UNIVERSITY OF DAR ES SALAAM

DEPARTMENT OF MEDICINE

TOPIC: CEREBRAL MALARIA AT MUHIMBILI MEDICAL CENTRE

A Clinical Study.

by:

EDINI ERASMO REVETA MARO, M.D. (Dar)

A Dissertation submitted in partial fulfilment for the Degree of Master of Medicine (M.Med) in Internal Medicine of the University of Dar es Salaam.

1985.

SUPERVISOR: Professor Donald G. McLarty, M.D.; F.R.C.P. (Glasgow)

Donald G McLarty

DECLARATION.

I the undersigned solemly declare that this dissertation is the result of my sole effort appart from my supervisor who constantly advised me on various aspects throughout the study and its write up.

I further declare that this same dissertation has never been submitted for a degree in any other University.

Eden E.R. Maro.

All rights reserved. No part of this dissertation may be reproduced, stored in any retrieval system, or transmitted in any form or by any means: Electronic, Mechanical, Photocopying, Recording or otherwise without prior written permission of the author or the University of Dar es Salaam in that behalf.

ACKNOWLEDGEMENTS.

Master of Medicine (Dar) promotes both clinical experience and also interest in research and scientific work. For the former I owe many thanks to my teachers. For the later I am particularly grateful to Professor D.G. McLarty, F.R.C.P., my overall supervisor, who encouraged and supervised me throughout the study and critically read through the manuscript giving necessary advice.

Many thanks to Professor S. Basinda, Dr. P. Pallangyo and Dr. A. Swai for their advice, guidance and constructive criticisms.

I am indepted to the Head of the department of Medicine Professor I. Mbaga, and Head of department of Parasitology Dr. C. Kihamia for the clinical and laboratory facilities put at my disposal.

I am grateful to Mr. B Ramji and Mrs. Vicky who helped me much with the laboratory work and Mr. Mmuni for his tireless Secretarial Services.

My relatives and friends missed me most of the day and night hours but accepted the inconvenience without complaint. May I express my sincere gratitude for their patience and understanding.

Finally, may I thank the staff of Mwaisella Medical Wards and everybody not mentioned by name who took keen interest both directly and indirectly in making this study a success.

TABLE OF CONTENTS.

	Page:
Abstract	1 - 2
Background to the study	3
Review of Literature	3 - 8
Objectives of the study	9
Patients and Methods	9 - 12
Results	12 - 31
Discussion	32 - 44
Conclusion and Recommendations	44 - 46
References	47 - 60

LIST OF TABLES AND FIGURES.

	Page:
• Number of patients with cerebral malaria admitted during each month of the study.....	18
• Age and sex distribution of cerebral malaria patients	19
• Place of birth of the cerebral malaria patients	20
• Length of time patients with cerebral malaria had lived in Dar es Salaam	21
• Occupation of the cerebral malaria patients.....	22
• Symptoms of cerebral malaria	23
• Signs presented by cerebral malaria patients	24
• Distribution of the cerebral malaria patients into 3 categories of altered cerebral function at the time of admission and relation to outcome	25
• Relationship between mortality rate and duration of disturbance of consciousness.....	25
• The parasite count per 8000 leucocytes	26
• Treatment given and outcome	27
• Complications recorded	28
• Results of in Vivo chloroquine sensitivity test	28 - 31.

CEREBRAL MALARIA AT MUHIMBILI MEDICAL CENTRE.

A CLINICAL STUDY.

ABSTRACT:

Between October 1, 1983 and September 30, 1984, a clinical study was done on cerebral malaria patients admitted to the medical wards of Muhimbili Medical Centre. The objectives of the study were to determine the clinical presentation, to assess the level of parasitaemia and clinical findings which could be used for assessment of prognosis and to assess the response of the parasites to chloroquine in vivo using the WHO standard field test.

During this period of the study 198 patients with cerebral malaria were admitted. The mean age of the patients was 18 years (range 7 - 54 years). 177 (89.4%) patients were between 7 and 30 years. There were 101 males and 97 females (M:F sex ratio 1:1). An increase in the incidence of cerebral malaria was noted from May to July, one month after the heavy rains in Dar es Salaam. 139 (70.2%) patients were immigrants from regions of high altitude (over 5000 ft. above sea level). 145 (73.3%) patients had lived in Dar es Salaam for four years or less. 70 (35.4%) patients were attending school and 30 (15.2%) were housegirls and houseboys.

The most frequent presenting symptoms at the time of admission to hospital were: fever, headache, confusion, body weakness, vomiting, loss of consciousness, convulsions, loss of appetite, dizziness and aggressiveness. The most frequent signs were: confusion, restlessness, tachycardia, high temperature (above 38.5°C), dehydration, pallor, coma, dilated pupils and thought disorders.

At the time of admission 119 (60.1%) patients had signs of acute organic brain syndrome, 73 (36.9%) had signs of diminished level of consciousness and 6 (3.0%) had signs of movement disorders.

The overall mortality was 12.7% being highest among those who were admitted with diminished level of consciousness.

Out of the total of 25 patients who died, 15 (60%) patients had the symptoms of cerebral malaria for more than 72 hours before they were diagnosed and treated. Among 17 patients with diminished level of consciousness who died, 13 (76.4%) patients remained in a state of diminished level of consciousness for more than 48 hours before they died. The identified causes of death were: pulmonary complications, hypoglycaemia and acute renal failure.

110 (55.6%) patients were treated with chloroquine only and 17 (8.6%) with quinine only. The remainder were treated either with chloroquine combined with cotrimoxazole or tetracycline, or with quinine and fansidar. In vivo tests of chloroquine sensitivity were carried out on 28 patients who had not received chloroquine prior to admission. 3 (10.7%) patients showed chloroquine resistance at RII level according to the WHO classification.

The commonest complications noted were anaemia, hypoglycaemia and persistence of the psychotic disorder for more than two weeks.

PART ONE:

A. BACKGROUND TO THE STUDY.

No studies have yet been published on cerebral malaria in adults in Tanzania. One year ago (1983), among 100 patients with non-traumatic coma studied at Muhimbili Medical Centre in the medical wards over a period of 7 months, cerebral malaria accounted for 37% of the cases[1]. Moreover, with the emergence of chloroquine resistance in Tanzania many of us working in the medical wards, had the impression that the number of patients admitted with cerebral malaria was increasing. Lack of local data on the clinical features of cerebral malaria and the observed increase in the number of patients admitted with a diagnosis of cerebral malaria prompted me to do this study.

B. REVIEW OF LITERATURE

1. Prevalence of cerebral malaria:

Malaria is still one of the world's major causes of morbidity and mortality in all age groups[2, 3, 4]. The disease which by 1983 was still a risk to 40% of humanity poses a continuing problem to health workers especially since the development of resistance by anopheles mosquitoes to pesticides and the appearance of plasmodium falciparum resistant to most drugs used in the treatment of the disease.

The situation in Africa is probably worsening despite the fact that the fatality rate due to malaria and particularly falciparum malaria can be reduced by early diagnosis[5] and early control measures.

Figures from Muhimbili Medical Centre show that malaria accounted for about 5 - 6% of all hospital deaths in 1983, but the frequency of cerebral malaria related to the total prevalence of malaria infection is unknown. It is known to range from 0.01% in Zimbabwe, 2% in

American troops in Vietnam, 2.5% in India and 16% in Uganda[6].

2. The complications and clinical features of cerebral malaria.

Infection with plasmodium falciparum is known to be associated with a high morbidity and mortality especially in pregnant patients, children and non-immune patients. These patients are more likely to have severe complications such as cerebral malaria, severe anaemia, acute renal failure, malaria nephrosis, disseminated intravascular coagulopathy, resistant pulmonary oedema and rarely splenic rupture. Two factors correlate well with the development of these complications. One is an overwhelming infection. Any patient with an intense parasitaemia (400,000 parasites/mm^3) is in danger of developing a major complication. The other is delay in treatment due either to misdiagnosis, to lack of a positive malaria smear or to patient's failure to seek medical help[7]. Of the complications, cerebral malaria appears more ominous than the others because its onset carries grave implications and death is the outcome unless prompt and adequate treatment is initiated.

The definition of cerebral malaria varies among authors, but for practical purposes, a patient with confirmed malaria parasites who displays signs of central nervous system dysfunction not explained by severe hyperpyrexia, anaemia, diabetic ketoacidosis, psychiatric illness or infections like meningitis and typhoid should be considered to have cerebral malaria[8]. Cerebral malaria, which commonly occurs in children and non-immune, is characterised by fever and altered states of consciousness ranging from confusional states to coma. Acute psychiatric disturbances including paranoiac and manic syndromes, hallucinatory delirium, schizophrenic-like states, depression, convulsions, pyramidal and extrapyramidal hyperkinesis, acute ataxia, psychosis and rarely focal neurological defi-

cit such as hemplegia, aphasia, optic neuritis, retinal haemorrhages and exudates may occur[9]. Spinal cord disorders and acute polyneuropathy have also been described. Probably in adults, the commonest cause of epileptic seizures is febrile illness due to malaria infection[10]. The exact pathophysiologic mechanism are not well known. Recovery without residual disability is the rule for the acute personality changes but permanent sequelae including deafness, blindness, hemiplegia, cerebral ataxia and choreiform movements have been described but they are rare[11].

3. Pathophysiology of cerebral malaria.

The pathophysiology of cerebral malaria is cerebral anoxia due to either thrombosis[12] or reduction of the oxygen carrying capacity of the infected erythrocytes[13]. The symptomatology is probably dependent on which area of the brain is anoxic and thus every neurological sign can occur. Currently it is believed that malaria affects the nervous system as the capillaries are damaged and blocked with parasitized cells, resulting in microinfarctions, anoxic oedema and bleeding diathesis from disseminated intravascular haemolysis. Toxic and allergic (immunogenic) damage by circulating antigen-antibody complexes to vascular endothelium especially the capillaries leads to leakage of fluid electrolytes and proteins. The intensity of the immune reaction associated with complement activation is important in the pathogenesis and may account for selective damage to cerebral vessels. Parasitized red cells tend to agglutinate and stick to capillary endothelium[14] and when they rupture during the process of asexual schizogony, they release vasoactive polypeptides including kinins. These polypeptides, kallikrein, kininogenases and prostaglandins causes functional

disturbance of the local circulation, altering the permeability of the blood-brain barrier which may be reversible.

As to why some patients develop coma and others do not is still unclear. In Africa, cerebral malaria occurs most frequently in children of pre-school age suggesting that a lack of immunity favors its development. Cerebral malaria is rare or virtually unknown in children under the age of one month as IgM antibodies against merozoites are transferred through the placenta and provide immunity[6].

4. Diagnosis of cerebral malaria.

Diagnosis of cerebral malaria is often difficult because the onset may be slow or appear with dramatic speed. The clinical manifestations are protean. The fever has no periodicity and parasitemia may be obscured by the tendency for the concentration of parasites to vary considerably from hour to hour[7].

