(*b*) *Vector-borne Group*

CHAPTER 7

MALARIA

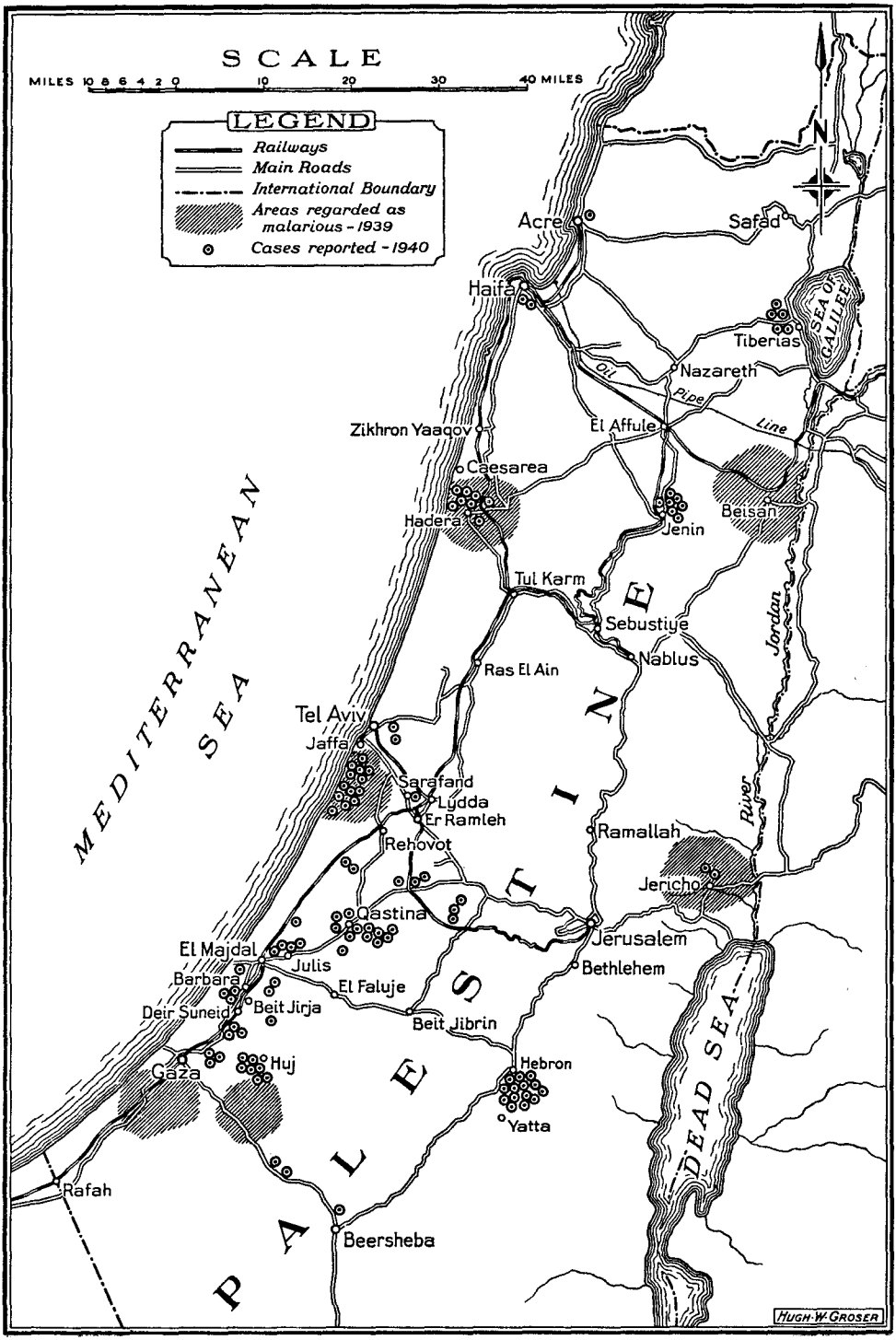
FROM the beginning of the 1939-1945 war till its end malaria was an important problem to the Australian forces.

MALARIA IN PALESTINE

When troops arrived in Palestine in February 1940 malarial control was good in the region of their camp sites, and here the risk was virtually nil, but there were areas known to be potentially dangerous, especially towards the northern border. Beyond this lay Syria, then held by the French, and known to be malarious. During 1940 there were 131 A.I.F. patients with malaria admitted to hospital from an average strength of 14,000 men in Palestine. Curiously, the first Australian soldier treated for malaria had a recurrence of a previous infection acquired in New Guinea. Most of the local infections came from suspected areas; some like Hadera in the north were known to be incompletely controlled, others, like the area south of Jaffa, were thought to be under control.

As the summer came on field hygiene sections reported finding anophelines breeding in additional areas. Some of these were in wadis near Arab settlements; most of them were adjacent to camps. In settled areas civil control was good, but it was soon evident that even troops in training might contract malaria, usually when on night manoeuvres. The incidence was undoubtedly small, but it was clear that active service conditions in areas not so well-controlled would tell a different story. Even so, it was not easy to prevent combatant units from using infected areas for night training exercises, and even in some camp areas mosquito breeding was occurring.

The vector mosquitoes for Palestine and Syria were *Anopheles elutus* and *superpictus,* and when later in the year Australian troops moved to Egypt other vectors were encountered, chiefly *A. pharoensis.* During the latter part of 1940 at the instance of Colonel M. J. Holmes, Director of Hygiene and Pathology, an attempt was made by the army medical services in Australia to have an entomologist appointed, chiefly to train a number of non-commissioned officers and for the nucleus of an entomological service. Unfortunately this far-sighted suggestion was not approved by the Adjutant-General. Later in the summer of 1940 instructions were issued that no camps should be sited within a mile of a village and none within two miles if over 20 per cent of the children were infected. Swamps were to be avoided, and due consideration given to the direction of prevailing winds. An excellent illustration of the difference in the malarial risk under military conditions as contrasted with the civil risk was given in the Wadi



Palestine: malarious areas.

Ghazza and surrounding areas. These were regarded as efficiently controlled from Hebron in the east to Rafah in the south, and no cases of malaria had been reported for three years, yet nearly one-fourth of the men who contracted malaria in 1940 had been infected while training in that area. At this time only limited equipment for personal protection was available; in fact anti-malarial measures were mainly confined to the avoidance of dangerous areas and the control of breeding in the vicinity of camps.

No general order was made at this time with regard to suppression. Quinine, 5 grains a day, was the recognised dosage in circumstances requiring the use of a suppressive drug; this could be increased to 10 grains if the conditions of transmission made it necessary in order to keep infections below the clinical level. In the treatment of clinical malaria in these early days an attempt was made to differentiate between the methods used for malignant and benign tertian infections. Plasmoquine was then in rather restricted supply and it was chiefly used for its gametocidal action on the crescents of the *falciparum* parasite, as there seemed better prospects of preventing relapses or recrudescences in this dangerous type than in benign tertian. Follow-up courses of quinine were also used with the same end in view. Benign tertian was chiefly treated with quinine and atebrin.[1]

It was, however, evident that a standard course of treatment for all types of malaria was desirable, and this was adopted, quinine, atebrin and plasmoquine in sequence being used. The routine was as follows: Quinine 10 grains 3 times daily for 3 days; atebrin 0.1 gramme 3 times daily for 5 days; and after an interval of 1 to 2 days, plasmoquine 0.01 gramme 3 times a day for 3 days, or 5 days preferably if supplies permitted. It was thought at that time that plasmoquine was more likely to have a toxic effect if it followed without break after atebrin. The dosage of plasmoquine was reckoned in terms of plasmoquine base. This treatment was based on extensive Indian experience, and was believed to offer the best chance of minimising relapses in all types.

MALARIA IN GREECE AND CRETE

In January 1941 the 6th Australian Division was engaged in the first Libyan campaign, in which malaria was not a significant medical problem. At this time the British offer of assistance to Greece made it probable that forces would be committed to a campaign in South-East Europe. Accordingly an appreciation of the malarial situation in that region was prepared by Colonels N. H. Fairley[2] and J. S. K. Boyd.[3] In this they pointed out that troops operating in Greece, Macedonia and the Balkans from June to

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[1] The term "Atebrin" is used throughout without distinction of its source. Whether referring to the original patent "Atebrin" produced in Germany, or the British "Mepacrine" or the American "Atabrine" the word atebrin came to be used in all Australian communications, and in this sense it will here be used, embracing the original and all identical or equivalent drugs.
Similarly, "Plasmoquine" includes all forms and substitutes of this drug, such as "Pamoquin".

[2] Consulting Physician to A.I.F. in M.E. and temporarily Consultant in Tropical Diseases to British Forces in M.E.

[3] Deputy Director of Pathology, British Forces in M.E.

September would face the hazard of a crippling incidence of malaria. Despite advances in therapeutic and preventive methods, they stressed the danger of non-immune troops being manoeuvred into some of the most malarious country in the world, where anti-larval measures had little chance of success. General Wavell, Commander-in-Chief, Middle East, was at first reluctant to accept the strategic limitations imposed by what seemed to him to be an unduly pessimistic opinion, but when all the facts were placed before him agreed that the malarial risks in these areas must be taken into consideration in all forward planning.

Early medical planning was undertaken at once. In March, 1941, when the 6th Australian Division, and, as at first believed, the 7th Division also, were committed to a campaign in Greece they were warned that preparations for anti-larval measures must be initiated at once, and anti-malarial stores obtained, including nets, repellent cream and drugs. Surveys were made by the British Force, the dangerous areas were noted, and labour was supplied for control work. From the beginning of April mosquitoes were beginning to bite, even up to the snow line, though only an occasional case of malaria was expected till the middle of April at the earliest. In the brief period before the Germans entered Yugoslavia as much was done as possible, but events moved with such speed that the end of this ill-starred episode was in sight before either men or material had been assembled. The plans to combat malaria were therefore never put to a test, as Greece was evacuated at the end of April. One unfortunate result of the forced abandonment of equipment was the loss of 60,000 mosquito nets. During the defence of Crete concern was felt by the medical units caring for troops on the island about the malarial risks in the summer. Conditions and meagre supplies offered little scope for purposeful action, but malarious areas were mapped out, and precautions enjoined in instructions. One such instruction laid down that "suppressive" quinine should be given in infected areas from the 1st June. However, at the beginning of June the campaign had ended with the evacuation of Crete. The incidence of malaria among the men who returned was negligible.

ANTI-MALARIAL MEASURES

Meanwhile anti-malarial training had been steadily pursued in Palestine and Egypt. Indeed from early in 1940 this had been organised in schools which used the resources of British and Australian services, and of the civil health administrations and with the help of the staff of the Hebrew University of Jerusalem. Didactic instruction was supplemented by work in the field. In April 1941, the possible importance of events in Greece on the military practice of preventive medicine emphasised the need for an authoritative account of malaria for the use of all medical officers. Arrangements were made for this to be compiled by Colonels Fairley and Boyd.

The publication of this account in June 1941 consolidated previous directions, and provided what was really a comprehensive though condensed textbook. Its scope and contents may now be briefly recounted, since they represent the basis of knowledge and standard of practice

adopted by the Australian medical services in the Middle East in 1941 From the clinical aspect its teachings laid the foundation of the highly successful handling of the many thousands of men who were later treated in Australian medical units for malaria.

The only varieties of malarial parasite of military importance in the Middle East were *Plasmodium falciparum* and *P. vivax,* producing malignant tertian and benign tertian fevers respectively. *P. malariae,* causing quartan fever was rare, and *P. ovale* was not seen in the Middle East. The life history and morphology of all the types were described in detail. The habits of the important local vector mosquitoes were described. *Anopheles elutus* bred well in valleys and in coastal swamps in brackish water, and *A. superpictus* in rocky hill streams or water near springs, while *A. claviger* (*bifurcatus*), seen mainly in North Palestine and Syria, was chiefly a house dweller and bred in wells and underground cisterns. *A. pharoensis,* the chief vector in Egypt, bred in swamps and rice fields, mainly in the delta and oases. The seasonal importance of malaria in the Middle East was emphasised. From May till October both M.T. and B.T.[4] were transmitted, but the peak of B.T. transmission was reached in the early summer, and that of M.T. in the later months. M.T. though not subject to the repeated relapses which are characteristic of B.T. sometimes produced recrudescences after a period of some six weeks. With the strains of B.T. met in the Middle East relapse was not usually manifest until after some months, often up to eight or nine months.

Full descriptions were given of primary and recurrent attacks and stress was laid on the fallacy of expecting a regular periodicity to be an early feature of malarial fever. Particular attention was paid to the varied manifestations of malignant malaria, such as hyperpyrexia, cerebral malaria with production of coma or simulation of other nervous diseases, algid malaria, producing the picture of severe shock, malaria imitating diseases of other systems, and the purpuric type. Special mention was made of the importance of M.T. as a cause of symptoms suggesting acute abdominal emergencies. The significance of anaemia, sometimes of severe grade and of jaundice in M.T. was pointed out. Diagnostic methods were described in detail; thick films were universally used, thin films only being used to verify plasmodial types. Facilities for the necessary laboratory procedures were available in all field medical units, whose physicians were competent to make a microscopic diagnosis. Giemsa and Leishman's strains were supplied and chiefly used. Field's method aroused interest about this time; extended experience in other areas later showed its value as a technique both rapid and reliable.

The chief considerations in making a diagnosis were listed as follows:

(1) blood examination for parasites, mononuclear cells, pigmented leucocytes and persistent leucopenia;

[4] The abbreviations M.T. and B.T. for malignant tertian and benign tertian malaria respectively will be used. The term "subtertian" for M.T. was used for a time in an endeavour to obviate the rather alarming implication in the name, but "malignant" tertian was too firmly established and became the official designation.

(2) the history of the patient, with special reference to periodic fever;
(3) demonstrable enlargement of the spleen and often of the liver;
(4) evidences of blood destruction, such as anaemia, jaundice and urobilinuria;
(5) the therapeutic test.

The standard treatment already mentioned was laid down in this memorandum as the official method. Intravenous administration of quinine hydrochloride was the rule whenever the patient could not swallow or retain quinine, or when absorption of the drug was in question, and in all severe or dangerous forms of illness due to malaria. Hyperinfection was included in the latter category; this was defined as an infection in which over 4 per cent of red cells were parasitised, or over 5 per cent of the infected cells carried multiple parasites, or in which pigmented asexual forms were present. Intravenous use of quinine was almost confined to the treatment of M.T., and with a safe dilution of the drug (one grain to one millilitre) and slow injection (two millilitres per minute) toxic effects were negligible. Intramuscular injection of quinine was very seldom used owing to the possibility of discomfort and necrosis of muscle. Atebrin was occasionally used for intramuscular injection, but where rapid action was required the intravenous use of quinine was pre-eminent.

Quinine was prescribed for suppressive treatment, but it was pointed out that even 10 grains a day could not do more than render an infection sub-clinical, and that the dose was better to be lower than this amount unless conditions in a hyperendemic area made it necessary. Stress was laid on the solubility of quinine, and where a mixture could not be given and tablets were used, only a soluble salt such is bihydrochloride, bisulphate or hydrochloride was advised. Special care was enjoined for wounded patients in a hyperendemic area. Therefore it was advised that quinine be given for fourteen days in suppressive doses of 10 grains daily or atebrin 0.3 gramme the first day and twice a week thereafter. Where blood transfusion was necessary and a donor was used who had been exposed to the risk of malaria, the donor received 10 grains of quinine or 0.2 gramme of atebrin six to twelve hours before his blood was collected if this was possible. The recipient was given 0.2 gramme of atebrin at once by mouth, or 10 grains of quinine by mouth or intravenous drip. If the donor was in fact found to be suffering from malaria a standard course was given to the patient at once. In all cases a follow-up course of 10 grains of quinine a day or 0.3 gramme of atebrin in divided doses, twice weekly, was ordered for two weeks.

This comprehensive brochure proved to be of great value, not only in the Middle East, but also in later operations. An official pamphlet on "The Prevention of Malaria" was also prepared and distributed for the information of all officers, combatant and medical alike.

MALARIA IN SYRIA

Meanwhile important events were occurring in other parts of the Middle East. While the brief Grecian campaign was hastening on, German infiltra-

tion was proceeding into Syria; this made it necessary to prepare a force for occupation. The division of France introduced peculiar political and military difficulties into this venture, which was undertaken following severe losses of men and material, and during the simultaneous pursuance of campaigns in other areas of the Middle East. The assembly and equipment of an adequate force were at the time not easy; supplies were taken straight from ships for the new force which comprised British, Australian, Indian and Free French troops. Though anti-malarial equipment was gathered for the force, there was no consultation with malariologists beforehand. On the eve of the entry into Syria a conference of medical leaders and malaria experts was held and a quick survey of Northern Palestine made, but these could not make good the lack of consultation in the beginning. Intelligence from Syria was sketchy; information about the medical conditions was limited and often unreliable, but it was known that the malarial hazard was considerable.

When the combined forces entered Syria on 8th June 1941, the malarial season was just beginning. Many of the troops, including the Australians, had not previously been exposed to malaria, and in addition were unacquainted with the risks of the country they were about to enter. Great efforts were made to educate all ranks in this respect, but it cannot be said that the troops entering Syria were "malaria-conscious". Some of the equipment was inadequate in quantity, such as the nets, which were also often ineffective in type. Nets from India to replace those lost in Greece went astray and were not available at the time when they were most wanted. The need of precautionary measures was felt before the campaign actually began, for even one night spent thus in the neighbourhood of the highly malarious Hula marshes, just south of the border between Syria and Palestine, constituted a definite risk.

Repellent cream was used: it was issued in bulk and distributed with some difficulty. Many of the troops did not have protective clothing. Quinine supplies were deficient at first, but its issue through the Army Service Corps with rations simplified distribution. The 7th Australian Division lacked some equipment, such as nets, but other protective measures were available, though their use was difficult to enforce. Even responsible officers sometimes showed a bad example by wearing unsuitable clothing after dark and in neglecting to take quinine. An Australian air force squadron in a malarious area in North Palestine had no nets, and no long-sleeved shirts were on issue.

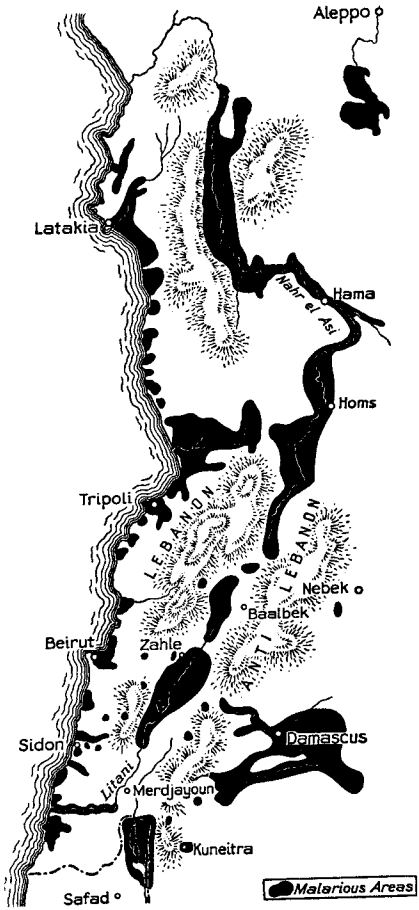
It was soon evident that malaria was occurring among the advancing troops. Malignant malaria appeared towards the end of June with a definite proportion of severe infections, and it was expected to assume epidemic proportions by August if prevailing conditions continued. Fortunately the brief but arduous campaign was over by the middle of July, but during the phase of action in Syria the casualties due to sickness had exceeded battle casualties and most of these were due to malaria. In the first month 500 patients with proved infections were admitted to two hospitals in Palestine, and the rush of malarial casualties was responsible for a good

proportion of the hospital expansion which was necessary during this campaign. The training of nurses in the taking of thick films from every man with a wound or with a rise in temperature was found essential. Then and in later years this was found a great aid to rapid diagnosis. In the Middle East it was found advisable to protect these slides from flies which quickly devoured the dry blood films.

It is hard to estimate just what effect the anti-malarial measures had on the incidence of malaria during the actual period of fighting. The ratio of B.T. to M.T. was about 4 to 1. This was expected, but when hostilities ceased in Syria the M.T. rate was rising. There were indications then that the troops were faced with the upsweeping curve of a typical epidemic of M.T. Without belittling the efforts of all concerned in anti-malarial measures, and the cooperation of military formations, we can attribute the improvement in the position as due rather to the cessation of hostilities, which allowed an accurate mosquito survey of the country and permitted stationing of troops in safer areas. All camp areas were then supervised and precautions tightened. Further, a dry summer hindered mosquito breeding, and transmission was not heavy enough to cause an epidemic, but a war of movement during the period August to October would have caused heavy malarial losses. As it was, from the entry of troops into Syria to the beginning of September 1,400 cases of malaria were reported to the I Australian Corps; the total of cases for the A.I.F. in the Middle East during 1941 was recorded as 2,331. The actual number of infections was greater than this. After their return to Australia many relapses were seen in men of the 7th Division whose primary attack had been suppressed, not observed, or mistaken for some other febrile condition. Early and unwarranted optimism as to complete cure of B.T. in Syria was shattered by this experience. The experience of individual units indicated heavy infection in bad areas: one brigade had 350 cases in 16 days without reckoning those suppressed by quinine. At first 5 grains of quinine daily was used as a suppressive dose, and later 10 grains. In September suppression was gradually stopped. The intensification of control measures in July was of course of great value. It was felt to be urgent at the time because there were grounds for suspecting a German attack from the north within a few months. Though skilled malariological work in Syria had been lacking before 1941, this was made good by the combined efforts of British and Australian experts. In July, on the advice of the British consulting malariologist, Colonel J. A. Sinton, the principle was accepted that camps should be only sited in safe areas. Night movements were reduced to a minimum. Vigorous propaganda was pursued by lectures and posters. In August long trousers and long sleeved shirts were issued, and orders concerning clothing, the use of nets and repellent cream, and controlling bivouac areas were laid down by the I Australian Corps.

The topographical problem in Syria was varied. The country was divided by two mountain ranges, the Lebanon and Anti-Lebanon Ranges, between which was a heavily cultivated plateau with streams and swamps. Coastwise was a narrow strip densely occupied and intensively tilled, while

in the interior lay the plains with slower running streams, and still farther eastward the desert. The vector mosquitoes were, as expected, *A. elutus,* and *A. superpictus,* and in habitations with wells and cisterns, *A. bifurcatus.* In July transmission of B.T. by *elutus* was lessening, but M.T. transmission was increasing. This mosquito was highly dangerous: it bred in swamps and still water, especially with floating vegetation, and had a long range of dispersal, three or four miles or even twice as far late in the season. *A. superpictus* was also a dangerous vector, breeding readily in hill streams at the edges or in pools. It was most prevalent in late summer and autumn, and had a range of two miles.



Syria: malarious areas.

Anti-larval measures included the oiling and dusting of breeding grounds with Paris green, and the canalising of streams so as to abolish breeding grounds. Anti-malarial control units were formed for the first time in the

Australian Army, and these and labour squads carried out numbers of extensive engineering feats with their own resources. Adult mosquitoes were attacked by sprays in dwellings and biting was reduced by the use of nets and repellent cream. Extensive surveys were made and much information collected as to the habits of vectors and infection rates of native populations.

Though malaria continued, the dry weather, good camp siting and energetic measures abated its incidence, and the winter came in Syria without serious trouble. The chief lesson of the Syrian campaign was the necessity of early planning, so that education of all ranks in malarial risks and anti-malarial discipline should be carried out, supplies obtained and even during a period of action preventive measures carried out as fully as military conditions permit. The organisation of malaria control was at first extemporised, but later made highly efficient. Its success emphasised the paramount need for the presence of scientific advisers who could apply the information gained on the spot. Syria showed too what malariologists know well, that only minute regional study of the conditions can make control effective; generalisations about such matters as the breeding or biting habits of mosquitoes, for example, are often dangerously misleading.

During the winter of 1941 and the first half of 1942 Northern Syria was held as a fortress area, and when summer came malaria returned. Even while the weather was still cold it was necessary to spray villages to kill hibernating mosquitoes. In the hot weather breeding was profuse. Atebrin was introduced as a suppressive, the dose being 0.2 gramme twice weekly. The movement of troops increased the risk perceptibly, and occasionally combatant units disregarded warnings about unsafe bivouac areas and other dangers and paid the penalty in malaria. In one battalion 315 men were exposed to the risk of infection in a highly malarious area near the Syrian border. Shortly afterwards this unit was transferred to Egypt, and through an error the dose of suppressive atebrin was halved. One hundred and sixty-three of these men needed treatment for febrile illness at first thought to be sandfly fever, but 46 were soon proved to be suffering from malaria and further investigation showed that the number with malaria was over 120. It is interesting to note that even when the full suppressive dosage of atebrin was restored (then only 0.4 gramme a week) it was insufficient to prevent overt infection.

IN THE MIDDLE EAST IN 1942

In Egypt before and during the Alamein battle, the general incidence of malaria was inconsiderable. Late in July sudden plagues of *Anopheles pharoensis* visited the Alamein region, but no outbreaks of malaria followed. These were thought to be due to air currents from the breeding areas in the Nile Delta. Dissection showed that the mosquitoes were poor vectors, and the absence of infection amongst those visited by the plague was correctly forecast by the malariologists. The return of the 9th Division to Australia ended the association of the A.I.F. with the Middle East.

During this period there were 131 cases of reported malaria in 1940, 2,331 in 1941 and 934 in 1942.

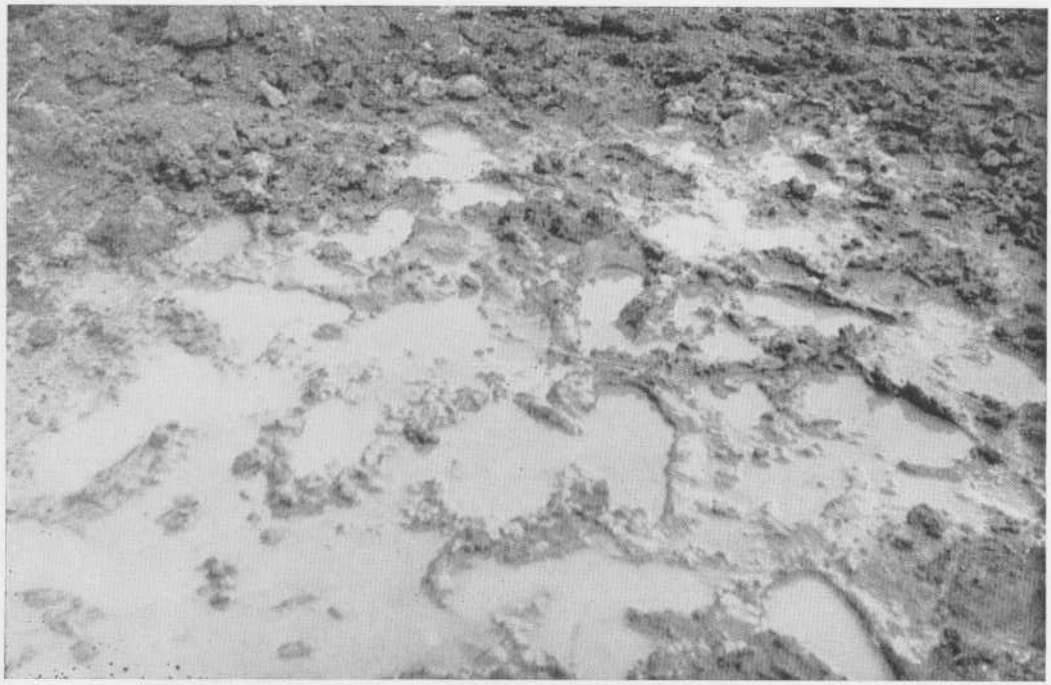
Before returning to the Australian arena, however, there are still some matters touching the military aspects of malaria in the East. In Colombo an A.I.F. hospital had been established as a halfway centre between the Middle East and Australia. Here also two returning brigades were stationed for a time. Malaria made up 14 per cent of the total admissions to the medical division of the hospital and local experience suggested that the strains of the *falciparum* parasite encountered there were more resistant to atebrin than to quinine. It was also claimed that quinine bihydrochloride instead of atebrin reduced the relapse rate greatly. It would seem likely that the question was one of absorption. The 2/2nd Australian Anti-Malarial Control Unit remained in Ceylon for a time, and did valuable work in an epidemic of malaria at Trincomalee, due to *A. culicifacies.*

MALARIA IN SOUTH-EAST ASIA

Meanwhile the 8th Division A.I.F. had been established in Malaya since early in 1941 and in February 1942 this force was involved in the bitter and tragic defence of the peninsula and Singapore. The experience of the 8th Division concerning malaria is of great value in retrospect. Unfortunately this experience, largely gained in captivity, could not be shared or applied in other fields of war, nor could the medical services do more than a limited amount to alleviate the invalidity or prevent the deaths that were inevitable in the conditions under which they worked. But it epitomises the military story of malaria under the shadow of defeat, though a constant medical rearguard action continued and undoubtedly saved the force from even greater losses. Although this part of the malaria story cannot be fitted into a chronological sequence with the accounts from the Pacific area, it is best told here so that it may show what malaria can do to a force striving with almost empty hands.

During the first phase of Malayan experience the incidence of malaria was low in the A.I.F. Control was good in the settled areas, and the influence of the Institute of Medical Research at Kuala Lumpur was most valuable. When jungle training began the incidence of malaria increased, particularly where troop movements were not correlated to anti-malarial measures. When the Australian troops took up battle stations, malaria became common. Then when the A.I.F. went into action at Gemas, the 2/4th Casualty Clearing Station, which treated large numbers of patients, found that medical casualties exceeded the surgical and most of them were due to malaria. The aftermath of this was seen in Changi after the capitulation when relapses of B.T. were frequent.

When the various working parties went out from Changi all of them had further experience of primary malarial infection. In the later phases of the war it was noticed when a hospital was set up at Thanbyuzayat at the northern end of the Burma-Thailand railway built by the prisoners of the Japanese, that new infections were moderate in number; but when in 1943 the line was pushed on through thick jungle country, the malaria



Human tracks making breeding grounds for mosquitoes.

Vehicle tracks making breeding grounds for mosquitoes.

(Australian War Memorial)

Malaria prevention—releasing Gambusia in stream in New Guinea.

(Australian War Memorial)

Malaria control—dusting with Paris green.

rate rose so high that whole units had practically all their men infected within a few weeks. Major W. E. Fisher found that when the different parties finally assembled in the terminal base at Nakom Paton, investigation in the large hospital there showed that 90 per cent of all the patients had had malaria. During their journeyings from one camp to another fresh infections were seen chiefly in the jungle camps, but in the base camps most of the attacks of malaria were recrudescent or relapsing.

It was evident that where conditions did not allow of any anti-malarial precautions infection rates were heavy. The accounts of medical officers unanimously show how futile all attempts were to employ protective measures. Night exposure was universal, most men did not return to their camps till after dark; in any case their quarters afforded no protection against mosquitoes. Even in the less uncomfortable base hospital camps where nets were available, these were often useless because mosquitoes had free access through the bamboo slats of the bed. In settled working camps medical officers were responsible for the malarial control of their camps, but mosquitoes usually entered freely from the neighbouring uncontrolled areas. Clothing, too, in the worst of the camps was almost non-existent. Drugs were always difficult to obtain and sometimes impossible. Quinine was usually supplied, but generally in inadequate amounts. The effect of this was twofold: clinical attacks were poorly controlled, or hardly at all, and treatment was perforce so inefficient that the camps were filled with men carrying parasites in their blood. Plasmoquine was virtually not obtainable after the fall of Singapore. A substitute was provided in small quantities on occasion by the Japanese, but it was toxic and unsatisfactory. The difference in areas where a reasonable supply of drugs was available was striking. Atebrin was sometimes supplied in small amounts and later was obtained through the American Red Cross.

In "F" Force and other forces in Thailand and Burma very heavy infection had been encountered on the road and practically the entire force was infected. Mosquito breeding was uncontrolled, chiefly of *Anophetes minimus* and *maculatus*; in other camps *A. barbirostris* and *phillipensis* were found. When enough supplies were obtained to treat clinical infections with adequate doses of quinine, beginning with 30 grains daily for 3 days, and of plasmoquine, the improvement in the chronic infections and in the longer spacing of relapses was apparent. Resistant infections were much benefited by the intravenous use of quinine. Cerebral malaria was not very common in the experience of most medical officers, but quinine given intravenously was found to be effective when available. Fisher thought that frequent small doses of quinine by mouth gave best results. The effect of inadequate treatment, which was more often seen, was depressing. Lieut-Colonel E. E. Dunlop in Tamarkan in 1943 was forced to use only 18 grains of quinine a day for 7 days, and 6 grains a day as a suppressive to the most severely ill. It is not surprising that blackwater fever occurred not infrequently. Major T. M. Pemberton, R.A.M.C., at Chungkai was even worse off, not being able to spare more than two or three days' treatment with quinine for each man. Relapses

were almost incessant in some of these enfeebled anaemic men, often occurring a few days after cessation of treatment. He graphically described "the large number of pallid, emaciated and tottery figures to be seen in the camps"—the toll of chronic malaria. Remonstrance with the Japanese here brought forth only 5 kilogrammes of quinine for a month's supply, which allowed each patient only 2 days on 15 grains a day. Pemberton justly pointed out that this was no more than a waste of quinine.

