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ASSOCIATION OF PARASITEMIA uJITH CLINICAL MANIFESTATIONS, BIOCHEMICAL CHANGES AND ANTIBODY TITRES IN ADULT PATIENTS LJITH PLASMODIUM FALCIPARUM MALARIA AT KENYATTA NATIONAL HOSPITAL.

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A DISSERTATION SUBMITTED IN PART FULFILMENT FOR THE DEGREE OF MASTER OF MEDICINE (MEDICINE) AT THE UNIVERSITY OF NAIROBI 198a.

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DECLARATION '

This dissertation is my original work and has not been presented for a degree in any other university.

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Ue certify that this dissertation has been submitted to the University of Nairobi with our approval as University Supervisors.

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A prospective study of 76 adult patients with Plasmodium falciparum malaria r=nd 76 adult healthy controls at KNH over six month period is described. There was no significant difference in age and sex between the cases and controls.* 81.6% of the patients hod bear to malaria endemic areas two weeks prior to presentation. The commonest presenting symptom was headache (71.rO followed by joint aches (33.8%) and dizziness (33.0 n O Fever occurpd in 92%, jaundice in 19% and splenomenally in 12%. 77.6% of thp patients had severe falciparum malaria with a mean parasitemia of 3.0%. 7 patients i.e. 10% had hyperparasitemia and only one of them had impaired consciousness. A total of 3 patients had impaired conscious level with a mean parasitemia of 10. 3 P - but none of them fitted into the WHO definition, for cerebral melar-ia. There was statistically significant differences in the mean serum sodium, B.U.N, and serum creatinine between the cˆses and controls. BUM nd serum creatinine showed a significant positive correlation with parasitemia but no significant correlation was demonstrated between the antibody titres and paras: teiriˆ.

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LI5T OF ABBREVIATIPNS

1. DIC - Disseminated intravascular coagulation

2. CSF - Cerebrospinal fluid

3. KEMRI - Kenya Medical Research Institute

h. FDP - Fibrinogen Degradation Products

5. P.A.3.A. - Para-arnino-benzoic acid

S. K.N.H. - Henyatta National Hospital

7. B.U.N. - Blood Urea Nitrogen

Q. WHO - Uorld Health Organisation

9. RBG - Red Blood Cells

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INTRODUCTION

Definaticn: Malaria is a protozoan disease transmitted to humans by the bite of anopheles mosquitoes and is characterised by rigors, fever, splenompgally, anaemia and a chrnnic relapsing ccurse (1).

Life Cycle in man: The infection is initiated when fpmale anopheles mosquito innoculate sporozoites during a blood meal. Sporozoites disappear from the circulation within one hour and by unknown mechanism enter the liver parenchymal cells where they proliferate into thousands of individual meruzoites. Development in liver cells requires about a week for Plasmodium falciparum and Plasmodium vivax and twc weeks for Plasmodium mclariae.

In Plasmodium vivax and Plasmodium ovale infections, some parasites (Hypnozoites) remain dormant in the liver cells for months to years before undergoing proliferation. The liver cells containing mature parasites (merozoites) rupture releasing the merozoites into thp blood stream, tD invade red cells. This initiates the erythrocytic phase of the infection. Development of the intrs-erythrocytic parasite follows one of two pathways i.e. asexual proliferation and differentiation into sexual parasite, the gamocyte (2).

Historical Background: The wurd malaria comes from Latin "m3l-aria" meaning "bad air". K^laria has been known since antiquity as evidenced by presence of terms denoting malaria in some of the ancient Egyptian papyri. Despite awareness Df its existence, the early physicians were totally oblivious of the aetiology of malaria. In 1031, Oenpc Boyle, a colonial surgeon to Sierra Leone put forward the "swamp .theory" to explain the cause of malaria. According to this theory, with the commencement of rains, the vegptations sprout overnight in the tropics and as quickly decays in thp stagnant ponds.

The heat and moisture combine to exite the deadly principles of malaria which are uafted in the early morning like smoke or steam over the streets of the nearby town to infect the inhabitants (3).

The discovery of Plasmodium as the cause of malaria was made by Laveran a French Physician in Algeria in 1880, and in 1907, he was awarded a Nobel price for the discovery. It was then thought that malaria was transmitted from one person to another by infected blood innoculations and mosquitoes were suggested as the natural vehicles. This theory was proved by Ross in 1898 for bird malaria and by Bignami, Grassi and Bastianelli at the turn of the century for Plasmodium vivax and Plasmodium falciparum (*·).

At unknown period in history, the curative value of cinchona bark was discovered in South America. According to the legends, an earthquake provoked great destruction at Loxa where many cinchona trees collapsed and fell into a small lake making its water very bitter. Yet an Indian with a violent fever drank the contaminated water and recovered from the fever within two days. The response of fever to cinchona provided the first specific diagnostic tool and this 'therapeutic test' was exploited by Torti (1775) to differentiate malaria from other fevers. The active principle of cinchone, quinine was isolated in 1820 by two French chemists Pellelier and Caventou (3).

Epidemiology:

Malaria transmission is indigenious in 102 countries of the world. About 2,700 million people (56% of the world's population) live in areas endemic for malaria. 2,265 million in countries where malaria ccntrol has been or is still practised and 398 million in countries where no specific measures are being or h3ve been taken against the disease. About 775 million people (16% of world's population live in areas where malaria has been eliminated over recent decades (5).

Of the four main types of human mp.laria, vivax malaria covers the widest geographical area but docs not occur in large areas of tropical Africa. Falciparum malaria however is the most frequently occuring ££om_ throughout the tropics and sub tropics.

All the four types of malaria parasites have been observed in Kenya (6). Plasmodium falciparum is by far the most common (80-85%) followed by plasmodium malariae (10-15%). Plasmodium ovale is only occasionally seen and Plasmodium vivax is reported infrequently.