In the non-immune (including visitors to the tropics) cerebral malaria must be considered in a patient with fever and symptoms of dysfunction of the central nervous system. However, since malaria infection is common in endemic areas, the finding of malaria parasites in the blood film does not necessarily confirm the diagnosis. Other causes of fever, such as typhoid, encephalitis, meningitis, Weil's disease, drug poison, brain tumour and heat stroke should be considered and excluded. Usually for cerebral malaria, apart from the examination of the blood films, no characteristic diagnostic findings are present in either the blood or the cerebrospinal fluid.

5. Treatment of cerebral malaria.

Treatment of cerebral malaria is a medical emergency and has been reviewed in detail by several authors[15, 16]. Administering

chloroquine (preferably intramuscular) or quinine intravenously is mandatory and is given for between 5 and 10 days[6]. In countries where there is resistance to chloroquine for example South East Asia, Asia, East Africa and parts of South America, quinine should be preferred as the drug of choice. The newer antimalarial drugs, mefloquine and quinghaosu are showing great promise[17].

In the last two decades, glucocorticoids such as dexamethasone were thought to be beneficial in reducing cerebral oedema and improving the prognosis in cerebral malaria but two years ago, in a well designed double-blind controlled trial, dexamethasone was judged to be deleterious[16]. There is no agreement on the value of heparin in the treatment of disseminated intravascular coagulopathy (DIC) in cerebral malaria. Low molecular weight dextran and mannitol may help to prevent stasis and coagulation in capillaries. Some authors have successfully treated malaria with DIC using antithrombin III, streptokinase[18] and prostacyclin[19]. There are also reports whereby patients with cerebral malaria with heavy malaria parasitaemia or complicated by full blown DIC after failing to respond to other forms of treatment were successfully treated by exchange transfusion[20, 21]. Anaemia may need blood transfusion. Additional management for the comatose patient (nutrition, fluid balance and careful nursing), pulmonary oedema, renal failure and circulatory collapse may be life saving.

6. Chloroquine resistant falciparum malaria.

The emergency of multiple drug resistant forms of plasmodium falciparum is a major public health problem with prophylactic and therapeutic implications[22, 23, 24]. After the first reports of chloroquine resistant falciparum malaria from South America[25, 26, 27] and later from South East Asia[28, 29, 30], a number of reports

appeared from various parts of Africa[31, 32, 33]. Cases of chloroquine resistant falciparum malaria acquired in East Africa have been reported since 1978. A number of cases have been documented in non-immune visitors returning from Kenya and Tanzania[34, 35, 36]. Some of them had been taking chloroquine chemoprophylaxis[37, 38]. Cases of RI, RII and more recently RIII resistance according to the WHO Scientific group criteria were discribed in these areas[39, 40, 41, 42].

Reports of suspected drug-resistant malaria continue to increase in Tanzania as in other African countries. Although these suspicions have not been confirmed, they create concern because of an increasing dependence in Tanzania on chloroquine for mass control of malaria in endemic areas and for individual treatment. Therefore it is essential to determine the magnitude of this problem and to seek alternative treatment regimens.

7. Prognosis and mortality due to cerebral malaria.

Certain predictive features of poor prognosis in cerebral malaria are known and these include high parasitaemia, deep coma acute renal failure, hypoglycaemia and pregnancy.

There is a wide variation in the incidence of mortality due to cerebral malaria. It ranges from 16% to 50% in tropical countries [11, 16, 43] and 3% to 10% in the United Kingdom in the last decade where over 1000 malaria patients were seen each year. The lack of uniformity in diagnostic criteria of cerebral malaria may explain this variation. The mortality of cerebral malaria at Muhimbili Medical Centre is unknown.

PART TWO:

1. OBJECTIVES OF THE STUDY.

The objectives of the study were:

a. To determine the clinical presentation of cerebral malaria patients admitted in the medical wards of Muhimbili Medical Centre.

b. To determine the level of parasitaemia and clinical findings which could be used for assessment of prognosis

c. To assess the response of the parasites to chloroquine in vivo using the WHO standard field test.

2. PATIENTS AND METHODS

The study was based on information obtained from a clinical evaluation of cerebral malaria patients aged 7 years and above admitted to the medical wards of Muhimbili Medical Centre between October 1st 1983 to September 30th 1984. I saw most of the patients myself, even though many of them were under the care of other doctors. The information was derived from a combination of a careful clinical history from the patient and/or relative who accompanied the patient to the hospital and confirmed when the patient regained full consciousness and also from the referral notes which showed the previous treatment. A thorough physical examination was done and then a specially prepared standardized questionnaire was completed. The patients were followed up until they recovered or died.

The diagnosis of "cerebral malaria" was made on a patient with confirmed malaria parasitaemia who displayed signs of central nervous system dysfunction, not explained by severe hyperpyrexia, anaemia, diabetic ketoacidosis, psychiatric illness (from past medical and family history) or infections like meningitis and typhoid.

During the follow up period, the complications of cerebral malaria i.e. diseases or accidents superimposed on cerebral malaria without being specifically related yet affecting or modifying the prognosis of cerebral malaria, were looked for. Those patients found to had a second disease, for example, hepatitis B, that could not be regarded as a complication, were excluded.

3. Assessment of parasitaemia.

On the day of admission, thick and thin blood films were obtained from all patients by finger puncture and stained by a standard Giemsa method. They were examined for the number of malaria parasites and the specie of plasmodium. Subsequently, thick blood films were obtained daily and parasite counts performed. An estimate of parasite count was made by recording the number of asexual parasites seen per 200 leucocytes. These counts were then converted to approximate numbers per mm^3 of blood by using a standard factor of 40 considering 8000 per mm^3 as an average count of leucocytes. After treatment, blood films of larger areas of the thick film were examined to confirm negative findings.

4. Other investigations and treatment.

Lumbar punctures were done to those patients who presented with neck stiffness, seizures and diminished level of consciousness i.e. drowsy, stuporous and comatose, so as to rule out meningitis or subarachnoid haemorrhage. The CSF was analysed for glucose, protein, cells, Gramstain, Ziehl-Neelsen stain and culture for pyogenic organisms and mycosis. At the time of admission blood glucose, urea and creatinine and haemoglobin were estimated. For patients who presented with fever and jaundice, liver function tests were performed to exclude viral hepatitis. Blood cultures were done for those

patients whose fever persisted for more than 72 hours despite the treatment so as to rule out septicaemia. Patients complaining of dysuria and those who had indwelling catheter, had their urine cultured to rule out urinary tract infection. Radiographs of the chest were performed to those patients who had pulmonary complications for example pulmonary oedema and aspiration pneumonia. Fluid input and output was recorded. Also patients with diminished level of consciousness had fundoscopy done after introducing a few drops of homatropine into their eyes.

For more than half of the study period, quinine was not available. Most patients were therefore treated with chloroquine 25mg base/kg in three days irrespective of the dose of chloroquine they had taken prior to admission.

5. In Vivo test of chloroquine sensitivity.

In those patients who had plasmodium falciparum species only and had not taken chloroquine two weeks prior to admission, urine was tested for excretion of antimalarial drugs using the Wilson and Edeson test before administration of chloroquine and at least one more time during the follow up period. Patients whose urine was positive for antimalarial drugs were excluded. The WHO field test for strain sensitivity of malaria trophozoites to 25mg/kg of chloroquine base in 3 days with a 7 day observation period ("7-day test") was performed on these patients. Thick blood films were prepared as nearly as possible at 24 hour intervals after the initial examination in order to calculate the total number of trophozoites. Again trophozoites were counted per 200 leucocytes and then converted to numbers per mm^3 of blood by assuming a constant leucocyte count of $8000/mm^3$. Those patients who had no progressive decrease in parasite count with clearance on day 7 were given another antimalarial drug.

The rainfall figures for Dar es Salaam City, were obtained from the Directorate of Meteorology - Dar es Salaam airport station.

RESULTS:

I. Seasonal incidence.

There was a marked increase in the number of patients with cerebral malaria admitted to hospital from February 1984 to July 1984. This coincided with the months of heavy rainfall. The wet season started early in March and ended in June 1984. The incidence of cerebral malaria was high during the rainy months, peaking two months after the onset of heavy rains and continued for a further one month (Figure 1).

II. Age and sex distribution.

Cerebral malaria mainly affected patients whose age ranged from 11 to 30 years. 177 (89.4%) patients were 30 years or less and only 21 (10.6%) were above 30 years. Overall, there was no significant sex difference. The male: female sex ratio was 1:1 (Table 1). There were more females than males among patients who were 25 years or less and more males than females for those above 25 years. This sex difference was significant ($P < 0.001$).

III. Place of birth.

139 (70.2%) patients were immigrants from high altitude regions ($\geq$5000 feet above sea level) of Tanzania, where malaria transmission normally occur for less than 3 months in a year. These patients came from Kilimanjaro, Morogoro, Iringa, Rukoba,

Songea, Arusha, Mbeya, Tanga and Musoma regions (Table II).

8 (4.0%) patients were born and had lived all their lives in Dar es Salaam where malaria transmission occurs throughout the year (holoendemic). Thus they would be expected to have a high level of immunity against malaria. Probably other factors apart from immunity may influence someone to contract cerebral malaria.

IV. Length of living in Dar es Salaam.

88 (44.5%) patients had lived in Dar es Salaam for a period of less than one year and 145 (73.3%) patients had stayed in Dar es - Salaam for 4 years or less. Only 27 (13.6%) patients had stayed for more than 4 years. In 26 (13.1%) patients, the duration of stay was unknown as they absconded or died before the information was obtained (Table III).

V. Occupation.

100 (50.5%) patients were non-immune young people from high altitude areas upcountry, who came to Dar es Salaam looking for employment (housegirls/boys) or to attend school. Their duration of stay in Dar es Salaam was less than 4 years. 8 (4.0%) patients were soldiers or policemen. The businessmen class consisted of 8 (4.0%) patients. Their duration of stay in Dar es Salaam was less than one year (Table IV).

VI. Clinical features.

The average duration of symptoms was 3.2 days. 191 (96.5%) patients complained of fever at the time of admission. The most frequent symptoms were: fever, headache, confusion, body weakness, vomiting, sudden loss of consciousness, convulsions, loss of appetite, dizziness and shouting or aggressiveness (Table V).

Among the 97 females with cerebral malaria 5 (5.2%) patients were pregnant.

The commonest clinical signs noted were: confusion, restlessness, tachycardia, a high temperature ($\geq 38.5^{\circ}C$), dehydration, anaemia, comatose state, dilated pupils reacting equally to light, semiconscious state and thought disorders (hallucinations and paranoid ideas) (Table VI). None of the patients had a temperature above $40^{\circ}C$. A patient was labelled as anaemic if the haemoglobin level was found to be less than 9 gm/dl. Three patients presented signs simulating those of tetanus. They were conscious and had trismus, twitches of the lips and limbs and opithotonus.