These multiplied experiences emphasised the importance of chemoprophylaxis. True, there was seldom enough quinine allowed for this purpose, and almost never enough atebrin, but in the instances where it could so be used the effect was most encouraging. There was evidence that atebrin was superior to quinine for this purpose. Fisher was so convinced of the value of suppression, largely through personal association with Field at Kuala Lumpur in 1941, that he strove to introduce it at Thanbyuzayat. The Japanese would allow only 3 grains a day of quinine for the purpose: this was futile and therefore not so employed. Later at Retpu the number of recrudescences was so large that the rules were disregarded and a daily dose of 6 grains was given. The result was almost to abolish active malaria in the hospital. At the base in Nakom Paton a fairly large scale experiment was carried out, after another convincing trial in a sectional group. Against considerable medical opposition in the area a suppressive dose of 6 grains a day was given to those who had completed treatment (seven days at 20 grains a day) for a third recent relapse. The number of relapses fell so sharply that in the group under this treatment which finally comprised 150 men, there resulted a saving of over 200 grains of quinine a day as compared with un untreated group. An experiment was also carried out on the effect on relapses of plasmoquine ordered early in 1945 at Nakom Paton by the Japanese. Analysis of the results showed little beneficial result in B.T. infections.

In this base area supplies sometimes ran out, and quinine was perforce reserved for the severest infections only. All care was taken to report mental clouding or the passage of darkened urine by patients. As a result of these precautions only three deaths occurred from cerebral malaria, and only one death out of the last seventeen cases of blackwater fever. Most of the attacks of blackwater fever began some days after the starting of treatment with quinine for a B.T. infection. Mixed infections with M.T. were of course common, and, as in all other fronts, it was found that the demonstration of only one type of parasite in the blood by no means precluded the possibility of a co-existing infection. Explosive onsets of blackwater fever were not common and anuria was rare. Haemoglobin figures below 40 per cent were also rare, and transfusions were usually withheld until haemoglobinuria had ceased. Several patients had more than one attack of blackwater fever.

One lesson which emerges from a study of the malarial experiences of the 8th Division is that thorough training of medical officers in all aspects of clinical and pathological diagnosis of malaria is essential. With regard to the latter an extraordinary amount of work was done in examining

slides, despite the scarcity of Giemsa, Romanowsky and Field's stains. Facilities for microscopic work were of course entirely lacking except in settled base areas. This made it all the more imperative to ensure that clinical diagnosis was of a high order. It is only to be expected that medical men whose previous clinical experience with malaria had been scanty or lacking should find difficulty, especially with M.T., the great deceiver. Men often arrived at a camp hospital with an indeterminate fever of some days' duration labelled "P.U.O.", but which was really malaria. Men might look reasonably well, but in a few hours might present the signs of serious illness, again due to malaria.

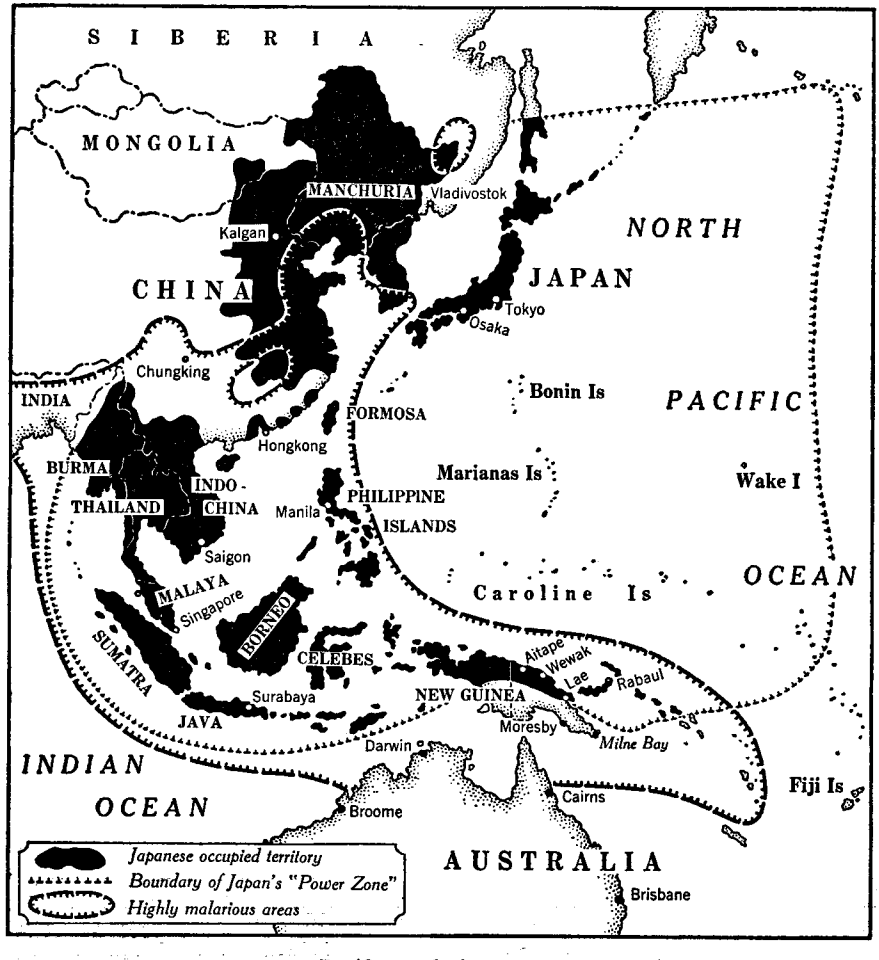
In the early days of training in Malaya prompt microscopic diagnosis was readily available, as in every well organised army, but the clinical picture seen in the jungle and in the working camps, where malaria was combined with all varieties of malnutrition and other tropical diseases was vastly different. The persistence of diagnostic ideas based upon descriptions of the so-called "classic" types of malaria has been referred to earlier. Under conditions prevailing in Burma and Thailand it is not surprising that difficulties in diagnosis arose. It was observed, for example, that in enfeebled men, suffering from malnutrition and other infections, response to treatment for malaria may not be as prompt as is usually taught and usually expected. Another lesson from Malaya was the need for further intensive education of all ranks in personal preventive measures. There is also a lesson for all communities in the disastrous effects and great danger of malaria when not under reasonable therapeutic control, and the futility of inadequate treatment. It is not surprising that malaria was an important cause of death among these men, weakened by disease and privation, but though the story is largely one of frustration, it shows that even with slender resources and devotion much may be done.

WAR IN THE PACIFIC AND THE THREAT OF MALARIA

When Japan entered the war in December 1941 and two divisions of the A.I.F. were recalled to Australia from the Middle East, events moved too swiftly for them to participate in the defence of the Netherlands East Indies, but an attempt was made to obtain a supply of quinine from Java, which produced 90 per cent of the world's supply. Urgent representations were made to the Australian Government setting forth a statement of the position by the Australian medical services with the object of obtaining an adequate supply while sea transport was still possible. Early in January 1942, 120 tons of quinine were paid for by the Australian Government but owing to probable fifth column activities none ever reached Australia, despite all endeavours of the advanced A.I.F. corps headquarters in Java.

While this was happening a grave warning of the danger of uncontrolled and untreated malaria was sounded in New Britain. The Japanese occupied Rabaul towards the end of January 1942 and part of the defending force, cut off and outnumbered, made their way back to New Guinea. Two hundred and fifty-two men of the 2/22nd Battalion escaped. Their medical

officer carried enough quinine for a month's treatment for the men, but after this was exhausted no less than 50 men died within the next five weeks. Almost all of the survivors were heavily infected with M.T. and B.T., and recovered only after many months' convalescence.



Pacific: malarious areas

This misfortune emphasised the importance of malaria to Australia. Before the war the civil health administrations of the Commonwealth and Queensland in particular were apprehensive of the dangers of malaria spreading on the mainland. Opportunity had been taken also for making surveys in New Guinea. Early in 1942 with a campaign impending in New Guinea and other islands to the north three problems relating to malaria faced Australia. These were: the prevention of malaria from spreading on the mainland; the control of malaria in New Guinea and other tropical islands; and the obtaining of malarial supplies from overseas.

THE MALARIAL RISK IN AUSTRALIA

Malaria was endemic in Cairns, and other low grade endemic foci were scattered through the north of the Australian continent. Below 20° south latitude the malarial risk was purely sporadic, but in North Queensland and the Northern Territory the epidemic risk was, and still is, considerable. In the past there had been epidemics, some of which were widespread and of considerable severity, a fact which their self-limited nature tended to obscure. In some of these the disease had been brought in, in others it originated in aborigines in whom there may be endemic foci and who are subject to the same periodic fluctuations of malaria as the other inhabitants. It was not likely that transmission would occur to any degree in the southern states, but north of 20° there was a real risk. Hence those concerned with preventive medicine clearly recognised the danger of introducing a concentrated military population into North Queensland or the Northern Territory where it could provide human material for an epidemic. All other factors were there; the climatic conditions, heavy rainfall in certain seasons of the year, the presence of both anopheline vectors and the parasite, whether intrinsic in origin, or as it might easily be with movement of men from endemic zones in the islands, extrinsic. The introduction of other vectors would also increase the risk.

In May 1942 a conference was held in Brisbane on mosquito-borne diseases. Here the Australian and Allied military representatives of preventive medical services and civil health authorities discussed the problems of dengue and malaria. It was agreed that further control measures were essential, and foundations were laid for future work. At this time a further effort was made to have entomologists attached to the army medical services. An appeal to the Acting Prime Minister through Professor Ashby, the Government's scientific adviser, was successful and four entomologists were appointed. Major I. M. Mackerras was appointed to take charge of entomological work at army headquarters, and later, with the rank of lieut-colonel became the Director of Entomological Services.

The Northern Territory was specially studied as a potentially dangerous area. Its history showed that malaria had smouldered there chiefly among the aborigines, with a few small epidemics of some severity that spread also to the white settlers. Between 25,000 to 30,000 troops were collected there early in 1942, and while they were not closely in contact with the usual inhabitants of the Territory, the aborigines supplied some labour on works like farms, and malaria among them was watched carefully, as the nomadic tribal remnants could spread the disease. The civilians in working camps made contacts with other groups of aborigines and in other ways were not easy to control from the point of view of public health. However, the chief danger of malaria lay in its introduction from outside Australia. Hundreds of refugees both from service and civilian sources had arrived in the Territory from Timor and other parts of the Netherlands East Indies; these were quarantined at Larrimah. The wisdom of this was shown by the occurrence of over fifty relapses of malaria, comprising many M.T. infections, in three months. An Independent Com-

pany and a R.A.A.F. squadron from Timor were found to be heavily infected. Americans from Timor were also believed to be infected. In addition certain A.I.F. units in the Northern Territory had served in Syria, and some of these produced a considerable number of B.T. relapses. The end of the wet season was expected to provide opportunity for more transmission by the anophelines of the Territory, which included a number of species. The most widespread was *annulipes,* which with *bancrofti* had been proved to be at least an experimental vector. *A. punctulatus moluccensis*[5] was also found and known to be a dangerous vector responsible for epidemics in Queensland and New Guinea.

The solution of this problem of the Northern Territory offered difficulties. It was certainly desirable to keep concentration of aborigines away from troops. The control of persons entering the country from overseas, by reason of the Japanese occupation, was not difficult—a matter of quarantine. Australian soldiers in the Territory who suffered from relapsing malaria were a menace; the only practical procedure here was to treat all relapses as they arose and to evacuate all men with proven infections south and not to allow them to return. The civil workers were also watched for evidence of fever, and similar measures taken. The destruction of larvae in so vast an area was not possible, but the neighbourhood of troop concentrations and air force establishments received special attention. These areas, at Darwin, Batchelor, Adelaide River, Katherine and Mataranka, were dealt with by malaria control units. Measures of personal protection and anti-malarial discipline in general were not easy to enforce in these widespread areas. Nets were barely sufficient, but their use was strongly advocated. The wearing of protective clothing was enforced as far as possible: some units, for instance, in the air force had none on issue. Repellent was scarce and its use half-hearted. All patients in hospital with active malaria were rigidly screened, and were evacuated south when their acute symptoms had abated. Further measures taken were to arrange for a conference between all Allied services involved so as to ensure uniform action, particularly with regard to the notification of all cases of malaria under two headings, those contracted outside Australia, and those contracted in Australia. Most important of all was to control the entry of possibly infected troops. Steps were taken to prevent troops leaving malarious areas from entering the Northern Territory, and, as just pointed out, to remove all infected persons from the Territory. This policy was strictly maintained: troops infected with malaria when coming out of New Guinea were taken direct to areas free of anophelines capable of acting as vectors.

The problem in Queensland was complicated by the need for terminals for movements of troops and supplies by land, sea and air. Townsville and Cairns, well equipped ports, were of obvious importance in this respect, but the malarial risk had to be considered. Cairns was within the

[5] There has been some confusion over the naming of the varieties of *Anopheles punctulatus.* The names *"moluccensis"* and *"typicus"* are used in this account as they were in general use by Australian medical officers and others. It is recognised, however, that the names *"farauti"* and *"punctulatus"* are accepted as correct.

malarial belt; Townsville was believed to lie within the belt also, but early surveys fortunately proved this not to be so. The epidemic hazards of Cairns and the other permanently endemic areas in the northern coastal districts emphasised the need for areas safe for troop concentration.

MALARIAL CONTROL IN CAIRNS

At the end of June 1942 a conference was held in Brisbane on the mosquito-borne diseases, at which Sir Raphael Cilento, Director-General of Health and Medical Services in Queensland, reported an extensive outbreak of malaria among civilians at Cairns. This outbreak had begun in March 1942; by the end of July some 500 cases were recorded, 50 of which were in service personnel, and the epidemic was increasing. Dr J. H. L. Cumpston, Commonwealth Director-General of Health, released Dr G. A. M. Heydon from the School of Public Health and Tropical Medicine in Sydney for a special investigation of the mosquito vector, which had never been accurately determined. Surveys of the area were also made by Colonels Fairley and Holmes, the Army Directors of Medicine and Hygiene. Major Mackerras and Captains A. R. Woodhill and F. H. S. Roberts were detailed for further entomological work in Cairns. The malaria in Cairns was benign tertian in type, as it had been in previous years, but it was thought possible that this extensive epidemic of 1942 was related to the influx of refugees from the north. The demonstration of sporozoites by dissection of the mosquitoes found in the field surveys proved that the vector at Cairns was *Anopheles punctulatus moluccensis,* identical with the vector in New Guinea. This discovery was of the first importance; it clarified questions of control and unified the vector problem so far as the Services were concerned. This mosquito did not favour the extensive swamps, such as those on the outskirts of parts of Cairns, but bred chiefly in other sunlit waters. Surveys showed that it did not extend south of Ingham. Other varieties of Anopheline, such as *amictus, annulipes* and *bancrofti,* were relatively scanty: they were potential vectors, but not responsible for this epidemic.

It was certain that a reservoir of gametocyte carriers existed in Cairns, since treatment of civilians usually consisted of the administration of quinine only, and was often incomplete and not medically controlled. Surveys of the population were carried out by the Queensland Health Department, and laboratory investigation was made available by the Commonwealth Health Services. All service patients in Cairns were now evacuated to Atherton, where, in a vector-free environment, full standard treatment was given. Attempts were also made to control civilian treatment, to some extent, by appeals for the abandonment of inefficient self-treatment, and by obtaining the cooperation of civilian practitioners to whom full laboratory service was available. A public meeting was addressed by the A.D.M.S. of the 5th Division stationed near Cairns, Colonel S. H. Lovell, and efforts were made by him and by Colonel Holmes, to disseminate knowledge among civilians. A house to house survey organised by Cilento, showed that of 3,000 persons a diagnosis of malaria had been

made in 6 per cent, though the actual figure was thought to be higher, about 7 per cent. Adequate supplies of quinine, atebrin and plasmoquine were made available at the Cairns District Hospital. In order to deal with the carriers of parasites a plan was devised for home treatment by drugs supplied through the army, which also provided help to carry out a campaign of adult mosquito destruction.

In June 1942 none of the Australian troops, except those who had had oversea experience, knew anything of malarial discipline. Protective clothing was not available in most units and was unpopular. Nets were obtained and were soon in use. The pamphlet "The Prevention of Malaria" was circulated among combatant officers and senior N.C.O.'s in the area and the subject publicised as much as possible. Fortunately the discovery of the vector saved much labour. The large swamps now did not require extensive spraying, though the actual breeding grounds needed close attention. These matters fell within the scope of army malarial control units, which carried the whole burden of the early control work at Cairns. Arrangements were made also to introduce *Gambusia* into the swamps in case *A. bancrofti,* which bred there, should be of importance.

The chief concern of the army medical services, of course, was not to deal with the civilian epidemic, but to control malaria in the Cairns area, as the possession of a malaria-free base in North Queensland was essential. This outbreak emphasised the suitability of the Atherton Tableland as a training area. With a bracing pleasant climate, well above sea level, well watered, offering forest and jungle country for training and yet convenient to the seaboard, it had many advantages. So much for the first Australian problem in malaria.

Meanwhile an occupation force had been in the Moresby area, and serious fighting was expected in New Guinea. It was essential not only to hold Port Moresby but to make it a safe malaria-free base. Medical surveys of Papua, the Mandated Territory of New Guinea, New Britain and other islands had been made before the war by members of the staff of the School of Public Health and Tropical Medicine.[6] These surveys had established that malaria was responsible for most of the morbidity and some of the mortality of the native population. Most of the infant mortality was due to malaria. Malignant malaria was the most common variety and benign tertian was also common: quartan, however, was rare. Blackwater fever was quite common and accounted for a number of deaths among whites. *A. punctulatus* and its sub species *typicus* and *moluccensis* were the most important vectors, and *A. bancrofti* was present too, especially in Dutch New Guinea, but it was a less efficient vector. Malaria was not found at an elevation of 3,000 feet or over, but since rapid transitions from mountains to coastal plains intensified the problems of prevention, there was no doubt about the formidable obstacle thus offered to military operations in these islands.

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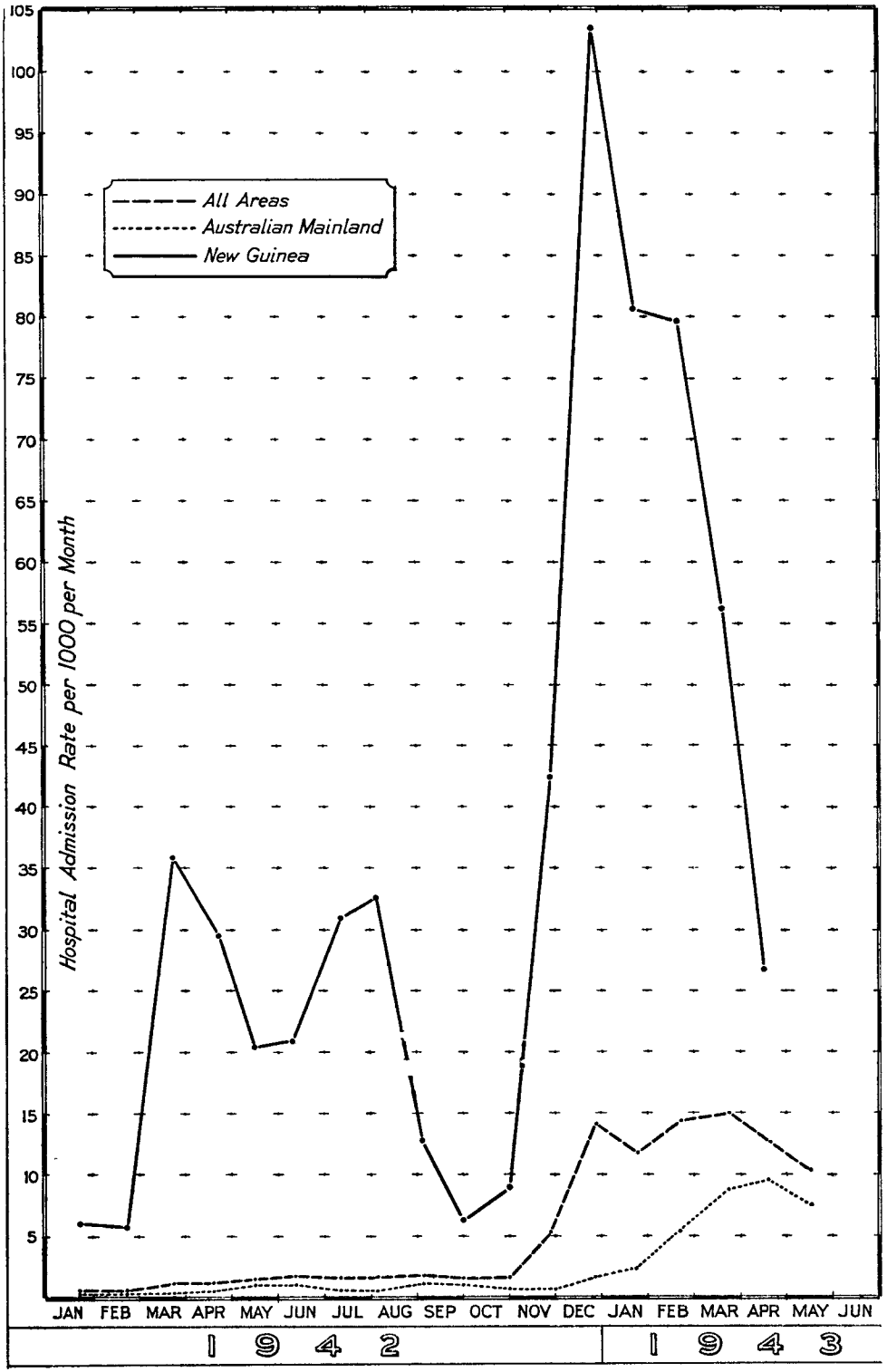
6 This school was established by the Commonwealth Health Department, following up and extending the original establishment of the Tropical Diseases Institute at Townsville. The University of Sydney had accommodated the building in its grounds, and its head, Professor Harvey Sutton, was a member of the professorial staff.

MALARIA IN NEW GUINEA IN 1942

Fortunately the Moresby area differed climatically from the rest of New Guinea. While the whole of the territory of Papua was a very wet area, receiving rain from both the N.W. monsoon and the S.E. trades, Moresby only had 38 inches of rain a year, with a dry season from May to January, thereby resembling many parts of Northern Australia. In June 1942 Colonel Fairley, and Major Mackerras visited New Guinea. They found a high spleen rate in native children in widely separated areas on the south and north coasts, and confirmed that the areas likely to be occupied by troops were hyperendemic. What was much more disturbing was the high rate of infection among troops stationed in and near the Moresby area, which before the war had been well controlled and relatively safe. During the first six months of 1942, out of a force ranging up to 7,700 men and then beginning to increase rapidly, 1,184 patients suffering from clinical malaria had been admitted to hospital. As suppressive quinine was being taken throughout New Guinea Force the probable undisclosed infection rate would at least equal these figures. Surveys of combatant and field medical units supported this. On this basis the malarial casualties which might be expected in the fighting which was undoubtedly approaching were assessed at about 50 per cent. A garrison force had been in the area since 1940 and this had consistently suffered from malaria. The type of fever had been almost all benign tertian, but early in 1942 the greater dispersal of troops into less settled bush areas caused malignant tertian to appear. Up till recent times laboratory facilities were practically absent, and searching technical methods such as the use of thick films had not been used. Arrangements were then being made for the distribution of microscopes and stains to all medical units, including the convalescent depot, and more hospital accommodation was provided. Plasmoquine had been lacking for treatment, an omission which possibly had some bearing on the carrier rate disclosed on making a local survey of troops. No less than 25 per cent of men had gametocytes in their blood at the end of a course of treatment of quinine and atebrin.

The control of *A. punctulatus* in the Moresby area was a formidable task, though this would be lessened somewhat as the dry seasons progressed, and the river levels fell, thus limiting mosquito breeding in back waters and pools and seepages into swamps. This vector preferred clear sunlit water on the whole, but it would also breed in hoof and wheel marks and tins so freely provided by military communities. In the immediate vicinity of Moresby control offered less difficulty and much valuable work had already been done. If personal methods of protection could be enforced, conservation of quinine was thought possible by ceasing suppression during the dry months, since supplies were meagre. Bombing raids by the Japanese had scattered the natives, and thus eliminated the great part of the native reservoir of infection, but unfortunately there had grown up a military reservoir among the troops themselves. Strict control of natives entering the area was instituted by A.N.G.A.U. (Australian and New Guinea Administrative Unit) and their segregation from the troop



Hospital admissions for malaria, Australia and New Guinea, 1942-1943.

areas was arranged. Plasmoquine was supplied for completion of treatment, and healthy carriers of gametocytes could be dealt with either by "blanket treatment" after surveys or by suspending suppression and treating the resultant overt attacks.

The particular importance of dealing promptly with the malarial problem in Moresby lay first in the necessity for having a malaria-free base on the island, and secondly, in realising that it was a seasonal problem which would inevitably be more difficult in the wet season when breeding would get out of hand, and thirdly in instituting a strict anti-malarial discipline before the wet season arrived and before troop numbers rose, as they must, to a much higher figure. In Moresby, as in Queensland, protective clothing was not available to all troops, and those who possessed it often did not wear it; they often cut off the sleeves of shirts and went about at night in shorts.

The middle of 1942 disclosed a serious position with regard to malaria in the troops in the South-West Pacific Area. Troops who should have been seasoned experts in avoiding malaria, and who had the advantage of being for months in a relatively safe area were without full equipment, deficient in anti-malarial training, and therefore without an active conscience. Technical medical aids to the diagnosis of malaria and the limitation of its incidence were still not adequate in amount. Supplies of mosquito nets were inadequate unless cotton could be specially diverted for their manufacture, and drugs were very short. Quinine supplies were rapidly becoming exhausted, atebrin and plasmoquine were scarce, stocks were dwindling, and neither drug was made in Australia. However, the areas where troops were concentrated were coming under better control, and by the middle of August 1942 the measures laid down in General Routine Orders were being carried out. These included the taking of 5 grains of quinine in the relatively safe areas and 10 grains in those more heavily infected, the actual taking of the drug being supervised by a non-commissioned officer. This and dress regulations were enforced by disciplinary action against offenders. These orders were repeated and implemented by force headquarters in Moresby and Milne Bay. Nevertheless, the medical appreciation of the situation prophesied heavy casualties from malaria when action took place at Milne Bay and in the Buna area on the north coast.

ANTI-MALARIAL SUPPLIES

While these preparations were being made, the question of medical supplies was sufficiently urgent to demand special action. In spite of urgent representations very meagre quantities of anti-malarial supplies had been received from overseas. Quinine of course was very scarce, since the fall of Java to the Japanese had removed the chief source of world supply, and very little had been received in Australia from the stock in the United Kingdom. Firm orders had been placed with the U.S.A. for atebrin and plasmoquine on behalf of Australia, the first country to use lease-lend for this purpose, but only small amounts had been received after considerable delay. Bobbinet netting of the standard type was very scarce, owing to

the diversion of loom workers in Great Britain to munitions and other wartime work. Good netting could be made in Australia, but unfortunately early orders had not been placed in England for the correct type of cotton yarn. Many of the nets then in use were unsatisfactory; either they allowed the female anopheline to enter, or else they impeded air-flow. Substitutes for bobbinet mosquito netting obtained from overseas or made in Australia had so far not been satisfactory. Pyrethrum was very scarce. Most of it was now produced in Kenya, since the pre-war output of Japan and of the Dalmatian coast were no longer available. This Kenya crop had been bought privately from America, and only two-sevenths were allocated to Britain, Australia, India, Africa and the Colonies, the remainder being absorbed by America, mainly for horticultural and civilian use.

Accordingly, in September 1942, General Sir Thomas Blamey, the Australian Commander-in-Chief, acting on the advice of the D.G.M.S., Major-General S. R. Burston, sent a military medical mission to Washington and the United Kingdom. Colonel N. H. Fairley, Director of Medicine A.A.M.C., Dr Adrien Albert, a research chemist with special experience in the acridines, and in the synthesis of atebrin, were appointed. The objects of the mission were to represent the truly serious position, particularly with regard to malaria in the South-West Pacific, to try to obtain adequate supplies of quinine, atebrin, plasmoquine and pyrethrum, and an efficient type of netting. The discussions in Washington and later in London had important results. It was essential to convince authorities in Washington and London of the serious urgency of the problem of malaria facing the Allied forces in the Pacific zone. Data collected from recent observations and past surveys were epitomised in a memorandum drawn up by Lieut-Colonel E. Ford, A.A.M.C., and illustrated by maps showing the extent of hyperendemic areas in which malarial transmission went on all the year. This was welcomed by the Medical Intelligence Branch of the Surgeon-General's Office, and the D.M.S., U.S. Navy and was widely circulated. In London copies were also circulated among the medical authorities of the services, the Ministries concerned and the Medical Research Council.

The position about quinine was faced. Just before the Japanese occupation Java was producing 1,000 tons of quinine a year. The Australian Commission strongly advocated the adoption of a 5 to 1 ratio quinine to atebrin in the calculation of world requirements; this basis was accepted and the Allied requirements were reckoned to be 200 tons of atebrin a year. Even if Java were retaken supplies of quinine might not be available, and if trees were destroyed some seven years would elapse before production of cinchona bark would be satisfactory. It was evident that the reserve of quinine, about one year's supply, must be conserved. In U.S.A. and Australia steps had been taken to restrict the sale, wholesale or retail, of quinine to its use for malaria; in the United Kingdom it could be obtained only on medical prescription, but could be used for any purpose. Later strong representations were made in authoritative quarters in England, and similar restrictions were introduced there. This was an

important matter, because without concerted action in the control of anti-malarial drugs it would be more difficult to have the distribution of these administered from an allied pool, by an allied committee. Obviously such a method of control would be an invaluable weapon in the critical struggle against malaria.

The possibility of using totaquine from the bark of trees grown in New Guinea was also discussed. Difficulties had been experienced in the insolubility of quinine sulphate in tablets, but it was found that if the salt was first exsiccated, some starch incorporated in the tablet and over-compression avoided, the trouble would disappear. It was clear in every way, however, that the Allied malarial war would depend largely upon atebrin. Most of the production had to fall on American industry. Britain could make 50 tons annually, but difficulties in manpower shortage, dangers of air attack on factories, and the necessity for importing several intermediary substances limited output. It was agreed that Australia could not make atebrin without a severe tax on the chemical industry: to make each ton of atebrin in Australia it would be necessary to import about 20 tons of raw materials. Australia was, however, able to help in effecting improvements in the synthesis of atebrin. Dr Albert made available his own experience and that of members of the drugs sub-committee of the Association of Scientific Workers, a body which had been engaged *inter alia* for two years past in improving the published methods of synthesis. As an outcome of their endeavours a team of twelve chemists had worked on this problem in the Universities of Sydney, Melbourne and Adelaide. The results of these researches were freely made available to manufacturers both in the United States of America and England, with some improvements in details of this exceedingly complex synthesis. The tabletting of atebrin had given occasional trouble through undue variation in disintegration rates. The difficulty was to ensure rapid disintegration in water without undue friability of the tablet. One American firm had used a waxy coating, but by an improved method a single coating of shellac was used which was satisfactory. A compromise disintegration time of 13 minutes maximum was adopted by agreement. Examination by the Medical Research Council in Britain in 1942 showed that no difference in degree of purity of the drug could be detected in the German, American and British products.

Plasmoquine was made entirely by one firm in U.S.A., 1½ tons a year, while two firms in the U.K. produced together about a ton. The Allied requirements were considered to be 2¾ tons a year, which was the amount expected to be made in one year. One interesting point which emerged from the commission's inspection of plants in England was that there were instances of one firm finding technical difficulties with processes which were easily compassed by another. It was suggested that pooling of methods would produce much increased efficiency.

One of the objects of the Australian commission was to advocate the quinine-atebrin-plasmoquine treatment for malaria, and the substitution of atebrin for quinine in suppression. The U.S. Army and Navy adopted a standard treatment of malaria which was identical with that used and

found effective in the A.I.F. in the Middle East. At this time the question of toxicity of atebrin and plasmoquine caused some doubts and anxiety. Experiments on volunteers proved that there was no difference in the toxicity of atebrin from any source. It was interesting that American medical students taking 0.2 gramme of atebrin twice a week often complained of mild alimentary discomfort, whereas only 2 per cent of prisoners in Sing Sing showed symptoms. Australian experience had been that 0.1 gramme seldom caused symptoms. Though considerable experience had accumulated about atebrin, both as a therapeutic and a suppressive agent, it had never been given a mass trial on a very large scale. General agreement was reached that it was now the only choice as a suppressive, but in addition to its much exaggerated alimentary effects there were some questions yet unanswered. Like most dye derivatives, it had its peculiarities in the amount of drug fixed to various tissues. The difference in individual degrees of skin pigmentation showed this. But the effects of prolonged administration were not fully known: it was concentrated in the liver to a considerable extent, but the desirable and maximum suppressive dose had not been absolutely established. The usual suppressive dose was 0.4 gramme a week, though 0.6 gramme a week had been used also.

A little nervousness was felt in some quarters about the toxicity of plasmoquine, but Australian experience was that this was negligible provided that the dose of 0.01 gramme of the drug, reckoned as plasmoquine base, was not exceeded. Its gametocidal properties made it a most valuable drug in M.T., not only in reducing the number of carriers, but also in controlling relapses to some extent. Although a great amount of research was proceeding both in U.K. and U.S.A. in the quest for an even better anti-malarial drug, preferably a true causal prophylactic, no rival to atebrin was yet in sight. Indeed the loss of Java had given atebrin the pride of place that once belonged to quinine.

In Britain the pyrethrum position was discussed. Even though active research was proceeding on mosquito repellents, it seemed likely that insecticidal substances like pyrethrum would be necessary for sprays. Attempts were made to secure samples of the seed for local growing in Australia: some was then on its way, but this was of the medium grade, the highly toxic variety with high pyrethrin content not being available. Some 70 tons of the flowers were sent to Australia for processing. This relieved the position for a time, as stocks of flowers were practically exhausted, even though the use in Australia of pyrethrum in insect sprays had been restricted to the services. The total Australian annual requirements were put down at 200 tons, but doubt was felt whether this would be sufficient. Even at this period of the war a great part of the world's pyrethrum was still used for horticultural and domestic purposes. The commission considered that it would be better for the war effort if the Kenya supplies passed out of the hands of private buyers and if priorities for the use of pyrethrum were imposed so that considerations of war necessity and civilian health should have highest ranking. An improved method of spraying with pyrethrum solutions had recently been developed

in America by the U.S. Department of Agriculture and the U.S. Army in association with the Westinghouse Company. This was a "bomb" or dispenser which used compressed freon gas to distribute a fine spray under pressure. Production at that time was not fully under way, but it was evident that the freon bomb would be most valuable for killing insects in confined spaces like houses, trenches or aircraft.

