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MALARIA IN KOREAN VETERANS

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THIS REPORT deals with the analysis of 152 cases of malaria in Korean veterans admitted to Queen Mary Veterans' Hospital during the year 1952.

The onset of hostilities in Korea in the early summer of 1950 introduced unforeseen problems with respect to malaria. Although it had been known to exist in Korea the Japanese, who had had considerable experience there, had not been greatly impressed by its incidence. For this reason the forces of the United Nations were thus somewhat unprepared for the relatively high incidence encountered. From the start of hostilities the United States forces were placed on suppressive chloroquine therapy and thus the severity of the problem was not realized until 1951 when men, rotated home on leave, discontinued suppressive therapy. The Commonwealth Division, of which the Canadian Brigade forms

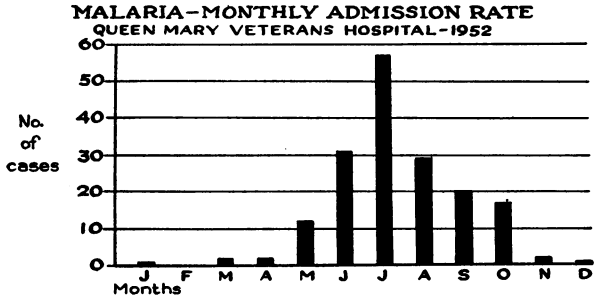

Fig. 1

a part, were placed on suppressive therapy with paludrine. As rotation leaves for Canadians serving in the war theatre did not begin until the spring of 1952, the problem of malaria in veterans hospitals throughout the Dominion did not become a major issue until the spring and summer of 1952.

From January until December 1952, there were 152 Korean veterans admitted to Queen Mary Veterans' Hospital with malaria. During this period approximately 1,350 veterans returned to this district from Korea which gave a malaria incidence of 11%, considerably higher than the incidence of 6.6% reported by the United States Far East Command.

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The type of malaria encountered in Korea is almost entirely benign tertian, although Eddleman[1] has reported one case of malignant tertian malaria. *Plasmodium vivax* parasites, characteristic of benign tertian malaria were found on direct blood smear in each patient in this series. Of the 152 patients 23 gave a history of having had malaria prior to admission to this hospital. Three had contracted malaria during World War II. The remainder had malaria either in Korea, Japan, or had an attack treated in some other hospital in Canada after leaving Korea.

The monthly admission rate of malaria (Fig. 1) is of some interest.

The monthly admission rate, although on a smaller scale, is similar to that given by the office of the Surgeon-General of the United States Army.[2] The explanation for the sharp fall of admission during the winter months lies in the fact that the so-called temperate zone *Plasmodium vivax* found in Korea has a long latent period of eight to nine months. For this reason, the individual infected during the summer months, which is the only time the disease is transmitted, does not manifest clinical signs of malaria until the following spring or summer.[3]

TABLE I.

SYMPTOMATOLOGY IN 152 CASES OF MALARIA ADMITTED TO Q.M.V.H. IN 1952

Chills fever	139 cases	(91%)
Headache	101 cases	(65%)
Anorexia, nausea and vomiting	59 cases	(38%)
Cough	23 cases	(15%)
Weakness	20 cases	(13%)
Pain in left upper quadrant	18 cases	(12%)

Miscellaneous.—(1) Low back pain. (2) Vertigo. (3) Joint stiffness. (4) Dark urine. (5) Diarrhœa.

CLINICAL FINDINGS

The ages of the patients in this series varied from 19 to 43 years, the average age being 24.8 years.

The interval between the last suppressive dose of paludrine and the onset of symptoms varied from slightly under 2 weeks to 10½ months; 75% of the attacks occurred within the first three months. This is in accord with the findings of a small group of cases reported by Aquilina and Paparella[5] and with the figures by Crawford.[4]

The duration of symptoms experienced by the patients prior to seeking medical advice varied from 12 hours to 35 days with an average of 6½ days. Table I lists the symptomatology as experienced by this group of patients.