VII. Categories of cerebral malaria and mortality.

The neurological signs in cerebral malaria were variable and changed with remarkable rapidity. Depending on the clinical features at the time of admission, the patients were divided into three categories. 119 (60.1%) patients at the time of admission presented features of acute organic brain syndrome some with acute personality changes. Their mortality rate was 6.7%. The second category consisted of 73 (36.9%) patients who were admitted with signs of diminished level of consciousness. Some with focal neurological signs. Their mortality rate was 23.3%. The third category consisted of 6 (3.0%) patients who presented signs of movement disorders. No patient in this group died (Table VII). The overall mortality was 12.7%.

VIII. Delay in diagnosis.

Delay in diagnosis was related to the mortality rate. A total of 25 patients died. 15 (60%) patients had the symptoms of cerebral malaria for more than 72 hours before they were diagnosed and treated.

10 (40%) patients had the symptoms for less than 72 hours before diagnosis and treatment (Table VIII).

IX. Duration of diminished level of consciousness (semiconscious/comatose state).

73 patients were in a semiconscious or comatose state at the time of admission. 17 (23.3%) patients died. Most of those patients who died had remained semiconscious or comatose for more than 2 days. 13 (76.4%) patients remained semiconscious or comatose for more than 48 hours before they died. Only 4 (23.6%) patients died after being semiconscious or comatose for 48 hours or less (Table IX).

X. Parasite counts.

All 198 cerebral malaria patients were infected by one species plasmodium falciparum. 72 (36.4%) patients had an initial parasite count of more than 2000/8000 leucocytes. Most (80%) were in coma. There were 8 patients whose initial blood slides were negative for malaria but subsequent slides were positive. These initial parasite counts do not reflect the true initial parasitaemia because most patients had taken chloroquine tablets before admission. There was no relationship observed between the parasite counts and mortality. 13 (6.6%) patients had a positive blood slide for malaria parasites but the total parasite count was not calculated (Table X).

XI. Treatment given and outcome.

Chloroquine alone.

110 (55.6%) patients were given chloroquine only (25 mg base/kg over 3 days) irrespective of the dose of chloroquine given before admission. From the history and referral notes, most of the 198 patients had chloroquine prior to admission but most had been under-dosed or were vomiting. Others had abstained from taking the tablets

because of their taste. Out of these 110 patients treated with chloroquine only, 28 were in coma or a semiconscious state and six died. 10 of 110 patients treated with chloroquine died. They died before completing the chloroquine course.

Chloroquine plus cotrimoxazole or tetracycline.

22 (11.1%) patients had been on chloroquine prior to the admission day and on admission they were given chloroquine plus cotrimoxazole or tetracycline in order to speed up the clearance of the parasitaemia.

Quinine plus chloroquine or fansidar.

49 (24.8%) patients were admitted when parenteral quinine was available and they were given a dose of 10 mg/kg 8 hourly for three days. Thereafter 25 mg/kg of chloroquine base was given in three days . Others were given fansidar 3 tablets on the third day instead of chloroquine whenever it was available.

Quinine only.

17 (8.6%) patients were given quinine parenterally only as their level of consciousness did not permit oral therapy. They had been in coma or a semiconscious state for more than four days (Table XI).

XII. In Vivo test results.

During the period of the study 28 of the 198 patients had not taken chloroquine 14 days prior to the admission day. Most were reported to have been unwell in the morning and later in the day had suddenly fallen and lost consciousness. Others had abnormal behaviour being confused and aggressive.

The mean asexual parasite count per 200 leucocytes was 20 - 40. The mean parasite clearance time for sensitive cases was 3 days. (Table XII). 3 (10.7%) patients out of the 28 had asexual parasitaemia which did not clear within 7 days but fell to 25% or less

of the original pre-test level during the first 48 hours of treatment. The parasites therefore in these patients were resistant at the RII level according to the WHO classification (Figure 2). None of the 28 patients died.

XIII. Complications.

Anaemia was the commonest complication noted in 22 (11.1%) patients and in 12 patients the anaemia was severe enough to necessitate urgent blood transfussion. 12 (6.1%) patients had a psychotic disorder persisting for more than two weeks after clearance of the parasitaemia. These patients were re-evaluated by a psychiatrist and later followed up in the outpatient clinics.

118 patients had their blood glucose determined at the time of admission and 9 (7.6%) patients had a blood glucose less than 40 mg/dl. In the remainder of the patients, blood glucose was not determined because they were on intravenous infusion of 5% dextrose or they had been given a bolus of dextrose at the casuality department.

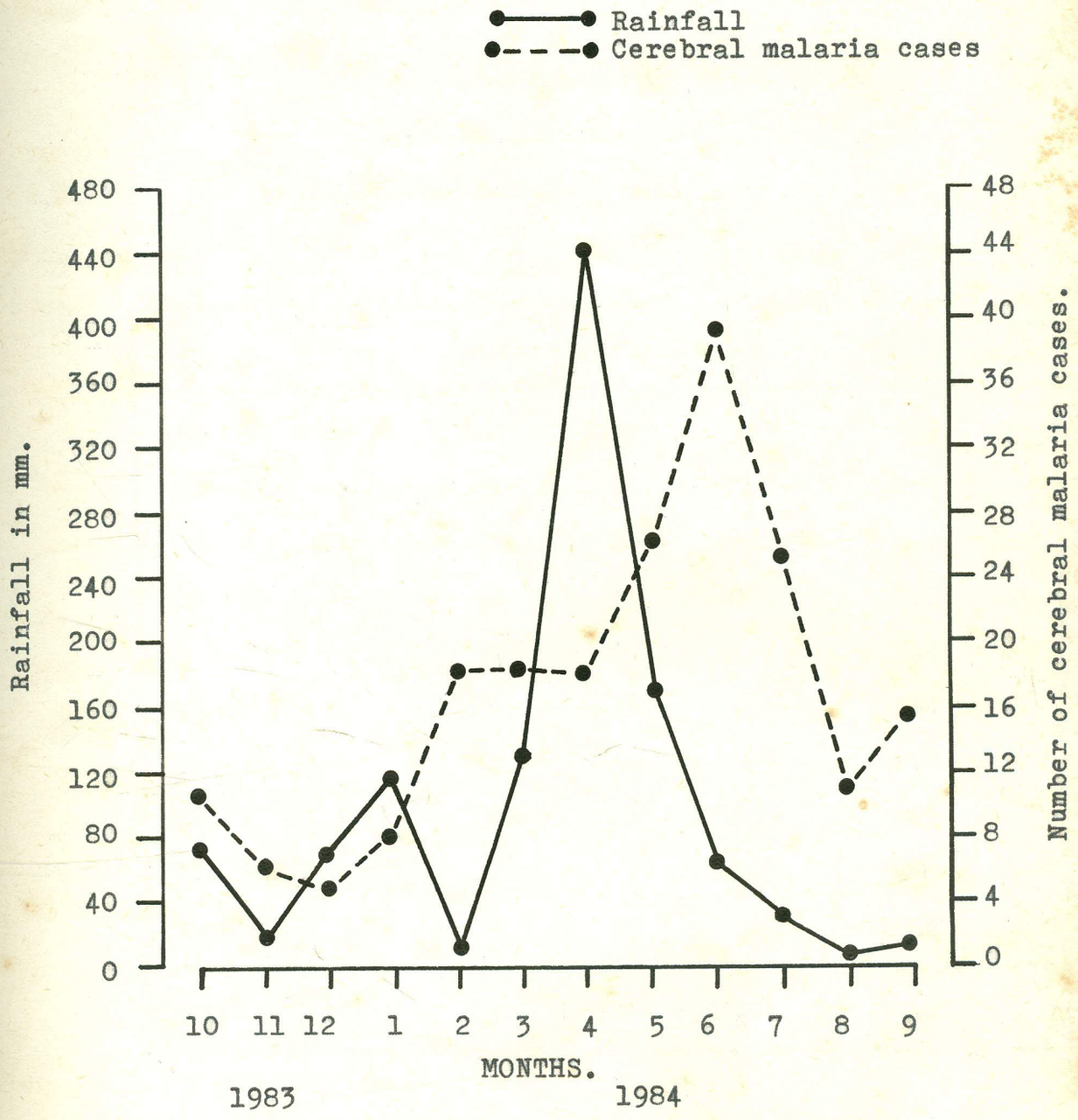


FIG. 1: NUMBER OF PATIENTS WITH CEREBRAL MALARIA ADMITTED DURING EACH MONTH OF THE STUDY. THE PATTERN OF ADMISSIONS IS RELATED TO THE MEAN MONTHLY RAINFALL.

Table I: AGE AND SEX DISTRIBUTION OF CEREBRAL MALARIA PATIENTS ADMITTED TO THE MEDICAL WARDS OF MUHIMBILI MEDICAL CENTRE.

Age (Years)	Males	Females	Total	%	Cumulation % of Total cases
6 - 10	5	8	13	6.6	6.6
11 - 15	8	23	31	15.7	22.3
16 - 20	31	36	67	33.8	56.1
21 - 25	28	18	46	23.2	79.3
26 - 30	12	8	20	10.1	89.4
31.-35	11	2	13	6.6	96.0
36 - 40	3	1	4	2.0	98.0
41 - 45	1	0	1	0.5	98.5
46 - 50	1	0	1	0.5	99.0
Above 50	1	1	2	1.0	100.0
TOTAL	101	97	198	100.0	100.0

Table II: PLACE OF BIRTH OF THE 198 CEREBRAL MALARIA PATIENTS.

Region	Altitude (feet)	No. of patients	%
Kilimanjaro	5000 - 12000	73	36.9
Morogoro	5000 - 7000	13	6.6
Iringa	6500	13	6.6
Dukoba	5600	12	6.1
Mtwara	4500	8	4.0
Dar es Salaam	10 - 500	8	4.0
Songea	5000	8	4.0
Arusha	5600 - 7000	6	3.0
Kigoma	3000	6	3.0
Tabora	3500	6	3.0
Mbeya	5000 - 8000	5	2.5
Tanga	4000 - 7000	5	2.5
Pwani	3000	5	2.5
Musoma	5300	4	2.0
Dodoma	3600	4	2.0
Zanzibar	600	3	1.6
Shinyanga	4500	2	1.0
Singida	4000	2	1.0
Mwanza	4000	1	0.5
Outside Tanzania	-	7	3.6
Unknown	-	7	3.6
TOTAL	-	198	100.0

Table III: LENGTH OF TIME PATIENTS WITH CEREBRAL MALARIA HAD LIVED IN DAR ES SALAAM.