Important information was also gained about insect repellents. Citronella was not proving very effective in the Australian Services, and its use was unpopular, partly owing to the greasy excipient. The Surgeon-General's Department in U.S.A. made available details concerning "Sta-way", "Indalone" and Ethyl-hexane diol, all synthetics of much greater potency. Sta-way, however, has been found to cause liver and kidney damage in animals, indalone stained clothing and was expensive; ethyl-hexane diol was effective for four hours, and could be applied as a cream, but it presented technical difficulties of manufacture in Australia where the resources of chemical industries were limited. On enquiry it was found by the commission that recent work on dimethyl phthalate showed that, although not so effective as ethyl-hexanediol, it proved very effective for both mosquitoes and mites ("chiggers"), as well as sandflies and fleas. The higher homologues of the ethyl and butyl series were not found to repel mosquitoes.

Dimethyl phthalate was introduced by the Standard Oil Company, who had patented it and issued a 25 per cent solution which had been found effective for some years in South America. Experiments showed that its toxicity was very low. This substance appeared to be the answer to Australia's needs, being twice as powerful as citronella, much easier to apply, and offering no difficulties in manufacture provided methanol could be obtained in quantity. Fairley and Albert aroused considerable surprise when they pointed out another virtue of this repellent which had been overlooked, its comparative cheapness.

The British view on repellents was that natural products should be favoured, so as to lessen the strain on their chemical industries. For Australia this attitude was not possible, as there was little chance of obtaining enough pyrethrum to use as a repellent as the British were doing. Accordingly a strong recommendation was made that dimethyl phthalate should be adopted as the standard repellent in Australia. British experts agreed to carry out further experiments on the toxicity of this ester. The importance of the South American work had attracted attention to it in Australia also at this time, and Captain Waterhouse had made some examination of dimethyl phthalate. R. N. McCulloch was thus able to start field work at an early date, and these independent studies were well advanced on Fairley's return. The first bulk supplies reached troops in New Guinea in March 1943.

The position about mosquito netting in U.S.A. and U.K. was not very encouraging owing to the scarcity of all cotton supplies. Looms were available in England, but not the necessary workers. A limited quantity only of the standard bobbinet netting could be obtained in America, and a

larger amount of a substitute netting of Nottingham or Lever's lace type. Unfortunately no army standard had been laid down either in Britain or U.S.A. for substitutes. There were many problems. Specifications were necessary to cover the size and shape of the aperture, anti-mildew processing, water-proofing, camouflage, shrinking and other details. Previous experience with substitute netting in the Pacific area had been unfavourable: nets sent to Australia both from India and U.S.A. had defective air flow, so that the troops would not use them. Further, their lack of camouflage made them impossible for use by forward troops, and they soon succumbed to mildew and rot in the tropics. The aperture of mesh was important. In substitute nets it was not octagonal, as in standard army bobbinet, but quadrilateral, and mosquitoes could wriggle through the longest diameter. A narrower aperture was necessary, and only "ungassed" yarn was to be used, in which the fine fibrils remained on the yarn and acted as a further impediment to the mosquito.

A difficulty arose over mildew-proofing for which there was no American Government standard, but, though production was held up for a time, it was agreed that the standard approved by the U.S. Quartermaster Corps would be adopted for all nets used in the South-West Pacific.

The discussion of these apparently small details had far-reaching effects for the Services of the Allied countries. Adequate supplies of netting were finally promised from America and England, and also of cotton yarn for manufacture in Australia. Difficulties were still being experienced in shipping priorities, through the complexities of lease-lend arrangements. These matters though not directly within the ambit of a scientific commission were of vital importance, as time was a crucial factor. In addition to the complicated procedure of procurement the International Supply Committee had recently introduced an additional check on the raw material exported, and this had caused further delays. The potential power of the War Department to repossess lease-lend material not shipped within 45 days was an additional source of anxiety. However, assurance was given by the British Ministry of Supply Mission in Washington that these difficulties were not formidable and could be overcome, and the closing months of 1942 gave promise of a much more satisfactory position with regard to anti-malarial supplies for the South-West Pacific zone. An appreciation of the serious position to be faced had undoubtedly been helped by the vigorous representations of this Australian commission.

Finally a most important matter was discussed and investigated. This was the problem of preventing the spread of malaria over Pacific areas hitherto free. The U.S. Navy had already had costly experience in the New Hebrides and heavy casualties from malaria were also being suffered in the Solomons. The danger of moving forces infected with malaria about the Pacific had been realised in U.S.A. A suggestion had been made to Field Marshal Sir John Dill of the British Joint Staff at Washington by Sir Philip Mitchell, Governor of Fiji, which was malaria-free, that malariologists should be appointed to various bases in the South-West Pacific. At conferences held in U.S.A. it was agreed that the problem was

that of the prevention of admission of anopheline vectors into this and other free areas. There had been a lack of coordination between some civil medical officers and some masters of American ships, and U.S. service officers, but recommendations were now drawn up to ensure the necessary action to prevent the spread of anophelines. On his way back to Australia Colonel Fairley stopped by arrangement at Fiji and found that energetic measures were being taken. In addition he suggested that any troops found to have malaria should be treated with plasmoquine, and that freon dispensers should be used in ships and aircraft, and that the services of an entomologist with experience in malaria be employed to advise concerning control measures near ports and airfields. These matters were duly reported to London and Washington.

MALARIA IN MILNE BAY

While these important steps were being taken overseas to secure and maintain anti-malarial supplies, stirring events were taking place in New Guinea. Two campaigns were proving how prophetic was the medical forecast of heavy malarial casualties in operations in hyperendemic areas. The first of these was at Milne Bay, the second included the terribly difficult action fought up and down the steep Owen Stanley Ranges and finally brought to a successful issue by forces converging on the north coast of the island at Buna and Gona.

Milne Bay is worth some detailed malariological study. The area is a roughly triangular one, occupied before the war by coconut and rubber plantations, bounded by hills and indented by the useful harbour of Milne Bay. It is virtually cut off from the rest of southern New Guinea to which access is gained only by sea and by air. Air communication is subject to weather delays and not without hazard. The terrain is flat and low; most of the area occupied by the Australians was only 25 to 100 feet above sea level. Jungle grew right up to the plantations, and many creeks fed the single river. The plantations were well drained before the war, there were sago swamps, neglected but originally harmless. Round the water front there was a good deal of malaria among natives; at Gili Gili, for example, the spleen rate was 90 per cent. It was in fact a hyperendemic area reasonably well controlled for white civilians. Both Australian and Japanese forces recognised the strategic value of its position at the south-eastern tip of the island. In July 1942 it was imperative that a force should defend it adequately against certain attack. Actually there was little time, and when the 11th Australian Division, as "Milne Force", occupied it, hurried preparations were made. Reinforcements arrived only in time for the action, and some field medical units had to settle in hastily selected areas. The wet season made the muddy area very difficult for vehicles on narrow and extemporised roads. Wheel tracks were everywhere, every one soon breeding mosquitoes. Slit trenches were also prolific breeding grounds for mosquitoes which attacked men seeking shelter during the frequent night air raids. Felled trees and palms blocked drains, so too did some of the roads and culverts hastily contrived by the engineers. *Anopheles*

punctulatus abounded, the *typicus* variety in small sunny waterholes, the *moluccensis* in the brackish water of the waterfront, among mangroves. Other anophelines were found such as *longirostris, subpictus* and *bancrofti,* but these were not of epidemic importance.

The first medical unit to arrive had some gear for malarial control work and early began the destruction of adults and larvae. One malaria control unit was in the area early, but its equipment was lost by the sinking of a ship. Up till September the Japanese had control of the sea by night.

The land action was only brief. Until 26th August when it began, the incidence of malaria was considerable but not crippling. The troops had had but negligible training in malarial discipline, but their newness at first saved them. Many of the reinforcements were in action within a period after landing not much greater than the incubation period of malaria. This was fortunate: it was after the successful conclusion of the brief sharp action that epidemic malaria attacked the force.

The malariologist's report on Milne Bay in July before hostilities had begun had stressed the need for at least twice the number of hospital beds usually provided in training areas in the north of Australia, for good laboratory facilities, reserve supplies of all kinds, an active malarial control unit, and provision of protection for troops. But at the end of August difficulties of transport and organisation still left the area with inadequate facilities. Brigadier W. W. S. Johnston, D.D.M.S. New Guinea Force, reported that the existing facilities of the whole New Guinea Force

"would not provide either for the best medical care of the troops or for the best means of maintaining the strength of the force, as bed space does not permit of retaining all cases on the island whose treatment can be carried out here."

This applied with special point to Milne Bay, where there was then no director of hygiene, thus adding to the burdens of the A.D.M.S., Colonel Maitland, who was severely handicapped without sufficient materials or labour. It was eight weeks after the loss of the malarial stores mentioned above before replacements arrived. This was due to lack of power to enforce priority of transport for such supplies; goods were later found to be lying in sheds at Townsville still waiting to be moved.

The R.A.A.F. in Milne Bay laboured under similar difficulties on a smaller scale. The secrecy of the original move of fighter squadrons to Milne Bay had been so closely preserved that adequate medical preventive arrangements could not be made. The Director of Hygiene and Tropical Medicine for the R.A.A.F., Group Captain Baldwin, was thus severely hampered, and anti-malarial discipline in the Milne Bay area was as unsatisfactory as in the army. The squadrons had only shorts and short-sleeved shirts, and the taking of suppressive quinine was not strictly supervised. Mosquito nets were issued but were quite unsuitable. In September it was necessary to rest these pilots, not only on account of their strenuous service against the enemy, but in part because of malaria.

It was not long before a dangerous reservoir of gametocytes was built up in the blood of the troops themselves. A little later a series of even apparently healthy soldiers was found to have as high a gametocyte rate

as 20 per cent. Concentrations of natives also increased the risk: in one area natives in camps within 500 yards of military areas were found to have high parasite rates, but after the administration of 0.02 gramme of plasmoquine for 3 days by an American unit, the local malaria rate was reduced. Even in medical units the medical officers and orderlies themselves increased the pool of available parasites. Where patients were accommodated on narrow stretchers they were frequently bitten through the nets, which touched them on either side if they moved.

After the occupation of Milne Bay the malarial incidence rose rapidly. Whereas in September when active operations concluded the rate was fairly steady at 33 per 1,000 per week, that is 1,716 per 1,000 per year, by December a sharp epidemic wave had begun which was responsible for 3,000 cases of malaria during the month. In September a bed allowance of some 7.5 per cent had seemed sufficient for the force, though medical authorities had all along advised a 10 per cent provision for areas with high sick rates. Now the rate for malaria alone was 82 per 1,000 per week, or 4,264 per 1,000 per year. During the week ending 25th December 1942, 1,083 men were admitted to hospital out of a strength of some 12,000. As Lieut-Colonel Ford[7] said with reference to epidemic malaria, an outbreak may be likened to a camp fire, but an epidemic to a bush fire. Medical units were overcrowded, many men were being inadequately treated in their lines, and others attempted covertly to treat themselves. Medical officers and others kept on their feet by taking increased suppressive doses of quinine. Had this alarming increase in rate continued, bounding upwards in geometrical progression as the parasite reservoir grew, the whole force would have been lost in less than two months. Evacuations of patients with malaria to the mainland were being made with a lamentable effect on morale. The only brightness on the horizon was the timely defeat of the Japanese invading force. Determined efforts by the medical service to obtain necessary supplies and native labour, and to tighten up loose malarial discipline produced only a weak response. An appeal was therefore made to General Blamey and, through the D.D.M.S., Brigadier Johnston, Lieut-Colonel Ford obtained an interview early in December with the Commander-in-Chief. He stressed the necessity for regarding the recent campaign areas as training grounds in malaria for subsequent operations. He pointed out the lack of consciousness of the destroying force in malaria among all Allied troops in New Guinea. Malarial discipline should be an integral part of unit discipline; "no officer is fit to command even the smallest body of men in a hyperendemic malarial area who does not have constantly with him the awareness of his responsibility". Personal protection must be enforced and breaches of discipline visited by punishment; the unfailing supply of all anti-malarial material, particularly suppressive quinine or atebrin was essential. Such responsibilities were incumbent on all troops right back to

[7] Lt.-Col. Ford officially was appointed Assistant Director of Pathology to New Guinea Force but unofficially was its malariologist. At that time the medical services had not been able to secure the appointment of malariologists, hence this device without which the effects of malaria on the force would have been even more serious.

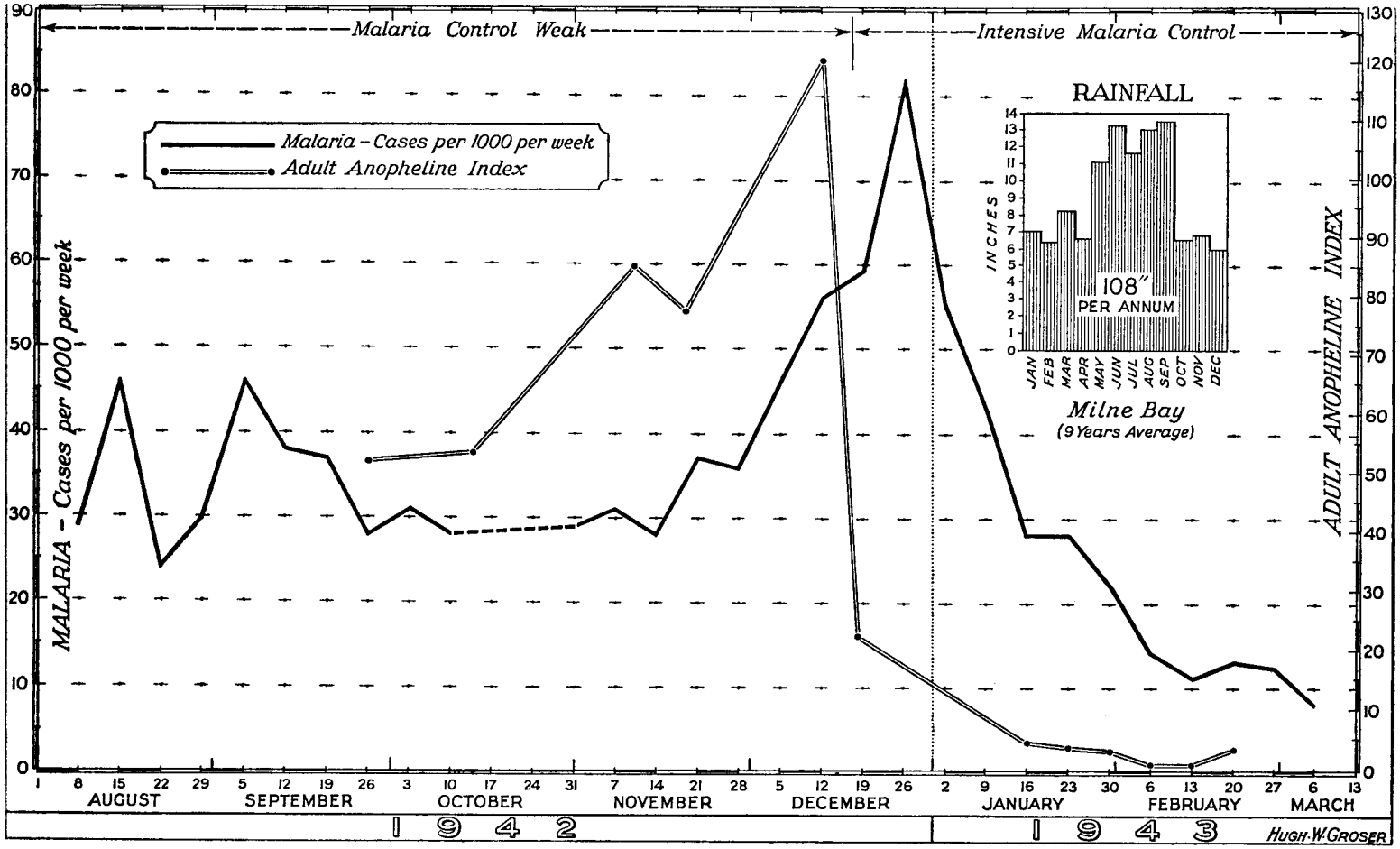
training areas. Ford pointed out that medical units in Milne Bay had been evacuating 300 men a week for weeks past, and 800 then awaited evacuation: about 5,000 men had been treated for malaria out of 16,000 in Milne Bay, and it was probable that practically the whole force was carrying infections temporarily held in check by suppressive drugs.

A request for higher priorities for all malarial work, particularly increased equipment and stores for malaria control, and for additional labour, amounting to 1,000 men, met with immediate response from General Blamey. By the middle of December intensive anti-malarial work began, 500 native labourers were made available at once, discipline was tightened and the wearing of protective clothing was compulsory under penalty. At the same time another malarial control unit arrived and delayed stores came to hand. A month later the 11th Division was replaced by the 5th, but even before this a dramatic fall in the anopheline index of the area began, and after the typical appropriate lag period, representing the incubation period of the infection, case incidence also fell sharply. There could be no doubt that the reduction in the malaria rate was due to reduction in infection by the mosquito. Three other important factors should be mentioned. The first was an order that no man would be evacuated from the area for malarial infection except for serious medical reasons; the second the segregation of native labourers and the third the resumption of plasmoquine in treatment. Some heavily infected units were also treated with plasmoquine in order to reduce the gametocyte reservoir. Mechanical methods of control such as engineering works, oiling, use of paris green and spraying were continued with vigour. The decrease in the infection rate continued when the 5th Division occupied the area. These men were already initiated into malaria control, having been in the Cairns area, and the incidence of malaria fell from 30 per week to about 10 a week within a month and diminished further.

In February 1943 many fresh R.A.A.F. units were moved into the Milne Bay area and concentrated efforts were made to institute malaria control. A mobile anti-malaria squad, with the help of allotted natives, joined in the preventive campaign. Unfortunately protective clothing was still inadequate in supply, but the figures of the R.A.A.F. for malaria soon began to show the same encouraging fall as in the army, and later in the year their rate fell to about 1 per 1,000 per week.

The malarial story of Milne Bay is one of a virtually closed community. The force, like some others in history, luckily fought an action while the malarial enemy was gathering strength; it was nearly extinguished by infection, but showed how remarkable a rehabilitation may occur once facilities are available and strong measures taken. It is fair to say that had not the medical services continued their undaunted struggles for control even when things were at the worst, so rapid a result could not have been attained later.

A month after the beginning of intensive malaria control in Milne Bay atebrin was adopted as the suppressive drug for the Australian armed forces, but the change was not fully implemented for a time. This aroused



Milne Bay: malaria in 1942-1943.

at first some of the doubts previously mentioned about the potential toxic effects of atebrin. Among aircrews in the air force, particularly pilots, there were at first serious questionings. An idea had gained a certain degree of credence that atebrin "lowered the ceiling" in high flying, owing to some interference with cell metabolism. Some pilots were averse to being bereft of their accustomed quinine. The experience of the U.S. Air Force indicated that there were no special drawbacks to atebrin. After some delays this reluctance was overcome and eventually atebrin was used by all services. The bogey of toxicity of plasmoquine was not so easy to lay. It was well known that the therapeutic dose is close to the toxic dose, that some people are sensitive to it, and that substitution in error of tablets containing 0.02 gramme plasmoquine base for the usual 0.01 gramme would cause abdominal discomfort and cyanosis due to the breakdown of haemoglobin. Such mistakes were due to the differences in strength of different preparations, poor packaging without clear description of the contents in large type, and lack of understanding of the actual potency of the different combinations of the base. The question was particularly important in Milne Bay for there, with malaria in the zenith and antimalarial morale at the nadir, plasmoquine so fell into disrepute that it was virtually abandoned when it would have been valuable in diminishing the gametocyte pool rapidly being built up in the force.

In order to cope with this situation a short treatment was introduced as a temporary measure. This was 5 days of quinine 30 grains a day, followed by 5 days of quinine 15 grains and plasmoquine 0.03 gramme a day. Atebrin was added to the course after the initial quinine as in the standard course if the medical officer considered it advisable. It was hoped that this would control attacks, maintain a presumed premunity and kill the gametocytes. Most of the gametocytes seen in films were crescents, for malignant tertian was the predominant type then in Milne Bay, comprising 90 per cent of the infections. The rest were benign tertian with an occasional quartan. Quartan malaria had a high incidence in native children but, as expected, was not often seen in soldiers, as *Plasmodium malariae* does not appear to be a ready or quick infecting type. This question of controlling the gametocytes after suppression of the primary fever was regarded as important in the Australian forces and will be referred to again presently.

It may be pointed out here that it is hard to present convincing statistical evidence involving calculation of gametocyte rates because of the laborious technique necessary in order to obtain accurate figures. If the standard of 8 to 10 gametocytes to 1 cubic millimetre of blood as the minimum infecting dose is accepted, one half or preferably one cubic millimetre of blood must be examined completely by thick films. This labour can only be appreciated by attempting it. Using this method, Mackerras found the following figures in an illustrative series.

	Number examined	Spleen rate	Parasite rate	Gametocyte rate
Native children . .	30	93%	70%	33%
Working natives . .	265	70%	15%	3%
Patients at end of quinine-plasmoquine course .	150	0	4%	4%
A.A.M.C. personnel (working) . . .	109	5%	6%	0
Infantry personnel (working) . . .	47	6%	25%	21%

The 47 infantrymen surveyed had not taken plasmoquine during previous attacks of malaria, owing to a prejudice against this drug which began in American units in Milne Bay and spread over most of the units in the area. Atebrin suppression had begun some weeks previously. The 109 A.A.M.C. men owed their freedom from gametocytes to their superior suppression.

Before leaving Milne Bay we should understand clearly the difference made by adequate control. Improved conditions were not only gained but maintained. The malarial rate fell to figures below 5 per 1,000 per week, there was no strain on medical units or on evacuation of the sick, unit discipline in the Australian forces was excellent, permanent road and drainage works made great improvements, such as the abolition of swamps, and making work in the jetty area safe and possible. Even with the improved conditions in the early months of 1943 malaria in Milne Bay caused 8,099 casualties in the period from October 23rd 1942 to April 24th 1943.

THE KOKODA-WAU-BUNA CAMPAIGN

Now we must turn to Central Papua. The arduous struggle on the Owen Stanley Ranges which ended in the repulse of the Japanese to the coast had not produced much malaria, for there was little transmission at the higher altitudes. But when Australian and American troops undertook the encirclement of the Japanese in the area including Sanananda, Buna and Gona three months of persistent fighting took place in swampy coastal country where malaria was hyperendemic. Once again the same cycle was seen; increase of breeding areas, increase of mosquitoes, rising infection rates, the creation of a reservoir of parasites in the blood of the troops, and finally an epidemic. Unlike the forces in Milne Bay these troops did not enter that ordeal after brief periods of establishment and action. They were already tired and undernourished, and were poorly equipped to protect themselves against infection. Suppression had been discontinued on the ranges, where mosquito transmission was unlikely, in order to conserve stores in that difficult country in which native carriers and air dropping were the only possible methods of maintaining supplies. Drugs, repellent cream and nets had not reached Kokoda, where there was a practicable airfield, before the action on the plains began. Even quinine did not arrive there for nearly a month.

Troops were also engaged in the operations on Wau and Bulolo, converging on the coast. The malarial danger in the high Wau area itself was slight, but lay in the precipitation of men from a safe area to the highly malarious areas in the Markham Valley with insufficient protection. Without great care the heavy epidemic of Buna and Sanananda might have been repeated. In this latter area between Kokoda and the coast the true incidence of malaria can only be guessed. Under existing conditions it was difficult to avoid infection. It was reported that at Soputa 90 per cent of the troops in the area were infected in a month. The declared overall rate for operational troops in the Buna and Wau actions was 22.5 per 1,000 per week, rising to a peak at the end of January 1943 when the rate was 48 per 1,000 per week, or 2,496 per 1,000 per year. Taking the same six months' period as for Milne Bay, 23rd October 1942 to 24th April 1943, the number of patients admitted with malaria to medical units was 11,638; this brings the total of cases of malaria reported in New Guinea for this period to 20,272. The total casualties for this period due to tropical diseases was 29,101 whereas battle casualties were 6,154, a ratio of 4.7 to 1.

Fairley has pointed out that the consolidated figures, even allowing for admitted understatement, give no idea of the impact of malaria on the forces. Many men admitted to hospital were suffering from hyper-infection, and severe M.T. infections were common. Blackwater fever was occasionally seen, and by no means always in men who had been for sometime, that is, a number of months, in the country. Thousands of men were treated in their lines or treated themselves.

Some idea of the widespread degree of infection may be gained from the results of surveys made on men after their return from the area. The 18th Australian Brigade was in action some 5 weeks in the Buna-Sanananda area and left there for a base area a few weeks later. Examination then showed that 7.3 per cent of the men who had had an attack of malaria still had parasites in the blood, while 26 per cent of those who had not had an attack also carried parasites. Some of these men had been in Milne Bay previously, but in proof that Buna was an equally dangerous area, similar surveys of men who had been only in Buna showed corresponding figures of 4.9 per cent and 29 per cent. Surveys were made later of men who had been in the sharp fighting of the Wau campaign in highly malarious areas. Less detailed examination was possible, but the frequency with which enlargement of the spleen was found in men who had no clinical history of malaria showed that a high relapse rate might be expected. In this series some interesting figures were obtained concerning the average time between the initial attack and the first and later relapses; these periods were 8.5 weeks, 8 weeks and 10 weeks.

Early in 1943 the divisions concerned in the actions at Milne Bay and Buna-Gona-Sanananda were withdrawn to Australia to rehabilitate and train in the more salubrious environment of the Atherton Tableland in North Queensland. There it was soon evident that practically the whole force had malaria, as most of the men had relapses of benign tertian fever.

It was apparent too that there was a sharp difference between these relapses and those seen after the Syrian campaign. Relapses now appeared earlier, and it was observed that the types of infection encountered in New Guinea were more severe and difficult to control.

We may anticipate here the happenings when the troops of the II Australian Corps were withdrawn to the mainland and they were allowed to proceed on home leave. It was inevitable that many would suffer from relapses of B.T. while in the southern States, as it was certain that suppressives would not be regularly taken during that period, although the taking of 0.1 gramme of atebrin thrice weekly was an order. Soldiers were instructed to report for advice to military hospitals or public hospitals or to the nearest area medical officers. Large numbers were admitted for malaria to military hospitals throughout Australia. Most of the "originals" who had been five months in New Guinea and had been in the Buna-Gona area were already infected, and after their return to their units presented the problem of latent malaria. Medical authorities thought that none of the original brigades would be fit for hard operational training for three months. Many of the men looked pale and tired. Anaemia was not uncommon, particularly in those who had a palpable spleen. Investigation in hospitals showed that eosinophilia was not infrequent and, as expected, this was found to be due to hookworm. Study of a considerable series showed that a recession of the eosinophilia was sometimes due to the occurrence of malarial relapses. The hookworm infestation was not severe, and it was not expected to be a serious factor in debilitating the men.

After several months relapses became less frequent and the condition of the men was obviously much improved. Malignant malaria was not common among these men. In one hospital in Queensland the first 1,000 cases of relapsing malaria produced 38 of malignant tertian, but in the second 1,000 there were only 3. Unfortunately, despite all warnings, a few deaths occurred among men who did not report when they fell ill. Others were seriously ill on admission to hospital but recovered rapidly. In a few instances too, rupture of the spleen occurred. But the problem was almost entirely one of relapsing tertian fever. In order to detect latent malaria suppressive drugs were suspended for a week and blood films were then examined. If parasites were found quinine and atebrin were given in a hospital, and the plasmoquine part of the course continued in a convalescent depot.

As the men became more physically fit for rigorous training there were several important problems to solve. The question of more intensive antimalarial training was, or should be, only one of organisation. But more serious immediate matters were involved when malarially infected troops were trained in the Queensland coastal areas. It was necessary to survey the most appropriate areas for bivouacs from the malarial point of view, for night exercises carried some risk of dissemination of malaria. Instructions were given that troops in moving to a bivouac area would proceed direct and not to be staged elsewhere in an area of potential risk. The men

were issued with mosquito nets before moving and took suppressive atebrin for a week beforehand.

At this time difficulties were occasionally experienced in various parts of the mainland and New Guinea in establishing prompt and complete control over the primary fever. Fever would recur even during a course of treatment, and parasites were sometimes then found in the blood. In some later series carefully observed, as in Nadzab, no parasites could be found in the blood even after prolonged search. In some instances it seemed likely that there was another cause for the fever, such as dengue fever, but in places like the southern States of Australia there was no dengue present. Where relapses occurred during or soon after completion of a course a variant of treatment was adopted. Intravenous quinine 10 grains on the first two days of the course, as well as 20 grains by mouth, 30 grains on the third day, 9 tablets of atebrin the fourth day, 6 tablets the fifth day, and then 3 tablets for three successive days. The most obvious explanation of these recurrences was that drugs were either not taken or not absorbed. There seems little doubt in carefully supervised series that the trouble was sometimes one of absorption. The question will be discussed later.

ANTI-MALARIAL DEVELOPMENTS IN 1943

By March 1943 it was necessary to review the whole malarial position. Some brief account of the measures taken is necessary, for it is really germane to the clinical study of the disease for whose understanding, treatment and prevention a penetrating knowledge of all the factors is essential.

One step had already been taken that was obvious and inevitable, but was even more important than was realised at the time, the adoption of atebrin as a suppressive drug. The dosage recommended was 0.1 gramme daily for six days a week in hyperendemic areas and 0.1 gramme daily for four days a week (or 0.2 gramme twice weekly) in areas where malaria was endemic, but not defined as hyperendemic by the D.G.M.S. or his senior representative in an area. The original suppressive dosages of atebrin were largely based on experiments carried out on semi-immunes in Malaya, thus accounting for their inadequacy to give full protection to fully susceptible whites under service conditions. The same fallacy had been observed in relation to quinine in the Balkans during the 1914-1918 war. The hesitation at first felt at abandoning quinine was reflected in one of the earlier orders which recommended a compromise in hyperendemic areas, in which the total weekly suppressive dosage was 30 grains of quinine and 0.2 gramme atebrin weekly. Hyperendemic or highly malarious areas were defined as those in which the splenic index was over 20 per cent or in which malaria assumed serious proportions in unseasoned troops.

In February 1943 the "New Guinea Allied Conference on Tropical Diseases and Hygiene" was formed under the aegis of New Guinea Force. This body was concerned with the educational aspect of preventive medicine. The subjects covered at its meetings ranged from purely scientific and technical reports to methods of propaganda to troops. Many of the contributions were of a high order and from its discussions flowed an

energising influence. Though the Allied Conference had no direct power of executive action its influence was well diffused. Methods of propaganda were particularly discussed at the earlier meetings, such as leaflets dropped from the air, posters and instructional films. Material was supplied for *Guinea Gold* and *Salt,* service magazines circulated among the troops. This was specially important, as articles had been published by well known writers, whose previous civilian experience was often not relevant and whose views were sometimes positively likely to do harm. Again and again it was found how far from military reality were the tenets of the pre-war civilian in the tropics. It was also pointed out later to New Guinea Force headquarters that a pamphlet "The Native Carrier" from the Allied Geographical Section advised seeking shelter in friendly villages, a course definitely not favoured by malariologists. Another pamphlet "Getting about in New Guinea" was found to contain dangerous advice about drinking water, and harmful information about malaria which contravened official instructions.

In March 1943 General Burston, on the advice of Colonel Fairley, made representations concerning the forming of a combined advisory body on tropical disease. Discussions took place between the American and Australian Medical Headquarters, and these resulted in the setting up of a body of experts who were to act in an advisory capacity to the Supreme Commander in the South-West Pacific Area, General MacArthur. This "Combined Advisory Committee on Tropical Medicine, Hygiene and Sanitation" comprised representatives of all medical services of both Allies, with Colonel Fairley as chairman and Colonel Holmes as chief executive officer. This committee, collecting information from many sources, had far reaching influence, and many important directives were made by General MacArthur on its advice.

During March another Australian mission was sent to U.S.A. and U.K. to coordinate the supply of medical requirements to Australia and the combat zones in which its forces were operating. This was done at the instance of the Medical Equipment Control Committee, a body that was fulfilling the important function of controlling supply and distribution of all medical material in Australia. Mr B. Egan, its representative on behalf of the Division of Import Procurement, and Colonel C. W. Ross, carried out this mission. As a result of the contacts made by this mission and by Lieut-Colonel J. A. Doull of the United States Army Medical Corps who visited Australia to investigate the control of supplies under "lend-lease", an improved flow of material soon was obtained, chiefly at first from U.S.A. for lend-lease and later by export from U.K. There was reason to hope that by the end of 1943 no lack of material would hamper the increased efforts made not only against the Japanese but also against tropical disease, in particular malaria.

Meanwhile additional medical units had been brought into New Guinea, preventive work was pushed on in the field and efforts were made to arouse the consciousness of the forces in the island to their personal responsibilities. The newly formed advisory committee as one of its first

acts placed before General MacArthur the lessons learnt to date in tropical warfare, particularly the dangers of beginning actions before anti-malarial supplies were available, and before anti-mosquito measures were established. The committee made recommendations as to the anti-malarial measures necessary for operational forces in highly malarious areas. These covered (1) training and instruction of troops in personal protection (clothing, nets, and repellents), suppressive use of atebrin and methods of destroying mosquitoes; (2) malaria control organisation within military units, including a recognition of the responsibility of commanders thereto; (3) issue of necessary personal supplies to soldiers before embarkation; (4) measures to be taken in connection with movement of troops to malarious localities, including the use of malariologists attached to such forces and the issue of necessary unit supplies; (5) discipline; and (6) priority of malarial supplies. The routine use of dimethyl phthalate as a repellent was advised through the whole South-West Pacific Area. Production was then proceeding in Australia with priority over munitions, and was expected shortly to supply the needs of the Australian Army and Air Force.