Transmission of malaria ip¥(¥laircbi where our study was conducted is less clear (7). Transmission can undoubtedly occur particularly in the low lying surburbs. However, the majority of Nairobi residents with malaria gave history of recent travel to an endemic area.

Literature review: It has always been taught here that with Plasmodium falciparum parasitemia of *2%* one would be very ill and infact in coma. It is also said that parasitemia of 100,000 parasites or more per mm^5 (approx. 2.5%) may result in death rates of about 20% and that cerebral malaria occurs when 5% or more of the erythrocytes are infected (Q). More recently, it has been stated that patients with parasitemia in excess of 5% to 10% are at increased risk of developing all the dangerous manifestations of falciparum malaria (9).

A case was however reportedˆin this hospital of a one year old boy who was only febrile but fully conscious with Plasmodium falciparum parasitemia of 2*+% (10). It is therefore apparent from theaabQOe finding that parasitemia may not correlate well with the degree of illness and that other factors may play part. It is in this background that the author undertook to examine the relationship between parasitemia and clinical manifestations including the complications of falciparum malaria in adult patients.

L _

Most fatal CASES of falciparum malaria have evidence of central nervous system disease, hours or even days prior to death. For purposes of clinical research, cerebral malaria has been defined as a state oˆ unarousable coma attributed solely to falciparum malaria (5).

In practice any degree of impaired consciousness could indicate central nervous system involvement and a paten*ˆal'y f.-.tal outcome. Four hypotheses have been advanced to explain the pathophysiology of cerebral malaria:-

a. Increased permeability of the blood brain barriers: According to this hypothesis, malaria infection is thought to act vie mediators which are probably kinnins to initiate an inflammatory process in thp cerebral blood flow. The cerebral capillary endothelium becomcs abnormally permeable allowing plasma, fluid and protein tc escape into the brain and CSF leading tc cerebral edema. This theory became widely adcpted and was the basis for the widespread use of corticosteroids in cerebral malaria. The- theory is based on experiments with rhesus monkeys and there is no evidence that a similar mechanism is operative in human cerebral malaria.

The hypothesis has received several criticisms.' First cerebral edema in the absence of a spinal block should lead tg raised intracranial pressure and therefore lumbar CSF pressure. But opening pressures at lumbar puncture in patients with cerebral malaria are usually normal. Secondly, papilloedema is rare and computerised tomography of the brain is usually normal and thirdly coma was found to be prolonged in patients treated with steroids.

«

tu Disseminated intravascular coagulation: It would be difficult reconcile a theory of widespread cerebrovascular thrombosis as the cause of cerebral malaria with the dramatic recovery which occurs in survivors. But the investigators who revived the idea that DIC was an important intermediate mechanism in cerebral malaria, argued that fibrin was rarely seen in cerebral vessels because fibrinolysis was accelerated and that regional intravascular fibrin deposition in the brain might be an acute temporary process (12). Some workers in 1966 showed modestly raised fibrinogen degradation products and increased fibrinogen turnover in the serum of patients with cerebral malaria and this seemed to favour the theory of D.I.C. (13). Although thrombocytopenia is common in cerebral malaria, it is also a feature of uncomplicated disease. Law platelet count and raised FDP have led some observers to argue that DIC occurs frequently in malaria (12.1ˆ,17). However, many of these published data are inadequate to diagnose DIC with certainty and when heparin was given to malaria patients alleged to have DIC on the basis of some of these results, the mortality was *15%* (11).

c. Immunologically mediated diseases: It has been observed that malnourished children seem less prone to develp cerebral malaria than those who are well fed (9,11). This observation was first made in Nigeria in 1967 (16) Other workers in Nigeria in 1973 made four major observations (19). First that malaria was apparently suppressed in normad and non-normad children during famine; secondly, that malaria was reactivated by refeeding, thirdly that cerebral malaria was restricted to non normads arid to no-mads refeedinj exclusively on grain and finally that the nomads drinking milk as the main source of food were apparently free of cerr-bral malaria.

They concluded that suppression of malaria by famine is not clear but that several factors might be operating. These include:

a. Deprivation of the parasite of the essential nutrients such as P.A.E3.A.

b. An unsatisfactory intracellular environment which does not favour multiplication of the parasite.

c. Premature death of the red cells from oxidant stress due to decreased glutathione peroxidase combined with the parasite load.

d. More vigorous phagocytosis in the face of protein defficiency

e. Increased interferon production and unavailability of iron in the ferrous (Fe^{2+}) form for the parasite use. Refeeding could correct these abnormalities some more abruptly than others permitting a recrudescence of the disease.

Cerebral malaria appears to be much less common in famine perhaps because of the synchronous combination of reduced parasite multiplication and suppression of cell mediated immunity or T cells function which interferes with the immune response essential for its production. The sparing of the underfed from the cerebral complications has been related to the atrophy of the thymolymphatic system (2D). Studies in hamsters showed clearly that neonatal thymectomy or treatment with antilymphocytic globulin prevented the development of cerebral malaria following infection of the animals with Plasmodium berghei (21,22). The workers prostulated that non-thymectomised animals developed agglutinin, in response to the malaria infection that causes microembolisation of the: cerebral capillaries with agglutinated parasitised RBC, and that neonatal thymectomy inhibits or delays the production of this agglutinin.

Circulating immune complexes are found commonly in patients with severe malaria compared to those with mild disease (23). However, studies of cerebral malaria in Thailand failed to demonstrate vasculitis, glomerulonephritis and other signs of immune complex deposition. Thus, there is no convincing evidence that immunopathological mechanisms are involved in cerebral malaria.

d. Systemic toxemia: A syndrome of severe multisystem disease which progressed to shock does occur in patients with falciparum malaria (11). It has been said that endotoxin is involved in the pathoqensis of malaria (16), and more recently two separate studies using limulus lysate gelation assay to look for endotoxic substances in human malaria found positive results in some samples 2ˆ,25). But because of the false positive results with which this technique is associated interpretation of these findings is difficult. The origin of endotoxin in malaria patients is unclear. Vascular stasis in the gut and failure of hepatic clearance of the absorbed endotoxins have been suggested gs passible mechanisms for systemic endotoxemia (26,27,20). There is no evidence that the parasites itself produces endotoxin. Other workers have reported secondary gram negative septicaemia in malaria (29,30) as the cause of endotoxemia in malaria. Finally haemolytic diseases of t'h which malaria is an example are known to predispose to invasive enterobacterial infections (31).