Duration (Months)	No. of patients	%	Cumulation % of Total cases
Less than 1 month	3	1.5	1.5
1 - 6 months	34	17.2	18.7
7 - 12 months	51	25.8	44.5
13 - 24 months	41	20.7	65.2
25 - 36 months	9	4.6	69.8
37 - 48 months	7	3.5	73.3
More than 48 months	27	13.6	86.9
Unknown	26	13.1	100.0
TOTAL	198	100.0	

Table IV: OCCUPATION OF THE 198 CEREBRAL MALARIA PATIENTS.

Occupation	No. of patients	%
Pupil/Student	70	35.4
Housegirl/boy	30	15.2
Office worker	19	9.6
Housewife	15	7.6
Peasant	12	6.1
Technician	11	5.6
Soldier/Police	8	4.0
Bussinessmen	8	4.0
Others	6	3.0
Unknown	19	9.5
TOTAL	198	100.0

Table V: SYMPTOMS OF CEREBRAL MALARIA.

Symptom	No. of patients	%
Fever	191	96.5
Headache	122	61.2
Confusion	104	52.5
Body weakness	74	37.4
Vomiting	67	33.8
Loss of consciousness	57	28.8
Convulsions	39	19.7
Loss of appetite	39	19.7
Dizziness	36	18.2
Shouting/Aggressive	35	17.7
Joint pains	25	12.6
Body pains	23	11.6
Excessive sweating	18	9.1
Urine incontinence	17	8.6
Cough	17	8.6
Diarrhoea	16	8.1
Abdominal pains	15	7.6
Visual/Auditory hallucinations	13	6.6
Chillness	13	6.6
Backache	8	4.0
Neck pains/Chest pains	8	4.0
Twitches of limbs and mouth	7	3.5
Insomnia	6	3.0
Photophobia	5	2.5
Jaundice	3	1.5
Constipation	2	1.0

Table VI: SIGNS PRESENTED BY 198 CEREBRAL MALARIA PATIENTS.

Sign	No. of patients	%
Confusion	116	58.6
Restless	97	49.0
Tachycardia (more than 100/min)	90	45.5
Dehydration	42	21.2
Pallor	39	19.7
Coma	30	15.2
Dilated pupils	29	14.7
Semiconscious	28	14.1
Thought disorder (hallucinations)	25	12.6
Neck stiffness	24	12.1
Over-talkative	24	12.1
Increased tone	22	11.1
Splenomegaly	22	11.1
Convulsions	18	9.1
Bruises (face/elbows)	17	8.6
Hyperreflexia	13	6.6
Dyspnoea	13	6.6
Twitches (limbs/lips)	13	6.6
Jaundice	12	6.1
Abdominal tenderness	10	5.1
Hypotension (diastolic B.P less than 40 mmHg)	9	4.6
Hepatomegaly	7	3.5
Sensory loss	2	1.0
Retinal haemorrhages	5	2.5
Fever (more than 38.5°C)	83	41.9

Table VII: DISTRIBUTION OF THE CEREBRAL MALARIA PATIENTS INTO THREE CATEGORIES OF ALTERED CEREBRAL FUNCTION AT THE TIME OF ADMISSION AND RELATION TO OUTCOME.

Category	No. of patients	No. died	%
1. DIMINISHED LEVEL OF CONSCIOUSNESS (Semiconscious and coma plus/minus. Focal neurological signs (Hyperreflexia, hemisensory disturbances and hemiplegia)	73	17	23.3
2. ACUTE ORGANIC BRAIN SYNDROME (Confusion, disorientation and intellectual deterioration plus/minus Acute personality changes (Paranoid and delusions)	119	8	6.7
3. MOVEMENT DISORDERS (Myoclonus, chorea, tetany and muscle twitches)	6	0	0.0
TOTAL	198	25	

Table VIII: DURATION OF SYMPTOMS IN RELATION TO MORTALITY RATE.

Duration of symptoms (Hours)	No. of patients	No. Died	%
Less than 24 hours	42	3	7.1
24 - 48	64	2	3.1
49 - 72	36	5	13.9
73 - 96	28	7	25.0
More than 96 hours	28	8	28.6
TOTAL	198	25	

Table IX: RELATIONSHIP BETWEEN MORTALITY RATE AND DURATION OF DISTURBANCE OF CONSCIOUSNESS (Semiconscious and Coma).

Duration in a Semiconscious or Comatose state	No. of patients	No. of death	%
Less than 24 hours	24	2	8.3
24 - 48	16	2	12.5
49 - 72	13	4	30.8
73 - 96	11	5	45.6
More than 96 hours	9	4	44.4
TOTAL	73	17	

Table X: THE PARASITE COUNTS PER 8000 LEUCOCYTES IN 198 PATIENTS.

No. of Parasites	No. of patients	%
0 - 500	26	13.0
501 - 1000	30	15.2
1001 - 2000	57	28.8
More than 2000	72	36.4
Unknown	13	6.6
TOTAL	198	100.0

Table XI: TREATMENT GIVEN AND OUTCOME IN THE 198 PATIENTS.

Treatment regimen	No. of patients	%	No. in Coma	%	No. Died	%	Absconded.
Chloroquine only	110	55.6	28	25.6	10	9.1	6
Chloroquine + Septrin	18	9.1	2	11.1	0	0.0	0
Chloroquine + Tetracycline	4	2.0	2	50.0	0	0.0	0
Quinine + Chloroquine	43	21.7	16	37.2	4	9.3	0
Quinine + Fansidar	6	3.0	2	33.3	0	0.0	0
Quinine only	17	8.6	8	47.0	11	64.7	0
TOTAL	198	100.0	58	-	25	-	6

Table XII: RESULTS OF IN VIVO TESTS IN 28 PATIENTS, RATE OF CLEARANCE OF THE ASEXUAL PARASITAEMIA.

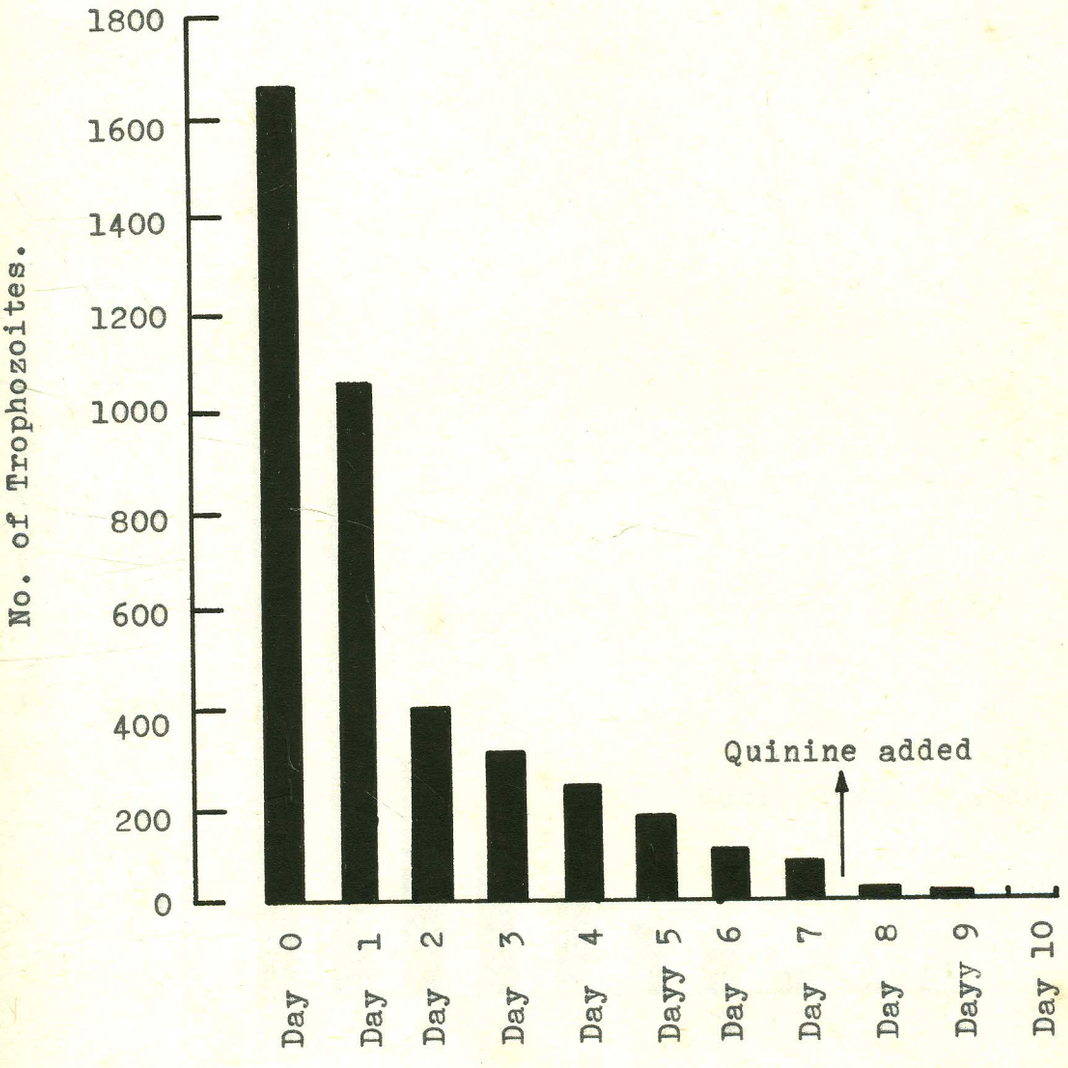
Day	No. of patients with asexual parasitaemia
0	28
1	26
2	20
3	8
4	5
5	4
6	3
7	3
8	2
9	1
10	0

Table XIII: COMPLICATIONS RECORDED IN 198 CEREBRAL MALARIA PATIENTS.