It might perhaps be thought that experiences in New Guinea to date would of their own relevance and force ensure that a striking reduction of malarial casualties would be effected in the next campaign. But human beings are not built like that, and in the early months of 1943 even officers of field rank could sometimes be seen in the Moresby area breaking the strict rules about clothing. Difficulties were still occurring with clothing in other ways. Men of the R.A.A.F. and R.A.N. were still arriving in malarious areas wearing shorts; the mobility of units of the air force created a particular problem, and some time elapsed before this service was equipped with protective clothing. Even under static conditions only strict supervision could ensure that suppressive drugs were taken or nets used. Engineering works still provided many breeding places for mosquitoes, many of which though avoidable were unheeded by the perpetrators. If there were those who were still careless of counsel there were also those who wished to follow their own notions. Striking at the appropriate time General Burston issued a new Technical Instruction No. 59, which consolidated and replaced all previous instructions. This was drawn up by Colonel Fairley and unified methods in all areas.

THE HANDLING OF MALARIA IN AUSTRALIA

The scene now shifts to the mainland of Australia, where the return of thousands of soldiers suffering occasional relapses of malaria aroused great public interest. This interest invaded the political spheres as was natural, and Sir Earle Page (himself a doctor) who had voiced some criticisms of the medical aspects of the campaigns, was asked by the Prime Minister, Mr John Curtin, to investigate and report. As a result of this investigation, for which full facilities were given Sir Earle Page in all areas, a complete report was presented covering the question of possible spread of infection in Australia, measures to prevent malarial infection, treatment of the

disease, including methods and places where it is best carried out, strategical considerations of malaria and army dietary in relation to health. The report emphasised the necessity for taking measures to control malaria in Australia, and with this end in view to treat malaria in the army in New Guinea and Queensland for preference, and not in potentially malarious areas. Priority for malarial supplies was advised and recommendations were made for improvement of army diet. This report amply vindicated the policy adopted for prevention and control of malaria by the Australian Army Medical Services, whose leaders welcomed the support thus given to their advice. Some important matters were also discussed with reference to the strategic aspects of malaria, such as the importance of malaria-free bases, the disposition of forces with relation to malaria, and the importance of keeping Northern Australia free from malaria. In this report the exploitation of night bombing to inflict malarial casualties on the enemy was mentioned. Such strategy may well come into the scope of military planners, but is quite foreign to the aims and practice of a medical service while it claims the protection of the Geneva and related conventions for the sick and for its own personnel. It seems strange that the Government should ask for the inclusion of strategic considerations in a report on medical matters.

The problem of preventing malaria from gaining a foothold on the Australian continent has already been discussed. It is now interesting to see how it was affected by the return of two malarialised divisions to North Queensland. More than ever was it necessary to ensure that no troops affected with malaria arriving at the mainland from an endemic area would be sent to a potentially malarious area in Australia. This policy was laid down in American and Australian orders, and strictly observed. All the troops arriving in Australia were kept on a suppressive dosage of atebrin for one month, which was discontinued under controlled conditions. All men developing malaria were admitted to hospital, and the full course of standard treatment with quinine, atebrin and plasmoquine was followed up with a further six weeks' administration of atebrin. In areas where vector mosquitoes were present, such as the Northern Territory and the coastal belt of Queensland, hospital wards housing patients with malaria were screened with wire. Notifications of malaria were required to state whether the disease was contracted in Australia or outside the mainland. During 1943, 135 soldiers contracted malaria believed to be due to local infections. These all took place in Queensland, and were of sporadic nature except in one outbreak of 18 cases at Sellheim, in a military camp through which men passed from New Guinea. About 60 to 70 per cent of these men in transit had previously had malaria, and many of them were sent to hospital. Here and in less important areas local transmission had occurred, and the vector was suspected to be *Anopheles annulipes*. Protective measures had not been complete, owing to the non-receipt of some essential supplies. Later in the year that irony attributed to fate was evident when another outbreak occurred at Canungra, which was a training area for jungle combat. The same mosquito was again suspect. In

addition there were 219 cases of infection in civilians contracted locally, most in Cairns. In none of these, or in others occurring in the Mossman shire in Queensland, was there any connection with the Services. Some local transmission of B.T. infection had possibly occurred in Brisbane, but the number of primary infections there was very small. In no instance was malignant malaria transmitted in Australia.

Cairns was now in 1943 a cause of even more anxiety than in 1942. It was agreed by the Allied forces that it was and would remain the most northerly of the important harbour bases for New Guinea and the north. Further, all troops arriving from New Guinea en route for the Atherton Tableland passed through there, and looked to Cairns for some at least of the amenities of a large centre. The yearly epidemics of B.T. in Cairns have already been described: it was now essential to control the large swamp areas on its outskirts. In July 1943 a conference was held between the U.S. Armed Services, the Australian Army and the Cairns City Council. All agreed to cooperate in carrying out the necessary control work, and the Queensland Government made a substantial contribution towards it. Mosquito breeding was free and took place even up to 2,000 feet above sea level in the Kuranda-Mareeba area and there was a heavy risk to the district if these mosquitoes became infected. It was most important to keep the military areas in the vicinity of Cairns free from infection, and to prevent transmission of malaria from servicemen to civilians in the Cairns district, which was already subject to seasonal epidemics, and was not a controlled area. The safety of Atherton Tableland above 2,000 feet contrasted sharply with Cairns. The United States forces also wished to develop the port facilities, which involved alterations in the swamp areas. After delays work was begun on the drainage scheme, though it took some time before the coordination of engineering schemes with anti-malarial requirements was effected. Up till June 1943 vigorous control work had been proceeding by army units, but the work could never have been finished without the help of the American engineer services and the Civil Construction Corps. In a general routine order the area north of 19° south latitude was proclaimed as "potentially malarious". This included Cairns, but not Townsville. Of course Cairns was actually malarious.

The effect of this proclamation was to stress the pressing danger not so much to the civil community, though the introduction of malignant malaria to Australia would have been deplorable, but to actual or potential battle stations. It drew attention too to the risk which had been incurred by the introduction of U.S., R.A.A.F. and R.A.N. personnel to these areas where the same vector and conditions lay in wait just as in New Guinea. For example, while serving in Ambon, a R.A.A.F. squadron had suppressed clinical malaria only by taking 10 grains of quinine a day: full precautions were impossible there. Most of the men were infected with malaria on their return, but their quinine was stopped in batches and treatment was carried out in those who then showed evidence of blood infection. Consternation had been caused to the medical advisers of the R.A.A.F. when squadrons were moved from New Guinea to Cairns and Darwin without warning.

No Australian troops were allowed to stay in Cairns and any contracting malaria in the district were promptly removed to the Tableland. The U.S.A. and other hospitals in the Cairns area took great care to prevent contact of vector and patient.

Sir Earle Page's report had stressed the importance of complete control of malaria on the mainland, and recommended the use of the Commonwealth Government authority to secure this. In particular he advised that the Government through the army and federal health authority take steps to implement a complete scheme for the drainage of Cairns, and also that power be sought to investigate and treat all civilians suffering from malaria. The Prime Minister, Mr Curtin, after obtaining the strongly favourable opinion of the army medical services, agreed to take the necessary steps. Accordingly, a National Security Regulation was proclaimed giving the power to the Director-General of Medical Services of the Australian Military Forces to carry out the examination of persons in a defined area in order to determine if they were infected with the malaria parasite and if necessary to prescribe treatment.

THE NORTHERN TERRITORY

In the Northern Territory even greater care was being taken to ensure that no extrinsic malaria was introduced which might blaze into an epidemic. Now that troops were being relieved from New Guinea this was all the more important. The occurrence of a localised outbreak at Katherine and Adelaide River outside the controlled areas showed again how the vastness of the country made general control impossible. The work of malaria control carried on by a keen but insufficient number was concentrated on the important areas. For instance, care was taken to keep a safe zone of a mile in radius round the hospital at Adelaide River. Aborigines were controlled by keeping them in compounds and areas free of mosquito breeding, and those used for labour were transported out and back between daylight and dark. It is not surprising that the army was criticised in some circles for these precautionary measures. Records were kept of all persons in the Territory who had been in a malarious area, and careful watch kept upon troop movements. Difficulties were sometimes encountered with "key personnel" arriving from malarious areas who were required to take suppressive atebrin for six months and have blood films examined regularly. Service units still needed to be carefully watched. For instance, an Australian air force squadron had been treating a number of their men for malaria contracted in New Guinea, but instead of evacuating all of them south had returned some to the unit. On one occasion the transfer of a body of malarialised troops was stopped at the eleventh hour through the vigilance of a member of the hygiene service. During the wet season anopheline breeding was slight because of the flushing effect of the heavy falls of rain experienced then and the rapid rise of the rivers. After the "wet" was over the lush growth of vegetation characteristic of many parts of the Northern Territory introduced fresh factors, and at this time breeding reached its peak. However, the principle was maintained in these

northern areas of Australia that control of the carrier was the unusual but quite practicable method of choice.

Meanwhile the already malarialised troops were stationed in safety at Atherton. Here the problem of malaria occurring in troops engaged in a war of movement did not arise, but that of controlling and treating relapses in returned troops had to be faced. Two general hospitals were stationed on the Atherton Tableland with the two divisions there undergoing rehabilitation and training, as well as other medical holding units and a convalescent depot. Now was the time to learn more about the medical problem of the hour. It was evident that relapses of benign tertian malaria were of great importance. It was desirable to discontinue suppressive drugs as soon as possible, yet important not to have military formations immobilised by men lost temporarily through relapses of malaria on the one hand and on the other hand to safeguard the men from risk of ill health due to post malarial anaemia and debility. It was also necessary to determine as accurately as possible the exact methods of action of the antimalarial agents available.

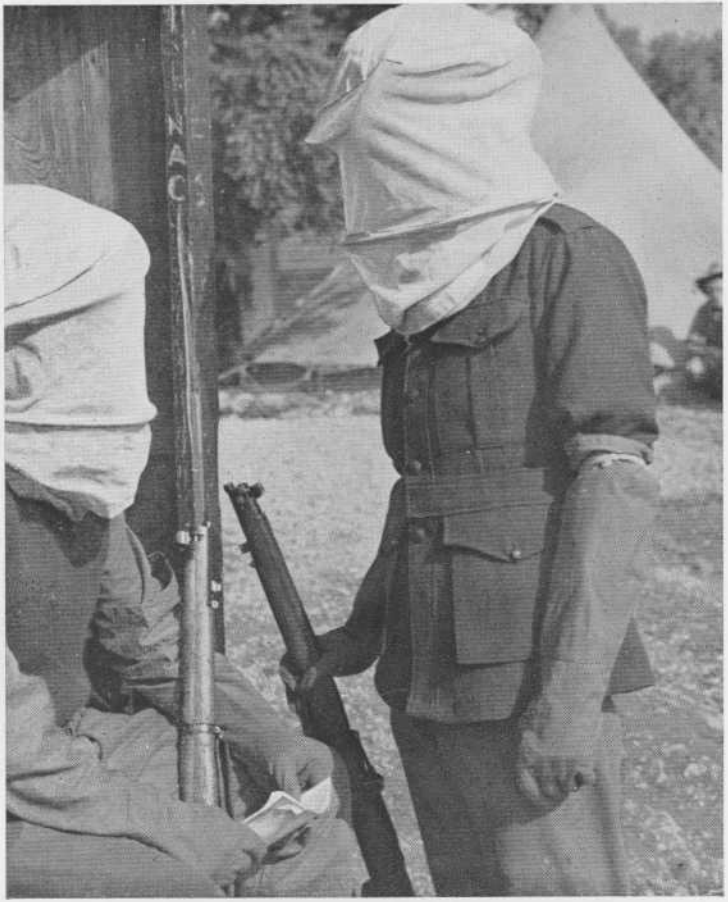
THE MALARIA RESEARCH UNIT AT CAIRNS

By June 1943 some 25,000 Australians had already contracted malaria in the South-West Pacific. It was imperative that further action should be based on accurate knowledge; therefore one of the most important steps of the war was taken in Australia in relation to malaria. The Commander-in-Chief, General Blamey, acting on the advice of the D.G.M.S., Major-General S. R. Burston, established the L.H.Q. Medical Research Unit at Cairns. The need for some such organisation solely devoted to the scientific investigation of malaria had been for some time apparent to the technical advisers of the Director-General. The plan evolved was really a cooperative project, but its original conception was due chiefly to Professor H. K. Ward (Professor of Bacteriology in the University of Sydney), Colonel E. V. Keogh (Director of Pathology and Hygiene) and Lieut-Colonel I. M. Mackerras. Colonel (later Brigadier) N. H. Fairley enthusiastically began the organisation and fulfilment of this project. With his long experience in tropical disease and especially in research he was chiefly responsible for the conspicuous success of this unit, and with his team of malariologists pressed home its teachings in the field. At Cairns the research unit had its own establishment as a military unit, and was attached to an Australian camp hospital. It was commanded by a physician with field experience of malaria, first Lieut-Colonel R. R. Andrew, later Lieut-Colonel C. R. B. Blackburn, and had a skilled staff of entomologists and pathologists. Associated with this unit was a research group attached to an Australian general hospital on the Atherton Tableland, thereby enabling therapeutic and other researches to be carried out independently. Similar investigations were also made at other hospitals at Atherton, and in New Guinea. By utilising also a convalescent depot farther inland, the staff could follow accurately the progress of men under observation. Special facilities were given the unit to ensure adequate supply of technical equip-

Malaria control—bivouac nets.

(Australian War Memorial)

Malaria research—collection of mosquito larvae for identification and research.



Malaria control—nets and gloves for sentries.

ment and stores, and also a special priority in transport. This latter was necessary to ensure the rapid transfer of patients and such biological material as mosquito larvae. The organisation also required the cooperation of the entomological services, and of physicians and pathologists in hospitals in New Guinea. The Commander-in-Chief approved of obtaining volunteers from the army for investigations on the action of drugs on experimentally produced malaria under a variety of environmental conditions.

The general plan followed in the research was to expose volunteers while taking anti-malarial drugs to bites of mosquitoes previously infected with malaria, and to study them throughout the incubation period of malaria. Later these men were sent to the hospital on the Atherton Tableland where further investigations were made to determine the success or otherwise of suppression. At Cairns mosquito-proofed wards were provided, and a special laboratory was prepared equipped for breeding and handling the mosquitoes. A special "humidity room" was made in which stocks of infected mosquitoes were kept. The mosquitoes used were anophelines bred from larvae and pupae collected in Queensland and New Guinea. During the early period of the work weather conditions were unusually dry and it was necessary to collect larvae from a wide area. Later a special collecting unit was stationed in New Guinea, which sent across to the mainland some 20,000 larvae a week by air. The entomological section of the unit under Major M. J. Mackerras was responsible for the collection of larvae and pupae, bred the adult mosquitoes from these and maintained the females, fed them on selected gametocyte carriers of malignant or benign tertian malaria and finally transmitted malaria to the volunteers by subjecting them to a known number of bites from mosquitoes. The sporozoite rate of these vectors was determined by dissection and examination of the salivary glands. Only the established vectors of malaria in Australia and New Guinea were used, *A. punctulatus typicus, A. punctulatus moluccensis* and *A. annulipes*. After some experience the *typicus* variation of *punctulatus* was found to survive best under laboratory conditions; it had a high average infection rate and bit most effectively, and was therefore used for most of the experimental transmission.

In collecting larvae it was necessary, especially in local areas, to reserve some breeding grounds from anti-malaria treatment, and care was necessary to ensure that general control of the area was not jeopardised. On emergence the adult mosquitoes were separated into species and kept in batches as large as convenient, each batch comprising as far as possible adults of the same age within a few days. They were fed on volunteer donors on the second day after emergence as nearly as possible, and separated again into experimental batches. Later feeds were given daily up to four to six days, different donors being used, but all carrying the same species of parasite.

Donors of blood were volunteers whose blood contained not less than one mature gametocyte of normal appearance to each ten fields of a thick film. Donors of B.T. infection were obtained on the Atherton Tableland,

but it was usually necessary to bring donors of M.T. from New Guinea. The volunteer recipients were drawn from convalescent depots in South Queensland at first. Only men who had never lived in malarious areas were suitable: they had to be physically fit and mentally stable, and free from venereal disease. Only men were accepted who had a record free of crime, and who had never had asthma or had not suffered from jaundice within the preceding year. Most of these men were of "B" class category, but for some aspects of the enquiry "A" class men were needed who were capable of undergoing strenuous exertion.

The clinical section undertook the medical care of the donors and recipients, supervised the administration of drugs under test and made accurate clinical study of the men's condition, of which full records were kept. Particular care was taken to observe accurately the diagnostic phenomena such as temperature, herpes, enlargement of the spleen and liver and other conditions such as anaemia and jaundice. If clinical malaria appeared treatment was carried out by various methods; the occurrence of relapses was recorded, and for this purpose each man was followed up carefully. Carriers of gametocytes were artificially produced at times by intermitting or modifying treatment so as to allow gametocyte production to proceed untrammelled after the primary trophozoite wave had subsided. Controls were always included in each group of volunteer recipients who received no anti-malarial drugs. These men were selected by lot. An incubation period of 23 days was chosen as a standard, after which men who had not acquired clinical malaria were sent to the hospital group at Atherton. Here, under Lieut-Colonel I. J. Wood, in charge of the medical division of the 2/2nd General Hospital, a special research ward was maintained, where the medical and nursing staffs were permanent so far as this was possible. Near the hospital full facilities were available for continued observation of men after suppressive treatment had been discontinued. The problems studied in this group were the method of action of anti-malarial drugs in volunteers infected by inoculation of blood containing trophozoites, and the investigation of men in whom malaria had not broken through after infection by sporozoites at Cairns. Observation was carried out over a period of at least five weeks after the cessation of suppressive treatment, during which a vigorous outdoor life was encouraged. Special investigations were also carried out to detect latent malaria and susceptibility and premunity to malarial infection. When a volunteer at the end of this final five weeks' period still failed to show any break through of malaria 200 cubic centimetres of his blood was injected intravenously into another compatible volunteer. Separate observations were made on infections with *Plasmodium falciparum* and *P. vivax* to elucidate the different mechanisms involved in the behaviour of these types in the human body. The possibility of a natural immunity to malarial parasites was investigated by injecting a determined number of parasites, from 100 to 800 million in infected blood, into volunteers who had failed to develop malaria after being subjected to mosquito bites.

The chief aim of the experiments was of course to test the efficacy of various anti-malarial drugs in suppressing or curing malaria in volunteers infected from mosquitoes. Several drugs were tested. Those first chosen were quinine, atebrin and the sulphonamides, especially in view of some evidence from animal experiments in America that sulphamerazine might act as a causal prophylactic. It was evident that if a drug could be discovered which truly would prevent malaria from obtaining a foothold at all, that is, with a lethal or inimical action on the sporozoite stage, the whole principle of malaria prevention would be immensely simplified. At the same time it was expected that sub-inoculation tests would give additional information about the erythrocytic and exo-erythrocytic cycles of the *vivax* and *falciparum* types of parasite.

In order to have accurate information concerning the effectiveness of the drugs used for the experiments blood concentrations were estimated in each case; a special study was also planned to show the building up of atebrin levels in the plasma during regular administration, and the receding of concentration after cessation of the drug. Finally an investigation was planned to show the influence of extraneous factors on the breaking through of malaria in men taking suppressive drugs. These factors were those encountered in jungle fighting, such as fatigue and cold, and in the case of aircrews in the air force, anoxia.

With this comprehensive programme the research organisation began its work; obviously its highly technical nature made quick results unlikely, and in the meantime another campaign was to be fought.

ADVANCES IN PROPHYLAXIS

In order to minimise sick wastage the Adjutant-General sent an instruction to all formations laying down the anti-malarial measures to be adopted by operational forces serving in malarious areas. This placed on the commander of a force the duty of examining all health hazards on entering a new area, and of using specially selected medical officers to make a preliminary survey of the area if circumstances permitted. It was further directed that a malariologist or equivalent officer should be attached for advisory purposes. Precautions were also outlined for the siting of camps, particularly in the region of native settlements, for the control of native labour, and for the limitation of breeding grounds for mosquitoes.

The official recognition of malariologists and the full organisation and utilisation of entomological services were two advances in the scientific equipment of the army that had far-reaching results. As told earlier, an entomological service was by now organised, and malariologists, found so valuable in tropical campaigns by the British Army, were appointed. A pool of malarial advisers was formed and attached to land headquarters for allotment to formations. Their functions included supervision of malaria control and advising on training of troops in the necessary measures.

Methods of training the troops had to be essentially practical. For instance, in one divisional area two creeks were used to create artificial breeding grounds which were demonstrated after the men had seen malarial

parasites under the microscope. In these areas track discipline and the pitching of tents were illustrated, and simple contour drainage was shown in a suitable boggy area. The jungle training area at Canungra was declared a malarious area for the purposes of training, and the most rigorous standards were exacted. Atebrin parades were part of the routine and were carried out under strict supervision. The use of mosquito repellent was ordered at the evening picture shows, and the Shell Company's film on malaria was shown. In order to bring the lessons of malaria control to the individual as a soldier an A.I.F. film on the subject was made. In April 1943 a special film unit was ready, and under the technical supervision of an experienced medical officer the taking of the film began. This was later completed and used for educational purposes. At the jungle training camp instructors in malaria control were also trained.

In the light of past experiences the general organisation of mosquito control was altered and improved. Mobile entomological sections were used to investigate field problems, of regional and general importance, to make field surveys, and to help the malariologists. Malaria control units allotted to formations were controlled by the malariologist or hygiene officer and, in addition to carrying out full local surveys, they planned and implemented control measures and trained anti-mosquito squads. If required, these units also undertook dengue control. Assistance was available in technical problems from the Universities of Sydney and Queensland and the Council for Scientific and Industrial Research. In the R.A.A.F. close contact was maintained with the army anti-malarial campaign and in New Guinea the principal medical officer, Wing Commander Fulton, and Squadron Leader J. Gunther, who had had tropical experience, greatly improved methods and discipline. A special handbook on malaria for medical officers was compiled and issued. For some time the supply organisation of the Air Board could not produce enough protective clothing to meet requirements in New Guinea, but where long trousers and long sleeved shirts were not available overalls were insisted on by official orders. The use of suppressives and repellent lotions was also supervised. An entomologist was appointed to carry out insect surveys and advise. Squadrons operating from Port Moresby kept their maintenance echelons there, so that only the aircrews operating from advanced flights near the front line or those forced down in combat ran serious risks of tropical disease.

In addition to these adjuncts to training special literature was circulated among those carrying responsibility, dealing with the incidence of malaria in the South-West Pacific and its prevention. At land headquarters a special Tropical Diseases Advisory Committee was formed to collect information from all sources concerning methods and supplies in order to integrate the measures adopted and to determine the quantities of materials required and available and the manner of their distribution. Drug supplies were reasonably satisfactory, and improved after the combined efforts of the commissions whose work has been referred to earlier.

Tests had been made of the new "Freon bombs"—insecticide dispensers —pyrethrum being used. These were small drums each containing the equivalent of one pound of pyrethrum flowers as 20 per cent concentrate in sesame oil dissolved in dichlor-difluoromethane, commercially known as "Freon" and used in refrigerators. A fine fog was projected by a gas pressure of 85 pounds per square inch and floating like smoke the contents of one bomb could kill all flies and mosquitoes in 100,000 cubic feet. They were found to be very effective, though rather extravagant and costly, and orders were placed for a supply. Dimethyl phthalate was being introduced as a mosquito repellent and efforts were being made to overcome difficulties and delays in its local manufacture.

Halfway through 1943 it was evident that although anxieties about medical supplies were not over, particularly those needed for the fight against malaria, there was every reason to hope that these medical munitions would be ready in sufficient quantities before the next campaign, which was expected to be undertaken in September.

In the course of studies of the position with regard to manpower a review of statistical methods and records was undertaken. Experience in the field had now shown that existing record systems did not disclose the true incidence of malaria or provide sufficient information. A research officer who was a trained actuary was seconded for the purpose of advising on statistical matters and in June 1943 an improved system was introduced. An administrative instruction detailing the alterations was circulated and the importance of this side of medical work in the field was stressed. An altered field medical card had an added page which provided a standard history sheet for cases of malaria. A new card was designed to give briefly the maximum data about diagnosed cases of malaria with the minimum labour on the part of medical officers. In this way information was gained about the probable source of infection, its type, clinical nature and degree of severity. For statistical purposes New Guinea was divided into various areas. Medical officers were reminded that unless such information was assembled, a number of important questions could not be answered such as the following: the relapse rate anticipated in B.T., the comparative results of various methods of treatment, the influence of re-infection on response to treatment, the comparative rates of infection in different areas, the influence of various military and environmental conditions on relapse rates, and the effect of delay in diagnosis and treatment on the end results of treatment. These problems were not merely of scientific importance; they concerned manpower both in operational areas and on the home front.

THE PROBLEM OF WASTAGE OF MEN

The incidence of tropical diseases had been, as has been shown, so high that the call made by malaria on manpower in reinforcements was the most serious of any. A considerable part of the reinforcement pool was perforce immobilised in hospital. During the early part of 1943 additional hospitals had been established in New Guinea. They provided for the

local treatment of men who could be returned to duty after a relatively brief period, thus saving wasteful evacuation to the mainland. It was best that such patients should be treated in New Guinea if possible, or alternatively in Queensland. The medical services had advised this for some time past, and Sir Earle Page in his report strongly supported it. The War Cabinet considered this question of manpower in 1943 in the light of the findings of a special sub-committee representing army and R.A.A.F. headquarters. With the air force the problem was not so acute: the force could be maintained at its strength in New Guinea, although its actual malarial rate was very high and comprised 89 per cent of the total casualties, but the army's larger demands in operational areas and its proportionately greater malarial risks involved great inroads on manpower. For the quarter ending 23rd January 1943 tropical disease had caused 14,011 casualties as against 4,137 battle casualties.

In order to maintain the size of the existing force for offensive operations, it would be necessary to review the order of battle, as reinforcements might have to be drawn from other sources. The medical services in reporting to the Cabinet hoped that, with the additional measures taken, the improved equipment and supplies and the heightened understanding and better anti-malarial discipline in the forces, operations could be undertaken in hyperendemic areas at a lower cost from illness than hitherto. Since malaria was responsible for about 90 per cent of the sick wastage due to tropical disease, the problem was largely one of control of malaria, and though it was believed on good grounds that the Japanese losses had been much higher than the Australian and their control measures much inferior, this gave no cause for over-optimism. Rumour was current at one time that the Japanese were immune to malaria, but this was completely untrue. Intelligence investigations revealed that such protective measures as they adopted were complicated and inefficient. It was most regrettable, and in fact a serious break of security that information was at this time published and broadcast in Australia concerning the work of Australian malarial control units and the use of modern methods of treatment and prevention of malaria. On the basis of experience in Milne Bay, even with improved facilities and methods, a rising malarial rate might be expected after three months of active fighting. It was hoped nevertheless that these heavy losses would not be repeated, for at Milne Bay the malarial rate of loss was 5 per cent of the force in the first month, and rose by 5 per cent each month up to 25 per cent in the fifth month. A maximum rate of 15 per cent for general sickness seemed more likely. The army sub-committee finally reported to the Cabinet that out of a military commitment of half a million a striking force of not more than 95,000 could be maintained in active operations in hyperendemic malarious areas only if large deficiencies were made good, if reinforcements were maintained and if no abnormal casualty rate was experienced.

The question of supplies was also considered. Enough quinine was held for immediate purposes, though more was needed. Quinine was now being reserved for therapeutic treatment only and enough atebrin was held to

keep the striking force on suppressive treatment for six months. More atebrin was expected to arrive shortly. Plasmoquine was held in quantities sufficient for present needs. The position about mosquito nets was still not satisfactory, as supplies promised had not yet reached Australia in May 1943. The Combined Advisory Committee on Tropical Medicine advised General MacArthur of these deficiencies and also recommended that the fulfilment of these orders should be expedited, and that replacements of nets for Allied forces in the Pacific areas should be increased, owing to the heavy wear and tear. As one of the earlier troubles about supplies had been their distribution to forward areas, a special instruction was issued by the Army Director of Supply and Transport to ensure the prompt despatch of anti-malarial stores. All these were specifically and indelibly branded with a description of their contents, indicating plainly that they were intended for anti-malarial use only. Where practicable important supplies were placed in the charge of a responsible conductor. So the next campaign was faced with the hope that the plasmodium of malaria would be overcome as well as the Japanese.

At the end of the period of preparation the malarial position in New Guinea was fairly satisfactory, but reports from some areas could be read as cautionary tales. The forces operating between Wau and Mubo showed reasonable infection rates. At the end of August their rate for all attacks was 9.5 per 1,000, but there was difficulty in getting figures from forward areas in country with such restricted communications. The rate for the whole of New Guinea was roughly half this local rate. In some other limited areas the position was less satisfactory. For example, a unit in the Buna-Oro Bay area showed heavy wastage due to fresh infections.

The position with clothing was still not quite satisfactory, but was improving. Some anomalies created discontent, as when senior staff officers visiting New Guinea appeared in shorts, or when new consolidated orders on dress permitted the wearing of shorts. As a matter of fact, though the malarial rate of Moresby was much on a par with other controlled areas the chief reason for restrictions there was the force of example.

In passing some reference may be made to anti-malarial discipline in hospitals and other medical units. The potential danger of a large infected pool of malarial patients in hospital was evident, and General MacArthur had ordered some time before this that all hospitals in malarious areas on the mainland should have wards protected with wire screening. In New Guinea this was not possible in the field, and even in base units screening was impossible on the scale necessary, at least in Australian hospitals, for the material simply could not be obtained. However, care and discipline minimised this risk. In over twelve months the 2/9th Australian General Hospital had admitted 24,000 patients, a great proportion of whom had malaria. Only two wards were screened, but nets were used continuously, patients being kept under them from dusk to dawn. Where exposure of a patient was necessary other precautions were taken. Only one case of malaria had occurred in the staff of this hospital, though infections had occurred in other units within half a mile of the site.

IN THE MARKHAM AND RAMU VALLEYS

On 4th September 1943 new operations began with the landing of the 9th Australian Division on the shore of the Huon Gulf with Lae as their objective. The next day American paratroops, Australian paratroop artillery and Australian engineers and pioneers took Nadzab, thus enabling the 7th Australian Division to move by air into the Markham Valley. A little over a week later the Australians had captured Salamaua and Lae, and a few weeks after this had taken Finschhafen, and Dumpu in the Ramu Valley. Further heavy fighting took place on the coast, and by the end of November 1943 the Japanese had been driven from the hilly country where they had taken up positions. By 10th February 1944 Australian troops had linked up with the Americans at Saidor, who had made a by-pass movement and established there earlier. Thence the drive continued up the coast and by the end of April Madang and Alexishafen had fallen.

The medical significance of these successful operations should be noted. To begin with, both the Markham and Ramu Valleys were highly malarious: so too were the coastal strongholds of the Japanese. Here and in the hills the enemy was dug in, and in coastal areas like Lae had suffered heavy malarial casualties. The advancing forces had to occupy areas defiled by the retreating enemy, and infested with heavily infected mosquitoes. The malarial experience of the divisions engaged varied. The 9th Division had had no real experience of malaria in operations, and only a small number of the troops had contracted malaria in Syria where they had acted as a garrison force. Their physical condition was excellent. The 4th Australian Infantry Brigade had been in Milne Bay, and had profited by the sound anti-malarial training of the 5th Division. Another brigade group, the 8th, only arrived in the later stages and had not had previous experience in a malarious area. The 7th Division had had operational experience in malarious country in Syria, and had been over the Owen Stanley Ranges into the Sanananda-Buna-Gona area where it suffered heavily from malaria. Since then the division had been well rehabilitated and reinforced.

It was disappointing to encounter a high malarial rate which at its peak was comparable with that experienced in the earlier campaigns. By December 1943 despite all endeavours, the position was again serious. Ten weeks after action began the malarial rate for all troops stationed in New Guinea, which of course included large numbers of men in base areas, was 17.2 per 1,000 per week, that is, 890 per 1,000 per year. The overall rate for the operational troops on the Huon Peninsula (some 30,000 men) was 55.3 per 1,000 per week (2,875 per 1,000 per year). The rate for the 7th Division in the highly malarious Markham and Ramu Valleys was 93 per 1,000 per week (4,840 per 1,000 per year). This peak coincided with the period of severest fighting in which most battle casualties were received. During this ten weeks 90 per cent of the total sickness casualties were due to malaria in the forward troops of the 7th Division, and 60 per cent in the 9th Division.

This result was a setback; both divisions had experienced a true malarial epidemic of the type familiar in hyperendemic areas where non-immunes had failed to take adequate precautions. However, the position was not so serious as the figures at first suggested. To begin with, the figures for the 7th Division were probably overstated owing to difficulties in diagnosis. Dengue fever was prevalent, and on reviewing medical affairs of the campaign later, medical administrators who saw conditions on the spot concluded that numbers of men with dengue had been classed as having unconfirmed malaria. It was evident, however, that greater efforts to reduce adult mosquitoes and minimise biting during the day would have decreased the wastage of men. The general health and nutrition of the troops were better, rations had greatly improved and, in spite of the high peak levels in the sickness statistics, the incidence of malaria was lower than in the Buna campaign. More adequate provisions for treatment in medical units lessened the bad effect of attacks of primary fever on health, and more control units were available with more and better equipment. Though some of the fighting was intense and hard, the severity and duration of combat were less, and reinforcements were available, at least to most of the formations. Transport conditions were also greatly improved, with a favourable effect on supplies and evacuation of the sick. Air evacuation had now become more firmly established and organised, thus lessening the strain on medical units in the forward areas and facilitating treatment. In the Ramu Valley at one period the strain on medical holding units became severe since the call on their accommodation had surpassed expectation.