Anaemia is said to be a universal feature of falciparum malaria (9). The main mechanism of anaemia associated with high parasitemia is direct destruction of the red cells by the parasites (2). In support of this, some workers (11) found that in uncomplicated falciparum malaria, haptaglobulins were reduced or absent while serum bilirubin and lactate dehydrogenase concentrations were high. However, other factors other than haemolysis may play an important role in the pathogenisis of severe anaemia sometimes encountered in patients with low parasitemia,, It is thought that in such netipntR_ nn™al a-. 1 , _. . ..

arertdestrayed mare rapidly than usual suggesting that autoimmunity may be involved. It has been suggested that malaria antigens released from parasitised cells can bind to normal red blood cells. Subsequently antibodies and complements combine with this surface bound antigen and thus make the affected red blood cell susceptible to pathocytosis and destruction by phagocytic cells and spleen.

Gastrointestinal symptoms such as nausea, vomitting and diarrhoea are common in malaria. Two studies have demonstrated abnormal xylose absorption in falciparum malaria (26,27). These studies also showed histological changes in small intestinal biopsies which included oedema and round cells for infiltration of the lamina propria, shortening and widening of villi and engorgement of the mucosal blood vessels

Hepatamegally and jaundice are common in falciparum malaria but the extent of structural and functional disorder within the liver is controversial. Histological abnormalities seem to be common in human malaria (32) but it is uncertain if these changes are associated with important alterations in liver function. These changes include Hupfer cell hyperplasia, mononuclear cell infiltration and granuloma formation.

Renal dysfunction is known to occur in association with Plasmodium Falciparum Malaria. The clinical pattern is that of reversible dysfunction which in minority of cases progress to established acute tubular necrosis. Some workers showed that the renal cortical blood flow is reduced during acute Plasmodium falciparum infection (32). Increased blood viscosity and hypovelemia have also been considered contributory® However the cause of renal failure complicating falciparum malaria is not clear. Pathological studies indicate that the predorminant lesion in patients dying of Plasmodium falciparum malaria wasacute tubular necrosis (33). Other studies have described medullary capillary engorgement in patients dying of Plasmodium Falciparum Malaria(3^{i}t).

In patients with black urine, acute tubular necrosis may be due to intravascular haemolysis. Haemoglobin itself is not nephrotoxic but other compounds released from lysed erythrocytes can induce acute tubular necrosis especially in presence c[r] dehydration and acidosis (35).

Antibodies to Plasmodium falciparum malaria are said to be protective. Passively transferred immune sera delay onset or abrogate acute malarial infection in children (14). Immunoglobulins of adult 'jJest Africans confer protection to East African m_laria (36).

Specific activity of malarial antibodies h=s been confirmed in various degrees in three immunoglobulins IgG, IgM, and IgA. No specific antimalarial antibody activity has been detected in IgD and IgE immunoglobulins (37). Prolonged exposure to malaria results in high serum IgG with certain protective substances. They seem to have their antiplasmodial effect at the time of Schizogony of the parasites when the merozoites escape from the erythrocytes.

Although anti-plasmodium specific antibodies are important during the eafly stage of infection and 'in the elimination of thp parasite in acute and chronic stages, there appears to be no direct correlation between protective immunity and antibody titres, or isotypes.

In highly endemic areas the p-rasite rate increases with age from D - 10'- during the first three months of life to 00-90% and the rate persists at high level during early childhood (35). By school age a considerable degree of immunity has been developed and asymptomatic parasitemia can be as high as lb% in primary school children (39). In areas of low ends-.mici ty where the immunity in the indigenous papulation is low, severe infection occur in all the age groups including adults. The immunity gained in Plasmodium Falciparum infections by frequent bites of infected anophelines can be partly lost if the person leaves the endemic area for a long period.

AIMS AND OBJECTIVES

1. Tn determine [f]he pattern of clinical presentation of Plasmodium falciparum malaria in adult patients at Kenyatta National Hospital.

2. To relate severity of illness tc parasitemia

3. To compare biochemical changes in **mElaria** patients to those of normal controls and to correlate the changes to parasitemj a.

U. To correlate antibody titres with parasitemia.

75 adult patii-.nts presenting at HNH Casualty between September 1987 ta February 19R8 with malaria were covered in the study. Patients who hud been on -'nti-maleria prophylaxis and those who hud recently ingested anti malarial drugs were excluded frnm the study. The stuˆy sl?c covered 76 healthy adults as controls. The controls comprised of relatives of the cases students, both frnm the Medical Training Centre and University ; Faculty cf Medicine, nursing staff, domestic staff and parents of sick children in the Poediatric Emergency Ward. Verbal consent was obtained from both the cases and controls.

The following information was recorded by the author on all patients:-

1. fr-me
2. Age
3. Sex
k. History of recent travel outside Nairobi
5. Mcin complainto

Full physical examination including temperature measurement usinij a centigrade mercury thermometer and blood pressure measurement using a mercury sphygmomanometer was done on all patients **by** the author. The temperatures were taken in the armpits and the blood pressures were taken cn the left arm.