Complication	No. of patients	%
Anaemia	22	11.1
Hypoglycaemia (Glucose less than 40 mg/dl.).	9	7.6
Psychosis of more than 2 weeks	12	6.1
Aspiration pneumonia	8	4.0
Pulmonary oedema	6	3.0
Bed sores	5	2.5
Urinary tract infection	5	2.5
Abortion	3	1.5
Spastic hemiparesis	2	1.0
Acute renal failure	1	0.5

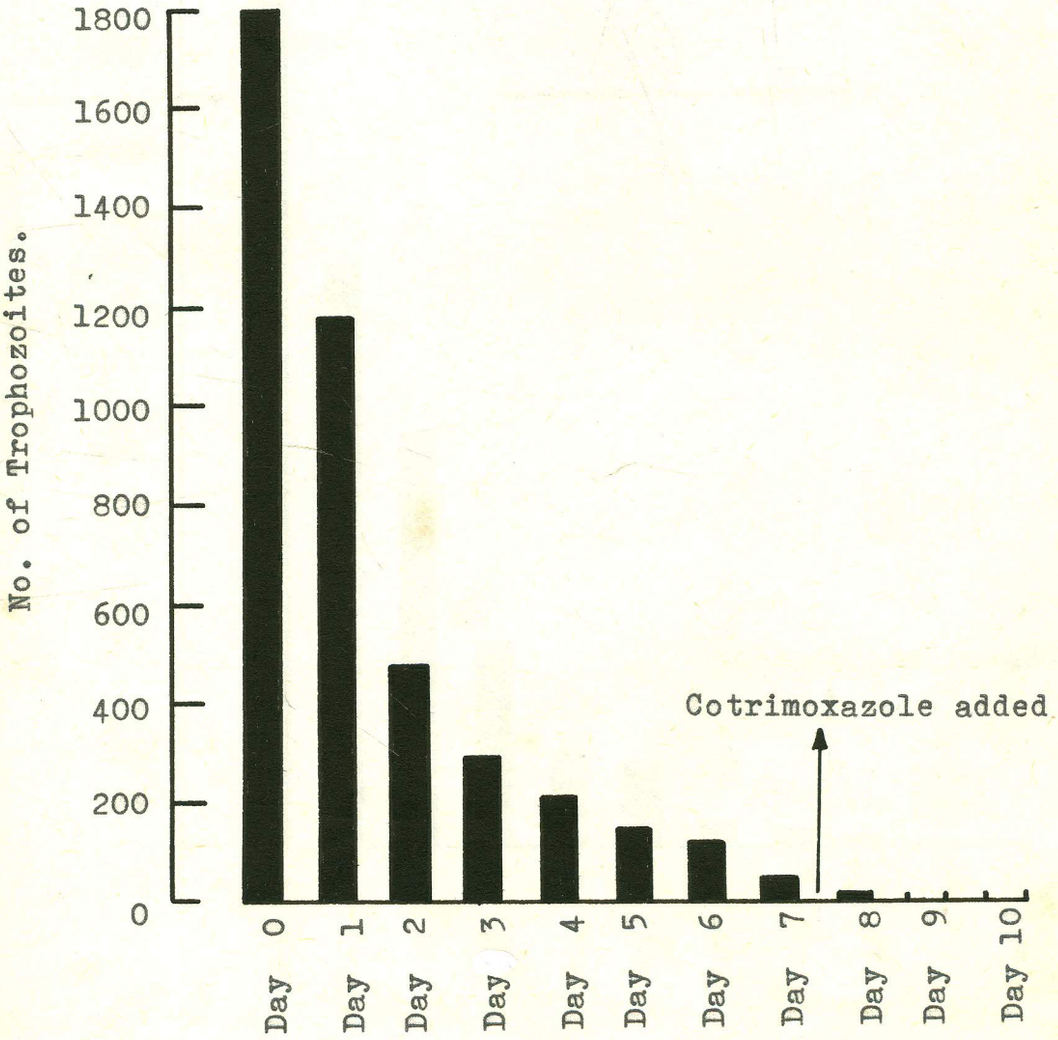
Figure. 2: PARASITE COUNTS IN THE THREE PATIENTS WHO HAD ASEXUAL PARASITAEMIA BEYOND THE 7th DAY.

Patient. A:



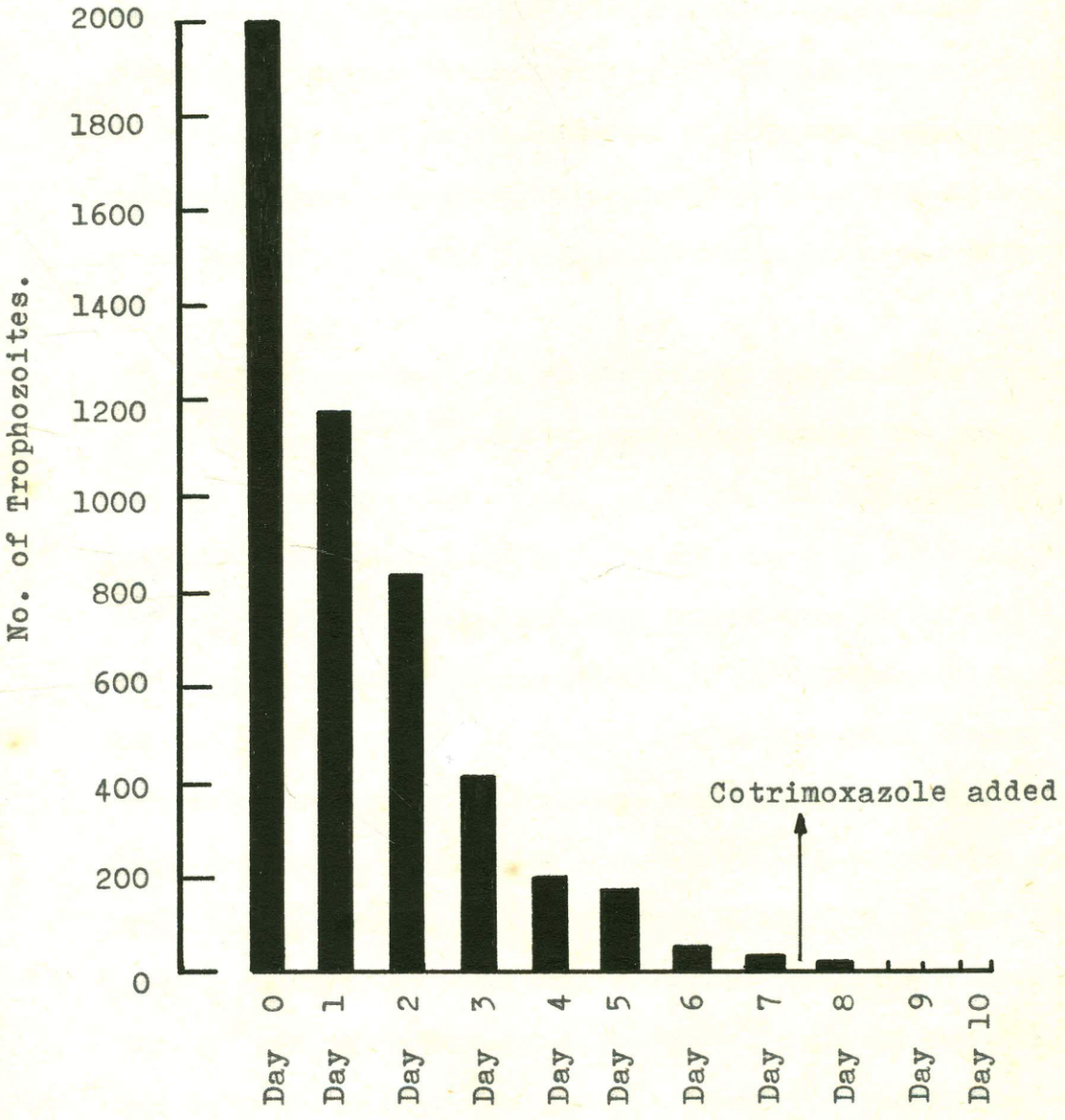
A. Mr. K.P. 21 years old from Kilimanjaro region duration of stay in Dar es Salaam 18 months. Occupation Technician on admission confused with visual and auditory hallucinations discharged on the 12th day.

Patient. B:



B. Mrs. C.M. 18 years old from Kilimanjaro region duration of stay in Dar es Salaam 11 months. Occupation housewife on admission semiconscious discharged on the 10th day.

Patient. C:



C. Mr. J.M. 12 years old from Morogoro region duration of stay in Dar es Salaam 4 months. Occupation houseboy on admission semiconscious discharged on the 20th day because of psychosis which persisted after regaining consciousness.

DISCUSSION.

During the period of the study 1983/84, 2,475 cases of malaria were admitted to the adult medical wards. 198 (8%) patients had cerebral malaria. The incidence of cerebral malaria was high during the rainy season, peaking in May to July, one month after the maximum rainfall in the years 1983/84. A similar relationship has been observed in southern Tanzania among children with cerebral malaria[44]. In Dar es Salaam, since the cessation of effective mosquito control measures, malaria transmission has continued at a high level throughout the year, with some accentuation during the months of May to July.

In Africa, cerebral malaria occurs most frequently in children of pre-school age[45, 46]. In Dar es Salaam, besides the pre-school age, the adults are also commonly affected. In this study 177(89.4%) patients were between 7 and 30 years and only 4 (2.0%) patients were above 40 years. A similar age range was reported in Thailand[47].

Overall, there was no significant sex difference. But below the age of 25 years there were more females than males because there were more non-immune girls than boys working as housegirls. Above 25 years there were more males than females because more non-immune young men were coming to Dar es Salaam looking for office work. Previous studies have shown cerebral malaria to be commonest in females[48] and others commoner in males[16, 47] with the explanation that males are at a greater risk of exposure than females.

In an area of stable malaria like Dar es Salaam[49], cerebral malaria is limited to infants, children and to adults recently residing in the region from non-malarious regions[14, 50]. 139 (70.2%) patients were immigrants from high altitude area s

(≥5000 ft. above sea level) of Tanzania, where usually malaria transmission occur for less than 3 months in a year. These patients came from Kilimanjaro, Morogoro, Iringa, Dukoba, Songea, Arusha, Mbeya, Tanga and Musoma regions.

Human malarial immunity is acquired only after repeated exposure to infection for many years and is directed against the erythrocytic stage of the parasite[51]. This immunity develops slowly[52], is often only partial and may be lost rapidly[53]. The reason for the sluggish development of the immunity is due to the existence among falciparum strains, a marked antigenic heterogenicity[54]. In this study 88(44.5%) patients had stayed in Dar es Salaam for a period of one year or less and 145 (73.3%) patients had stayed for four years or less. Probably this exposure period was not enough for them to develop adequate immunity to protect them from malaria.

In this study 8 (4.0%) patients had resided in Dar es Salaam, a malaria endemic area, since birth yet they developed cerebral malaria. Similar findings were observed in Zambia[55]. Most likely, there are certain individual differences in the ability to develop immunity against malaria from early childhood to adulthood due to as yet unidentified genetic and environmental factors[56, 57, 58].

The differences in intensity of infection with regard to age might be due to exposure frequencies to the bite of anopheles mosquitoes and to occupational differences. In adult population, it is generally adult policemen, miners, prospectors and soldiers who are likely to contract cerebral malaria[59]. In this study 8 (4.0%) patients were soldiers and policemen but the majority 100 (50.5%) were students attending school and housegirls and house boys. In urban environment these two groups are more exposed to mosquitoes during evening hours when they are reading or when

finishing domestic works. Moreover, the majority of these two groups cannot afford to buy mosquito nets to protect themselves from mosquito bites.