The fact that some of the patients did not seek medical advice for 4 or 5 weeks indicates the benign nature of the symptomatology in some instances. While many of the patients had the typical 48 hour peaks of fever associated with benign tertian malaria, others ran a continuous fever. In some no fever was recorded in hospital. In general the pulse rate was elevated when fever was present.

Many of the patients in this series were admitted to hospital as diagnostic problems, with such diagnoses as pneumonia, acute tonsillitis, infectious mononucleosis and infectious hepatitis. These facts are mentioned not to cast any reflection upon the diagnostic acumen of referring physicians but simply to point out that in many instances the diagnosis is far from simple. It is well known that individuals who discontinue suppressive therapy and later develop malaria do not always conform to the clinical pattern usually associated with malaria.[6] The disease may have an insidious onset with malaise and headache. The fever may be continuous, not relapsing and early in the disease chills need not be present. Even more confusing is the fact that blood smears in a delayed primary attack may often contain very few, if any, parasites. This is in direct contrast to the smears in relapses where the parasites are usually easily found.

Splenomegaly was present in 84 of the 182 patients (55%). This is the result of examination by different observers and is lower than that reported by some who state that the spleen is palpable at some time during the disease in 90% of cases. However, our figure is larger than that reported by Schwartz *et al.*[7] and Aquilina and Paparella.[5]

Hepatomegaly was found in 37 patients (24%). This is considerably higher than that reported by Schwartz *et al.*[7] In only 5 patients was hepatomegaly unassociated with splenic enlargement.

Laboratory Findings

Of 150 hæmoglobin determinations done, 35 fell below 80% giving an incidence of anæmia of 23% (Fig. 2). The lowest recorded hæmoglobin was 55% with a red blood count of 2.98 million. The patients with severe anæmia were kept in hospital and reticulocyte counts were followed. All showed a reticulocyte count varying from 4 to 8% and all showed improvement in the anæmia with or without benefit of iron therapy.