This great wastage in the 7th Division called for some strong measures, and fortunately by this time, December 1943, the work of the research unit at Cairns was sufficiently advanced to give the answer. Experiments on suppressive drugs had shown that experimentally produced malaria would not break through to cause a clinical attack while 0.6 to 0.7 gramme atebrin a week was faithfully taken. The official dose was already 0.6 gramme a week, therefore it appeared that most of the men were not actually taking this full amount. To ensure that they received a full suppressive dose the weekly rate was doubled: acting on medical advice and with the concurrence of General MacArthur the 7th Division troops were ordered to take 1.2 grammes of atebrin every week. During the next month the fighting was less severe, and the more heavily infected component units of the division were assembled in rear areas to await return to Australia. Even allowing for these factors the difference in the malarial rate was striking: a weekly rate of 43.7 per 1,000 during December became in January one of 14.3 per 1,000, in other words, the annual rate of 2,270 per 1,000 fell to 740 per 1,000.

The effect of these and similar factors in lowering the fighting capacity of a formation engaged in operational activities is well illustrated in a contrast between 9th Division and 4th Infantry Brigade at the end of 1943. The former had not been in New Guinea before, the latter had been in Milne Bay eight months. Their periods of severe fighting on this front were relatively six weeks and two weeks, but the division had

received 3,400 reinforcements in five months, whereas the brigade had received none. Their malarial wastages were the same, 44 per cent of the division, including reinforcements, and 43 per cent of the brigade. The 9th Division, with its advantages of reinforcements and starting its task fresh from training, was still an efficient fighting force a month after active operations had concluded. The 4th Brigade, coming to its new role after a considerable period of tropical service, had its three battalions reduced from 1,658 to 952 men, and many of these were tired and not fit for further hard fighting without a rest. One comforting fact emerged from an analysis of the malarial casualties that relapses in men who had been infected during the last campaign were not increased in number or frequency by the strain of operations. The rate of relapsing attacks remained steady at about 3.5 per 1,000 per week, which was regarded as a satisfactory figure.

THE LESSONS OF 1943-1944

Turning to the factors more directly concerned with the incidence of malarial infection we find that a number of points become clear. The staging areas for troops committed to an operational task in the tropics are of importance; ideally they should carry a low malarial risk and be well controlled. This does not mean, however, that men cannot contract malaria there; it is a matter of discipline. In some areas dress discipline was still poor, men bathed after dusk and failed to carry out other precautions such as the use of repellent. Slackness during the day had unfortunate results, as dengue was prevalent in these areas. In the areas of occupation there is no doubt that the Japanese had been severely attacked by malaria. As a rule the objectives were taken quickly in these actions; this lessened the risk, for although there was an abundance of infected mosquitoes on the wing at the time of each assault, the time elapsing before reasonable control was begun and made effective was brief. This last condition was not always fulfilled. The malaria control under the command of the 7th Division was not employed in the operational area until nearly two months after the campaign had begun.

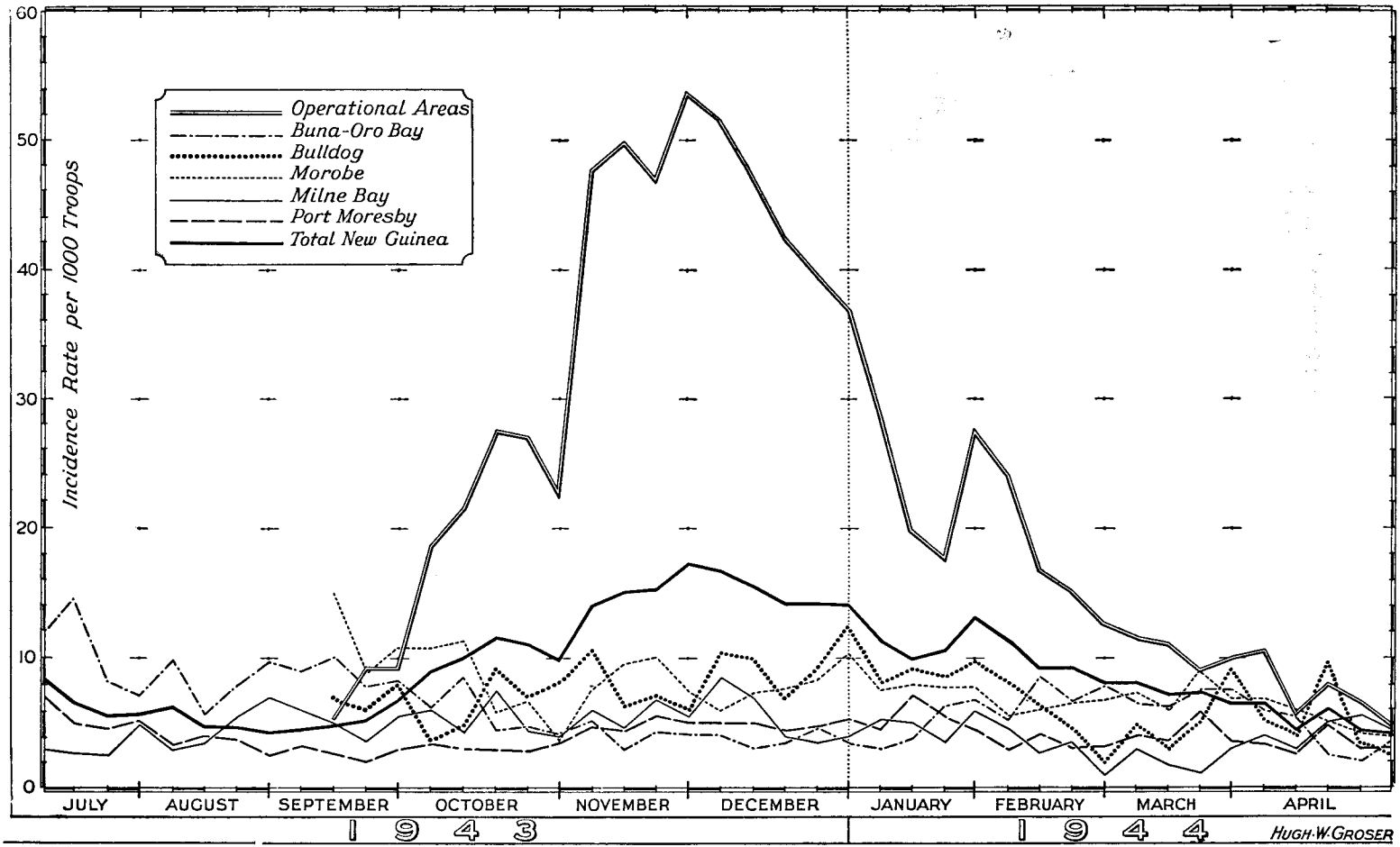
Once areas were occupied the malarial risk was dependent on the life of the mosquito, a factor varying with climatic conditions, the intensity of breeding, and the supply of gametocyte carriers. The last mentioned could come from neighbouring Japanese troops, or native population or from the Australian troops themselves. With regard to the last source of parasites, medical units sometimes created more risk than desirable because they did not always have enough nets for the number of patients they held, and the units sending the patients often did not send nets with them. Natives usually retired to the hills, but carriers were, under operational conditions, quartered near the troops and the suggestion was made that they should be treated with plasmoquine.

Anti-malarial supplies during operations were usually adequate, but atebrin did not always arrive regularly, a few packages being lost or mislaid during the early stages of the campaign. Freon pyrethrum "bombs" were used, but up to that time their even distribution and training in their

use were not satisfactory. Sprays were not always on hand when wanted, and difficulty was experienced at times in bringing them forward from rear areas where they had been left. The work of the malaria control units was good. Lae and Finschhafen could not have so quickly been used as bases had they not been made safe by skilful and well organised control work.

In several such instances the value of possessing bases and forward bases with low malarial risks was evident. This was all the more important with units whose malarial discipline was not of very high grade. One battalion in the coastal area had 175 fresh infections of malaria out of 600 men within ten days in a malarious area, another battalion similarly lost 100 out of 850 in a week. The standard of malarial discipline varied greatly among units; it became apparent that it was necessary that a responsible officer should each night notify to the formation headquarters that all malarial precautions had been taken. There was no doubt in the minds of medical administrators on the spot that the use of repellent lotion was often neglected, and that failures to take atebrin one or two nights a week were common. Mosquito nets were often found discarded along the way. There were several faults. The nets were often of unsuitable type and quality, insufficient supervision was imposed, and deficiencies were not promptly made good. Worst of all, men were allowed to occupy captured areas for as long as a week or ten days without nets to exclude the throng of infected mosquitoes. Enquiry showed that in the Lae operations 90 per cent of a number of men questioned had not used nets for some period, which in the aggregate was usually part of a week. Only two-thirds of these men used repellent all the time, though on the whole the new repellent was well used and appreciated by the troops. Unfortunately in many dangerous areas in New Guinea there were few pest mosquitoes whose noise and painful bites gave warning of their presence, whereas the silent anopheline often did its damage unnoticed.

These breaks in discipline and lack of appreciation of the importance of ordered routines were not necessary and that they could be overcome was proved by the 15th Australian Infantry Brigade. During the first week in January, following the heavy malarial losses of the 7th Division in the Ramu Valley, this brigade was brought in to drive up to Madang on the coast. It had already been engaged during the five preceding months in the Wau-Salamaua area. Recognising the risks involved, Brigadier Hammer, the commander, and members of his staff had evolved an organisation for the enforcement of anti-malarial precautions. The essence of this was that the responsibility for carrying out these procedures was cast directly upon the unit commanders and sub-unit commanders, who daily informed headquarters that all personal methods of protection had been carried out, including the taking of atebrin. During the first quarter of 1944 this brigade was engaged over a wide area in the operations which resulted in the capture of Madang and Alexishafen. Its average malarial rate was 7.6 per 1,000 per week (395 per 1,000 per year). This rate was no higher than that attained at Lae after control had been instituted.



Incidence of malaria in New Guinea and in dissected areas in 1943-1944.

and was easily the best figure achieved by any formation engaged in this campaign. It was most heartening to the medical services to see this practical demonstration of control, and to read the commander's description of the precautions laid down by the medical authorities as "sound and practicable" measures which "can be readily accepted and put into operation by all commanders". The routines established in this brigade had a potent influence in determining a general disciplinary standard for the future.

By April 1944 this twofold campaign was over, and there remained the tasks of clearing up the areas and later pressing farther along the coast. But for the present the objectives had been gained and the time was come for appraisal and criticism. As pointed out above, the impact of malaria on these forces was much less severe than at Milne Bay and Buna-Gona, and, though in need of rest and rehabilitation, the troops were not hit hard physically. The difference between the incidence of malaria in quiet areas and in those where fighting was going on was again apparent. This was exemplified in other areas also. For instance army and R.A.A.F. forces in Merauke and Tanah Merah were in highly malarious areas, and the rising rates gave concern in early 1944, approaching 1,000 per 1,000 per year. Here there were local difficulties such as a heavily infected native population, but these were overcome to some extent by improved control. Had action taken place there at this time, there is no doubt that losses would have been serious.

THE ATHERTON CONFERENCE ON MALARIA

On June 12th and 13th an important conference was held at Atherton to discuss the position. Malaria had proved as dangerous an enemy as ever, but there were two important weapons to hand, one that of military discipline, the other that of science, for by this time important conclusions had been reached in the research unit at Cairns. The Atherton conference on "Prevention of Disease in Warfare" was held under the chairmanship of Lieut-General V. A. H. Sturdee, then G.O.C. First Australian Army. The Adjutant-General, Major-General C. E. M. Lloyd, in opening proceedings pointed out that during the period September 1943 to the end of February 1944 there were 3,140 battle casualties in an average strength of 98,050 men, and 47,534 were evacuated sick. Brigadier Fairley described the results obtained from research on anti-malarial drugs. The work of the research unit will be dealt with later in greater detail; the most important finding was that concerning atebrin. It had been found that volunteers proved to be inoculated with malaria infection would remain well without the onset of malarial fever while they took 0.1 gramme of atebrin with complete regularity. Once an adequate concentration in the blood was built up, and while it was maintained, these volunteers could engage in laborious occupations and be submitted to fatigue or to exposure to extremes of temperature without any break-through of malaria. Further such a regimen would not only suppress benign tertian while atebrin was taken, but it would cure malignant tertian. If the experimental results held

good in the field it was thus possible to keep a fighting force free from overt malaria by maintaining a blood concentration of atebrin such as could be obtained by the regular taking of 0.7 gramme a week. Four weeks after such a force was returned from a malarious to a safe area the risk of malignant malaria was small, and the use of atebrin could then be discontinued. Relapses of benign tertian were sure to occur, and their percentage would be some indication of the lapses in personal measures of protection. The incidence of benign tertian would of course depend partly upon the efficiency of external control methods. One most important conclusion came from the unexpected finding that malignant malaria was cured by the taking of an invariable suppressive dose; it was that the faithful following of this routine would abolish blackwater fever and reduce the death rate from malaria to zero. Major J. C. English, the malariologist of the I Australian Corps, described fully the practicable methods of prevention of malaria in the field, and Major C. E. Cook described the measures by which intestinal diseases such as dysentery and cholera could be prevented. Major-General S. R. Burston, D.G.M.S., summed up the discussion by pointing out to the divisional and brigade commanders that the measures which would prevent malarial wastage were their responsibility, and ended with the historic words, "Gentlemen, the ball is now in your court".

This conference was a milestone along the way of malaria control, and from it sprang an extensive and intensive campaign of education by all available methods. Operations were planned for the latter part of 1944 and 1945, and in preparation for these it was essential that all ranks be acquainted with the necessary measures. Responsibility also rested with all ranks, but close and constant supervision was necessary as the lessons of past campaigns had shown. From early in 1944 the principle had been adopted to which reference has been made before, that the responsibility for carrying out the measures of malaria control rested with commanders and sub-commanders of units. There is a vast difference between the tacit and the actual implicit acceptance of responsibility in the army and other armed forces. This was now not a matter of personal keenness, it was an obligation of duty, and as such, neglect carried appropriately severe penalties.

FURTHER ADVANCES IN MALARIA CONTROL

The Atherton discussion emphasised the vital importance of the maintenance of suppression, steady and unvarying from day to day, and of the close attention to every detail of control. Months before General Burston had said that "it must be ensured that every soldier carries a month's supply of atebrin tablets as a reserve, and loss of these tablets should be regarded as seriously as the loss of a rifle". He further advised that stockinet nets should be withdrawn from units actively engaged in operations and replaced by the lighter and less absorbent bobbinet nets. These should be discarded by the soldiers only on the order of the unit commander, who should take the responsibility for the decision. Such dis-

carded nets should be protected from the weather if possible and kept in an accessible place.

During 1944 another advance was made in mosquito control by the introduction of D.D.T. (Dichloro-diphenyl-trichloroethane). This substance had been under investigation since 1943. This new insecticide was effective both as a killer of adult mosquitoes and their larvae, and its remarkable potency even in incredibly high dilutions made its use possible by aerial spraying. In May limited quantities were available for field trial with a view to using it for the spraying of areas immediately after a landing. There was an immense demand for D.D.T. in America and England, and production in Australia was then only in the pilot plant stage. There was good reason to hope that when further active operations began over a wide area in November this important aid to mosquito control would be ready for full use. By July spraying of D.D.T. from aircraft was accepted overseas as well past the experimental stage, and its efficacy in destroying many varieties of insects, including the louse vector of epidemic typhus made it one of the great discoveries of the war period. An early trial of D.D.T. in Alexishafen soon after its capture showed how rapidly control could be effected and how the work of control units was likely to be revolutionised.

Meanwhile Australian troops were holding the ground gained in north-eastern New Guinea and steadily pressing on up the coast, where Hansa Bay was occupied in June 1944. In the first quarter of 1944 there had been 11,074 cases of malaria out of an average strength of 91,000 men; in the second quarter out of 70,000 men there were 3,261. The rate per 1,000 per week had thus fallen from 9.3 to 3.6. During the next quarter it fell to 1.5 per 1,000 per week. Of course conditions in operational areas had become much quieter, but the improvement was encouraging.

Malaria control units were re-organised into three different types, according to requirements, and a special tropical scale was provided for jungle operations. Intensive training of officers and men for this work proceeded, and using the standard methods now proved effective the infested areas of New Guinea were cleared up and kept under control. Bad areas like Lae, full of mosquitoes at the time of its capture, were made as safe as Moresby. Entomological surveys and experimental work supplemented these methods and, although 1944 provided less action than the preceding period, there were a number of proving grounds, such as the operations from the Ramu to Bogadjim, and from Finschhafen to Hansa Bay and the mouth of the Sepik River. In the forward bases of New Guinea then there was evidence of a general lowering of the malarial rate, and it was demonstrated too, that malaria-free bases could be established from which fresh advances could be made.

In November 1944 the combined rate for troops in both base and forward troops in New Guinea was 26 per 1,000 *per annum,* whereas a year earlier it had been 740 per 1,000.

Meanwhile the 7th and 9th Divisions, so severely attacked by malaria in the recent campaigns, had returned to Australia between February and

April 1944. What was to happen there while they rested and underwent further training? To what extent would recurrent malaria attack these forces and how would their experiences affect their fighting efficiency? By this time knowledge gained in the field and in the medical research unit could forecast that a great wave of benign tertian malaria would sweep over the resting divisions, and that malignant malaria would occur in small and rapidly disappearing numbers owing to the curative action of suppressive atebrin. With the arrival of the 7th and 9th Divisions in Queensland the total rates of relapsing malaria did in fact rise promptly after the troops had ceased to take atebrin. The wave of B.T. reached a peak between June and August 1944 and then rapidly fell so that by November the malarial rates of these troops and those then operating in New Guinea were comparable and satisfactorily low. The physical condition of the troops soon reached a high pitch and prompt and adequate treatment dealt with the relapses. Although the malarial figures for the campaign had been disappointing, the impact of the disease on the force was much less severe than before, and after due rest the divisions committed to operational roles in 1944-1945 were fit and ready.

During the third quarter of 1944 more rigorous measures of hygienic training were adopted, by the use of visual and practical educational methods, and insistence on strict invariable routines. The principles enunciated above, whereby commanders assumed the full responsibility for the carrying out of preventive measures, were put into effect. "It was not only a question of organisation" as one malariologist said, "our results were better because we all knew more".

RESULTS OF MEDICAL RESEARCH

A digression must now be made to describe what scientific advances had been made. The initial programme laid down for the Cairns medical research unit has been outlined earlier, and the methods employed. The first task undertaken was a comparison of the value of various drugs in the suppression of malaria.

Reliable methods were established of producing experimental malaria either by the bites of infected mosquitoes or by the inoculation of infected blood, that is producing either sporozoite-induced or trophozoite-induced disease. Methods of estimating the concentration of anti-malarial drugs were elaborated. Fantl's modification of Werner's method was used for the sulphonamides, and in later estimates Marshall's method. A laboratory of the U.S.A. medical corps helped in the early stages in carrying out the plasma-atebrin estimations, until a Coleman photo-fluorimeter was obtained which was used for quinine and atebrin.

The first drugs to be tested were the sulphonamides. Reports had been received earlier of the effectiveness of sulphamerazine in particular as a prophylactic in bird malaria and one field test in West Africa also seemed promising. For some years it had been known that some of the earliest produced members of the group acted on the parasites circulating in the blood, and while it did not seem likely that the long wished for causal

prophylactic would be of one of this series the possibility had to be explored. Sulphadiazine, sulphamerazine and sulphamezathine were tested in daily doses of 1.0 gramme. Sulphamerazine showed the highest and best concentrations in the plasma, and maintained a higher and more constant blood level, and was relatively free from toxic manifestations. For these reasons it was selected for manufacture in Australia. In the malarial experiments with each drug the same broad lines were followed. Volunteers were exposed to infective bites carrying *Plasmodium falciparum* and *P. vivax* in separate series. The number of bites varied in different experiments, in most instances being higher with *vivax* species than *falciparum.* Some of the volunteers acted as controls and received no drug: they invariably developed overt malaria within the usual incubation period. Sub-inoculation experiments were carried out to find out if the men in whom malaria had been successfully suppressed and who had not demonstrable parasites in their blood at the time could transmit malaria. This reinforced the clinical evidence of successful suppression. Other sub-inoculations on these same volunteers after the experiment was over were made with blood containing the same species of parasite to prove that the men were susceptible to malaria. Thus a successful experiment established that a drug had the power to suppress malaria of a known type in men proved to be susceptible to infection by that type. As time went on the value of sub-inoculation to demonstrate blood infections after given periods was worked out more in detail. Observations on the sulphonamides proved that in M.T. these drugs can kill schizonts in the blood, provided they are given over a sufficiently long period. In practically all instances the disease was successfully suppressed. In B.T. the results were much less favourable. In both sporozoite and trophozoite transmitted malaria these drugs exerted a very slight suppressive action. Therefore it was clear that their value was limited.

When atebrin was similarly tested the results were surprising. In fact the hopes for sulphamerazine at the time led the experimenters to try the effect of atebrin alone and of atebrin in combination with sulpha drugs. Two groups of volunteers were tested, one receiving 0.6 or 0.7 gramme atebrin weekly, and the other 0.6 gramme atebrin and 1.0 gramme sulphamerazine daily.[8] The administration of atebrin was begun from 22 to 46 days before the beginning of the experiment in order to ensure maximum concentration of the drug in the plasma; with sulphamerazine a period of two days was sufficient. The drugs were continued for 23 days after the period of exposure. Fifty volunteers were used in the experiments on M.T., half receiving infective bites and half sub-inoculations—no infections occurred. Sub-inoculations showed that the blood some 7 to 9 days after exposure was infective in spite of the fact that parasites were not demonstrable. Later sub-inoculations proved that the infections had been cured with the continued suppressive dose of atebrin. The tests of B.T. showed that atebrin prevented the disease from breaking through, that is, from

[8] Further details and figures are available in Fairley's article published in May 1945 in *Transactions of the Royal Society of Tropical Medicine and Hygiene.*

becoming overt, but in every case after discontinuing the drug the volunteers developed clinical malaria with demonstrable parasites in the blood. During the administration of the drug no parasites could be found in the blood, but in a few men in each group tested mild symptoms of disturbance occurred, including transient slight fever, headache and abdominal discomfort, sometimes associated with tenderness and enlargements of the spleen or liver. Other groups were tested to find the action of atebrin alone or with sulphamerazine on B.T. produced by blood inoculation, that is, trophozoite-produced B.T. The disease was completely suppressed in every instance and, what is even more interesting, cure was effected, as it could not be transmitted by further blood inoculation, no parasites appeared in the blood and no relapses followed. In these series of observations the action of atebrin was so positive that no advantage could be detected by adding sulphamerazine. Concentrations of the drugs were found to be maintained well: the group receiving atebrin only showed an average mean of 21.3 microgrammes per litre, while the group receiving atebrin and sulphamerazine showed an average mean of 23.1 microgramme per litre.

These results indicated that atebrin was a reliable and effective suppressive when taken in doses of 0.6 gramme a week. This dose would suppress B.T., and would suppress and cure M.T. Sporozoite-transmitted B.T. was not cured by a suppressive dose, but the trophozoite-produced form was cured.

Further experiments were now indicated. It was evidently highly desirable to try to reproduce the conditions under which men acquired malaria in the field, and also to ascertain what would be the effect of smaller doses of atebrin, such as were already being given for suppression in areas where malaria was endemic only to a moderate extent. In the previous experiments, as above described, a number of infective bites, ranging from ten to over twenty, had been received by the volunteers over a period of one week or less. It was now planned to carry out a "field type" of experiment, in which the men were subjected to the biting of infected mosquitoes repeatedly over a period of months. As prolonged exposure to infection was found to produce mixed infections with M.T. and B.T. under jungle conditions in New Guinea, both *falciparum* and *vivax* types of parasite were allowed to infect these men. The universal experience had been that if men broke down and showed signs of clinical malaria while exposed to prolonged risk and while taking atebrin only *P. falciparum* was found in the blood. On the other hand, when troops who had been exposed to such risks of infection resumed static conditions or were returned to Australia, the cessation of suppressive atebrin was frequently followed by relapses, which were predominantly due to *P. vivax.*

Over fifty volunteers were subjected to this experiment. The men were divided into three groups who received 0.1 gramme atebrin daily, 0.1 gramme atebrin and 0.1 gramme of sulphamerazine daily, and 0.2 gramme atebrin daily respectively. Drug administration was begun at appropriate intervals before exposure as before, and continued throughout the period

of exposure and for 28 to 34 days after. These volunteers were exposed to heavy infection, in fact to much heavier infection than could occur under service conditions. Some volunteers received 200 infective bites at Cairns in two months; to parallel this in the field it would be necessary to be bitten by impossibly huge numbers of mosquitoes, since the sporozoite rate of average vectors is reckoned as high if it reaches 3 per cent, and is probably nearer 1 per cent in the average of mosquitoes in the jungle where the troops fought. Anophelines of species *punctulatus typicus* were used, and were infected from carriers showing a high gametocyte count in the blood. Daily dissections were made to ensure that the salivary glands were heavily infected; as a rule more heavily than would be expected under ordinary conditions. The number of infective bites varied from two to thirty-five each session, and during the period of exposure which was from 49 to 92 days, there were 10 to 20 sessions. As a rule the exposure to *falciparum* was twice that to *vivax*. A control volunteer was used for each new batch of mosquitoes. During the period of experiment, some three to four months, each volunteer's blood was thoroughly searched for parasites; only in 4 out of 55 men were they found. In 2 of these the plasma atebrin level was only 10 to 12 microgrammes per litre at the time, and in the other 2 it was inordinately high on the following day, 50 microgrammes in one instance, 74 microgrammes in the other. In the latter 2 there is no doubt that evasion of atebrin was followed by the taking of a massive dose. Only one other instance of atebrin evasion was found. In not one man of these 55 did malaria break through, a break-through being defined as having occurred if there was fever of over 100°F. with parasites present in the blood, causing illness sufficient to make the patient go to bed. The health of these volunteers was excellent, and was interrupted by only a few minor disorders.

It is interesting that 15 of the men had minor indisposition of transient nature, with a temperature over 100°F. Such findings are not uncommon in the tropics, apart from overt malaria, and it must be remembered that Cairns has a tropical climate, and that much of this work was carried out during hot weather. It may be remarked, however, though the numbers are probably too small to be statistically significant, that more of these transient disturbances occurred in men taking 0.1 gramme of atebrin daily than those taking 0.2 gramme; a palpable spleen and liver were also more frequently observed amongst them. Slight fall in the red blood cell count was noticed during the period of the experiment and slight lowering of the haemoglobin value, the average decrease of the latter being 1.1 gramme per 100 cubic centimetres. The average arithmetic mean level of atebrin in the plasma of men taking 0.1 gramme daily was 22.9 microgrammes per millilitre, and this was assumed to be adequate to prevent the occurrence of malarial fever. Individual plasma levels were subject to considerable variation. A dosage of 0.2 gramme daily was found to be superior to 0.1 gramme, the average mean plasma level being 44.2 microgrammes per litre. The average minimum plasma content for 0.1 gramme dosage was 12.8 microgrammes, whereas that for 0.2 gramme dosage

was 27.3. After atebrin had been suspended an average period of about 30 days elapsed before a relapse occurred. There was considerable variation here, ranging from 14 to 58 days. At this point the atebrin content in the plasma was 3.4 microgrammes per litre.

The results of these experiments confirmed the value of atebrin as a suppressive, and showed that the drug could prevent the occurrence of overt attacks even when infective bites were received over a considerable period of time. The experiment also reproduced the manner and type of infection found to occur in a hyperendemic area. When an uninfected volunteer was bitten on the same day by equal numbers of anophelines harbouring *falciparum* and *vivax* the resulting fever was found to be malignant tertian, just as in the field. Thick smears revealed *P. falciparum,* but *P. vivax* remained latent, being a less rapidly increasing type of parasite. Later, however, after treatment had completely cured the malignant tertian disease, benign tertian still remained latent, breaking out later in the form of relapses. In the infected volunteers who were taking suppressive atebrin the drug completely cured the malignant tertian, and it was demonstrated that if double infection occurred, atebrin administration continued for a month after the last exposure would remove all trace of malignant tertian infection, leaving only relapses of benign tertian to be dealt with in a proportion of the volunteers. Even if this proportion was high, as was the case in New Guinea, the position gained by the use of atebrin as a suppressive was very favourable. The death rate from malignant malaria should be negligible, severe forms such as cerebral attacks should not occur, and blackwater fever should be abolished. These results were somewhat surprising, and surpassed what had been expected. In view of the importance of maintaining an efficient level of atebrin in the body, a study was made of the plasma atebrin levels in thirty-five volunteers taking 0.1 gramme daily over a long period. Considerable individual variation was found, but a curve constructed from mean geometric levels showed that the equilibrium was reached at the end of the fourth week and was well maintained over a period of seventeen weeks. In other work done on this subject a progressive fall was noted after a long period of administration, but these figures were for blood levels. The Cairns figures for plasma levels showed a drop but not of significant degree. Actually the curve rose to an average of about 26 microgrammes during the fifth to sixth week, and then receded to the level of equilibrium, which was 20 to 21 microgrammes. After administration ceased the atebrin concentration fell rapidly, but did not reach zero till about the end of the sixth week. This "die-away" is approximately of the order of a daily decrease of 10 per cent.

A further investigation was undertaken to ascertain the factors which might possibly be responsible for a break-through of malarial suppression. Two series of volunteers were studied. Men in the first series after infection were given daily exercise requiring considerable output of energy, such as walking, swimming and playing games, one group being subjected to unusually heavy exertion such as chopping wood and walking over the hills during the hottest time of the day. In the second series men were

infected more heavily than others and subjected to very heavy exertion throughout the day in humid heat. Some men in this series were also used to investigate the effects of injections of adrenalin and insulin, chill and anoxia. Adrenalin has sometimes been used in other parts of the world to make manifest parasites in the blood, by contraction of the spleen, and its use was also suggested by the possibility of suprarenal stimulation occurring through psychic stress in jungle combat. Doses of 0.5 cubic centimetre of 1 in 1,000 solution of adrenalin given hourly for four doses or two hourly for six doses failed to produce any malarial parasites in the blood. Similarly the possible occurrence of a fall in the level of the blood sugar under combat conditions was imitated by injecting up to 25 units of insulin once or twice a day. Even lowering the level to 70 or even to 40 milligrammes per 100 cubic centimetre failed to produce overt malaria or demonstrable parasites in the blood. Chill was produced by placing volunteers in a refrigeration chamber at — 9°C. for one hour. Though the men wore only boots and trousers and remained at rest during the test period no break-through occurred. The exertion undergone by some of the men in the fatigue tests was extreme; they worked to the point of physical exhaustion without inducing a breakdown of malaria. Some groups even marched over 80 miles in three days over mountainous country, ranging up to 2,500 feet above sea level, where the nights were cold despite the great heat of the day. The men slept out at night without blankets, but in spite of all this malaria was not produced.

Though anoxia is recognised as a cause of relapse in persons with latent malaria, it was not found possible to produce a break-through experimentally. A special group of 18 volunteers was flown to Melbourne and tested in the experimental decompression chamber at the University of Melbourne by No. 1 Flying Personnel Research Unit under the supervision of Group Captain Baldwin, the air force Consultant in Tropical Medicine and Hygiene. After resting five days and moving about normally under quite cold weather conditions they were tested in two sections and spent one and a half to two hours a day for five days at 15,000 feet without supplementary oxygen at 65°F. After a week's rest they were given runs at altitudes of 15,000 to 18,000 feet at 28°F., being allowed to wear overcoats. Volunteers in one group were subjected to a "bends" run at 35,000 feet at 65°F., using supplementary oxygen. In none of these tests did clinical malaria appear, nor were parasites found in the blood after careful search. As the men were taking different doses of suppressive drugs, 0.1 gramme atebrin with and without 1.0 gramme sulphamerazine, and 0.2 gramme atebrin observations were made on their response to anoxia. No difference could be detected which could be attributed to the drugs. After the tests all the men were well and their blood was free from demonstrable parasites.

The suppressive value of lower doses of atebrin (0.3 and 0.4 gramme weekly) was next investigated. Three groups of volunteers who were taking different amounts of atebrin were subjected to infective bites of mosquitoes harbouring *P. falciparum* or *P. vivax*. The usual check observations were

made. Two groups of men were subjected to heavy exertion. Blood estimations showed that a weekly dose of 0.3 gramme atebrin produced an arithmetic mean blood level of 8.8 microgrammes per litre; 0.4 gramme weekly gave a level of 10.3 and 0.7 gramme weekly a level of 24.0 microgrammes. Trophozoites appeared in the blood of 6 out of 7 men taking 0.3 gramme weekly, and in 3 out of 7 taking 0.4 gramme a week. No parasites appeared in the men taking 0.7 gramme a week. Thus atebrin in dosage of 0.3 gramme weekly failed to suppress malaria, and a dosage of 0.4 gramme only partly succeeded.

A further interesting study was carried out on gametocyte production, which incomplete suppression might be expected to favour. In both of the partially suppressed groups of volunteers gametocytes were found in the blood. Vector mosquitoes fed on one of these men were found later to be heavily infected with sporozoites of *falciparum* and were used to infect volunteers in other experiments. It is also interesting that benign tertian parasites were never found even after extensive search of the blood of those who were infected by this type.