The importance of early diagnosis of cerebral malaria has been stressed by many authors[60, 61, 5]. The mean interval between the onset of symptoms and the start of treatment was 3 days. In Thailand it was 4 days[16]. Several factors accounted for this delay: 4 (2.0%) patients were attended by local traditional healers before admission, and these were mainly indigenous people of Dar es Salaam. Also, as a result of the varied clinical presentation, patients with cerebral malaria were misdiagnosed at all levels of health care. At dispensary level 36 (18.2%) patients were misdiagnosed. At Muhimbili Medical Centre - Casuality department 24 (12.1%) patients were misdiagnosed. Mistaken diagnoses included: Psychosis (6), epilepsy (4), hepatitis (3), typhoid fever (3), gastroenteritis (2) tetanus (2), pneumonia (2) and anaemia (2). In other studies, 57% of deaths in children in Nigeria were misdiagnosed in life[14] and 44% in Ethiopia[48].

The clinical recognition of cerebral malaria is not always easy, since acute mental disturbance may occur in any severe infection making the diagnosis difficult. Unfortunately cerebral biopsy to confirm the presence of parasites plugging the cerebral capillaries cannot be performed, hence we rely on the blood smear results. There has been much, often heated controversy over the years as to the existence of cerebral malaria in the absence of asexual parasites in the peripheral blood films. Idnsay[62] states "A negative blood film has sent many to the grave". This view is supported by Khan[63] who reported finding segmenting parasites in the brain at autopsy of 6 cases in whom the blood was repeatedly

negative during life. Edington[64] recorded a case of a child in whom no parasites were present in the peripheral blood vessels, yet malaria granulomata containing parasites were demonstrable at autopsy. On the other hand, other authors[65, 66] insist that parasites are easily found in all severe cases. This has been my experience also, but very occasionally it has required more than one film to demonstrate the parasites. As with schistosomiasis, not even after repeated blood smears will every case of cerebral malaria show the presence of the plasmodium parasite. The blood positivity in malaria is between 80 and 90%[46]. It should be remembered that in light infections (especially if they have been exposed to intermittent chloroquine), the blood films may be intermittently negative.

In Dar es Salaam, where the malaria picture is of the stable holoendemic type, all four species of plasmodium occur[49] but plasmodium falciparum comprises over 93%. In this study all 198 patients had plasmodium falciparum. There have been reports of cerebral malaria due to plasmodium vivax[48, 67]. The consesus opinion is that cerebral malaria is caused by plasmodium falciparum species.

Lumbar punctures were not done routinely except when indicated for example patients in coma or with signs of meningeal irritation. Completely normal cerebrospinal fluid results were obtained except for a slight increase in pressure and in the number of lymphocytes in a few patients. Previous reports vary with some authors sharing my experience[46, 60, 50, 66], while others have reported pleocytosis and protein increase or both.

The clinical course of cerebral malaria can evolve over a number of days or may appear suddenly with rapid development of coma. In this study the course in most cases was rapid and dramatic as in Zambian adults[55]. Sphincter incontinence and hiccoughs have been

reported to be an "alerting signal"[69] but in this study none of the patients presented with hiccoughs. 17 (8.6%) patients presented with urine incontinence. Other warning symptoms of the development of cerebral malaria were change in mood, mental clouding and non-purposeful actions.

In cerebral malaria, all kinds of neurological signs may be present and can change rapidly[56]. In this study the most frequent sign was confusion observed in 116 (58.6%) patients. Others were restlessness, tachycardia, dehydration, paleness, comatose state, dilated pupils reacting equally to light, semiconscious state, thought disorders and high temperature. Fever is not a constant feature in severely ill patients[2] and in this study at admission 22 (11.1%) patients were afebrile and only 83 (45.9%) had temperature above 38.5°C. The pattern of the fever was irregular rather than tertian i.e. the pattern is unpredictable and was accompanied by profuse sweating.

Splenomegaly is considered to be one of the outstanding features of malaria infection, but it is by no means always palpable in early infections[70]. In this study unlike Sothe's [68] observation where all his patients had hepatosplenomegaly, the spleen was palpable in 22 (11.1%) patients. Usually splenomegaly is found in about a third of the case and more so in children and much less often in adults[71]. 7 (3.5%) patients had hepatomegaly and all these had jaundice too. Jaundice usually occurs in severe malaria attacks[72] and the main differential diagnosis is usually infectious hepatitis. The fever in infectious hepatitis, however, usually subsides with the appearance of jaundice unlike in falciparum malaria.

Hypotension was noted in 9 (4.6%) patients. According Hall[2], this occurs in malaria due to vasodilatation caused by anoxia and haemoglobinuria leading to acute tubular necrosis. Increased insensible fluid loss, sweating from pyrexia and decreased fluid intake also contribute. Retinal haemorrhages which are thought to be common in cerebral malaria and a sign of prognostic significance were noted in 5 (2.5%) patients and all were in coma. In other studies the incidence has been as high as 15%[73].

Unlike Daroff's[43] series, in which a diminished level of consciousness was the commonest manifestation of disturbed cerebral function, in this study acute organic brain syndrome was the commonest manifestation of cerebral disturbance. 119 (60.1%) patients had acute organic brain syndrome. 73 (36.9%) patients had diminished level of consciousness and 6 (3.0%) patients presented with signs of movement disorders. Among those with signs of movement disorders three patients presented features clinically indistinguishable from tetanus (trimus, opisthotonos, neckstiffness and twitches). One patient had such signs while upcountry and he was treated for tetanus but eventually it was realized that he had cerebral malaria.

The two most widely used drugs in the treatment of cerebral malaria are quinine and chloroquine[2, 11, 74, 75]. For severely ill patients, parenteral quinine given by slow intravenous infusion is mandatory and should be continued until oral therapy is possible[76]. The comparative efficacy of chloroquine and quinine both given as intravenous infusion, against chloroquine sensitive plasmodium falciparum has not yet been precisely determined. Ansdell[77] found that quinine was more effective than chloroquine in some patients from Africa. There is evidence of antagonism between chloroquine and quinine[78]. The two drugs should therefore

not be used simultaneously. Sequential treatment may be satisfactory in certain circumstances.

Chloroquine resistance has already been described in parts of Africa and recently in Tanzania[36, 38, 79, 80]. The only antimalarial which was constantly available was chloroquine and parenteral quinine was available for some few months only. In this study 66 (33.3%) patients were treated with intravenous quinine until oral therapy was possible when chloroquine or fansidar were added. The mortality in this group was 22.7%. The cause of this high mortality was not known.

Most patients, 132 (66.7%) were treated with chloroquine, intramuscularly initially and then oral therapy later. Cotrimoxazole or tetracycline were added in some patients in order to speed up the clearance of the parasitaemia. The mortality in this group was 7.6%. Steroids were not used[16].

Normally if the parasite count is excessively high or the patient is severely ill, it is advisable in areas of suspected chloroquine resistance not to attempt the in vivo test of chloroquine sensitivity. Quinine which is recommended for cerebral malaria should be given. Due to unavailability of quinine, 28 patients who had not taken chloroquine 14 days prior to admission were subjected to in vivo test for chloroquine. Three (10.7%) patients demonstrated RII level of resistance according to the WHO criteria. Because of doubts about drug absorption after oral administration, some authorities now suggest that evidence of resistance is only reliable when effective serum drug levels have been measured[37]. Even if this is demonstrated to be a real drawback to the standard field test, such objections were minimized in these 28 patients by the use of intramuscular

administration. Distinction between sensitivity and resistance at the RI level was not possible to evaluate because of inability to follow the patients for 28 days.

Once chloroquine resistance appears in an area it does not follow that all or even the majority of patients in that area will be chloroquine resistance. The first documented case of chloroquine resistance reported in Tanzania must not be the trumpet call for the abandonment of chloroquine. In Tanzania chloroquine remains the cheap and easily available drug of choice for the treatment of uncomplicated malaria and complicated malaria when quinine is not available. A close watch however, must be kept on the response to therapy and intervention with alternative drugs should be carried out if there is delay in clearance of parasitaemia. It is important to remember that failure to respond to chloroquine may be due to poor compliance on part of patient to take the drug, underdosage or in some cases, failure to absorb it due to vomiting or diarrhoea. It may even be due to misinterpreting the blood film if the continued presence of gametocytes is thought to indicate resistance. An appreciation of the time interval between the onset of treatment and the clinical and parasitic response is vital. After a successful therapeutic course of antimalarial drugs, the average time interval between the initiation of treatment and the clearance of fever is about 48 hours, while the average parasite clearance time is around 77 hours[76]. In this study the parasite clearance time was 72 hours. Unless this is recognized premature condemnation of a perfectly effective and adequate therapy may be made. Careful monitoring of parasitaemia is a mandatory concomitant investigation when assessing the effect of treatment.

The usual supportive therapy given to unconscious patients are vital in cerebral malaria. These include: blood transfusion when haemoglobin is less than 5 gm/dl., diazepam if patient is convulsing, antipyretic and tepid sponging if the patient is hyperpyrexic, oxygen by nasal catheter if the patient becomes dyspnoeic or cyanosed, antibiotics, preferably cotrimoxazole if there are secondary bacterial infections and strict monitoring of fluid intake and output. Patients must be kept on their sides to minimize the risk of aspirating vomitus. Prompt coordinated action on the part of the ward nurses is necessary.

The most frequent complication noted in these patients was moderate to severe anaemia seen in 22 (11.1%) patients. 12 (54.5%) of the 22 patients required blood transfusion. It is always difficult to determine the degree to which malaria contributes to anaemia, because several factors are compounded. These factors are: the rapidity with which a high parasitaemia may develop in non-immune patients, variability of the clinical course with respect to racial background, age and immune status and the presence of multiple pathology, including iron and folate deficiency and associated bacterial or parasitic infections. Since anaemia in malaria is due to direct damage to the red cells by the parasites, haemolysis as a result of immune destruction of red cells and depression of erythropoiesis[81, 82, 83, 84], and not due to iron deficiency[2], iron therapy is not helpful in such cases. It is therefore important to distinguish iron deficiency anaemia from the anaemia of malaria for the purpose of treatment. If the cause of the anaemia is iron deficiency and you then administer iron , you may speed up the multiplication of existing

parasites[85, 86] if the antimalarial drug is not effective.

Hypoglycaemia is now a well recognized complication of falciparum malaria. However, its overall incidence in cerebral malaria is unknown because diagnosis in such patients is difficult since changes in the level of consciousness or deepening coma are usually attributed to cerebral malaria in which signs, such as sweating and tachycardia are common. Delay in diagnosis of this complication may well contribute to a high mortality. This complication has been attributed to exhaustion of the host's hepatic glycogen reserves by the parasites enormous metabolic demands for glucose, increased metabolic demands related to high fever and prolonged fasting. Also in the presence of microcirculatory obstruction and tissue anoxia, the switch to anaerobic glycolysis may considerably increase the amount of glucose required to preserve energy status and would also generate large quantities of lactate.
In this study among 118 patients whose blood glucose was determined at the time of admission, 9 (7.6%) patients had a blood glucose less than 40 mg/dl. In one patient blood glucose was as low as 10 mg/dl. He died in spite of the administration of intravenous glucose. These patients gave no history compatible with previous hypoglycaemia or recent quinine intake since quinine has been shown to stimulate insulin secretion.