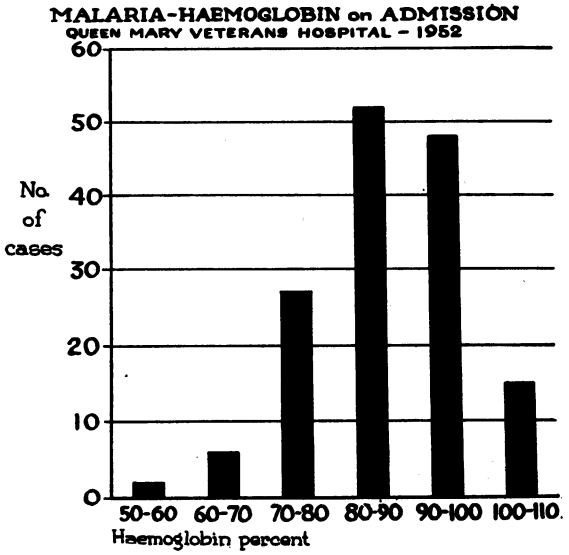

Fig. 2

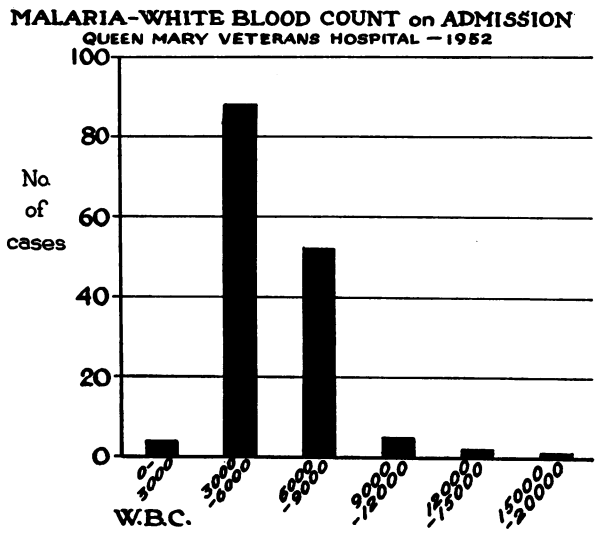

Fig. 3

The white blood count varied from a low of 2,350 to a high of 17,000 (Fig. 3). 61% of patients had leukopenia with white blood counts below 6,000 and 95% of patients fell within the range of 3,000 to 9,000 (Fig. 3). Of the three patients with a white blood count above 12,000 one had non-specific urethritis, one had infectious hepatitis and in the other no organic disease was found. In general when the white blood count was repeated during treatment it was found that it tended to rise, sometimes to quite high levels (10,000 to 15,000). This has been reported as a toxic effect of Primaquine or Pamaquine therapy[8] but it was noted as frequently in those treated with chloroquine alone. The dif-

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ferential white blood count was of little aid in diagnosis. Regardless of the total white blood count the differential was within normal range in 17% of patients; there was a relative lymphocytosis in 53% and a relative polymorphonuclear leucocytosis in 30%.

It has been known for some time that the standard liver function tests are frequently disturbed in malaria. However, the fact that the liver plays an active rôle in the life cycle of malaria has only recently been established.[9, 10] One or more liver function tests were done on 162 patients, which includes the 22 cases readmitted to hospital with a recurrence. Of these 89 showed an abnormality of at least one of the tests. The highest percentage of positive results was obtained with the cephalin cholesterol flocculation test (Table II).

TABLE II.

LIVER FUNCTION TESTS IN MALARIA

Test	*No. of tests*	*Neg.*	*Doubtful*	*Positive*
C.C.F.....	146	15	71	39 (41%)
Bil.....	117	78	0	39 (33%)
B.S.P.....	68	46	0	22 (33%)
T.F.....	47	28	7	12 (26%)

C.C.F.—Cephalin cholesterol flocculation
Bil.—Bilirubin
B.S.P.—Brom sulphalein
T.F.—Thymol flocculation

It is of interest that the number of positive thymol flocculation tests is considerably lower than the number of positive cephalin cholesterol flocculation tests, for which no explanation is offered. In only one case was the thymol flocculation positive where the cephalin cholesterol flocculation was negative. In an article published recently by Wahi and Arora[11] 90% of patients with acute malaria were found to have abnormality in a battery of liver function tests, the highest percentage of positive results being obtained with flocculation tests. One wonders if impaired liver function tests in malaria actually represent liver dysfunction. The elevated bilirubin can easily be explained by the process of hæmolysis. The flocculation tests depend on changes in gamma globulin which may occur in disturbances of reticulo-endothelial cells. Bromsulphalein retention too may be due to dysfunction of the reticulo-endothelial cells. One can thus explain derangement in liver function tests without invoking damage to the liver parenchyma. However, liver enlargement with tenderness in some patients can hardly be overlooked and there is very likely some liver damage in patients with malaria.

Out of the total number of patients in this series 140 were given a Kline exclusion test within 3 days of admission to hospital. In 48 of these (34%), where the Kline was found to be doubtful, Wassermann and Kahn tests were done. The breakdown of the Wassermann and Kahn reactions in this group is of considerable interest (Table III).

The figure of 34% is somewhat low when one considers the reports of Beerman[12] and Moore and Moh.[13] However, some interesting work in this regard was done by Kitchen *et al.*[14] They noted that the maximum frequency of positive results were found in the third week following the last paroxysm of malaria. This would help to explain our low results as our tests were done much earlier than this; also it would tend to confirm the statement that the more frequently the tests are made the higher the percentage of positive results. Another possible explanation for our low figures may be the fact that the Kline exclusion test in malaria gives rise to less false positives than the Wassermann or Kahn.[15, 16] In one of the patients in this series where a Kline Wassermann and Kahn were done on the same blood sample the Kline was subsequently reported as negative while the Wassermann and Kahn reactions were both positive. Of the 22 patients with definitely positive Wasserman and Kahn reactions 18 were subjected to further tests. In 16 the tests became negative in a period varying from one to five months and 2 were doubtful at the end of 1 month.