After this work on atebrin similar investigations were made into the suppressive power of quinine. Two groups of volunteers were used, one taking 5 grains of quinine sulphate daily in a mixture, the other 10 grains daily. Each group was exposed to mosquito-borne infection by *P. falciparum, P. vivax* and both parasites. An intense degree of infection was induced in these tests as in other experiments, that is, the number of infective bites was higher than might be expected even in hyperendemic areas. In all these tests quinine failed to suppress the strains of parasites used. It was thought possible that either the virulence of the strains used or the intensity of biting might have been too high for quinine to be effective. But there was no doubt whatever that quinine was an ineffective suppressive compared with atebrin. Even 10 grains a day which had been used in heavily malarious areas was insufficient to give protection, though it appeared to delay somewhat the break-through in the experiments.

This work now placed in the hands of the services a method of suppressing both M.T. and B.T., and of curing M.T. by a full suppressive dose, thus eliminating carriers of M.T. and preventing its serious lethal complications. It was now possible to see clearly why quinine had failed to control the heavy infections of Milne Bay and Buna-Gona, and why it was that when malaria broke through suppressive atebrin it was always M.T., and why B.T. came to light later with relapses. The fighting up to the end of 1943 and early 1944 had produced heavy malaria that was plainly due to breakdowns in method and discipline, and the much lessened rate during the latter part of 1944 showed how the same measures could be successful if properly and faithfully applied. The much lower overall malarial rate of 26 per 1,000 per year in November 1944 proved that success was in the grasp of the forces.

Field experiments in the U.S. Army carried out by Colonel M. C. Pincoffs, Chief Medical Consultant U.S. Army S.W.P.A., confirmed the laboratory findings. No volunteers exposed for 40 days in malarious areas

in New Guinea developed malaria while taking 0.6 gramme atebrin weekly, while 64 per cent of a control group acquired clinical infections. After atebrin had been suspended in the first group some 30 per cent of them developed malaria in two to ten weeks after stopping the drug. The effect of atebrin in preventing relapses of B.T. while it was taken was well shown in the 7th Australian Division. Before this division was returned to New Guinea and while the men were in a non-malarious area on the mainland and not taking any suppressive drug the relapse rate was 20.5 per 1,000 per week, 288 men being sent to hospital each week. Maintenance atebrin 0.6 gramme a week was then begun and the division was sent to New Guinea. In three weeks the rate had dropped to 4.5 per 1,000 per week and remained at this level while the troops were stationed in the controlled area of Moresby.

ATEBRIN DOSAGE AND POSSIBLE TOXICITY

Earlier in 1944 attention had been directed to the advisability of using atebrin more intensively, that is, both for suppressive and curative purposes to build up the concentration in the body more quickly than the hitherto used more gradual method. In the Australian forces the question of administering suppressive atebrin in weekly or bi-weekly doses had been considered, but daily dosage was thought to be better as a regular drill, particularly under conditions of jungle fighting. Intensive atebrin treatment had been used, starting with 1.2 grammes in the first 24 hours, 0.8 gramme in the next 24 hours, then giving 0.4 gramme daily for four days, a total of 3.6 grammes in six days. Observations on this and other curative routines will be described later. Where suppressive atebrin was begun in troops previously resting and not exposed to malarial hazard, the procedure favoured was to give 0.4 gramme daily for three days if a speedier "build-up" was desired, or 0.2 gramme daily for seven days, or 0.1 gramme daily for three to six weeks. For motives of security it was desirable to have an alternative. The question of motion sickness arose too, for in combined operations it was important to know if air or sea sickness would be more readily induced in troops who had been taking enough atebrin to give the desired plasma level. The R.A.A.F. carried out swing tests which disposed of this doubt, as atebrin caused no increased tendency to sickness. Tests were also made of dark adaptation in men taking atebrin, and no deterioration could be detected.

A further question was raised in England as to the possibility of greater susceptibility to atebrin after previous period of administration. As toxic manifestations from atebrin taken in standard doses were rare in Australian troops any enhancement of such effects would readily be observed, but no ill effects were noticed when troops returned to New Guinea and resumed regular dosage of atebrin.

During the Huon Peninsula campaign the suppressive dose of atebrin was doubled for some formations, as above related. It was important to know if 1.2 grammes of the drug per week would cause toxic symptoms, and reports from New Guinea Force in June 1944 indicated that such

symptoms were negligible. Evidence from seven battalions and three field ambulances indicated that only a few soldiers complained of discomfort, which at the most consisted of headache, some abdominal uneasiness and occasional nausea. These symptoms were transient, passing off two or three weeks after the increased dosage was begun. Two instances were reported of possible atebrin psychosis in men who had on their own initiative taken excessive quantities of the drug. During 1943 and 1944 a lichenoid eruption of the skin and mucous membranes was reported in numbers which, though not substantial, were increasing. There were reasons for suspecting some connection with atebrin, but pending fuller enquiry care was taken not to allow rumours to arise which might have imperilled the scheme of malaria control. The subject is fully discussed in the section on dermatology and later in this section.

Another and more serious matter was the rumour, entirely false, that atebrin caused impotence. This canard was no novelty. The same had been said at one time of quinine, and in India and Africa atebrin had previously been similarly blamed. The extraordinary pervasiveness and persuasiveness of rumours in communities, particularly when under stress, is well known, and though the suggestion was made that anti-atebrin stories arose from "fifth column" activities there seems little need to invoke a cause apart from that which lies deep in the personality of human beings. Counter-propaganda was issued, pointing out that the hard conditions of warfare in the tropics lessened the responses of men to the usual stimulating effects of normal life. Further, failure to take atebrin produced the dangerous alternative of chronic malaria, with all its debilitating influences on health and vigour.

The whole question of the possible toxicity of atebrin had been most carefully considered by the medical services from the beginning, not merely because of the known peculiarities of this drug in its selective absorption by different tissues of the body, but because of the general principle that toxicity can only be established by prolonged clinical trial. Up to the beginning of 1944, however, it was certain that atebrin in ordinary suppressive doses even when taken over a period of months was practically non-toxic. If occasional instances of idiosyncracy did occur, their number could confidently be regarded as too small to cause a loss of reliance in a drug which could, if properly used, reduce the wastage of armed forces by malaria to a minimum.

D.D.T. AND AERIAL SPRAYING

Early in 1944 keen interest was centred on D.D.T. Experiments were carried out with oily solutions, which were found to be highly toxic to anopheline larvae. Small scale observations showed that one minim deposited from a pipette killed all larvae in one square yard of heavily infected pools. Large bodies of water could not be treated in this way, but in one swamp of half an acre in extent no living larvae could be found after treatment which consisted simply of pouring in a pint of 4 per cent D.D.T. in oily solution 2 ounces at a time at points round the bank. A

spray also controlled larvae, 22 fluid ounces per acre being used. One great advantage of this method was the great reduction in bulk of the fluid used, which was about 1/150 of the oils used hitherto. A cycle of seven days was necessary for effective spraying as D.D.T. would not kill pupae and had a slower and less lethal action on 4th instar larvae. Even with the use of the spray method great economies of men and time resulted, and its value in new areas was obvious. Survey of the Madang-Alexishafen area, for example, showed that some areas were healthy, and others most unhealthy and dangerous. Tactical necessity might demand that unhealthy areas be occupied, and in this event temporary control could be quickly established until such man-made breeding places as wheel ruts, blocked drains and bomb craters could be dealt with mechanically. Actually in the example quoted, Madang, a rate of 1-2 per 1,000 per week was achieved, though this was also due to high atebrin dosage, rigid discipline and the advantages of settling into safe areas under stable conditions.

In May 1944 the project of controlling mosquitoes by spraying an area with D.D.T. solution from aircraft was discussed. In America excellent results were reported from spraying D.D.T. in oil from a Piper Cub, but no particulars had been received in Australia of trials in which fast operational types of aircraft were used. Data concerning weather, the behaviour of aerial sprays and their droplet pattern on the ground were likewise not to hand. A joint committee of the Australian Army and Air Force undertook an investigation of the behaviour of oil sprays in the air under varying conditions of wind and elevation of the aircraft. No. 1 Aircraft Performance Unit carried out modifications of an aircraft, arranging that the outer wing tanks could be used to distribute the oil through jettison valves, and supplied crews for the experimental work. The only suitable machine readily available was the Beaufort Bomber, which fortunately proved most satisfactory, as it provided good visibility to the pilot, was easily manoeuvred, and had good carrying capacity. At first attention was paid rather to the production of large droplets on the ground, but later experiments accorded with the findings then coming to hand from overseas that small droplets were more lethal to mosquitoes. The oversea work, however, related only to laboratory experiments, the results of which were not applied in Britain or America to actual spraying from aircraft. In New Guinea the Australian Services used these results in practice and found it advantageous to regulate flying times so as to utilise downward movements of air to deposit spray where it was most needed. Under optimum conditions a dosage of 2 to 2½ quarts per acre of 5 per cent D.D.T. in oil was found to give better than minimum effective distribution. The malariologists of II Corps reported very satisfactory results from 300 gallons of spray per square mile although the penetration of spray through foliage could not be checked accurately. The ideal method was for the aircraft to fly 100 feet above tree level in straight line runs 100 yards apart, and though cross-wind runs were preferred the flight pattern dictated by the topography could be followed with good results. Accurate flying was called for, especially when steep turns were necessary to avoid

obstacles. The results were very satisfactory. Larvae were killed and did not reappear for a week. After an initial substantial drop the adult mosquito population tended to rise again, owing mainly to reinforcements from outside areas, especially if the area sprayed was small. A light wind was found preferable to calm, but more than half the early mornings in New Guinea were found suitable during this investigation. There was still a world shortage of D.D.T., but manufacture in Australia was being expedited. Obviously control of the air was necessary to make the use of this now new weapon practicable, but its tactical value in stabilising the hygiene of new areas was evident. Australian experience was found helpful in Britain in calculating the supplies needed for military formations.

Before the planned combined operations were carried out early in 1945 the routines for air spraying of D.D.T. had been well worked out. In general it was not carried out where the planes would risk exposure to hostile anti-aircraft fire, or where the enemy might suspect a gas attack. The indications were the presence of presumably infected anophelines in a newly occupied area, an outbreak of dengue fever, difficulty in applying other control methods to inaccessible areas, and an outbreak of dysentery in an area infested with flies. Areas for spraying were selected rather for their proximity to concentrations of native population or to areas recently occupied by the Japanese than for the presence of suspected breeding grounds. A zone of 200 to 300 yards around these camps was included in the spraying. No particular advantage was found in adding pyrethrum to the spray solution. Dosage of 1.8 to 2 quarts of 5 per cent solution per acre was recommended; spraying for adult insects was done only at dawn to ensure the correct drift of tiny droplets, in the region of 5-15 microns diameter, but anti-larval spraying, for which larger droplets were effective, could be done at any time during the day. The lines for the run were clearly indicated to the members of the R.A.A.F. carrying out the spraying, preferably by smoke markers laid by a malaria control unit. In most particulars the details were worked out in the preliminary experiments. The results were very satisfactory on the whole. A 95 per cent kill or better of adult mosquitoes resting out of doors was usual; practically all larvae died within twenty-four hours except occasional late 4th stage larvae. Pupae were not killed though the adults sometimes did not survive emergence. Eggs were not killed. Larval destruction was not so satisfactory with *Aedes scutellaris* or *albopictus,* vectors of dengue. Mosquitoes in dwellings were much less affected, this was particularly so with *Aedes aegypti.* Flies were killed off almost entirely, but the larvae and pupae were unaffected. Heavy vegetation reduced insect destruction to some degree, but the penetration of fine droplets was remarkable. The frequency of spraying depended on the genus and species of insect.

In the early stages of an operation it was not considered wise to rely on D.D.T. spraying alone, since planes could not always operate so soon, accurate marking was difficult, and adult mosquitoes resting indoors were little affected. Pyrethrum spraying by hand or by Freon bombs was carried out as widely as possible on the day of the landing, particularly in native

quarters. Power sprays or knapsack sprayers were used to produce an atomised mist in affected areas out of doors, and D.D.T. solution was sprayed on the walls of shelters in order to kill resting mosquitoes by its delayed action. This last manoeuvre was of value in reducing sporozoite and transmission rates, quite apart from reduction of mosquito populations, since the resting mosquitoes were already engorged with blood. The same technique was found useful in the treatment of vegetation with heavy dosage of D.D.T. in oil, spraying two or three gallons of 5 per cent solution per acre. In New Guinea the reduction thus produced in mosquito populations lasted for about one week, much less than the three weeks' period reported from Burma. In any case some reduction in sporozoite rates resulted, though the method used a considerable amount of D.D.T.

The order of priority for spraying after landing was as follows: treatment of the beach maintenance area and a fifty yard zone around, and thereafter native compounds, main dressing stations of field ambulances, rest camps, casualty clearing stations and transit areas for troops.

MALARIA IN NEW GUINEA IN 1944-1945

In November 1944 fresh operations were begun. The action areas were now widely spread. Troops were maintained at base areas in New Guinea in reduced numbers, the chief areas now being on the north coast, at Lae and Madang. Here conditions were now well stabilised. At Morotai, north of the Halmahera island group a forward base was established from which combined operations were planned in Borneo, and carried out after April 1945. A divisional group pressed on along the north-eastern coast of New Guinea to capture and hold the Aitape-Wewak area. In New Britain, following up previous Allied actions, a division established a base sub-area and in the Solomons a larger force operated and stabilised the position. In each of the operational groups there were numbers of new units without previous experience of malarious terrain, and the troops in all these islands north of the Australian mainland totalled about 188,000. There was a high malarial risk in all these areas, though some of them were well controlled.

Previous experience had shown that New Guinea and New Britain were as a whole hyperendemic, though there was considerable difference in various areas. Not even in the controlled base areas could precautions be relaxed. In the Solomons the malarial hazard was equal to that in New Guinea, for the ascertained native spleen rates were high. The experience of nearly 800 Japanese prisoners concentrated in Fauro Island had paralleled the earlier experiences of the Australians escaping from Rabaul, in New Britain. These men coming from non-malarious Nauru Island, with their own medical service, came in contact with other heavily infected troops, with the result that an epidemic swept swiftly through them and killed over 200 men. Borneo was known to be malarious along the coast except for the controlled commercial areas. Even these, under Japanese control, were likely to be still hyperendemic. These multiple proving grounds were a challenge to the anti-malarial organisation. At the begin-

ning of these active operations the overall malarial rate for areas outside Australia was 0.5 per 1,000 per week, or 26 per 1,000 per year. In January the annual rate per 1,000 rose to 75, but fell again to 39 in March. It was essential that the wastage of men through malaria should be kept as low as possible, for at 31st January 1945 a review of the records showed that since June 1943, 67,172 men had had malaria, suffering 132,014 attacks of the disease, and spending in all 2,545,585 days in hospital. At this point there was a serious interruption in the steady low rate owing to an outbreak in the 6th Australian Division in the Aitape-Wewak sector. This force had aimed at producing a record low rate in these operations, and the breakdown, which was responsible for 300 to 400 cases of malaria a week in May and June 1945, was a great disappointment to all concerned. This epidemic is of such interest and importance in the whole story of malaria that it will be discussed at some length.

Excluding the 6th Division at Aitape-Wewak and base troops, about 130,000 troops were exposed to malarial infection for periods of from six to twelve months, and out of this force only 1,256 attacks of malaria were reported over a period of nearly one year. In the Solomons the rate was 22 per 1,000, and in New Britain 18 per 1,000, while in the forces at Morotai and Borneo the incidence was only 3.7 per 1,000. In the Solomons heavy fighting went on under difficult conditions, and yet the usual average weekly rate was consistently low with few exceptions. In a few instances localised outbreaks occurred. For example, some 60 cases were reported in a fortnight at Bougainville from units of one brigade which were found to be lax in supervision. The overall rate for these campaigns was seldom above one per thousand per week.

In the Borneo operations forecasts were difficult to make beforehand, as local conditions were not clearly known and the degree of enemy resistance could not be surely estimated. By this time, 1945, organisation was good, supplies were adequate, and sea and air control had been gained, but even so the malarial rate was gratifyingly low. Out of a body of troops never less than 70,000 during a period of five months, 17,000 admissions were made to medical units and of these only 218 of the patients had malaria, less than 1.3 per cent. Only 97 of these 218 attacks were primary, and mainly due to malignant tertian, the rest being due to subsequent attacks. One death occurred at Labuan from cerebral malaria. Incidentally it was interesting that the admissions for skin disease were ten times the number for malaria.

Even admitting that some of these operations were carried out against less sustained resistance, remembering the high incidence of malaria in previous years in some relatively safe base areas, these results were highly gratifying. The introduction of D.D.T. spraying from the air must have had a salutary effect on the incidence of all insect-borne disease, and the whole of the Borneo operations in particular were a tribute to preventive medicine. It must be pointed out too that the incidence of relapses of B.T. fever among the troops exposed to risk in this campaign was also low. After the 7th and 9th Divisions returned from their campaigns in 1943-1944 it

will be remembered that their relapse rate was very high after they ceased to take atebrin, reaching a peak of 37 per 1,000. It will be recalled too that experience both in the field and the laboratory showed that it was M.T. that broke through to cause overt malaria in combat areas and B.T. that appeared later. These relapses after the men returned to non-malarious areas were an inexorable witness to the fact of infection, even though that infection had been latent under the controlling influence of atebrin. But in the 1944-1945 campaigns the relapse rate in the Atherton areas after all the troops returned south even at its peak in the end of 1945 never reached 15 per 1,000 per week. Moreover, not all these relapses were due to infection during the recent campaigns. Of course these latter figures do not represent the total number of men who had relapses of malaria acquired in these campaigns, but they are reasonably comparable with the figures for the preceding year.

Brigadier Fairley in an analysis of the experiences of one brigade (6th Australian Infantry Brigade) has pointed out how high an ultimate benign tertian rate may be expected after exposure. This brigade was twelve months in Buna and Lae areas in New Guinea, and nine months in New Britain. Early exposure in Buna produced a very high malarial rate, but improvements in control lowered this, until in August 1944 the average weekly rate was below one per thousand, and had not risen higher than 5 per thousand. After its service in New Britain the formation was disbanded piecemeal, and exact figures are not obtainable, but the percentage of men suffering relapses in three battalions was about 45. The rate rose to 125 per 1,000 in one week. Even taking the figures for two months after the cessation of suppressive atebrin, a period too brief to include all relapsing attacks, Fairley estimated that the ultimate infection rate for benign tertian would be at least 70 per cent. Previous experience in New Britain suggested that transmission of M.T. was considerably greater than B.T. in the regions where Australian troops were exposed. If this be so the value of atebrin as a suppressive agent is evident, and its capacity to cure M.T. is demonstrated. When the war ended the Australian troops were on the whole in good health, and their rehabilitation from the point of view of physical condition in general and of malaria in particular was not difficult.

THE AITAPE-WEWAK EPIDEMIC

The methods evolved for controlling malaria in the field were vindicated by the excellent results obtained in the last year of war. Yet there is a chastening experience still to be described, that of the epidemic in Aitape-Wewak among the 6th Division, and to a lesser extent the 3rd Australian Base Sub-Area, which caused 6,906 casualties. Operations began in the Aitape area in November 1944. The force had to fight back along 100 miles of coast and also in the mountainous inland sectors. Wewak was occupied in May. The malarial hazard was high over the whole area, particularly so on the coast. In some of the mountainous parts transmission was relatively low, but there was no doubt that the area as a whole was hyperendemic throughout the year. The coastal area was narrow

and flat, and intersected by a number of rivers and innumerable creeks, which fed swamps and towards the foothills ran through dense rain forest. There were concentrations of natives in different parts of the area as the campaign progressed with variable degrees of contact with the troops. Considerable infection existed in the native groups, especially among the infants, as will be shown later. There was also a pool of infection among the Japanese. Mosquito breeding was found to be heavy, the most abundant vector was *A. punctulatus moluccensis*. Many breeding grounds existed particularly near the coast, and there were innumerable bomb craters filled with water. Malaria control units worked with good effect, and eventually reduced the mosquito population to 5 per cent of its initial total in areas where such work was possible. Owing to the nature of the campaign there was a constant lag in the application of control to active areas. The spraying of D.D.T. from the air was used more extensively than in any campaign hitherto, but it was never possible to spray areas before or even soon after their occupation. Shortage of supplies also restricted the use of the method towards the end of the period. It was recognised from the beginning that control must rest on a firm basis of personal protection and the taking of atebrin.

In December an undue malarial rate was noted in certain units of one brigade, the 19th. The whole 6th Division was already working under very strict hygiene orders, but the commander made prompt enquiries and, finding evidence of slackness in anti-malarial discipline, took firm disciplinary measures. As a precaution the whole brigade group concerned was placed on a double dose of atebrin, 0.2 gramme daily for three weeks.

At the end of January the Commander-in-Chief, General Blamey, held a conference at divisional headquarters at which the position was discussed, and even more strict drill at atebrin parades was adopted and the rigid enforcement of all control measures emphasised. Three teams of medical and combatant officers were appointed to make searching survey of all relevant matters. Thorough investigations were made on the spot by representatives of army medical headquarters and it was concluded that conditions of infection were not more severe than elsewhere, that atebrin was not at fault in composition or action, and that the outbreak was due to faulty atebrin suppression. It was admitted that the divisional orders relating to the administration of atebrin were strict to the point of actual harshness. The method of atebrin administration included the actual placing of the tablet in each man's mouth, and the inspection of his empty mouth after swallowing. Nevertheless there was evidence that there were slips in the use of repellent lotions and loopholes in attendance at atebrin parades, and even in the generally excellent dress discipline (one very high officer was observed not to be wearing gaiters).

The 19th Brigade went back to rest at the end of January, and by this time malaria had increased rapidly, the rate reaching 44.8 per 1,000 per week. Accordingly the suppressive dose was raised to 0.2 gramme daily for the whole division. The brigade in question reverted to 0.1 gramme after a month, but the other two brigades, 16th and 17th, con-

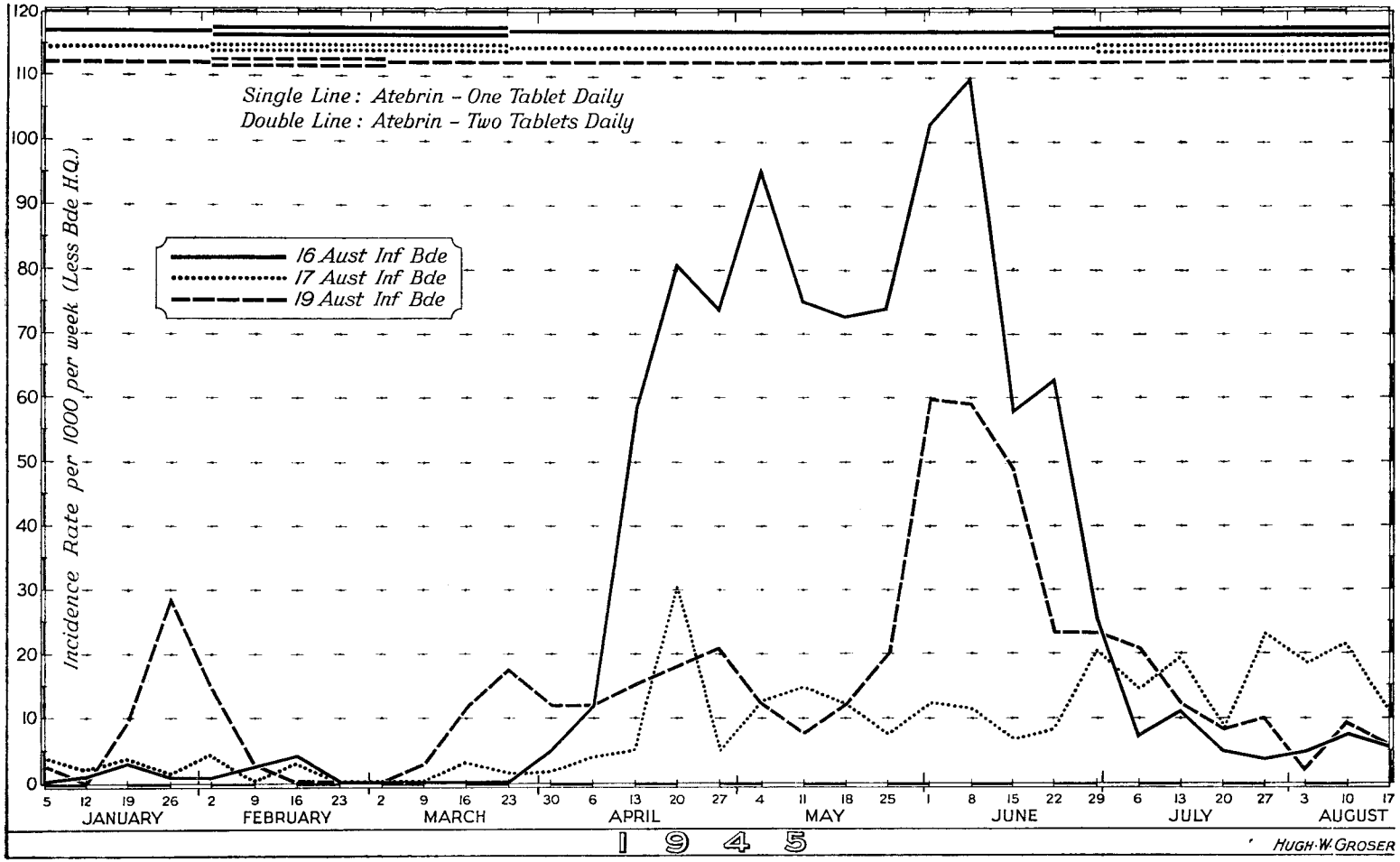
tinued the higher dosage for another month, during which the 17th moved into the Torricelli Mountains, and remained chiefly in the higher ground for the remainder of the campaign. Here transmission was apparently at a lower level, probably accounting for the lower incidence of overt malaria experienced by this formation. At the end of March the whole force was back on the usual suppressive dose of 0.7 gramme a week. The sharp outbreak just described subsided by the end of February. It attracted great interest and caused not a little anxiety. No parallel existed on other fronts. In the Solomons, with the exception of a brief rise to a rate of 47 per 1,000 due to a localised breakdown in control, the incidence was uniformly low, so too in New Britain. In both these areas high rates of transmission and incidence were known to exist, yet the rates were better than those previously obtained in some relatively settled areas.

The divisional commander, General J. E. S. Stevens, and his responsible officers were very keen to be able to show a record low malarial rate, for, though many of the troops were reinforcements who had not had previous experience in the tropics, the background and tradition of this, the first division of the A.I.F. to be formed and to enter action, were powerful influences.

By March the situation was thought to be under control, but in April a large-scale outbreak began. The graph illustrating the steep rise and high level attained is characteristically that of a malarial epidemic. The three brigades were not equally attacked. The 17th Brigade, chiefly in hilly country, reached a maximum of 30 per 1,000 per week in July, the 19th reached 65 per 1,000 per week in the beginning of June, and the 16th reached the peak of 113 per 1,000 per week in the first week of May. The initial rise began in each brigade at approximately the same time. Double suppressive dosage of atebrin was ordered for the 16th in June when some fall in rate had begun, and the epidemic terminated in July. Increased dosage was ordered for the 17th Brigade, but its rate, never very high by comparison, did not subside for some weeks. The 19th Brigade continued taking the usual dose and after a sharp rise the rate fell at the same time as that of the 16th.

THE EPIDEMIC ANALYSED

It will be seen that there were some inconsistencies hard to explain. Out of a force of 17,500 men, 4,838 individual soldiers were recorded as having one or more attacks of malaria. Some 78.2 per cent of the total cases were due to M.T. or Mixed M.T. and B.T. infection, and 10.7 per cent to B.T., 11.1 per cent were not confirmed by the finding of parasites. The attacks were on the whole very mild in nature, though four deaths occurred. During the period when the epidemic took place and until the end of the war in August 1945 the malarial rates in other operational areas remained consistently low. Here was a problem posed for solution. Was it simply due to breakdown in malarial discipline and control, or were there other factors? An extraordinary amount of argument



Epidemic of malaria in Aitape-Wewak

took place and intensive enquiries were made within the affected formation, by higher formations and by the medical directorates at army headquarters, and finally by research teams under Brigadier Fairley. Commanders of a combatant and a medical unit were sent to tour other operational areas, but they found no evidence of anything done there which was left undone in the Aitape-Wewak sector. Fairley has made a detailed statistical survey of this epidemic and has also described the findings of work done on the problem by the Medical Research Unit at Cairns and by a field section of this unit which was specially set up to make local investigations. The information available falls into three categories, a statistical survey, an account of the special scientific investigations made in New Guinea and at Cairns, and a consideration of other circumstances and relevant material bearing on the question. Some of the factors mentioned are beyond dispute, others are more imponderable and speculative.

The nature of the epidemic was of itself not unusual, the steep rise suggests the combination of factors such as a degree of non-immunity of those affected, a high concentration of vectors, and heavy breeding, a high transmission rate, and the provision of a pool of gametocyte carriers. The last may be left for the present; the other factors are understandable provided control measures were inadequate, or if a race of parasite was present less amenable to suppression than any hitherto encountered in the islands. The majority of infections were by *P. falciparum,* as might be expected in such an epidemic. It would follow then on the basis of previous experience that latent infections by *P. vivax* would be manifested later. But if for reasons of faulty control, principally deficient atebrin dosage, it would be expected that M.T. would break through and not B.T., since the latter requires substantially less atebrin for its suppression. Both experimental and field work have shown this. If primary B.T. infections occur it will be surely due to a defective atebrin level in the blood below that given by taking 0.1 gramme atebrin a day.

Such an outbreak of B.T. did occur here, and whether it was primary or not, a rate of 4.6 per 1,000 per week is hard to explain except by assuming too low an atebrin level. The rates of M.T., B.T., and mixed M.T. and B.T. fluctuated after the same pattern during the outbreak. It should be remarked that the total consolidated percentages recorded of the types encountered (78.2 per cent M.T. and 10.7 B.T.) are much lower than those found at a mobile bacteriological laboratory, where 98 per cent of 298 cases were M.T. This high percentage was unique in army experience in New Guinea, and suggests that the B.T. was being suppressed while M.T. broke through. What exact significance can be attached to the total B.T. figures for the whole period is thus doubtful.

Consideration of multiple attacks is also interesting. Fairley points out that in troops of the 6th Division the average of attacks per patient was 1.3 and in the base sub-area 1.15 over a period of eleven months. Medical officers in hospitals reported an unusual tendency for recrudescent attacks of M.T. to occur; some of these could not have been fresh attacks as they occurred within a few days of completing a course of treatment. The

2/11th Australian General Hospital reported 390 attacks in 250 men, and the Medical Research Unit 160 in 97 men, and a battalion survey gave 45 in 34 men, a total of 595 attacks in 381 men. It will be seen that this ratio of 1.6 to 1 is higher than that above quoted, which is derived from base records.

The question of the cause of these recrudescences or relapses arises at once: it has been touched on earlier in this account. There seems no doubt that this was a genuine experience, but how much of it was due to deficient taking of atebrin in hospital may be questioned. In two hospitals the institution of stricter methods, such as the inspection of the patients' mouths, reduced the number of recurrent cases in some instances. Reliable observers on this and other occasions have stated that under strict conditions recrudescences did occur after or even during follow-up maintenance courses. Parasitaemia of a transient order has also been observed. A clinical impression held by some medical officers was that these phenomena were more frequent at Aitape-Wewak. No controlled figures can be given; some observers considered that controlled atebrin intake definitely lessened the number of recrudescences, but this cannot be proved.

While speaking of hospitals, some figures may be mentioned obtained in a survey of 500 patients. More patients were drawn from amongst those who had served 40 to 49 months than any other period, and 7 months in the area. It was also observed in Lae base sub-area that though 31 per cent of the patients with malaria came from Aitape-Wewak, 96 per cent of those developing relapse after five days in hospital came from this area. Pursuing more closely the question of relapses, we find that the percentage of individuals contracting subsequent attacks was much the same as that found in the divisions which campaigned in the Huon peninsula. The percentages for the 7th and 9th Divisions were 28.3 and 21.3 respectively, that for the 6th Division in this campaign being 22.7. This will be discussed further presently in connection with the possibility, already mentioned, of a parasite relatively resistant to atebrin.

Another important statistical fact emerged in the incidence of malaria in officers and other ranks: only 15 per cent of the officers with the 6th Division were admitted to hospital with diagnosed attacks of malaria. This is only half the incidence in non-commissioned officers and men. This may be due in part to greater opportunities for avoiding malarial infections, but is certainly in many instances due to higher atebrin dosage. Numbers of officers took more atebrin on occasion, especially if they suspected the nature of any indisposition. Moreover, it was more important for them to keep on their feet owing to the strictness of the disciplinary measures. C. H. Selby, a commander of a field ambulance, has pointed out it might perhaps be thought an indication of bad discipline that many officers took more than the standard dose because of the threat of court martial and disgrace should they contract malaria.

It will be evident now how important it is in the understanding of this epidemic to know just how much atebrin was taken by officers and men of this division. Was there a widespread laxity in taking atebrin on the one

hand, or was the standard dose insufficient for some unknown reason, or was the better result obtained by some formations due in part to higher, if unofficial, atebrin dosage? Officers could more easily have access to atebrin than other ranks. Lieut-Colonels Jaboor and Selby, in visiting other fronts officially, found that in Bougainville and New Britain more than one tablet a day was frequently taken. Instances occurred of units taking additional atebrin when carrying out special work to avoid being disciplined for contracting malaria or to retain a previously good reputation. Commanders finding their rates rising would take similar action to keep the rates down. It has been suggested that one reason for better results in Bougainville and New Britain may have been a higher or at least a more consistent atebrin level in the blood obtained by these means.