Pulmonary complications were common and were the major identifiable cause of mortality. Pneumonia is a well known complication of cerebral malaria but pulmonary oedema seen in 6 (3.0%) patients is a recently recognized complication. These patients were dyspnoeic and had bilateral rhonchi. Hypotension with sinus tachycardia was also present but arrhythmias were not recorded. Some were

Although rare, permanent sequelae following cerebral malaria have been noted. Usually recovery is the rule but permanent cerebral damage is possible and this might take the form of a monoplegia, hemiplegia or mental illness[66, 90]. In this study, the neurological complications were spastic hemiparesis in 2(1.0%) patients and in 12 (6.1%) patients a psychotic disorder persisted for more than two weeks after clearance of the parasitaemia. There are reports in which the psychotic symptoms have persisted from days to months and occasionally beyond a year[12]. Each of these patients, at the time they became psychotic were awake and alert and neurological examinations revealed no neurological abnormality.

Due to different definitions of cerebral malaria, the comparison of studies from different areas is difficult[11, 69]. Figures at Muhimbili Medical Centre in 1983 have shown that malaria accounts for about 4 - 5% of all hospital deaths. Several authors have reported the mortality rate of cerebral malaria to range from 4% to 50%[16, 70]. 18% among 66 children in Southern Tanzania[44], and 33% in a Harare Hospital[46]. Usually in cerebral malaria, deaths occurs within 48 to 72 hours[16, 69]. In this study, the overall mortality was 12.7%. When however you divide the patients into three categories according to mental status, mortality rates were related to the nature of the cerebral disturbance. First there were those who had disturbance of consciousness (semiconscious and coma). There were 73 patients in this group and 17 (23.3%) patients died. Secondly there were those who had acute organic brain syndrome (confusion and disorientation). There were 119 patients in this group and 8 (6.7%) died. Among the third group, those who had movement disorders none died.

Delay in diagnosis was related to the mortality rate. 15 (60%) patients out of the total 25 patients who died had the symptoms of cerebral malaria for more than 72 hours before they were diagnosed and treated. Also remaining in a state of semiconscious or comatose for a duration of more than 48 hours was related to the mortality rate. 13 (76.4%) patients out of the total 17 patients with diminished level of consciousness who died, had remained in a semiconscious or comatose state for more than 48 hours.

The identified causes of death were hypoglycaemia, acute renal failure and pulmonary complications in which respiration ceased before the heart stopped beating.

CONCLUSIONS AND RECOMMENDATIONS.

The mortality rate in cerebral malaria was related to delay in diagnosis and the duration of diminished level of consciousness. Health education to the public stressing the symptoms and signs of cerebral malaria is important so as to reduce the hours of delay in diagnosis.

Measures to decrease the incidence of cerebral malaria should be carried out. These include an increase in living standards, mass clearing of the environment, removal of marginal vegetation, clearing of drains and canals and larviciding accompanied by residual spraying in selected peripheral parts of the city in order to reduce the number of mosquitoes. Funds should be allocated to control and fight malaria together with the training of manpower at national level for mosquito control.

Hypoglycaemia is a potentially lethal but treatable complication

of cerebral malaria that may be unsuspected because the features simulate those of cerebral malaria. Hence blood glucose estimations during admission is mandatory and probably later daily, since it is at present impossible to predict which patients will develop hypoglycaemia.

This study does not dispute the fact that quinine is the best drug for cerebral malaria patients. It has shown, however, that in Tanzania, when quinine is not available chloroquine is still an effective drug for the treatment of cerebral malaria despite the existence of a few strains of malaria parasites which have developed resistance to the drug. It is advisable in patients suspected to have chloroquine resistant plasmodia to add drugs of other types such as cotrimoxazole and tetracycline. Probably a study whereby the chloroquine dose is raised from 25 mg to 30 mg base/kg for 3 days should be carried out in near future.

The public should be advised to take the proper chloroquine dose under doctors instructions instead of determining their own dosage. Some patients often vomit chloroquine and repeat doses are not administered because they dislike the taste or they fear vomiting. This information should be sought when treating a patient with persisting parasites following chloroquine treatment before the drug is condemned. If an individual has had an infection with chloroquine resistant malaria it should not be concluded that subsequent malarial infections will also be chloroquine resistant.

The present WHO recommendations for chemoprophylaxis of non-immune residents is chloroquine 300 mg base weekly. If this fails the dose should be increased to 600 mg base weekly and if this fails fansidar should be taken. To decrease the incidence of cerebral

malaria not only in the underfives and pregnant mothers, non-immune immigrants from the highlands of mainland Tanzania should be advised to take malaria prophylaxis when they come to Dar es Salaam for at least 5 years since 73.3% of the total patients had stayed in Dar es Salaam for 4 years or less.

Enquiry as to which region the patient comes from and for how long he/she has stayed in Dar es Salaam is important in the evaluation of any patient with features of central nervous system dysfunction. This will give a clue whether you are dealing with cerebral malaria or other disease.

REFERENCES.

1. Rwiza H.T.
The aetiology and prognosis of non-traumatic coma in Dar es Salaam.
Dissertation for Master of Medicine in Internal Medicine. (Unpublished) 1 - 2.

2. Hall A.P.
The treatment of severe falciparum malaria.
Transactions of the Royal Society of Tropical Medicine and Hygiene, 1977 ; 71: 367.

3. Wilcocks, C. and Manson-Bahr P.E.C.
Disease caused by protozoa (malaria).
In Manson's Tropical Disease, 17th edition 1972; 1:62-63.

4. Kingston, H.
A new look at malaria.
British Medical Journal; 195:9

5. Fisher, G.U.
Fatal falciparum malaria in the United States of America.
Journal of Infectious Disease 1969; 119:215.

6. Osuntokun, B.O.
Neurology of malaria.
Postgraduate Doctor 1983; 5 : 12; 420 - 426.

7. Sheehy, T.W. and Reba, R.C.
Complications of falciparum malaria and their treatment.
Annals of Internal Medicine, 1967; 66:4; 807 - 809.

8. Blocker, W.W.; Kastl, A.J. and Daroff, R.B.
The psychiatric manifestations of cerebral malaria.
American Journal of Psychiatry, 1968; 125:2 192 - 196.

9. Kiselev, V.B.
Secondary lesions of the CNS in some infectious and toxic allergic condition in Zambia.
Medical Journal of Zambia 1975; 9:5.

10. Osuntokun, B.O. and Odeku, E.L.
Some aspects of epilepsy in Nigerians.
Tropical Geographical Medicine, 1970; 22: 3 - 19.

11. Marsden, P.D. and Bruce-Chwatt, L.J.
Cerebral malaria.
In: Hornabrook R.W. ed. Topics on Tropical Neurology
Philadelphia Davis, 1975; 29 - 44.

12. Arieti, S.
Histopathological changes in cerebral malaria and their relationship to psychotic sequelae.
Archives of Neurological Psychiatry, 1946; 59: 79 - 104.

13. Regdon, R.H.
Lesions in the brain associated with malaria.
Archives of Neurological Psychiatry, 1945, 53: 191 - 198.

14. Attah, E.B. and Ejeckam G.C.
Clinico-pathologic correlations in fatal malaria.
Tropical Geographical Medicine, 1974; 26: 359 - 362.

15. Gilles, H.M.
The treatment of malaria.
Postgraduate Doctor, 1982; 4: 68 - 74.

16. Warrel, D.A.; Looareesuwan, S.; Warrel, M.J.; Kasemsarn, P.; Intaraprasert, R.; Bunnag, D. and Harinasuta, T.
Dexmethasone proves deleterious in cerebral malaria.
New England Journal of Medicine, 1982; 306:6 : 313 - 319.

17. Jiang, J.B.; Li G.Q.; Que, X.B.; Kong, Y.C. and Arnold, K.
Antimalarial activity of mefloquine and quinghaosu.
Lancet, 1982 ; 2 : 285 - 288.

18. Edwards, J.R.
Malaria with disseminated intravascular coagulation and peripheral tissue necrosis successfully treated with streptokinase.
British Medical Journal, 1980; 280 : 1252 - 1253

19. Weston, M.J.; Jackman, N.; Rudge, C.
Prostacylin in flaciparum malaria.
Lancet, 1982; 2 : 609.

20. Nielsen, R.L.; Kohler, R.B.; Chin, W.; McCarthy, L.J.; Luft F.C.
The use of exchange transfusion: a potentially useful adjunct in the treatment of fulminant falciparum malaria.
American Journal of Medical Science, 1979; 227:325-329.

21. Kurathong, S.; Srichaikul, T., Isarangkura, Phanichpant, S.
Exchange transfusion in cerebral malaria complicated by disseminated intravascular coagulation.
Southeast Asian Journal of Tropical Medicine and Public Health, 1979; 10: 389 - 392.

22. WHO.
Chemotherapy of malaria and resistance to antimalarials.
World Health Organization Technical Report Series.
1973: 375.

23. Peters W.
Antimalarial drug resistance: an increasing problem.
British Medical Bulletin 1982; 38: 187- 192.

24. Bruce-Chwatt L.J.
Chemoprophylaxis of malaria in Africa: "The spent magic bullet".
British Medical Journal 1982 ; 285: 674 - 676.

25. Moore D.V. and Lanier J.E.
Observations on two plasmodium falciparum infections with an abnormal response to chloroquine.
American Journal of Tropical Medicine and Hygiene
1961 ; 10 : 5 - 9.

26. Young M.D. and Moore D.V.
Chloroquine resistance in plasmodium falciparum.
American Journal of Tropical Medicine and Hygiene.
1961 ; 10 : 317 - 320.

27. Box E.D.; Box Q.T. and Young M.D.
Chloroquine resistant plasmodium falciparum from Porto Velho, Brazil.
American Journal of Tropical Medicine and Hygiene.
1963 ; 12 : 300 - 304.

28. Eyles D.E., Hoo C.C., Warren, McWilson and Sandosham A.A.
Plasmodium falciparum resistant to chloroquine in Cambodia.
American Journal of Tropical Medicine and Hygiene
1963 ; 12 : 840 - 843.

29. Young M.D., Contacos P.G., Stitcher J.E. and Millar J.W.
Drug resistance in plasmodium falciparum from Thailand.
American Journal of Tropical Medicine and Hygiene
1963 ; 12 : 305 - 314.

30. Montgomery R. and Eyles D.E.
Chloroquine resistant falciparum malaria in Malaya.
Transactions of the Royal Society of Tropical Medicine
and Hygiene 1963 ; 57 : 409 - 416.

31. Iasch E.E. and Ng'uyen T.L.
Observations on an apparent chloroquine resistant strain
of plasmodium falciparum in West Africa.
British Medical Journal 1965 ; ii: 1219 - 1222.