TABLE III.

Wassermann positive....	Kahn positive.....	22 cases
Wassermann negative....	Kahn positive.....	3 cases
Wassermann doubtful....	Kahn positive.....	8 cases
Wassermann doubtful....	Kahn doubtful.....	12 cases
Wassermann negative....	Kahn doubtful.....	3 cases
Total.....		48 cases (34%)

In 71 patients the stools were examined on one or more occasions for ova and parasites. The examinations were negative in 61. In the remaining 10 patients 5 showed infestations with *Ascaris lumbricoides,* while the remainder showed one of the following: *Entamœba histolytica, Giardia lamblia, Trichosis trichiura, Iodamœba butschlii, Ancylostoma duodenale.*

TREATMENT

Of the 174 patients, including the recurrences, 77 were treated with chloroquine alone, 93 were treated with chloroquine and primaquine, 2 were treated with paludrine and 2 with quinine alone. Unfortunately the dosage of chloroquine (diphosphate) varied somewhat at the discretion of the individual consultant on the ward but was generally 2.5 to 3.5 grams of the diphosphate salt given over a 2 to 5 day period. Chloroquine and primaquine together were used according to a plan recommended by the Directorate of Medical Services in Ottawa. (Chloroquine 1.0 gram stat 0.5 gram q.6 h. x 5 doses; 4th day start chloroquine 0.5 gram and primaquine 15 mgm. and continue daily for 10 days). The rather high dose of chloroquine in this latter schedule was tolerated well and there was only an occasional instance of nausea and vomiting which may well have been connected with the disease itself. There was no toxicity noted with respect to nausea, abdominal cramps, or liver disturbance with primaquine. One patient receiving primaquine was noted on the 7th day of treatment to be quite deeply cyanosed. As methæmoglobinæmia is reported to be one of the toxic effects of primaquine when used in higher doses,[17] a methæmoglobin test was done on this patient and this was reported negative but an arterial oxygen saturation was only 87%, suggesting interference with the normal oxygen uptake. The cyanosis cleared gradually in 10 days. Unfortunately it was impossible to detain this patient for further investigation. As no other cause could be found it was felt that this represented a toxic reaction to primaquine probably in the form of methæmoglobinæmia.

The term recrudescence is sometimes used for attacks occurring within 2 months of the original infection and relapses for attacks occurring after this time.[18] For this reason and in order to avoid confusion, all patients readmitted with malaria, regardless of the time interval, are designated as recurrences. There were 27 recurrences (35%) in those treated with chloroquine alone and 1 recurrence (1%) in those treated with chloroquine and primaquine. It is quite possible that the recurrence rate in both groups may be higher for, although letters were sent out to over 100 patients, only 61 replies have been received to date. However, as most of the patients in this series were from Montreal or the surrounding district it is likely that the majority would be readmitted to this hospital with a recurrence. Thus the figures that are submitted above are felt to be reasonably accurate. It is well known of course that recurrences in vivax malaria can occur up to three years. However, for comparable periods of follow-up, the difference in the recurrence rate with the two forms of therapy is quite striking.

There was no difference noted in the recurrence following varying doses of chloroquine which is in agreement with Gordon *et al.*[19] Of the 28 recurrences 9 became evident within the first 2 months and 18 within the first 3 months, which is also the experience of Gordon[19] and his group. The one relapse on chloroquine and primaquine therapy occurred in 9 weeks.