Menous blond specimens were taken for the various investigations as follows:-

1. 2 millilitre of blood in sequ˜strine for making twon thin smears on slides and for coultergram. The ccultergram was obtained on the coulter counter model 5, in the Haarr.atol egy Department. The thin slides were stained with Giemsa in the department of medicine after which the parasites were counted against 5?PR3Cs in six fields. The average number of parasites/ 500 f?3Cs was used to calculate percentage parasitemia using the R3C count from the ccultergram.
2. 3 miliilitres of bloou in-a plain bottle for urea and electrolytes. These ware dene in our chemical pathology laboratory using the SNA IT computer controller, multichannel biochemical analyser.
3. 3 millilitres of bland in a plain bottle for determination of the antibody titres. The procedure used in detection of malaria specific antibodies is described here in details.

Materials:

1. B multiwell slides
2. Tris-buffered Hanks solution

Prepared from:

a. 10mls of 0.15M Trio-huffpr PH 7.2
b. 10Cmls of Hanks solution
3. Co- ting buffer prepared by adding 1.5gm of Naˆ CO,,, 2.93gm rJaHCO_3 and 200mg Nal¥l$_3$ in 1 litre and PH 9.6

U. *1%* Glutaldehyde.

Indirect Immunofluorescence nntjhody (IFA) test

Procedure :-

Infected erythrocyte (E) monolayers

1. 31nnd specimen sontaining more than $10^{\sim 7}$ porasit^{c}mia (2) cells washed x 3 with Tris-buffered Hanks.
2. Dilute the CFIIS to give t$^{n/}$ suspension, use normal red blnod cells or controls.
3. Apply one drop of costing into 8 multiwell slides and incubate for 30 minutes.
   ˆsnirate the casting buffer and add one drcp of 1% red blood cell suspension and incubate for 30 minutes at room temperature.
5. LJash off unbound erythrocytes by shaking the slides immersed upside down in petridish cont2ining Tris-buffered hanks.
6. Quickly cover the red blood cell monolayers with 1-2mls of glutaraldehyde for 10-20 seconds in P3G.
8. After decanting, repeat step 1 and then wash with H0, airdry and then stare at 20° C till used.

DETECTION AND TITRATION OF ANTIBODY

1. Label 3 tubes, neat, 1/10,1/20 and dilute the patient's sera accordingly.
2. Add one drop pf the diluted sera onto each well of the above prepared slides and incubate at room temperature foi 30 minutes.
3. Wash excess sˆra with Tris-buffared hanks and add ens drop of diluted fluorescent conjugated anti-human e.g. immunoglobulin (anti 1GG, Anti IgA, Anti IgM). Incubate in the dark ˆor 30 minutes.