32. Hippo B. and McCallum J.B.
Possible chloroquine resistant malaria in Zambia.
Medical Journal of Zambia 1967 ; 1 : 31 - 35

33. Stevenson D.J.D.
A case of malaria not responding to chloroquine.
Transactions of the Royal Society of Tropical Medicine
and Hygiene 1966 ; 60 : 276 - 277.

34. Fogh S., Jepsen S. and Effrose R.
Chloroquine resistant plasmodium falciparum in Kenya.
Transactions of the Royal Society of Tropical Medicine and Hygiene 1979 ; 73 : 228 - 229.

35. Kean B.H.
Chloroquine resistant falciparum malaria from Africa.
Journal of American Medical Association 1979;
241 : 395 - 396.

36. Campbell C.C. , Collins W.E.; Chin W., Teutsch S. and Moss D.M
Chloroquine resistant plasmodium falciparum from East Africa.
Lancet 1979 ; ii : 1151 - 1154.

37. Faehlmann, M., Rombo L. and Hedman P.
Serum concentration of chloroquine in a patient with a late recrudescence of Kenyan plasmodium falciparum malaria.
Transactions of the Royal Society of Tropical Medicine and Hygiene 1981 ; 75 : 362 - 364.

38. Gardner A.L. , Weinstein R.A. and Lincoln L.
Failure of chloroquine prophylaxis in plasmodium falciparum from East Africa.
Journal of American Medical Association 1981 ; 264 : 979 - 980.

39. Weniger, B.G., Blumberg, R.S., Campbell, C.C. Jones, T.C. Mount, D.L. and Friedman S.M.
High level chloroquine resistance of plasmodium falciparum malaria acquired in Kenya.
New England Journal of Medicine, 1982 ; 307: 1560-1562.

40. Kihamia C.M. and Gill H.S.

Chloroquine resistant falciparum malaria in semi-immune native African Tanzania.

Lancet 1982 ; ii : 43.

41. De Cook M.K. ; Armitage J. and Markey A.C.

Possible case of RIII chloroquine resistant malaria from East Africa.

Lancet 1983 ; i : 773 - 774.

42. Public Health Laboratory Service malaria lab.

Malaria prophylaxis.

British Medical Journal 1983 ; 286 : 787 - 789.

43. Doroff R.B., Deller J.J., Kastl A.J. and Blocker W.

Cerebral malaria.

Journal of American Medical Association 1967; 202 : 8 679 - 683.

44. Schmutzhand E. and Gerstenbrand F.

Cerebral malaria in Tanzania. Its epidemiology, clinical symptoms and neurological long term sequelae in the light of 66 cases.

Transactions of the Royal Society of Tropical Medicine and Hygiene 1984 ; 78 : 351 - 353.

45. WHO

Development in malaria immunology.

Technical Report Series 1975 ; 379 : 45.

46. Gelfand M.

Neurological complications of parasitic disease.

Tropical Neurology Textbook by John D. Spillane

London Oxford University Press 1973 ; 2407-2455.

47. Chipman M., Cadigan F.C. and Benjapongse W.

Involvement of the nervous system in malaria in Thailand.

Tropical Geographical Medicine 1967 ; 19 :8.

48. Menghistu M., Maru, M. and Ahmed Z.

Malaria in Gondar, Ethiopia 1975 - 1978; a review of 435 cases with special emphasis on cerebral malaria.

Ethiopian Medical Journal 1979 ; 17: 3: 57 - 62.

49. Clyde D.C.

Malaria in Tanzania Textbook.

Oxford University Press, London 1967 : 15.

50. Hutton P.W.

Neurological disease in Uganda.

East African Medical Journal 1956 ; 33; 6: 209-223.

51. Cohen S.

Mechanisms of malaria immunity.

Transactions of the Royal Society of Tropical Medicine and Hygiene 1977; 71; 4 : 283 - 285.

52. McGregor I.A., Gilles H.M., Walters J.H., Davies A.H and Pearson F.A.

Effects of heavy and repeated malaria infections in Gambian infants and children: effects of erythrocytic parasitization.

British Medical Journal 1956; 2 : 686 - 692.

53. Maegraith B.G.

Malaria . In: Woodruff A.W. ed. Medicine in Tropics. Edinburgh: Churchill Livingstone 1974: 27 - 73.

54. McBride J.S., Walliker D. and Morgan G.

Antigenic diversity in the human malaria parasite plasmodium falciparum.

Science 1982 ; 277: 254 - 257.

55. Flamin A.H.

Cerebral malaria in adult Zambian Africans.

East African Medical Journal 1981 ; 58 : 2: 124-129.

56. Adams and Magraeth.

Clinical Tropical Disease 5th edition

Blackwell Scientific Publications Limited

Oxford and Edinburgh 1971 : 248.

57. McGregor I.A.

Studies on the acquisition of immunity of infections in Africa.

Transactions of the Royal Society of Tropical Medicine and Hygiene 1964 ; 58: 1

58. Mukherjee A.P.

Falciparum malaria associated with jaundice, renal failure and anaemia.

Transactions of the Royal Society of Tropical Medicine and Hygiene 1971; 65 : 6.

59. Gelfand M.

The sick African: a clinical study

South African Medical Journal 1957 ; 11: 64.

60. Most H. and Moloney H.E.

Falciparum malaria.

Journal of American Medical Association 1944; 121:71.

61. Hall, A.P.

Preventing deaths from malaria.

British Medical Journal 1978 ; 2 : 877.

62. Idnsay D.K.

Guidance notes of falciparum malaria.

Transactions of the Royal Society of Tropical Medicine and Hygiene 1943 ; 37 : 63.

63. Khan M.U.

Cerebral malaria.

Journal of the Royal Army Medical Corps 84 : 263.

(Abstract. Tropical Disease Bulletin 1945;42: 861).

64. Edington G.M.

Cerebral malaria in the Gold Coast.

Annals of Tropical Medicine and Parasitology 1954; 48; 300.

65. O'Holohoen D.R.

Clinical and laboratory presentation of malaria.

Journal of Tropical Medicine and Hygiene 1976 : 79 : 191 - 196.

66. Musoke, L.K.

Neurological manifestations of malaria in children.

East African Medical Journal, 1966 : 43 ; 561.

67. Hill, G.J.; Knight, V.; Courtney, G.R. and Lawless, D.K.

Vivax malaria complicated by aphasia and hemiparesis.

Archives of Internal Medicine, 1963; 112 : 863.

68. Rothe, H.

100 cases of cerebral malaria.

East African Medical Journal, 1956; 33; 10: 405.

69. Fitz-Hugh, T.; Peppa, D.S. and Hopkins, H.U.

The cerebral form of malaria.

The Bulletin of the U.S.A. Army Medical Department,

1944; 83: 39 - 48.

70. Manson-Bahr, P.E.C. and Apted, F.I.C.

Manson's Tropical Desease 18th edition

London : Bailliere Tindall, 1982; 38 - 69.

71. Gelfand, M.

Clinical falciparum malaria - its severity, types,

splenomegaly, association with malnutrition and criteria

for diagnosis.

The Central African Journal of Medicine, 1983; 29: 12

233 - 237.

72. Gilles, H.M.

Malaria.

Medicine, 1974 ; 26 : 1522.

73. Looareesuwan, S.; Warrell, D.A.; White, N.J.; Chanthavanicne, P. Warrell, M.J. and Chantaratherakitti.

Retinal haemorrhages, a common sign of prognosis significance in cerebral malaria.

American Journal of Tropical Medicine and Hygiene. 1983; 32; 5: 911 - 915.

74. Bruce-Chwatt, L.J.

Essential Malariology Textbook.

Hainemann London, 1980 ; 196.

75. Rollo, M.J.

Drugs used in chemotherapy of malaria.

In: The Pharmacological Basis of Therapeutics.

Gilman A.G.; Goodman L.S. and Gilman A. (Editors)

New York: MacMillan, 1980 : 1038 - 1060.

76. Hall, A.P.; Doberstym, E.R.; Mettaprakong, V. and Sonkan, P.

Malaria treatment.

British Medical Journal, 1975 ; 2 : 15.

77. Ansdell, V.E.; Boosey, C.M.; Geddes, A.M. and Morgan, H.V.

Malaria in Birmingham, 1968 - 1973.

British Medical Journal, 1974 ; ii : 206 - 208.

78. Hall, A.P.

Quinine and chloroquine antagonism in falciparum malaria.

Transactions of the Royal Society of Tropical Medicine and Hygiene, 1973 ; 67 : 425.

79. Mahoney, J.L.

Chloroquine resistant malaria in Africa.

Journal of Tropical Medicine and Hygiene, 1980;

83 : 207 - 209.

80. Nieuwveld, R.W.; Malkett, J.A. and Spracklen, F.H.N.
Drug resistant malaria in Africa:
A case Review and review of the problem and treatment.
South African Medical Journal, 1982; 62; 173 - 175.

81. Kuvin, S.F.; Deye, H.K.; Stohlman, F.; Contacos, P.G. and Coatney, G.R.
Malaria in man. Infection by plasmodium vivax and the B strain of plasmodium cynomolgi.
Journal of American Medical Association, 1963; 184 : 1018 - 1020.

82. Srichaikul, T.; Wasanssomsith, M.; Poshyachinda, V.; Panilburt, N. and Rabieb, T.
Ferrokinetic studies and erythropoiesis in malaria.
Archives of Internal Medicine, 1969 ; 124: 623 - 628.

83. Srichaikul, T.; Siriasawaikul, T.; Poshyachinda, M. and Poshyachinda, V.
Ferrokinetics in patients with malaria : normoblasts and iron incorporation in vitro.
American Journal of Clinical Pathology, 1973; 60 : 166 - 174.

84. Woodruff, A.W.; Ansdell, V.E. and Pettit, L.E.
Malaria.
Lancet, 1979; 1 : 1055 - 1057.

85. Masawe, A.E.J.; Muindi, J.M. and Swai, G.B.R.
Infections in iron deficiency and other types of anaemia in the tropics.
Lancet, 1974; 2: 314 - 317.

86. Murray M.J., Murray A.B., Murray M.P. and Murray C.J.
Diet and cerebral malaria: The effect of famine and refeeding.
British Medical Journal 1975 ; 2 : 1113 - 1115.

87. Gilles H.M., Lawson J.B., Sibelas M., Voller A. and Allan N.
Malaria, anaemia and pregnancy.
Annals of Tropical Medicine and Parasitology 1969 ; 63 : 245 - 262.

88. Molyneux M.E.
Malaria again.
Medical Quarterly 1983 ; 15 : 1 - 2.

89. Makhab D. and Samir N.B.
Malaria in pregnancy.
Southern Medical Journal 1982 ; 75 ; 8: 957 - 962.

90. Guyer O.K.G.
Report on a case of cerebral malaria.
East African Medical Journal 1943; 20: 139.

WEO THE
RC 157
.M3
1985
copy 1