In view of these considerations it is of great interest to see what happened when a unit was introduced into the Ataipe-Wewak area which had earned a reputation for excellent anti-malarial discipline in other hyperendemic areas. The 8th Infantry Brigade was moved from the Madang-Alexishafen-Hansa Bay sector to Wewak during July. This brigade had carried out long advances along the coast, and after some early breakdown in two units had maintained a low rate. Two battalions took over fixed positions at a late stage of the campaign, and within several weeks of this they both showed a definite increase in the incidence of malaria. This was particularly so in one battalion, whose rate rose to 38 per 1,000 per week in August. Following the administration of double dosage of atebrin a prompt fall occurred to a low level. This example pointed to the probable existence of some other factor. Thus the doubts that had arisen that 0.7 gramme of atebrin might not always suppress malaria in this sector called for fuller investigation. Several senior officers had contracted malaria, including a brigade commander and the commanding officers of two field ambulances. Numbers of instances occurred in which the most reliable N.C.O.'s and men in units had overt infections. Such happenings had been observed before, reported by responsible and reliable persons, and here an impression was widely held in the field medical units that more malaria was occurring than they believed could be accounted for by failure to take atebrin. The mild nature of the cases has been commented on already: it was suggested that this was due to the partial protection of atebrin. On more purely hypothetical foundation was the idea that some degree of premunity existed in many individuals and that this might explain how out of an epidemic of mild nature numbers of cerebral infections would appear, as they did, with occasional deaths. This suggestion assumed that an infection which otherwise might have been more dramatic and severe, had not lost its peculiar property of causing such local manifestations as cerebral malaria.

Some doubts were also expressed as to the efficient absorption of atebrin. Was there some other factor such as hookworm hindering absorption? An increased incidence of hookworm was noted in hospitals in the field, but it was not certain that similar findings might not have been made before if more intensive search was undertaken. Besides, in Bougain-

ville, hookworm of unusual intensity of infection had been found, but without any special obvious reflex on malarial incidence. The question of intercurrent alimentary disease in relation to the absorption of atebrin had also been raised. Interesting observations were made by 1st Lieutenant J. Maier, 1st Lieutenant F. B. Bang and 2nd Lieutenant N. G. Hairstrom of the American Malaria Research Unit (3rd Medical Laboratory). With clinical assistance from the 2/7th Australian General Hospital they determined the plasma atebrin levels in patients with infective hepatitis, and diarrhoea. No difference could be found in the plasma atebrin content of these men and of controls in either instance. Thus there was no evidence that these infections would hinder absorption of atebrin.

The same team also investigated plasma levels of men in the field. Among men claiming to take atebrin regularly they found considerable individual variation in the plasma atebrin concentrations. This was thought to be due to failure to take the prescribed suppressive dose in the great majority, though it was recognised that daily variations in the analytical method, or in individual response to the drug, or a variable ratio of free to bound atebrin in the blood might also cause some fluctuation in the estimations. The plasma concentration of atebrin bore only a rough relation to the free and presumably active drug in the plasma. It appeared also that the malarial rate did not vary in proportion to the expected efficiency of atebrin suppression in an infected group, though there was no question that a high malarial rate could be possible only if atebrin suppression was poor.

INVESTIGATIONS AT CAIRNS

The research units set about elucidating the following problems. Was atebrin correct in composition and tablet dosage? Was it adequately absorbed? What were the average atebrin plasma levels in men on reputedly standard dosage? Did malarial strains isolated from soldiers in this area behave in a manner different to strains encountered hitherto in the islands? Forty selected patients with overt malaria were flown to Cairns and hundreds of specimens of blood plasma also for atebrin estimations. These specimens were taken without warning from soldiers on atebrin parades, those selected having varying degrees of pigmentation so as to secure a representative cross section. Lieut-Colonel Mackerras in addition carried out special investigations dealing with epidemiology with reference to control. Definite answers were obtained to these questions.

The atebrin tablets contained never less than 0.101 gramme of atebrin hydrochloride. The distintegration times were within effective limits, though one type of tablet took from five to fifteen minutes to distintegrate in water. An occasional tablet could be held in the mouth for a time without dissolving. Evidence was obtained that a few men of unsatisfactory or unstable temperament practised some means of evasion, perhaps with the help of chewing gum. Specimens of plasma collected by the field research section were analysed for atebrin by a standard method. Very close agreement was obtained between the plasma levels of these men

who stated that they were taking 0.7 gramme atebrin a week, and those found in volunteers at Cairns who were known to be taking the same dosage. The geometric mean of the level in microgrammes a litre was 21.56 for Aitape-Wewak and 20.12 for Cairns, standard deviations being 1.37 and 1.59. The patients with overt malaria were found to have higher levels, 27.57 mean, due probably to their taking extra atebrin when they felt unwell. Agreement was not found between the plasma levels of men alleged to be taking 1.2 grammes a week at Wewak and volunteers known to be taking this amount at Cairns. The mean level for volunteers was 43.1 microgrammes, that for the Wewak men was 31.7.

It will be realised that the same certainty cannot be felt concerning the actual dose taken by the New Guinea men as that taken by the volunteers. Despite the correspondence of the 0.7 gramme a week levels there is no proof that these men were not taking an occasional extra tablet. It seems likely that the lower levels with the 1.2 grammes weekly dosage was due to irregular intake. In general this evidence points to a sufficient dosage of atebrin in the division to ensure protection against the strains previously investigated at the research unit.

Study of spleen rates and parasite rates indicated a high general rate of infection estimated at 90 per cent at the time of review. After Milne Bay and Buna-Gona campaigns high parasite rates were recorded in men who were apparently well, as has been previously told. Rates of 16.0 per cent and 12.0 per cent for blood parasites and gametocytes respectively were found in these men, and though these unprecedented rates were not approached in the Aitape-Wewak area, the rates there were 5.0 to 5.5 per cent and 2.0 to 2.5 per cent, while the figures for Bougainville were 1 per cent and 1 per cent and for Morotai-Borneo only 0.17 and 0.05. Some men at Wewak were doing their usual work while carrying large numbers of parasites in their blood, and did not contract overt malaria. *Plasmodium falciparum* was found in the blood of men who were well and whose plasma contained a theoretically adequate concentration of atebrin. This occurred only in the Aitape-Wewak area, and had not been seen before by the staff of the research unit. This pointed again to the possibility of an atebrin-resistant strain. Soldiers thought to be the most likely subjects of infection by such a strain were flown to Cairns, particularly those with attacks of M.T. repeated within a short time during the administration of a maintenance course of atebrin, those with cerebral malaria and those with hyperinfection. Seven out of nine strains isolated from these soldiers were found to be unusual in their resistance to atebrin. Volunteers infected from mosquitoes carrying sporozoites from these strains contracted malignant tertian malaria which was either not suppressed by 0.1 gramme atebrin daily or if suppressed not cured by this dose. In some instances the disease was suppressed but not cured by 0.2 gramme of atebrin daily. In several volunteers recrudescences of M.T. occurred after a standard course of treatment while maintenance doses of atebrin were being taken. Larger doses of atebrin and higher blood concentrations were more effective in dealing with this type of parasite.

Other drugs then under trial at Cairns were tried. No alteration in sensitivity was found with quinine, "Resochin", sulphadiazine or "Paludrine", but in two volunteers "Santochin" as well as atebrin suppressed but did not cure the infection.

Whether this atebrin-resistant quality could be lowered by successive passage through mosquitoes and men could not be ascertained: one instance suggested the possibility. No similar results could be obtained with the strains of *Plasmodium vivax* isolated from the Aitape-Wewak area. All these strains behaved like the others previously tested at Cairns. Thus definite proof was obtained of an atebrin-sensitive strain of *P. falciparum,* but no proof of any such strain of *P. vivax.*

It was of particular interest to determine how prevalent this strain was in the Aitape-Wewak area, and whence it was derived. Fairley has pointed out that the incidence factor of secondary attacks in the 6th Division was 1.3, and that therefore failure to obtain radical cure of M.T. in the area must have been rare, the prevalent strain producing overt attacks being atebrin-sensitive. From considerations of the number of recrudescences and relapses experienced he argued that the chance of acquiring a recrudescent form of malaria in Aitape-Wewak was not greater than in the Ramu or Markham Valley, all the figures being similar, hence that the percentage of men affected with the resistant strain would not be higher than about 20 per cent. There is, however, a possibility that an undetermined proportion of men who had had one attack of M.T. took more atebrin thereafter, thus reducing their liability to recurrence. Although the recrudescence rate may be higher than 1.3 as pointed out above, this figure may be a near approximation. Even this cannot be stated with certainty, however, as exact evidence about atebrin intake and plasma levels in the division does not cover all classes of officers and men, for instance those who had had an overt attack of malaria.

FURTHER ENTOMOLOGICAL RESEARCH AT WEWAK

How did this strain arise? It was suggested that insufficient atebrin intake may have caused this characteristic of resistance to appear in a proportion of *falciparum* parasites. A similar phenomenon is familiar with drugs like sulphonamides and penicillin. If this were so, from what gametocyte pool did the epidemic arise? Interesting epidemiological evidence was accumulated by Mackerras and Aberdeen in the Aitape-Wewak area. They made a study of the naturally occurring and uncontrolled infection in the native community. The spleen rates and parasite rates were estimated in adult men and women, children and infants drawn from a population of over 1,000 in the neighbourhood of Wewak. These were compared with similar observations made on Japanese prisoners in Wewak and on Australian soldiers in the area. The highest spleen rates were in infants and children, of course, up to 93 per cent; the parasite rates were much higher also, but a point of interest is that they were very

much higher in infants than in children. The following figures taken from Mackerras and Aberdeen's table are of interest:

	Hwain natives				
	Infants	Children	Adults (men)	Japanese	Australians
Parasite rate .	92%	59%	29%	47%	5%
Infection rate .	130%	71%	32%	57%	5%
Gametocyte rate	49%	16%	6%	22%	2½%

Mosquito dissections showed a 2 per cent sporozoite rate in the Hwain villages, but 0 per cent in the troop encampments in Wewak in July. Particular attention was paid to the possible sources of infection in the military community. These sources were, in terms of this survey, for *P. falciparum* infants, Japanese and the Australian troops, in that order of importance, and for *P. vivax,* Japanese and children. Contact of troops with infants and children was slight, but with Japanese was close, especially in forward units where clinical malaria was prevalent. This survey is of course a localised one: parasitological and immunological differences were found in surveys of different areas, such as Lae. Mackerras and Aberdeen concluded that the troops acquired most of their infections in the coastal zone from the Japanese and probably also in the hills, where the Japanese were numerically preponderant. It was further pointed out that in the hours before dawn an off-shore drift of air would bring the mosquitoes in from the infected areas. Malaria pickets patrolling camp areas at night spraying tents were instructed to look specially for "large bare surfaces" of skin in contact with nets.

These points have been raised here as they have some bearing upon the origin of an atebrin-resistant parasite. The hypothesis has been put forward that this strain arose through being circulated among troops who were taking inadequate amounts of atebrin. It is hard to reconcile such a suggestion with the findings of this local epidemiological survey. If such a strain originated among the Japanese its transfer to Australian troops was easily possible, particularly in this campaign, both in the coastal sector and the hills. In the mountainous areas it was not uncommon for opposing forces to be on ridges separated by difficult barriers of ravine and jungle though actually close by direct distance.

CONCLUSIONS ON AITAPE-WEWAK

It is evident that there were breaks in malarial control and discipline, but it is certain that the same applied to all other areas at one time or another, despite a generally high standard. The question of morale has been raised: it is difficult to assess. Some officers thought that fatigue due to difficult fighting was a factor, combined with the feeling that the campaign, though strenuous, was not of major importance. There is no evidence that such a feeling was more prevalent there than elsewhere. The rules of atebrin administration were very strict: it is hard to see how there could

have been more loopholes than in other formations, though some undoubtedly occurred. If anything, the measures adopted were too harsh, and these may have reacted unfavourably on the men.

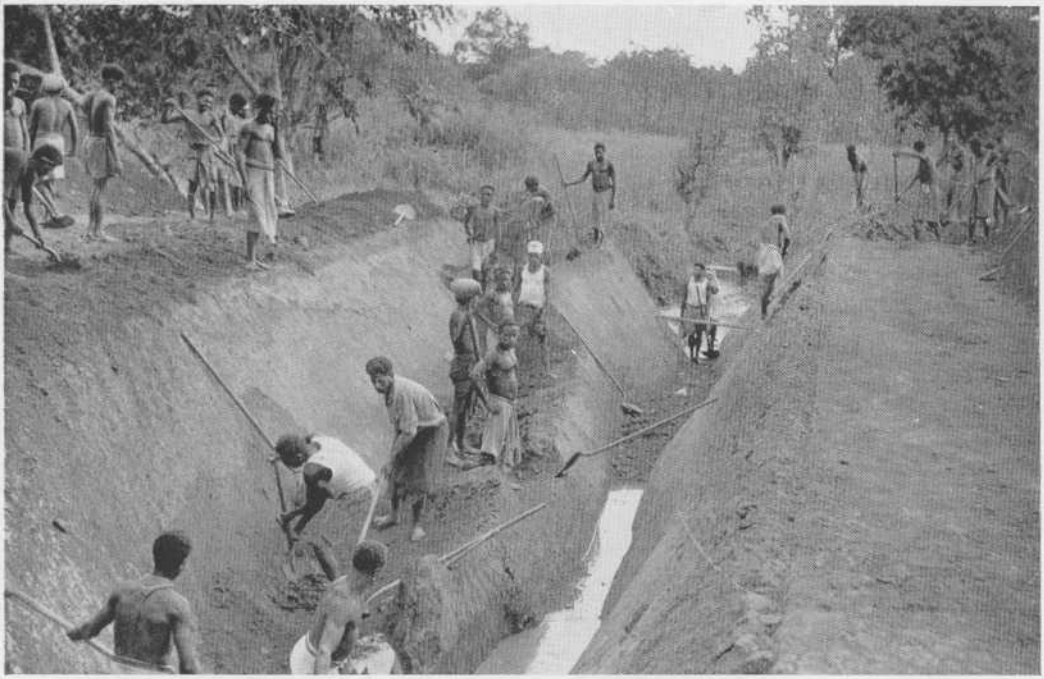
It is interesting that Lieut-Colonel English, malariologist to First Army, reported that of 1,500 men from many areas, but not including 6th Division, some 15 per cent still believed that atebrin would cause impotence or sterility. Quite apart from this, senior medical officers of the 6th Division considered that the emotional and intellectual attitude towards suppression of malaria was a factor of importance. In this connection it will be remarked that, although the possible causes of break-through of malaria in men taking an adequate dose of atebrin were very thoroughly investigated at Cairns, the laboratory results are not necessarily applicable to field conditions. In some convalescent depots on the mainland men have been known to court relapses by prolonged cold showers. Medical officers have in some cases believed that relapses more frequently followed such action, but this is only an opinion unbacked by controlled evidence. It must be admitted that the psychological component of fatigue, or the effect of distress, anxiety or other more or less turbulent emotion of stress cannot be reproduced experimentally. Such possible factors can only be regarded as imponderable, but no physician will question their importance.

Summing up, this epidemic had the usual features of a swiftly increasing outbreak of malaria in a closed community. It occurred in troops of excellent fighting qualities operating under strenuous and difficult conditions in a highly endemic area where transmission of malaria was well established before their arrival. Ground control was good, but owing to military conditions was always catching up, except in settled areas. Personal protection was not always first-rate, in which it probably did not differ from other areas. The slightest laxity would cause infection, in point of fact some 90 per cent of the troops in the area were infected. It must be remembered in connection with high rates of suppressed malarial infection that sub-inoculations prove that M.T. infections can be transmitted by injection of blood on the seventh and ninth days after mosquito-borne infection of volunteers taking atebrin, even though no parasites appear in the blood. An atebrin-resistant strain of *P. falciparum* was demonstrated in the area; it is likely that this characteristic was not firmly or long established, but this is unproven. Its mode of origin is not certainly known: epidemiological evidence indicates that it is very improbable that it arose among Australian troops who were not taking full doses of atebrin, but rather among Japanese. Rigid discipline was imposed, particularly in the taking of atebrin: it is possible that psychologically such discipline can be too rigid. Nevertheless some breakdown must have occurred: it may or may not have been greater than the degree occurring elsewhere. The proportion of men with overt malaria infected by the atebrin-resistant strain is uncertain. The elaborate and time-consuming nature of the very thorough and accurate researches made could cover only a small number of selected patients. This difficulty is innate in the investigation of

Malaria control—swamps to be drained near Port Moresby, New Guinea.

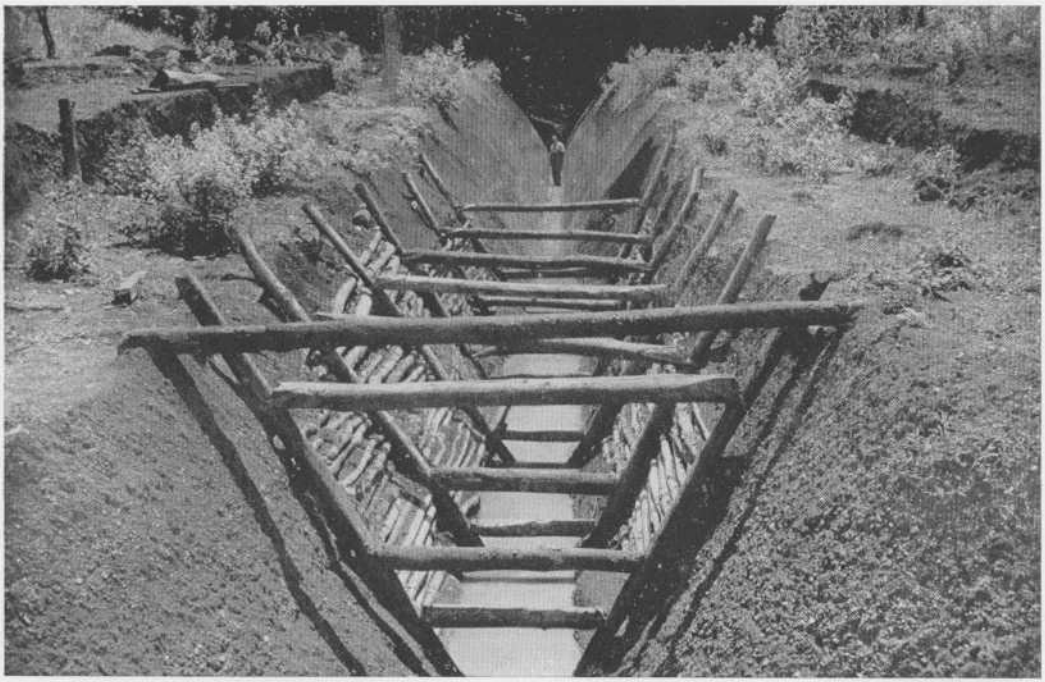
(*E. Ford*)

Draining a swamp near Port Moresby, New Guinea.



(Australian War Memorial)

Draining a swamp near Port Moresby, New Guinea.



(E. Ford)

Malaria prevention—canalising stream.

epidemics of acute disease. However, it seems certain that the atebrin-resistant strain was not the prevalent strain in the area.

On the credit side are the facts that the division was able to carry out its assigned tasks with complete success and that atebrin was successful in suppressing overt malaria in two-thirds of the force. The lessons of the Aitape-Wewak campaign are the military necessity for continued striving to attain perfection of personal as well as mechanical control of disease, realisation of the great number of variables involved in unravelling the scientific problems encountered, the need for constant local technical investigation in every operational area, and the desirability of having at hand more than one reliable suppressive drug for use in the field.

SUMMARY OF THE WORK OF THE MALARIA RESEARCH UNIT

A brief summary may now be given of the work done at the Cairns Medical Research Unit, pertaining to malaria in general.

Some of the already known facts about malaria were confirmed. A test of latent malaria was necessary in order to establish whether volunteers apparently cured of malaria were completely free of infection. For this purpose a larger amount of blood was used for sub-inoculation tests than the usual 10 cubic centimetres: instead 200 cubic centimetres, some 4 per cent of the blood volume, were given usually by direct transfusion. In *falciparum* infections sub-inoculations produced malaria in a fresh volunteer within twenty-three days if latent infection was present. In *vivax* infections this could not be relied upon, since the cycle during which tissue forms of parasite exist (in distinction to those found in the blood) is much more persistent in this form of the disease.

The possible existence of natural immunity was also investigated in volunteers who failed to contract malaria when exposed to infection. Intramuscular injection of a determined dose of parasites from a malaria donor never failed to produce disease, thereby excluding the possibility of premunity in the donor and natural immunity in the second volunteer. No evidence of natural immunity was found in these experiments. The results of sub-inoculation were also used to investigate the erythrocytic and exo-erythrocytic forms of parasite. It was found that if a volunteer is bitten on one arm by a mosquito carrying either *P. vivax* or *P. falciparum,* blood taken from the other arm after seven minutes will infect a fresh volunteer, proving that sporozoites are still in circulation. In one instance direct transfusion of 500 cubic centimetres of blood taken while biting was in progress produced malaria. After thirty minutes sub-inoculation was no longer effective: the sporozoites had left the blood. This gives some idea of the time taken by the sporozoites to become fixed away from the blood stream in the reticulo-endothelial system, as is generally believed. After infection of a volunteer with *P. falciparum* his blood failed to transmit malaria till the seventh day when it was capable of infecting another volunteer, in spite of the fact that for one to three days after no parasites could be found in thick films. The same held for *P. vivax,* but here the

blood was incapable of transmitting the infection for eight days. In *vivax* infections prolongation of this period of non-infectivity of the blood could be produced by the administration of plasmoquine. This is believed to be due to inhibition of the intracellular development of sporozoites and early tissue forms. Prolongation of the incubation of *P. vivax* could also be produced by giving a large daily dose of plasmoquine during a period extending from before exposure to five days after.

Fairley concluded from these experiments that support is given to the hypothesis that an exo-erythrocytic phase of B.T. is persistent, and that asexual parasites are shed from these tissue forms from time to time to cause relapses. The erythrocytic form in M.T. is vulnerable to atebrin, and the non-persistence of an exo-erythrocytic form is probably due to the tissue stage being a very brief one or vulnerable also to atebrin. Very sharply defined limits were found to the negative and positive sub-inoculation results, and it was suggested that if the tissue cycle was forty-eight hours there might be four cycles in *vivax* and three in *falciparum* before the erythrocytic forms were shed into the blood stream. These results also suggested optimum times for administering drugs under test for their action on sporozoites, early tissue forms and schizonts. An interesting clinical observation was made by R. R. Andrew at Cairns, that the first detectable sign in experimental mosquito-borne malaria was distinct tenderness of the liver on the ninth day after biting by infected mosquitoes.

Incidentally, during sub-inoculation experiments some valuable information was collected regarding the phase of the parasite on which a drug was acting. In connection with work done at Cairns on the cultivation *in vitro* of New Guinea strains of *P. falciparum* and *P. vivax* some observations were made on the behaviour of cultures exposed to the action of anti-malarial drugs. The second generation was not seen in *vivax,* and in *falciparum* this did not develop beyond large rings and amoeboid forms. Postulates made from this work have some bearing on the action of these drugs on the metabolism of the parasite, for example, the hypothesis that they prevent the use of pyrodoxine by the plasmodium. These studies at Cairns have borne fruit in further research since the war, particularly the demonstration of the tissue stages of parasite at the London School of Tropical Medicine and Hygiene.

ENTOMOLOGICAL RESEARCH

Further scientific observations had been made during 1943 and 1944 on the bionomics of mosquitoes, and in particular on their habits of breeding and biting. The latter was most important, and local observations were essential in new areas. An interesting and important finding about *punctulatus* was that intermediate types were found between *moluccensis* and *typicus varieties.* At a meeting of the Allied Conference in New Guinea discussion showed how unsafe were generalisations based on studies in a single locality. The U.S. Navy malariologist at Guadalcanal found there that the conditions with regard to *punctulatus* were almost the reverse of those found in New Guinea. In the Solomons intermediate types had not

been recognised, yet at Aitape there were few pure strains, the majority being intermediates. The importance of exact local observations was proved again and again.

Scientific research was also being pursued in the field. In the course of local surveys a considerable volume of useful entomological work was produced, though this was always related to the military problems in hand. In addition, a whole section of the Division of Economic Entomology of the Council for Scientific and Industrial Research in charge of Captain D. F. Waterhouse was made available for biological and chemical studies of control methods. Arrangements were also made for systematic identification of mosquitoes to be done by D. J. Lee at the Department of Zoology in the University of Sydney, where the staff of the School of Public Health and Tropical Medicine also gave assistance.

Besides the work already mentioned Major A. R. Woodhill carried out investigations on the subspecies of *Anopheles punctulatus*. The existence of what appeared to be a hybrid emphasised the value of study of the exact habits of a vector in a given locality. Contributions made to the meetings of the Allied Malaria Control Conference, such as those of Captain D. O. Atherton and Lieut-Colonel Orth (U.S.A.) helped to spread information concerning habits of flight, breeding and biting of local mosquitoes and its application to problems of control. Studies were made on the behaviour of adult anophelines at Cairns, and various places in New Guinea by F. H. S. Roberts and P. J. O'Sullivan, and I. M. Mackerras examined the "vector qualities" of Australasian anophelines. This latter study dealt with the susceptibility of infection, abundance, association with man, avidity for human blood and length of life. *Anopheles punctulatus* (*typicus*) was outstanding in all these qualities and was therefore the most dangerous vector, next to which came *Anopheles punctulatus moluccensis,* more correctly styled *"farauti"*. Under favourable conditions *A. annulipes, bancrofti, subpictus* and two varieties of *amictus* were potential vectors, and unknown, but the most locally significant were *A. meraukensis* and *novaguinensis.* Considerable research was also carried out in the field of methods of control.

CLINICAL INVESTIGATIONS IN ARMY HOSPITALS

Turning to clinical considerations we may note that the resources of army hospitals were used to study and compare various methods of treatment with particular reference to their effectiveness in relieving fever and clinical symptoms, and in clearing the blood of parasites, their toxic properties if any, and their capacity to control relapses. Amongst the combinations tested were the following:

1. Quinine 10 grains and plasmoquine base 0.1 gramme three times for ten days. Two hundred and eighty-eight showed a relapse rate of 7.3 per cent: more patients who had not had previous courses of treatment seemed to relapse. Mild nausea and occasional vomiting were observed in a few patients, but only in two (members of the nursing service) were these symptoms severe.

2. A special course of quinine, atebrin and plasmoquine base was compared with an intensive atebrin course. The doses were respectively (1) quinine 30 grains a day for three days and atebrin 0.9 gramme, 0.6 gramme each one day, 0.4 gramme for three days, and plasmoquine 0.3 gramme daily for three days; and (2) atebrin 1.2 grammes for one day, 0.8 gramme for one day and 0.4 gramme four days. 2,088 patients were studied who had an average of slightly more than one attack previously treated, acquired in New Guinea. Clinical response was good with each method, and no distinction could be drawn. The rate of parasite clearance was much faster with the intensive atebrin course, but there was no significant difference in the recrudescence rate, which was low (0.2 per cent to 0.5 per cent). The latter course enabled patients to leave hospital more quickly, but its toxic effects were more pronounced.

Excessive vomiting was more frequent with intensive atebrin therapy and 1 per cent of the patients had a confusional state, which was severe in three cases. This aspect was also studied at another hospital, and is discussed later.

3. Observations were made on the blood levels of quinine and atebrin in the "Q.A.P." intensive course used in these experiments. Very satisfactory concentrations were found, the average quinine level was above the effective therapeutic level (5 microgrammes) for six days, and more than double this during the first three days. Parasite counts rapidly fell and were negligible by the third day. The same was true of the atebrin levels, 80 microgrammes at least for six days, and 125 on the third day, the effective therapeutic level being taken as 30 microgrammes.

4. Groups of over 1,000 patients with malaria were compared to test the results of standard malarial treatment (quinine 30 grains daily for three days, atebrin 0.3 gramme daily for five days and plasmoquine base 0.03 gramme with 15 grains quinine daily for three days) and a moderate atebrin treatment (0.6 gramme daily for two days and 0.4 gramme daily for four days).

No striking difference was found in the clinical response, or in occurrence of recrudescences. Parasite clearance was better with the atebrin treatment, though control of fever was identical. This apparent discrepancy was probably due to the fact that there the concentration of parasites was often too low to cause fever. Toxic effects with both methods were inconsiderable.

It was evident from this carefully controlled work that the usual standard methods were efficient, and that abbreviated courses in which higher atebrin dosage was used, were quick and effective. The position about relapses was not so sure, as the determining causes, if any, were obscure. However, the standard course of quinine, atebrin and plasmoquine followed by a maintenance course of atebrin seemed to give results as good as any other method.

THE INTRODUCTION OF "PALUDRINE"

The advent of "Paludrine" changed the whole outlook, though the proving of this drug was completed too late for it to be used in extensive field trials under operational conditions. The Medical Research Council in Great Britain which had controlled malarial research there, arranged for clinical trials of promising drugs. In 1944 F. M. Rose and F. H. S. Curd, working in the laboratories of Imperial Chemical Industries, synthesized two very promising members of a new series of anti-malarial drugs. D. G. Davey found that these not only killed malarial parasites in the blood of birds, but acted as a causal prophylactic, this is, could prevent infection from being established. The better of these (code name M 4888) was submitted to clinical trials early in 1945, and its pharmacology was studied. The Medical Research Unit at Cairns was asked to investigate its prophylactic and therapeutic action on human volunteers infected with South-West Pacific strains of malaria. Later the drug was styled "Paludrine": some confusion occurred about this name which had already been used for the less successful compound M 3349. The name has since been adopted for the drug M 4888, which is also called "Chlorguanide" in U.S.A. Since the war the name "Proguanil" has been used in Britain.

Tests were carried out at Cairns on some 200 volunteers with experimentally-produced infections, and clinical trials were made on soldiers suffering from malaria contracted in the South-West Pacific Area. Paludrine was proved to destroy parasites of malignant malaria inoculated by mosquitoes before they passed into general circulation. One gramme of the drug taken by mouth by a volunteer three hours before being bitten by a mosquito carrying *P. falciparum* would prevent him from developing malignant tertian fever. A dose of 0.1 gramme given on the second day and for three days thereafter would also prevent the disease from developing. Thus paludrine is a true causal prophylactic for malignant tertian malaria. Complete suppression of M.T. was achieved in volunteers by administering 0.1 gramme daily, no matter how many infective bites they received or what exertion, fatigue or cold they endured. Sub-inoculation experiments proved that the infection was cured. Thus paludrine was able to destroy both the erythrocytic and exo-erythrocytic forms of *P. falciparum.*

With benign tertian malaria paludrine was completely successful as a suppressive, and inoculation of the blood of a volunteer infected with *P. vivax* did not produce malaria in another volunteer who was taking paludrine. Thus the drug acted as a partial prophylactic, but relapses were prone to occur on cessation of ingestion of the drug, as with atebrin, since the exo-erythrocytic forms of the parasite still survived.

When used in the treatment of frank clinical malaria, paludrine controlled both M.T. and B.T. infections as efficiently as quinine and atebrin. Culture experiments by Captain R. H. Black showed that the drug inhibited nuclear division of *P. falciparum* grown *in vitro.* Consequently the drug acted more slowly than other drugs, especially quinine, and allowed a

rigor to occur before control of the parasite was gained. The minimum effective dose necessary to control fever was extraordinarily low, one dose of 0.1 gramme. No comparable schizontocidal effect had been observed in other drugs. Observation of patients treated showed that 64 out of 65 patients with M.T. were cured by taking 0.3 gramme a day for ten days. Relapses were not entirely controlled, but the experiments indicated that they were reduced in number and could be suppressed by one or two tablets of 0.1 gramme per week.

The atebrin-resistant strain described above was found to be extraordinarily susceptible to paludrine, for 0.025 gramme was found to suppress the disease in infected volunteers. Further experiments indicated that a combination of paludrine and plasmoquine might be potent in acting on the persistent exo-erythrocytic forms of *P. vivax*. Gametocytes were studied in respect of their vulnerability to paludrine. The drug did not inhibit the usual gametocyte wave, which was observed after the administration of 0.3 gramme daily for ten to fourteen days. Though no obvious change was produced in the gametocytes of *P. falciparum*, they were unable to infect a mosquito allowed to bite a patient taking paludrine. Even a single tablet of the drug taken by a gametocyte carrier an hour before he was bitten by a mosquito would prevent the development of oocysts in the insect's stomach; they formed but did not grow. Even traces of the drug in the volunteer's blood were sufficient to produce this effect, for the organism died off in the mosquito even up to ten days after paludrine administration had been discontinued. Similar results were obtained with *P. vivax*: gametocytes disappeared from the blood by the seventh or eighth day of treatment, and though they were unchanged in appearance the presence of paludrine in the blood as shown by M. J. Mackerras was associated with a remarkable carry-over which prevented the development of the oocyst in the mosquito.

Finally, in all the experiments at Cairns and in hospitals the drug showed a very low degree of toxicity, and its therapeutic dosage range was wide. It had the further advantage that it did not stain the skin.

Other drugs were tested at Cairns. For example, SN-6911 was tested and the results presented to the National Research Council U.S.A. in November 1944. This drug did not stain the skin or upset digestions, suppressed and cured M.T., but did not act as a causal prophylactic. *Vivax* infections were suppressed by it just as by atebrin. However, no drugs tested gave the performance of paludrine.

FURTHER EXPERIENCES IN THE TOXICITY OF ATEBRIN

More anxiety was probably felt in the beginning about the possibility of atebrin having toxic properties than later, when definite knowledge had accumulated. In spite of a wide use of atebrin in the treatment of malaria before the war, it had not been employed on a large scale over extended

periods of time as a suppressive. Experience with all drugs has proved that time is an important factor in producing toxic effects.

Toxic hepatosis was at first thought to be a possibility, owing to the accumulation of atebrin in the liver, but lesions of that organ were very rare. Aplasia of the haemopoietic system was also thought possible, and though this occurred it was also rare.