h. Wash end mount with PBG-glycerol

When monolayers of glutaraldehyde fixed and air dried parasitised

'Iqure 1: Showing Age and Sex Distribution for the Cases

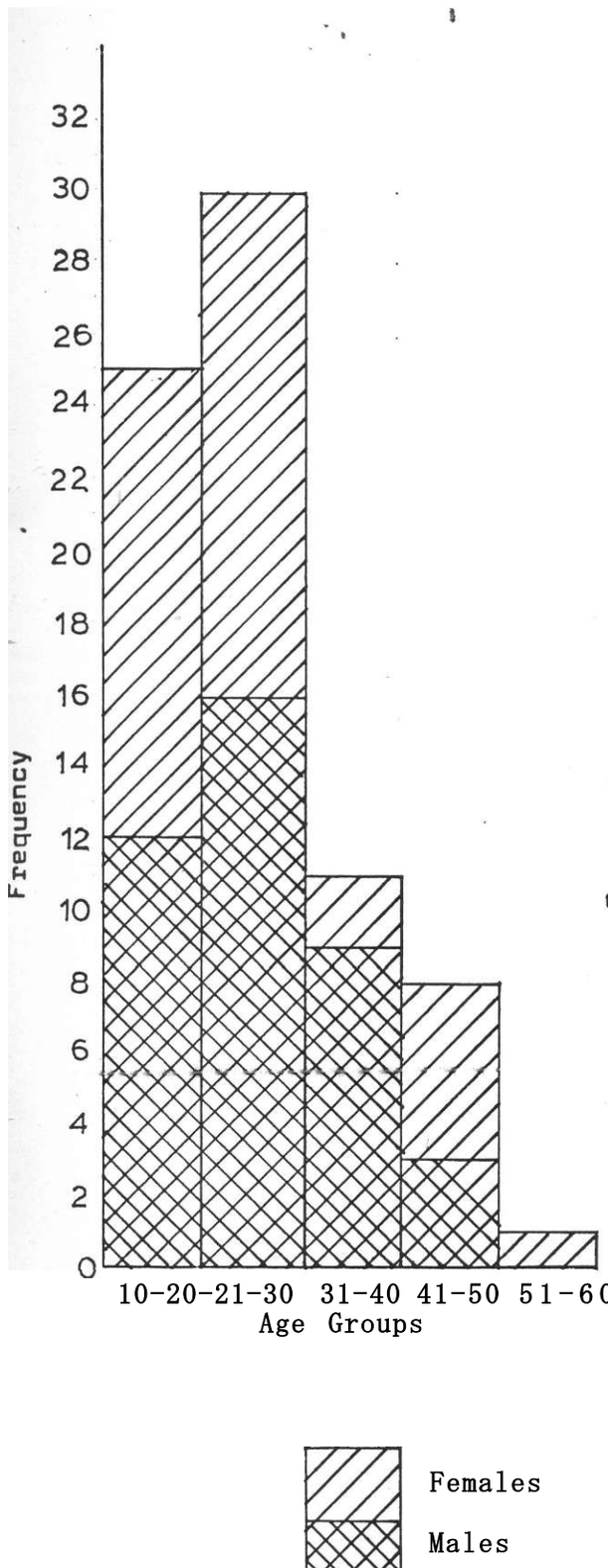


Figure 2: Shotus the floe and Sex Distribution for the Controls

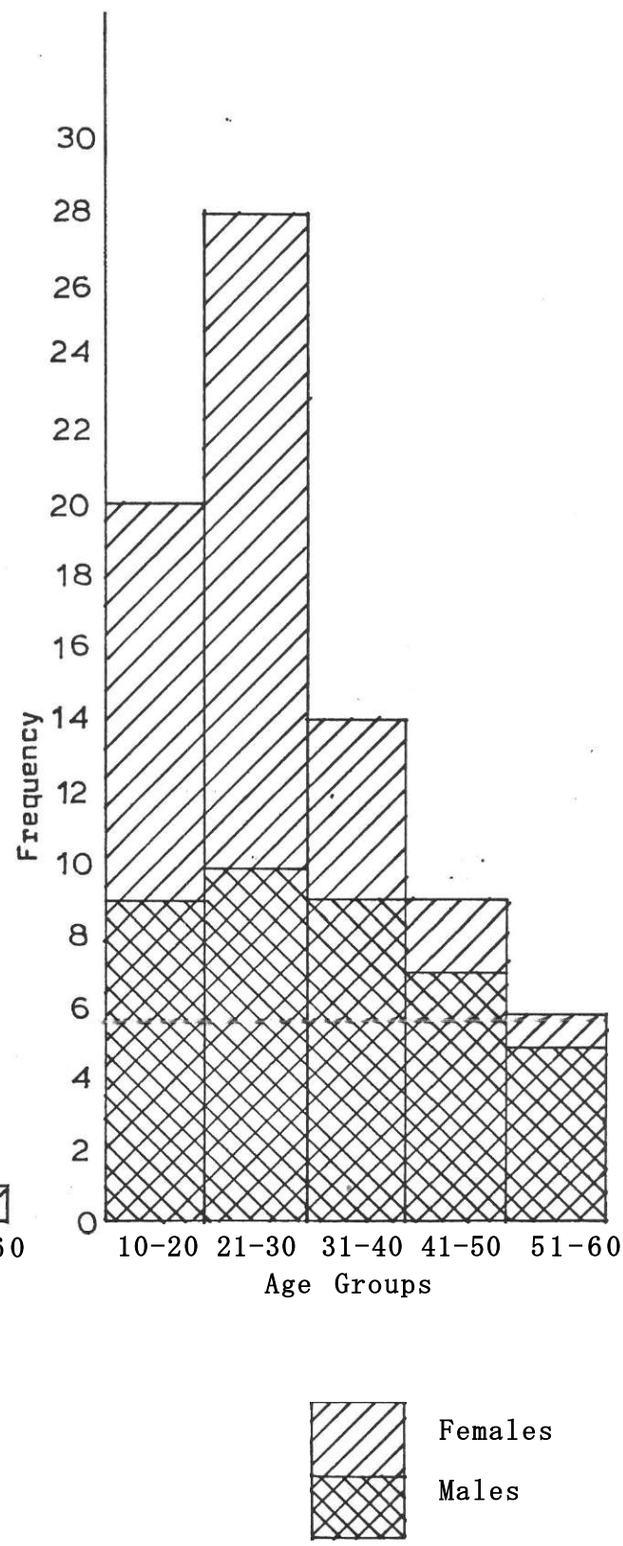


Table 1: Comparison for age in cases and controls

	Cases	Controls	T Test
Mean Age (Yrs)	27.7+10.3	30.6_+12.1	P 0.05

Table 2: Comparison for mean aqe and sex in cases and controls

	Mean age for females	Mean age for males	T Test
Cases	27.5+11.6	27.9+9.0	P 0.05
Controls	29+10.0	30.9+8.0	P 0.05

HI2Ti. V GF RECENT T'.,VJEL TL THL COUNTRYSIDE

Only 14 patir nts (18.4=0 denied having travelled outside Nairobi 2 weeks prior to the onset- of illness. 62 patients i.e. 81.6% had been to various districts as shown in table 3 at least 2 weeks prior to the onset of illness.

Table 3: Shows the districts soma of our patients had visited

District	No. of Patients	%
1. NAIROBI	1u	18.4
←. K -K^MEGA	13	17.1
3. KISUML)	8	10.5
4. KISII	6	7.9
5. MAGHr.K05	6	7.9
6. MURANGA	5	6.6
7. LI•YA	£	5*6
B. MOMBASA	4	5.3
9. BUSIA	4	5.3
10. TR-N5-NZOIA	3	4.0
11. BUNGOMA	2	2.6
12. KITUI	2	2.6
13. SOUTH KYmNZA	1	1.3
14. HI ,MBU	1	1.3
15. MERU	1	1.3
16. KAJIADO	1	1.3

THE Fr.TTEPN OF CLINICAL MKN IFE ST-'': TIGNS

The majority of cur patients had mare than one symptom with a maximum of three. The commonest symptoms were headaches, joint aches and dizziness with 3 patients i.e. 4' unable to give history due to impaired level of consciousness.

The main finding on clinical examination in majority of the patients was fever in *32%* followed by jaundice (19£) and splenomegally (12 P/ J. Table 4 and 5 shows the pattern of clinicalmmanifestati ons.

TARL T ^ 5HOUING THE PATIENTS SYMPTOMS

SYMPTOM	No. of Patients	1
1. Headaches	54	71.1
2. Joint aches	26	33.8
3. Dizziness	25	33.0
4. Vomitting	16	21.0
5. Diarrhoea	15	20.0
6. Shivering	12	16.0
7. Loss of appetite	3	4.0
S. Epistaxis	2	3.0
9. Unable to give history	3	' 4.0

TABLE 5: SHOUING THE CLINIC';L SIGNS

SIGN	IMC. OF PATIENTS	%
Fever	7N	92
Jaundice	14	19
Splenomegally	9	12
Hypotension	5	7
Dehydration	5	7
Pallor	5	7
Impaired consciousness	3	4

PARASITEMIA

This ranged between 0.2 - *23.0%* with a mean **of** 2.55+3.6. Ue looked at tnpan parasitemia in 10 year age groups as shown in table 6 brrlow and there was no statistically significant difference P= over 0.05.