The prevalence of malaria during World War II stimulated great interest in the treatment of malaria and a number of new drugs were found. Of these chloroquine and paludrine are in common use at the present time. Both of these are excellent drugs, lacking in toxic effects, but the recurrence rate following treatment with them is high. With paludrine it is rarely less than 35% and with chloroquine it is perhaps even higher.[20] Pamaquine, one of the newer 8-aminoquinoline compounds has had extensive trial. The recurrences with this drug are believed to be low but it produces occasionally a hæmolytic crisis in the Negro race. Primaquine, also an 8-aminoquinoline, was synthesized at Columbia University during World War II. Clinical tests with it were done at Stateville Penitentiary[17] and revealed that the drug was safe in the therapeutic range. Further studies by Hockwald *et al.*[21] revealed that in therapeutic doses it was non-toxic in the Negro race. The efficiency of the drug in preventing recurrences in Korean malaria is indicated by the study of Garrisson *et al.*[8] This drug is not yet available for general use and our supply was obtained through the courtesy of the United States Army Medical Service. It is hoped that primaquine fulfills the advanced prophecy in the treatment of *Plasmodium vivax* malaria but it will be some time before a complete assessment can be made.

SUMMARY

The war in Korea has revived considerable interest in malaria in Military and D.V.A. Hospitals throughout Canada. During 1952 there were 152 veterans, recently returned from

Korean Military Service, treated for *Plasmodium vivax* malaria in Queen Mary Veterans' Hospital.

Anæmia was present in 20% of patients and leucopenia in 61%. The differential white blood count was within normal range in 17%, there was a relative lymphocytosis in 53% and a relative polymorphonuclear leucocytosis in 30%.

One or more liver function tests, including bilirubin, bromsulphalein, cephalin cholesterol flocculation and thymol flocculation, showed abnormality in 55% of patients. The highest percentage of abnormal results was obtained with the cephalin cholesterol flocculation test.

34% of patients showed abnormality of the Wassermann or Kahn serological test and 16% showed definitely positive reactions in both tests. The greatest percentage returned to normal within one to five months without therapy.

One group of 77 patients was treated with chloroquine alone while another group of 91 was treated with a combination of chloroquine and a new 8-aminoquinolene compound, primaquine. In a three to six month follow-up period there were 35% recurrences with the chloroquine group and only 1% with the group which received chloroquine and primaquine. Sufficient time has not yet elapsed for a full evaluation of the two forms of therapy and a further follow-up study is planned.

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AN EPIDEMIC OF ACUTE NEPHRITIS*

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THE OCCURRENCE of acute nephritis in groups of associated individuals has been described under a variety of circumstances. It has frequently been recognized among soldiers and referred to as trench or war nephritis.[1, 2] Fleming[3] has reported an outbreak among the adult inhabitants of congested tenement buildings where cold, damp environment and poor nutrition have been suggested as possible contributory factors. In this outbreak, which reached almost epidemic proportions during 1945-46, the majority of 159 hospitalized cases in the group were from 20 to 40 years of age. As a rule, the maximum incidence occurs between 5 and 20 years of age.[4] Kemp *et al.*[5] described an outbreak of acute nephritis in a private school in which they found 4 cases of clinical nephritis and 20 cases of microscopic hæmaturia among 96 boys from 11 to 14 years of age. No direct relationship could be established with hæmolytic streptococcus infections. Multiple cases of acute nephritis have been observed in the children of one family,[6 to 9] and a "familial predisposition" to the disease has been suggested.[10] Nephritis has frequently developed following scarlet fever, and to a lesser extent, other streptococcal infections. The opinion is widely held that, in some obscure manner, nephritis is related to streptococcal infections.

This report deals with an outbreak of acute nephritis which occurred in a sharply localized rural area. The presence of numerous cases of acute nephritis at Lower West Pubnico, N.S., was first brought to our attention in the middle of February, 1952, when the Provincial Department of Health was asked to investigate the outbreak. Up to this time there had been 19 cases of nephritis since October 1951, and 2 deaths in uræmia had occurred. The most recent

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