Skin lesions, whose possibility was also suspected owing to the fixation of variable amounts of dye in the skin, were by far the commonest manifestations of atebrin intoxication, yet these too occurred only in relatively moderate numbers, not significant when compared with the necessity of using the drug. Toxic confusion due to atebrin also occurred rarely. It was only in the later part of 1943 and beginning of 1944 when cases of a lichenoid affection of the skin appeared in any number. In view of the great military importance of a retention of faith in atebrin by the soldiers the patients were handled very discreetly; dermatologists agreed that this was a lesion resembling *lichen planus,* but of a type not seen in civil practice. Fuller account of this condition is given in the section on dermatology; here a brief description will suffice. The skin pigmentation caused by atebrin varied greatly. The skin had a curious greenish yellow tinge best seen on parts not sunburnt. In some persons deep pigmentation of a brownish colour occurred which faded very slowly on suspension of atebrin. Such persons were not necessarily affected by any skin disturbance. Pigmentation of the conjunctivae was as a rule minimal or absent, but it sometimes occurred, causing a deep pseudo-icteric tinge. The mucosa of the mouth was sometimes stained with dark patches of bluish or brownish colour, and occasionally the nails sometimes showed bluish pigmentation. Hypertrophic changes occurred at times in the skin of the palms and soles. When the lichenoid eruption was well established horny thickening of patches of skin on the trunk and elsewhere were an occasional feature, to which was added in a few instances a deep almost black pigmentation. When it became evident that a lichenoid eruption was an entity appearing in many parts of the tropical operational areas, it was naturally connected with the wide and continued use of atebrin, particularly in higher dosages. Yet it occurred only in a minority of persons taking continued large doses, that is, 0.2 gramme daily. Cases such as that described by Lum illustrate this. A man who had taken 0.1 gramme a day for six to nine months died from a rapidly developing hepatitis in four weeks. He also had a typical "tropical lichenoid" eruption.

This eruption assumed different characters, but there were constant basic features. Papules or plaques appeared, erythematous or violaceous with some hypertrophic reaction, scaly, or even verrucous. Pigmentation was common, so too were atrophic manifestations such as deficient sweating and alopecia. Mucous lesions were seen in the eyes and mouth. In some patients fissuring appeared, with eczematous weeping. Rarely a severe bullous form occurred, somewhat pemphagoid in type. The trunk was less affected than other parts as a rule, but the limbs, buttocks, genitals, feet, hands and neck were commonly involved. Itching was sometimes

slight, but sometimes quite troublesome. The exudative lesions rarely were precursors to a general exfoliative dermatitis. It should be pointed out that exfoliative dermatitis as a lesion *per se* was certainly due to a number of causes. It was seen sometimes at the close of 1942 before atebrin was used as a suppressive; a few such conditions were probably due to sulphonamide drugs, the cause of others was unknown.

Perhaps "wishful thinking" led at first to some reluctance to incriminate atebrin, even if such admission was made with great secrecy, but there can be no doubt that atebrin was at least the chief cause. Obviously some degree of idiosyncracy must have been necessary. Other possible factors suggested were a hot moist climate, nutritional deficiency, contact irritation, photosensitivity or some unknown infective agent. Some of these could be readily dismissed. Cases occurred on the Australian mainland in men who had been in a good cool climate for some time, not unduly exposed to the sun, and taking a satisfactory diet. While there may have been some other factors, not omitting the influence of the central nervous system on skin sensitivity, there was only one common factor, the taking of atebrin.

Skin patch tests with atebrin sometimes caused reactions but these were also seen in controls, and were little help in diagnosis. Extended investigations were not carried out, but the general results of observation concorded with the findings and opinions of work done elsewhere. By the end of 1944, for example, the Malaria Research Unit of the 3rd Medical Laboratory, U.S.A. Army Medical Services, had established that in this skin condition the mean plasma atebrin level was higher than that given by a weekly dose of 0.7 gramme, the skin atebrin concentration did not differ from that of persons with no skin lesions, and there was no demonstrable relationship between dietary insufficiency and the lichenoid disease. The experience quoted by Williams is significant. Amongst 18,000 New Zealand troops in Fiji, Tonga, New Caledonia and other Pacific Islands free from malaria no lichenoid was seen, and no atebrin was taken. Among the men in malarious islands, such as the New Hebrides, cases of lichenoid occurred within two and a half months; the men here were taking 0.6 gramme atebrin a week. In general improvement took place following withdrawal of atebrin, but after a latent period. Where atebrin medication was continued for treatment of malarial fever, recrudescence of the skin lesions was not always observed, but over longer periods of time it appeared that the generalisation was true that improvement was quicker and better after atebrin was suspended.

When this eruption was most common in the Australian Army skin diseases as a whole were also most prevalent, but it must be conceded that where the risk of malaria was greatest conditions productive of skin disease were also present. Improvement was noticeable about the time that the atebrin pigmentation began to leave the skin. No special treatment seemed to be effective. The time taken for full recovery varied to a good extent according to the previous duration of the dermatosis; long established lesions might take a year before they were completely resolved, but those

less firmly established sometimes cleared up completely in three or four months.

Reverting to hepatic lesions, acute toxic necrosis of the liver is occasionally seen in any community, but the number attributed, and probably correctly so, to drugs has grown of recent years. Since liver atrophy and aplastic blood disorders have rarely occurred in the army, but have been seen in connection with tropical lichenoid dermatitis, it is likely that this association is more than coincidental.

Psychoses related to high atebrin dosage have been mentioned previously. The episodes observed in hospitals during tests of high atebrin therapy were usually mild, and though varied in type, were confusional in general pattern. One patient had a maniacal outburst and two had epileptiform convulsions. Most of these patients had psychological defects of temperament, evident from their record, past history and subsequent examination. The condition was not constantly related to the atebrin blood level, and no parasites were observed in the blood during the episodes. There was no evidence during these tests that ordinary suppressive doses of atebrin, 0.1 gramme a day, caused any psychic disturbance. D. M. Ross described seven cases regarded as confusional states due to atebrin intoxication, seen in the psychiatric wing of an Australian general hospital, which treated 331 psychotic patients during the period under review. The pattern of symptoms was unlike the recognised psychoses; the patients seemed to have insight into their own condition, were worried by their peculiarities of behaviour and usually sought advice spontaneously. A confusional state allied to disordered action was the usual type seen. This always began within three weeks of commencing suppressive atebrin, especially when a larger dose was ordered to build up the blood level quickly. Temporarily raising the daily dose from 0.1 gramme to 0.2 gramme caused no unusual effects, and there was no evidence of the standard dose of 0.1 gramme daily causing mental disturbance.

Euphoria associated with hyperactivity was not specially noted in this series, but was occasionally reported in others. Australian experience with atebrin has revealed very few instances of mental disturbances due to toxic action. Perhaps mild symptoms might have occurred rather more frequently in association with high dosage than official reports indicate, as some of these may pass unnoticed, but on the whole the incidence has been negligible. Gastro-intestinal symptoms have, as previously mentioned, been unimportant and only a rare cause of trouble during high atebrin dosage, and then as a rule transitory only.

THE VALUE AND TOXICITY OF PLASMOQUINE

The toxicity of plasmoquine was periodically a subject of discussion during the war. Despite reports of abdominal pain and of haemoglobinuria from overseas, especially associated with previous administration of atebrin, the Australian experience was not unfavourable. Extensive clinical investigation showed no cause of uneasiness about the drug, although occasional complaints of abdominal pain were made. For a long time

there was a belief that plasmoquine was toxic if taken while a therapeutic concentration of atebrin was present in the body. The original pause of a day or two between the giving of atebrin and plasmoquine in the standard course of treatment was later omitted with no bad result. An enquiry was carried out in a military hospital to see if patients taking plasmoquine immediately after atebrin suffered any symptoms such as abdominal pain, but it was soon found that questioning the men suggested the very symptoms which were being investigated. Undoubtedly a minority of people were somewhat sensitive to plasmoquine, and it is admitted that the margin between therapeutic and toxic doses is not great, but in Australian experience it has proved a safe and useful drug. No doubt was felt concerning its gametocidal properties. Before the war its gametocidal action on M.T. crescents was established: this was confirmed at Cairns. M. J. Mackerras showed that a single dose of 0.02 gramme completely sterilises all M.T. crescents in the blood within less than 24 hours. Australian experience also coincided with the general agreement in most countries that it has some action in controlling relapses. The value of a course of quinine and plasmoquine for relapses had been pointed out by Sinton in 1937; only later during the war did this receive attention which it merited. Nevertheless it was necessary at times to represent strongly the need for this drug which was of specific value and was also an important component of a standard treatment which, with occasional modifications for special purposes, gave excellent results throughout.

CLINICAL ASPECTS OF MALARIA

About the purely clinical aspects of malaria there is not much to be said, although individual differences in bedside manifestations are as characteristic of malaria as any other infective disease. The death rate was extremely low, less than 0.5 per 1,000 owing to prompt diagnosis and treatment, not to any mildness of the disease. It was the duty of commanders of army field medical units to ensure that all the medical officers on whom devolved the care of men with malaria should be certified as competent to make the microscopic diagnosis. Large numbers of technicians were similarly trained. Diagnosis of course cannot be made with certainty except from blood films, and there can be few Australian medical officers with tropical field experience in this war who were not familiar with the use of Field's stain on thick films. Chemical suppression by drugs made diagnosis more difficult, and the coexistence of dengue in some areas introduced another element of doubt, particularly where transport for the evacuation of sick was subject to delay.

The only types of parasite of importance were the *P. falciparum* and *P. vivax*. The *tenue* subvariety of *falciparum* was observed with some frequency among natives on the north coast of New Guinea, but no particular significance can be attached to this. *P. ovale* was occasionally seen. For practical purposes it was regarded as similar to *vivax,* and was not of importance, but the identification of the ornate trophozoites when stained by Giemsa or similar stain was of interest. *P. malariae* was so rare as to

be negligible. Nevertheless quartan infections were not infrequently seen in native children and a nephrotic type of nephritis was observed in at least one such child. The rarity of this parasite was in part due to its peculiarities in transmission.

The advantages in relegating to the clinical background the descriptions of the classic types of malarial fever have been mentioned before. This phenomenon should resemble the once well-known remissions of pernicious anaemia in one sense, that the disease should be recognised too promptly for them to be seen. The different clinical patterns of M.T. and B.T. sometimes enabled a bedside distinction to be guessed, but minor points such as the occurrence of herpes were unimportant compared with the warnings of a conscience alive to the facts of pathology which reminded the medical officer of the facts, such as the capacity of M.T. to thrust B.T. aside when break-through of suppression occurred, and the real and great dangers of the former infection. Patients with M.T. were not necessarily very ill: it has been pointed out that in Aitape-Wewak mildness was a striking feature. But often such patients were very ill and showed those familiar multiform characters of severe infective illness which cause anxiety to a doctor or a nurse, and which are understated by the medical slang phrase that the patient "was very toxic". Fever which was not promptly controlled, or evidence of hyperinfestation, or suggestions of a possible metastatic complication of M.T. fever were indications for the use of the intravenous injection of 10 grains of quinine. The immense value and the safety of this measure are firmly established in the minds of those who had to treat large numbers of men very ill with malaria.

Of all the complications of *falciparum* infections cerebral malaria and the extremely severe infections just described were most common. The latter, of course, is not truly a complication. Cerebral malaria took all its usual forms, in particular coma and convulsions. Care was taken not to overdo treatment, a real danger which should not occur. The capacity of cerebral malaria to strike suddenly was not infrequently demonstrated, and illustrated, too, the imitative nature of the disease. In such cases treatment was not allowed to wait upon diagnosis. Cerebral malaria was fortunately infrequent and owing to suppressive atebrin and prompt treatment the death rate was low. Medical officers of the 8th Division experienced cerebral malaria under unfavourable circumstances. In Changi it was uncommon; but was much more frequently seen in Thailand and still more so in Burma. In Burma Hunt described two chief types, one with violent delirium and the other with drowsiness increasing to coma. Lumbar puncture was tried therapeutically, but withdrawal of spinal fluid had no effect on convulsions; the pressure was never raised but was often low. In Changi neurological sequels such as aphasia with spastic palsy of the right arm, and heminanopia were seen.

Abdominal forms of malaria were less common, but they occurred. In one instance in the Sanananda sector a medical officer asked for transport to move a patient whose symptoms suggested an abdominal emergency.

As it was night and all movement was difficult and at the time dangerous, the trial of intravenous administration of quinine was suggested. In the morning the man was well. Symptoms of shock with sudden onset and no elevation of temperature were also encountered. These so-called "algid" types have been attributed in some instances to coronary vascular lesions due to *P. falciparum* and these have been described at autopsy. No certain demonstration has been made in this series.

Sudden convulsive seizures occurred on all tropical fronts and aroused much interest. While some were undoubtedly due to malaria, others were not, so far as could be determined. Typhus was a probable cause in a few cases, but in others no explanation could be given save that they may have been true epileptiform seizures occurring as a single phenomenon in an exhausted individual. Death occurred in a few instances, but autopsy did not always give the reason. Medical officers were informed that where the facilities for full autopsy were inadequate, smears of the cortex could be made on slides and examined for parasites. This condition is discussed in the section on nervous diseases.

Jaundice associated with malaria always suggested the possibility of a relatively severe M.T. infection. Opportunity occurred during the first Papuan campaign for a study of this problem, as jaundice was then not uncommon in troops returning from the coastal areas. Undoubtedly infective hepatitis was occurring at this time, and on occasion there was reason to believe that the two infections coexisted. Indeed at this time the old advice never to diagnose two diseases in one patient was misleading and often proved fallacious. There was a gradation of severity leading up to the more serious M.T. infections in which the appearance of urobilinogen and then bile in the urine would be followed by haemoglobinuria. When the latter occurred it was regarded as threatened blackwater fever and treated accordingly. With the realisation that a degree of hepatitis was invariably present, came the doubt whether atebrin might be less easily dealt with by a damaged liver, but no evidence of this was found. As a matter of fact many such patients were regarded as showing indications for parenteral administration of quinine. In a different category were the patients with malaria who were deeply jaundiced but who were clinically only slightly ill. These in many instances had a virus hepatitis as well as a controlled malaria.

BLACKWATER FEVER

Blackwater fever was seen with increasing rarity as time went on. Numbers of men in whom haemoglobinuria was observed and who were treated as possible sufferers from early blackwater fever recovered promptly and were never classed other than as malarial subjects. Whether less careful handling and less forethought might have swelled the numbers of blackwater fever or not was a matter for conjecture. Evidence of haemolysis was regarded as a sign of great potential danger. A technical instruction was issued in the army based on the facts that death in blackwater fever was most commonly due to anuria and uraemia, and that

haemoglobin can be excreted by the kidneys with little disturbance of structure or function when the urine is alkaline in reaction, with pH 8.0. In order to stop the conversion of haemoglobin into methaemoglobin and acid haematin in the kidneys and to obviate mechanical blackage of the renal tubules rapid alkalinisation of the urine was advised. Sodium bicarbonate in saturated solution and 4 x molar sodium lactate solution were combined in ampoules of 10 cubic centimetres and two such ampoules were injected into a vein at once and at intervals of a quarter to half an hour as required. Glucose-saline solution was used to dilute the alkalies if immediately available. Alkalies were also given orally if tolerated. The same treatment was recommended for incompatible blood transfusion, fortunately exceedingly rare in war experience.

Treatment by alkalisation has not been without its critics who, like Maegraith and Havard, have pointed out that acid haematin is most easily precipitated in a slightly acid medium and that anuria may begin while the urine is alkaline. Alkalosis and alkaline urine do not necessarily coexist. However, without too great an insistence on mechanical theories of anuria, which are surely not the whole story, there is reason to believe that whatever may be the precipitating cause of the blood crisis that determines blackwater fever, red cell equilibrium seems to be favoured by alkalisation. As with other forms of the lower nephron syndrome, early action is imperative. The service practice was one of caution on the whole, both with regard to the dosage of alkalies and the use of blood transfusion. It was felt that the latter had its place if blood destruction was severe and if great care was taken both with cross-matching of the blood and with the conduct and close supervision of the transfusion. The official instruction gave warning of the risks of producing alkalosis and of the need for watching for signs of tetany. Blackwater fever in service practice has been an excellent example of preventive medicine, since its existence was reduced to a very low figure, especially in the later years of war, and insistence on prompt and early treatment produced what was often anticipatory action. Recovery from established anuria is recognised as rare. The traditional association of blackwater fever with quinine was not always borne out in service experience: several cases have been seen in which no quinine had been taken before the onset of haemoglobinuria, but only atebrin. On the other hand instances occurred in which the patient had been taking quinine as a suppressive. Blackwater fever was observed on one occasion in a volunteer patient taking plasmoquine experimentally.

Anaemia was common in some degree after severe attacks of malaria, but did not necessarily demand special treatment. A healthy man after a sharp attack of M.T. would soon recover with a period of convalescence on good diet. But with the added factors of prolonged exposure to fatigue, and of a monotonous diet, and probably repeated malarial infection a frank attack would reveal an anaemic state needing treatment. Early in 1943 this was frequently found, and in various phases of the war also. The existence of hookworm infestation was an additional cause of anaemia, so too was dietary deficiency. The diet in operational areas was often

lacking in variety and in fresh components by the time it reached the fighting soldier, particularly in the early periods. Even in hospitals on the mainland except in large centres it was difficult to obtain fruit and fresh vegetables. In one hospital in Queensland in a series of 300 men who had just completed treatment for malaria contracted in New Guinea the mean haemoglobin value was below 13 grammes, and about one-third of the men had a value of 12 grammes or under, the normal average being 15.4 grammes. At the time scale preparations of iron were restricted in output, and ferrous salts were also far from plentiful. With severe anaemia transfusion of blood was the quickest method, but this was seldom necessary. It was, however, of great value for some of the debilitated men arriving in Moresby from the Kokoda trail.

A rare but serious complication of malaria was rupture of the spleen. On occasion this has happened spontaneously while the patient was at rest or even in hospital. Hughes and Niesche described one case in which the patient vomited and collapsed: he had pain above the left clavicle (Kehr's sign) but no rigidity. Pullen, Bowden and others have also reported cases occurring in men who had B.T. In several of these death occurred. On one occasion spontaneous rupture apparently took place during the night in a soldier on leave in an Australian city, who died before anything could be done for him. A possible precursor to rupture of the spleen was described by Andrew, who studied ten men who had what he considered a spontaneous subcapsular haemorrhage. Sudden severe pain was felt in the left upper quadrant of the abdomen with local tenderness and muscular rigidity lasting some days or even weeks. None were submitted to operation, no abnormality was found in the thorax, and all recovered. It seems unlikely that the syndrome was due to an infarct in the spleen because no such history is associated with infarction in conditions where it can be proved *post mortem*.

In 1942 the growing number of cases of malaria introduced the occasional problem of false positive serological reactions for syphilis sometimes observed in the serum of patients with malaria. An army technical instruction was issued on this subject, which stated that the incidence of frank reactions was about 10 per cent, and of doubtful reactions about 25 per cent. Such reactions were observed with all the usual complement deviation and precipitation tests in common use, and lasted for several months. Therefore a warning was given that immunological evidence of syphilis in patients with malaria was not necessarily trustworthy. The Kahn verification test was carried out at headquarters in Melbourne as a means of distinction from syphilis, but was not found of significant value. Actually in field practice not much difficulty arose from this fallacy. Cox and Durant made some observations on these tests in connection with malaria and found that there was little risk of calling malaria syphilis if repeated examination was made at intervals by both Wassermann and Kline techniques. They could detect no relationship between "false positives" and relapses, and could not differentiate between false and specific reactions. Francis and Wannan also found that simultaneous observation of Wasser-

mann and Kline tests enabled the serological distinction to be made between malaria and syphilis. (See section on venereal diseases.)

TRANSMISSION OF MALARIA BY BLOOD TRANSFUSION

Difficulties with blood transfusions from donors possibly suffering from latent malaria have been mentioned previously. A technical instruction was issued late in the war on this subject as it was realised that increasing numbers of men with latent or relapsing B.T. malaria would be potential blood donors in both military and civil communities. The instructions pointed out that when blood containing malaria parasites is injected direct into the circulation of a person with no premunity to that type of parasite the recipient usually has a rise of temperature within twenty-four hours. This fever is mild and transitory if parasites are scanty in the transfused blood, but it recurs after a few days. The danger that *P. falciparum* might be transmitted thus was emphasised, especially when the recipient was already suffering from a condition which of itself might cause fever, such as a septic wound. Available evidence indicated that blood infected with malaria cannot be made safe for transfusion either by the addition of quinine or by cold storage. Fortunately, however, trophozoite-induced infections are easily cured, and even B.T. does not recur if a course of treatment is given, in contrast to the history of sporozoite-induced infections. In general the advice given was if possible to use blood from donors resident in a non-malarious area. Where this could not be done, careful selection of donors was advised, and thorough examination of thick films of blood. Before a transfusion was undertaken in a malarious area, it was important to ensure that the donor had been taking suppressive treatment and advisable if time permitted to give him 0.3 gramme of atebrin four hours before blood was taken. The recipient of such a transfusion was given continuous suppressive atebrin, beginning with the therapeutic dose if previous administration had been irregular. Any suspicious sign or symptom was an indication for examination of blood films, and if *P. falciparum* was found or even suspected, intravenous quinine was administered.

Braithwaite in recording experiences of transfusion in highly malarious areas (Aitape-Wewak), compared the results of using blood from local donors and stored blood. Stored blood was brought by air and road from Australia, and by the time it reached the forward area, though not haemolysed, caused an undue proportion of reactions. Therefore its use was abandoned. With careful selection and premedication of donors, giving atebrin as a routine measure to the patients and following the transfusion with a full therapeutic course, satisfactory results were attained. Here not only donor but patient was probably already infected, and despite precautions a number of patients contracted overt M.T. The invariable use of a routine high atebrin therapeutic course solved this problem in an area where parisitaemia was so common that *P. falciparum* was found in the blood of fourteen out of forty apparently healthy soldiers, including combatant and medical officers.

CRITERIA OF CURE

A few points remain to be mentioned connected with the clinical aspects. The criteria of cure adopted underwent alterations corresponding to changes in circumstances. For some time blood films were examined at the conclusion of treatment, but this practice was discontinued as it was seldom of value and threw a burden on the pathological services. A single thick film was therefore examined on the third day after the end of treatment, and if possible also on the fourteenth and twenty-first day. At the end of 1942 a maintenance course of atebrin was introduced, consisting of 0.1 gramme for six days in each week for six weeks. This made the examination of slides unnecessary as a criterion of cure, and the practice was therefore given up. Similarly examination of the blood of troops returned from malarious areas was discontinued unless clinical symptoms were manifest.

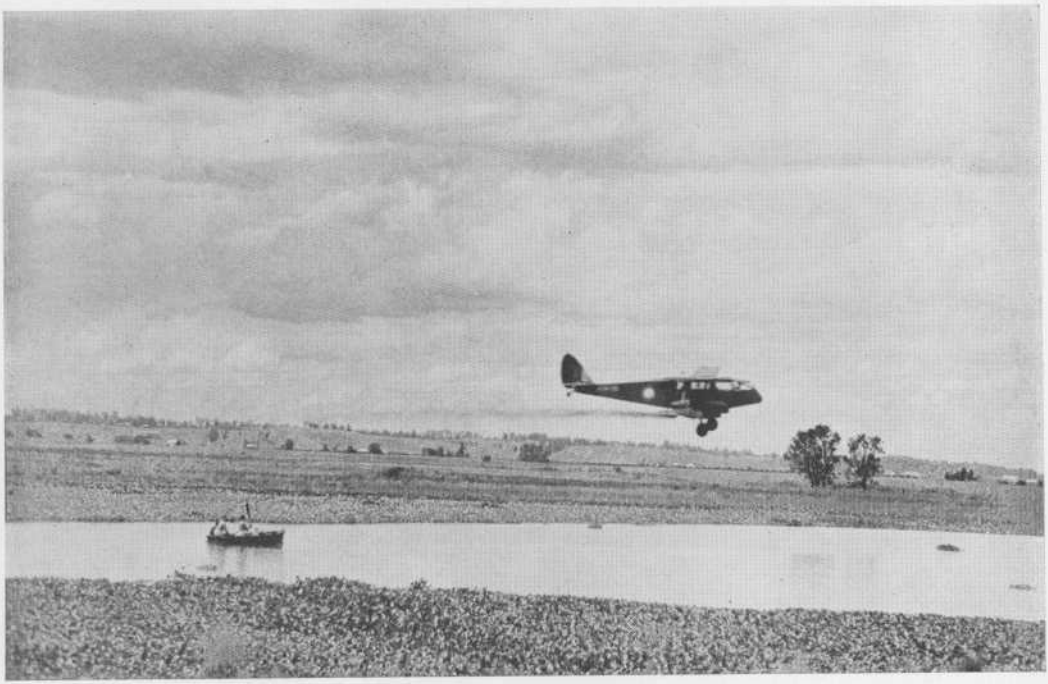
RESULTS OF TREATMENT

An army technical instruction which was of definite value to medical officers was one setting forth the results of malarial treatment. This embodied some of the findings of clinical research teams, and pointed out that the low death rate (under 0.5 per 1,000 for uncomplicated malaria) was due to early diagnosis, the use of intravenous quinine when indicated and suppressive treatment. Malignant malaria was found to recrudesce in 2 to 6 per cent and a second course of treatment had cured this minority in nearly every instance. The completed eradication of M.T. was the keynote of prevention of blackwater fever. Studies of relapsing B.T. infections indicated that only a minority of men would require more than two standard courses for clinical cure, and that not more than 5 to 10 per cent would be candidates for a chronic relapsing malaria. Latent malaria was common, chronic malaria was rare. Emphasis was laid on the need for prompt diagnosis and good treatment, for poor response to standard treatment was found to be associated with exposure to infection under conditions where these desiderata were not easily obtained, and where repeated infection would occur.

The various aspects of malaria in the civil population of Australia were carefully considered by the health authorities concerned. Indigenous malaria has already been discussed, with special reference to Queensland and the Northern Territory. The risk of exogenous malaria was minimal. As has been pointed out, in the potentially malarious areas of Australia the movements of malarialised troops were carefully controlled, and the vector position watched. Occasional cases of transmitted malaria were reported in different parts of Southern Queensland and New South Wales, but these were negligible. Contact with returned soldiers and civilians was established in several instances, and in one at least *Anopheles annulipes* appeared to be the vector. This occasional vector was also found breeding at one time in the neighbourhood of Concord Military Hospital in Sydney. As expected the transmission of malaria apart from the recognised areas was exceedingly rare. Among demobilised servicemen malaria has become

(*E. Ford*)

Spraying malarial breeding grounds with oil



(*R.A.A.F.*)

Mosquito control—spraying from aircraft.

(R.A.A.F.)

Aircraft spray equipment.

a diminishing problem, though in 1947 the Repatriation Commission found by questionnaire that in New South Wales it was still one of "appreciable magnitude". This was considered to be due to the failure of men to report for the correct sequence of pathological diagnosis, two weeks' treatment in hospital by paludrine and plasmoquine, and a follow-up course of paludrine for six months. This method has given encouragingly good results.

CONCLUSION

In conclusion it is of interest to look back over the six years during which malaria control played an increasing part in the campaigning of the Australian Armed Services, in particular the army. Several features of the constant struggle stand out. The organisation of control measures became more and more adequate and complete and rested on two foundations. One of these was the background of science, the other the principle that guidance was the role of the medical services, but that responsibility for carrying out measures for which disciplinary control was necessary rested with the combatant commanders and their deputies. The entomologist supplied information of a peculiarly technical and detailed kind, the malaria control specialist used this and other data in a characteristic mixture of entomology, hygiene and engineering, the malariologist combined the outlook of the doctor experienced in the pathological and medical aspects of malaria with a first-hand knowledge of military requirements. The clinical research teams patiently applied the complex techniques of combined biological and pharmacological experiment and submitted their results to field trial, the statistical experts collected and analysed figures and corrected unwarranted deductions, and the clinical workers at the bedside gave the benefit of their experience to patients and planners alike. This organisation was won by effort and trial not without opposition. As the result of these labours are there gaps in knowledge remaining, and are there weaknesses in the military method by which the knowledge is applied?

There are gaps of course. The loss of quinine to Japan was a blessing in disguise. Quinine still has first place as an antipyretic, lethal to the blood-borne cycle of the malarial parasite, and is unassailed for quick and reliable results in dangerous complications. But we have learned that it is a poor suppressive. Atebrin saved the day, and even though it yields the stage to paludrine and other and better anti-malarials, it has proved its ability to control massive infection, with a remarkably low price to pay in toxic reactions. Some of the doubts and difficulties with research on atebrin will be helpful in future work with other drugs. Since the introduction of the sulphonamides the estimation of blood concentrations has been firmly established as an index of effective dosage. The curiously unequal distribution of atebrin in the tissues of the body may be an indication of some of the difficulties in gaining certain knowledge of the mode of action of this and other drugs. The Australian research work used the generally accepted criterion of the plasma level of atebrin. Considerable variations are known to occur. Whether these are due to idiosyncracy, or to varia-

tions in absorption or whether there may be other occasional extrinsic factors such as occur in the peculiar conditions of jungle warfare, is not known with certainty. Factors governing degradation of atebrin in the intestine, and its absorption, may need further enquiry. Reid has suggested that variations in atebrin blood levels found in volunteers in certain stages of experimental M.T. infections may be related to transference from a storage depot in the liver. Plasma levels have been accepted as an expression of equilibrium of atebrin between the plasma and the tissues, though the validity of this has been questioned by some workers. Great advances are to be expected in the future in the attaining of accurate standards and measures of chemotherapy.

Of course there remain still the variables connected with human behaviour. It is evident that there are some disparities between biological human experiment in the laboratory which as yet cannot be reconciled. We cannot duplicate the effects of fear and anxiety by experiment, and exhaustion, with its physical and mental components, is not the same as fatigue. It was not found possible to produce break-through of malaria in volunteers in Cairns, though clinical impressions, statistically unconfirmed, strongly suggest that relapses may be induced by environmental traumata. There would be few if any who would deny that break-through of M.T. in the field does occasionally occur in persons who have unfailingly taken the dose of atebrin proved to be effective as a suppressive. Whether this may be an anomaly of absorption or due to some factor such as was present in Wewak, a relatively resistant strain of parasite, or to some other factor or factors unknown, we do not know. Under combat conditions in hyper-endemic areas such apparent anomalies may also be due to chronic and repeated infection associated with imperfect application of chemo-therapeutic suppression and personal protection. Again there must be some exciting causes for relapses of B.T.: though the existence of the tissue phase has been demonstrated since the end of the war the emergence of the parasites into the blood remains a mystery, yet it cannot be fortuitous.

Gunther has said that new concepts of malarial control alter our outlook on the problem: atebrin is passing, paludrine and its congeners rule in its stead, and chemical larval control may alter anti-malarial work radically. We now are better equipped than before in the war against this most destructive of protozoal diseases, but we still have to reckon with the recalcitrance of that possessor of high intelligence, man, who seems bent on destroying himself. It cannot be said that the very high overall rate of actual infection in the servicemen and servicewomen exposed to malarial hazards is entirely creditable. In theory we know how to prevent their infection, and how to suppress and partly to cure the resultant latent disease; and we have almost enough knowledge to cure the overt disease entirely and invariably when it occurs. In practice we have not successfully done all these things. Yet the manhood of Australia has suffered surprisingly little from the attacks of this dangerous enemy, and successful military operations have been made possible by the scientific knowledge

gained and its earnest application. Less spectacular, but highly successful, was the achievement of preventing the introduction of the island strains of malaria into the potentially malarious areas of Australia.

APPENDIX I.

September 1944.

General Routine Order.

By

General Sir Thomas Blamey, G.B.E., K.C.B., C.M.G., D.S.O., E.D.
Commander, Allied Land Forces in S.W. Pacific Area, and Commander-in-Chief, Australian Military Forces.

(a) COs will be held personally responsible for ensuring the strict observance of the instructions contained in this order and they, and all other officers, will at all times be vigilant and unremitting in the enforcement of such instructions.

(b) Neglect to comply with such instructions will be treated as a serious offence and will be punished accordingly.

(c) The occurrence of cases of malaria in a unit which has been directed to take the dosage of atebrin prescribed in this order will be regarded as *prima facie* evidence that the CO has failed to ensure the observance of such instructions.

APPENDIX II.

South-East Asia Command Headquarters.

From: The Supreme Allied Commander, South-East Asia.
Date: 14th February 1945. Ref.: SC5/398/E.
To: Commander-in-Chief, East Indies Fleet.
Commander-in-Chief, Allied and Forces, South-East Asia.
Allied Air Commander-in-Chief, South-East Asia.
Copy to: Commanding General, United States Forces, India Burma Theater.

Subject: ANTI-MALARIAL PRECAUTIONS:

I have already drawn the attention of Commanders-in-Chief to the importance of malaria discipline in my Directive of 1st January, 1944. Despite this the incidence per thousand men of malaria in South-East Asia Command is still very much higher than in the South-West Pacific Area. This I cannot accept.

2. Although there are certain factors operating in the South-West Pacific Area which render the task of controlling malaria in that area somewhat less difficult than in South-East Asia Command, the incidence of malaria in the South-West Pacific Area has been reduced, not by new method but solely by the high standard of anti-malarial discipline maintained in both the Australian and the American Armies, backed by comprehensive and extremely forceful routine orders rigidly enforced. Copies of these orders were forwarded in my letter PAO/MED/15.A of 26th September, 1944, with the suggestion that you should issue similar orders.

3. I now direct that if you have not already done so you will issue very strict orders on the lines of those given in Appendix A attached thereto. Owing to the varying problems of the Services regarding such matters as the definition of areas and the conflicting problems in dress, certain difficulties may arise in the interpretation of the orders attached hereto. If agreement cannot be reached locally, any such problems will be referred for decision at one of my meetings with Commander-in-Chief. I must emphasise that this is a matter of discipline designed to maintain fighting efficiency for which every Commander is personally responsible.

/s/ LOUIS MOUNTBATTEN,
Supreme Allied Commander.

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