TABLEI 6: SHCwS MEAN PARASITEMIA FOR THE DIFFERENT AGE SREUPS

AGE Gll'L'P	MEAN PARASITEMIA	NO OF CASES
10-19 yrs	2.20	16
20-29 yrs	2.05	33
30-39 yrs	3.1	13
L0-U9 yrs	1.5	12
50-60 yrs	2.5	2
Total No. of Cases		75

Looking at the level of parasitemia, we found majority of our patients (90.8%) to have parasitemia below 5.0% as shown in Table 7 b[r]:low.

TˆGLE 7: SHCUS THE DUTRI3IJTICN OF PARASITEMIA

Range of parasitemia in %	No. of Patients	%
0.1-5.0[n/]	69	90.8
5.1-10.0%	m	5.3
10.1-20. *Or'*	*2*	2.6
Over 20"'	1	1.3
TOTAL	76	100%

We compared the level of Parasitemia between the males and females as shown in Table 0 and there was no statistically -significant difference. P over 0.05

TABLE 8: PUT' I3i;TIC[r]: OF THE D IFFERENT LEVELS OF PARAGITO", IA I" LE AND FEir^Lt P^TIEiYTS

Range of Parasitemia ("Q	No. of males	No. of Fem"les	Total
n.1-5.0	35	33	£9
5.1-1H.0	3	1	U
10.1-20.0	1	1	Z
Over 2 0	0	1	1
TCT'.L		35	7s

Going by the clinical features and applying the WHO guidelines, the patients were divided into two groups i.e. severe falciparum malaria and non-severe falciparum malaria. Patients with the following features were considered to have severe manifestations of Plasmodium falciparum malaria.

a. Any degree of impaired consciousness attributable solely to Plasmodium Falciparum malaria,

h. Clinically detectable jaundice

c. Hyperthermia: Defined as rectal body temperature above 39'[n]C.

d. Hypotension: Systolic blood pressure of less than 90mmHg[t] and diastolic blood pressure of less than SOmmHg.

Bleeding

f. Fluid, electrolyte or acid base disturbance requiring I.'J. flyids.

Using the abeve criteria 59 patients (77.6"-) had severe Falciparum malaria (Table 9) and only 17 patients (22.^) had nr-n-severe malaria.

TABLE 9: SHOx'S THE DISTRI3UTION OF SEVERE MANIFESTATIONS

Clinical Feature	No. of peticr.ct.	% of those with severe malaria	% of the total No.
Hyperthermia	37	62.7%	43.7%
Jaundice	U	23.7%	18.4%
Hypotension	5	*B.t***	6.5%
Dehydration	Ꝯ	8.4%	6.6%
Impaired consciousness	3	5.1%	4.0%
Bleeding	2	3.4%	2.6%

Hyperthermia was the commonest severe manifestation occuring in more than hˆlf (62.7%) of those with severe Falciparum Malaria. Sliqhtly less than one quarter (23.7%) of those with severe Falciparum Malaria had clinically detectable jaundice.

CLINICAL MANIFESTATIONS IN RELATION TO PARASITEMIA

The mean value of parasitemia for the severe and non-severp Falciparum Malaria were compared and there was a statistically significant difference. P less than 0.05 Table 10 shows the maon values of perasitprnia for severe and nan severe Falciparum Malaria.

TABLE 10: SHCˆS f_ ·N PTRASITEMIA FOR SEVERE AND NL'N SEVERE FALCIPARUM MˆLARĨ*

SEVERITY	ME-N PARASITEMIA
Severe Falciparum Malaria	3.00?a
Non severe Falciparum Malaria	1.00%

The mean level of parasitemia was higher (3%) in patients with severe Falciparum Malaria as compared to that of patients with non-severe Falciparum Malaria (1%)

HYPERPARASITEMIA; (Parasitemia above 5%

There were 7 patients (approximately 10° -) uiith parasitemia above 5%. The parasitemia in these patients ranged between 5.1 to *23%* with a mean of *11.U+U.1.* All the seven patients had features of severe falciparum malaria. The symptoms and signs were as shown on Table 11 and 12.

T.—.3LE 11: SHCiJS THE V^I^US SYMPTOMS AND THEIR PROPORTIONS IN PATIENTS UIITH HYPERPARA3 ITEM IA

Symptoms	No. of Patients	% of patients with hyperpara-sitemia	% of the total (76)
Headaches	5	*71.1*%*	*6.6%*
Dizziness	U	57. *V*	*5.3%*
Diarrhoea -	2	*23.5%*	*2.6%*
Loss of aopetite	1	1*4.2% ,	1.3%
Unable to give history	1	1*4.2%	1.3%

71.*4% of the patients with hyno parasitemia complained of headaches, 57.1% of dizziness and 28.5% of diarrhoea.

Hyperthermia and jaundice were found in 85.7% of them.

Only one patient had impaired level of consciousness. ¥

CC* T—..-L NERVOUS SYSTEM MAP] IFEST-MICIf; 5

° nly 3 patiants (*+%) had impaired level of consciousness. Of them only 1 had hyperparasitemia and the other 2 had parasitemia less than 5%. Their level of consciousness were assessed and graded according to the Edinburgh method thus:-

Grade 1: Drowsy but responsive to vocal commands

Grade 2: Unconscious but responsive to minimal painful stimuli

Grade 3: Unconscious but just responsive tD strong painful Stimuli

Grade U: Unconscious with no response in stimuli

There uere 2 patients in grade 1 level of consciousness with a mean parasitemia of 13. while 1 patient was in grade 2 with parasitemia of There were no patients in grade -3 and as shown in table 13.

