

Early in 1946 some 5,300 Japanese (Camp I) were being employed on an important engineering project in Tennassarin but the sick wastage was so high that work was being seriously curtailed. An average of 30 men were going down daily with malaria. It was decided therefore to give these men suppressive treatment. The results were carefully observed and the diagnosis investigated by microscopy in all cases. The course given was 0·3 gramme (per man) daily for five days and 0·1 gramme (per man) daily thereafter. The results in this instance are not complicated by extraneous factors. No DDT was being used and mosquito nets and repellent ointments were conspicuously absent. Spleen rates in neighbouring villages ranged from 70 to

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80 per cent and larval breeding of *A. minimus*—the most important local vector—was observed at the time.

The population at risk remained fairly constant throughout the period concerned so that the trend of events could be fairly represented in terms of actual cases recorded. The data are presented in fig. 4. At Point A mepacrine administration commenced. A breakdown of supply resulted in the dosage being discontinued for two days (Point B). When the work was completed the drug was discontinued (Point C). At a later date the drug was administered again (Point D).

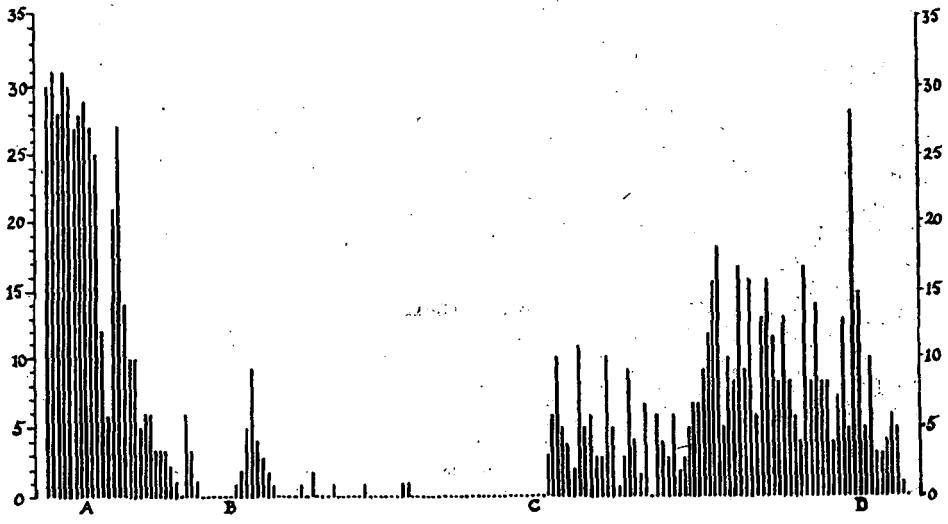

FIG. 4.—Japanese Camp I. Number of Malaria Cases admitted to hospital each day.

Several matters of interest arise from a perusal of these data:

(*a*) The "notch" that occurs on the fourth day under the 0·3 gramme daily treatment. In fig. 2 a similar notch may be seen. The explanation is probably that under 0·3 gramme daily overt malaria is being *treated* so that men do not report sick. When on the sixth day the 0·1 gramme course is substituted the rate immediately rises and then falls as true suppression makes itself manifest.

(*b*) The immediate effect observed when the course is interrupted (Point B).

(*c*) The reappearance of malaria as soon as the course is stopped (Point C). This is not necessarily in conflict with the data presented in fig. 3. In the first place the Japanese prisoners had been on suppressive treatment for a shorter period than the Rangoon troops. In the second place, the Japanese were being exposed to infection while taking mepacrine, whereas the troops in Rangoon had not been exposed to infection for some months before suppressive treatment was stopped. Grouping the daily numbers of cases it is found that the maximum incidence occurs during the fourth and fifth ten-day periods after mepacrine is stopped.

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No well-defined peak is to be expected as infection was still being contracted. The gratifying results in control obtained in the case just given were seen again in the case of another group of Japanese. In a camp 2,000 strong, located in the foothills near Toungoo, high malaria casualty rates were recorded in March 1946 (Camp II). Between 5 and 10 per cent of the strength were ineffective at any one time from malaria. Some 6 to 8 cases of blackwater fever were occurring each month. 20 per cent of the personnel had parasitæmia and 16 per cent had enlarged spleens. Towards the end of May 1946, this group was put on suppressive treatment. Fig. 5 shows the results expressed by

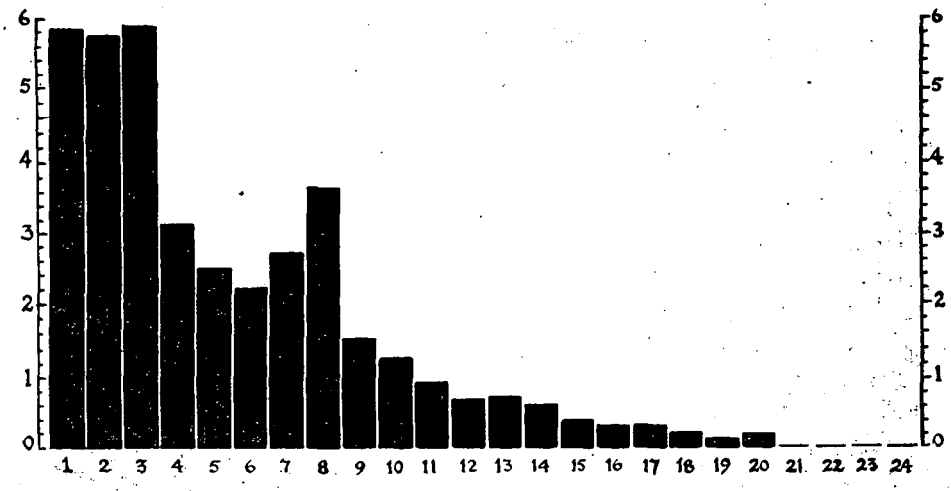

FIG. 5.—Weekly percentages ineffective because of malaria at Japanese Camp II. Suppressive mepacrine started at end of week 2.

way of percentage of strength ineffective because of malaria. Blackwater fever ceased to occur under the suppressive regime. This group, like the previous one, had not the advantage of any concomitant measures such as DDT or personal protection against mosquito bites. The results obtained in both these cases can only be ascribed therefore to the effect of suppressive mepacrine.

SUMMARY.

The effects which followed the use of suppressive mepacrine in malaria among Imperial troops and Japanese Surrendered Personnel are described.

The value of this method in reducing sick wastage from malaria, particularly where other methods of control cannot be applied, is unquestioned.

I wish to acknowledge my debt to Lieut.-Col. D. R. G. Fox, I.M.S., for much information and guidance on the question of malaria in Burma. Much of the material has been culled from official reports written by numerous officers,

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