TABLE 13* SNOWS THE LEVEL OF CDNSC-IOUSNESS OF THE THREE PATIENTS JJITH CENTRAL NERVLUG SYSTEM MANIFESTATIONS

GRADE	No. of Patients	% of those with CNS manifestation (3)	% of the total
1	2	66.7%	2.6*
2	1	33.3	1. y
3	0	00.0	0.0%
U	0	oo.0	0.0%

None of our patients had grade U level of consciousness which is the equivalent of the WHO definition for cerebral malaria.

The mean level of parasitemia for the patients with impaired conscious level was 10.3%

UREA AND ELECTROLYTES

The values were compared between cases and controls The parameters looked at include sodium, potassium blood urea nitrogen and serum creatinine.

SODIUM

The mean value of sodium in malaria cases was 13.S+.ommol/litre. and for the controls was 136.9+6.2mmal/litre. The values were compared using the T-test and there was a statistically significant difference in the mean value of sodium between the cases and controls (Table 10. P=Q.0131

TA3LE : SHCSG THE Ml ¥f! VALUE OF 30D1UM BOTH IT; C,~;SES AND CONTROLS

	Cases	Controls	T Test
MEAN V/ALUE FOR SODIUM	13*».3+ˆ.0	136.9+6.2	P less than 0.05

There wasn't any significant difference in the meep value of sodium between the controls and the cases when divided in 10 year age groups except in patients aged above itO years where there was a statistically significant difference (Table 15).

TABLE 15: SHCLJS A COMP.AIXN IN MEAN SODIUM VALUES OETuJEEIM CASES ND CONTRUG IT:TO 10 YEAR AGE 5ML UPS

Age Group	Mean Sodium Value for cases mmol/litre	Mean sodium value controls mmol/litre	T Test
10-19 years	13ˆ+2.6		F over 0.05
20-29 years	13U.g+<».5	136.5+_6.1	P over 0.05
30-39 years	135.7+ˆ.0	133.1+7.5	P over 0.05
Over 'i0 years	m.0+3.9	138.ˆ+6.8	P less than 0.05

RELATIONSHIP TO PARASITEMIA

Using Pearsons correlation co-efficient, there was no correlation between parasitemia and serum sodium (Figure 3).

POTASSIUM

There was no statistically significant difference in the mean serum potassium as shewn in Table 16.

Figure 3: Scatter Diagram Showing the relationship betueen serum Sodium and Parasitemia

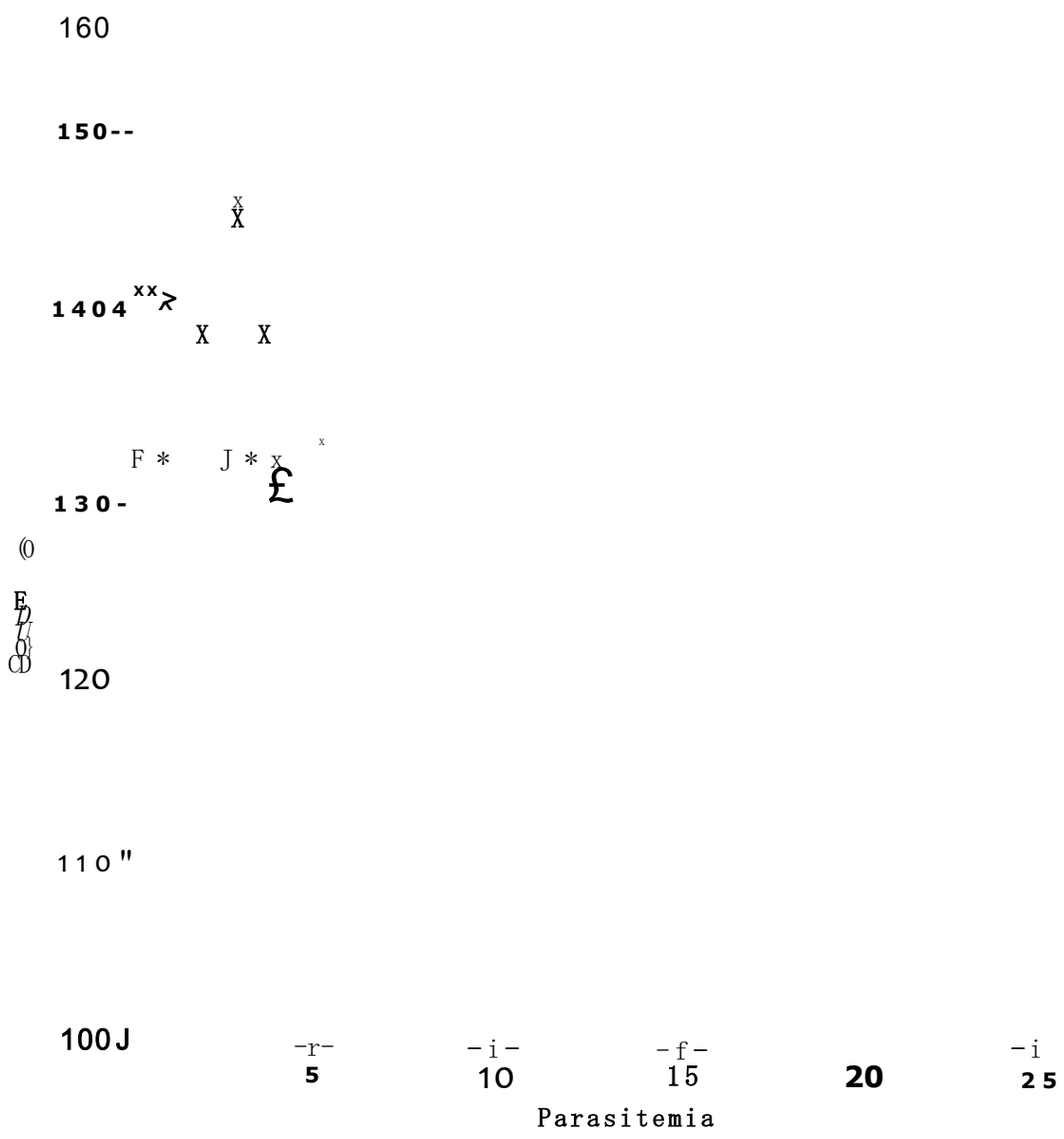


Figure k: Scatter Diagram showing the relationship betueen Serum Potassium and parasitemia

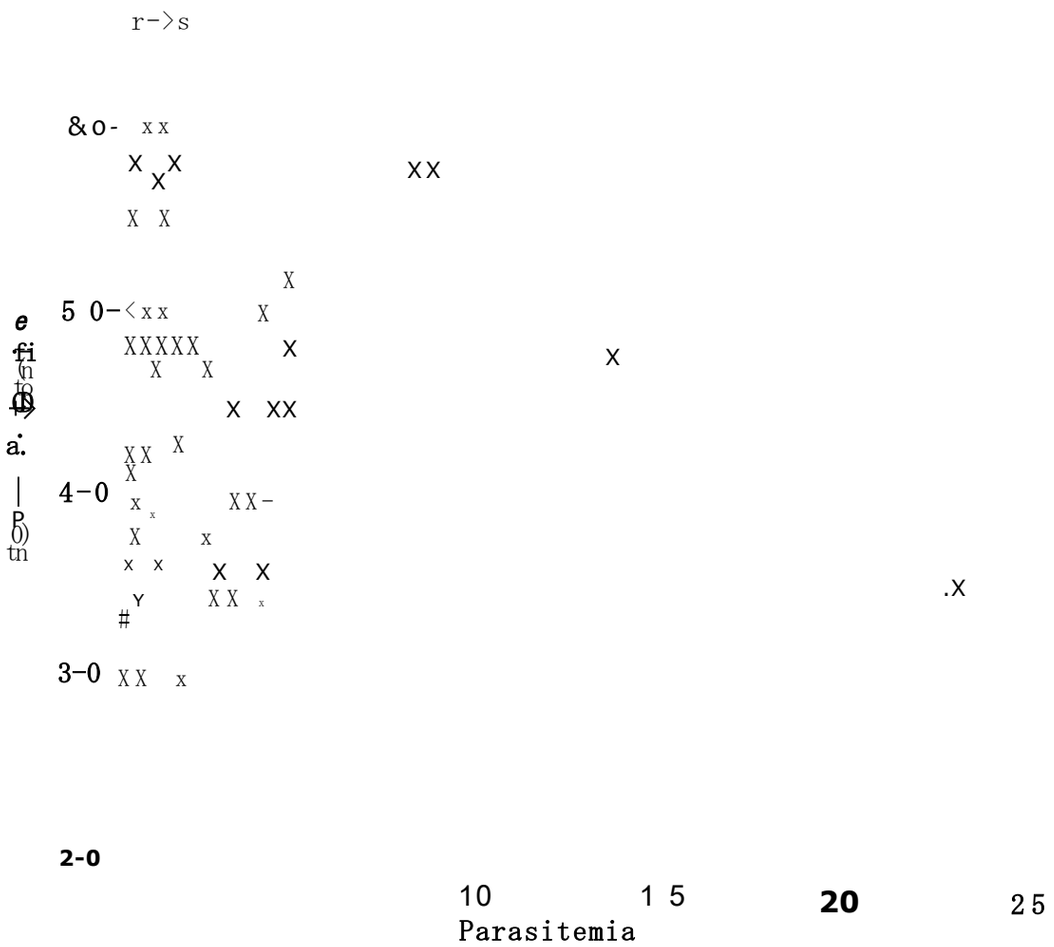


TABLE 15: SHC'JS A CCMPARISCN OF THE MEAN SERUM POTASSIUM BETWEEN CASES AND CONTROLS

	Cases	Controls	T Test
Serum Potassium mncl/1	<+.5+0.8	<·.5+0.9	F over 0.05

There was no statistically significant difference in the mean values of serum potassium between the cases and contrds in the 10 year age groups as shown in Table 17.

TABLE 17: KE^R N VALUES OF SERUM PETASSIUK IN THE 10 YEAR AGE GROUPS

AGE IRuL'Pwi (In years)	KE-.N SERUM POTASSIUM FOR THE CASES mmol/litre	MEAN SERUM POTASSIUM FOR THE SOrJTRCLS mmol/litre	T EST
10-19	<·.8+0.8	<·.7+0.9	P over Bo05
20-29	<·.3+0.8	<·.3+_1.0	P over 0.05
30-35	[illegible]	5+0.9	P over 0.05
Over ˆ0	'·.8+1.0	<·.5+0.3	.P over 0.05

Relationship of Serum Potassium to Parasitemia

There was no correlation between serum potassium and parasitemia using Pearsons correlation co-efficient. The reiatianship is shown in Figure <·.

BLDDD UREA NITRUGEN

There uas a statistically signific . difference *i-* the mean blood urea nitrogen levels betwee the cases and controls. P=0.0003 i.e. less than D.D5 (Table 18},

TABLE 18: SHObJS THE MEAN BUN GF THE CAGES AND CuNTRLLS

	CASES	CONTRLLS	T TEST
Mean BUN mmol/litre	5.57+2.0	4.56+1.1	P less than 0.05

There was a positive correlation between parasitemia and BUN using Pearsons correlation co-efficient. Figure 5 demonstrates the relationship.

SERUM CREATININE

There was a statistically significant difference in the mean value of serum creatinine between the cases and controls (P=0.0000) (Table 19). Using Pearsons correlation co-efficient, there was a positive correlation between the serum creatinine and parasitemia (Figure 6).

TA3LE 19: ft COMPARISON OF MEAN 5ERUM CREATININE BETUEEN CASES AND CLNTKOLS

	CASES	CONTROLS	T TEST
Mean Serum Creatinine (mmol/litre)	110.5,+ 29.3	69.0+/14.1	P less than 0.05

Figure 5: Scatter Diagram showing the relationship between Parasitemia and BUN

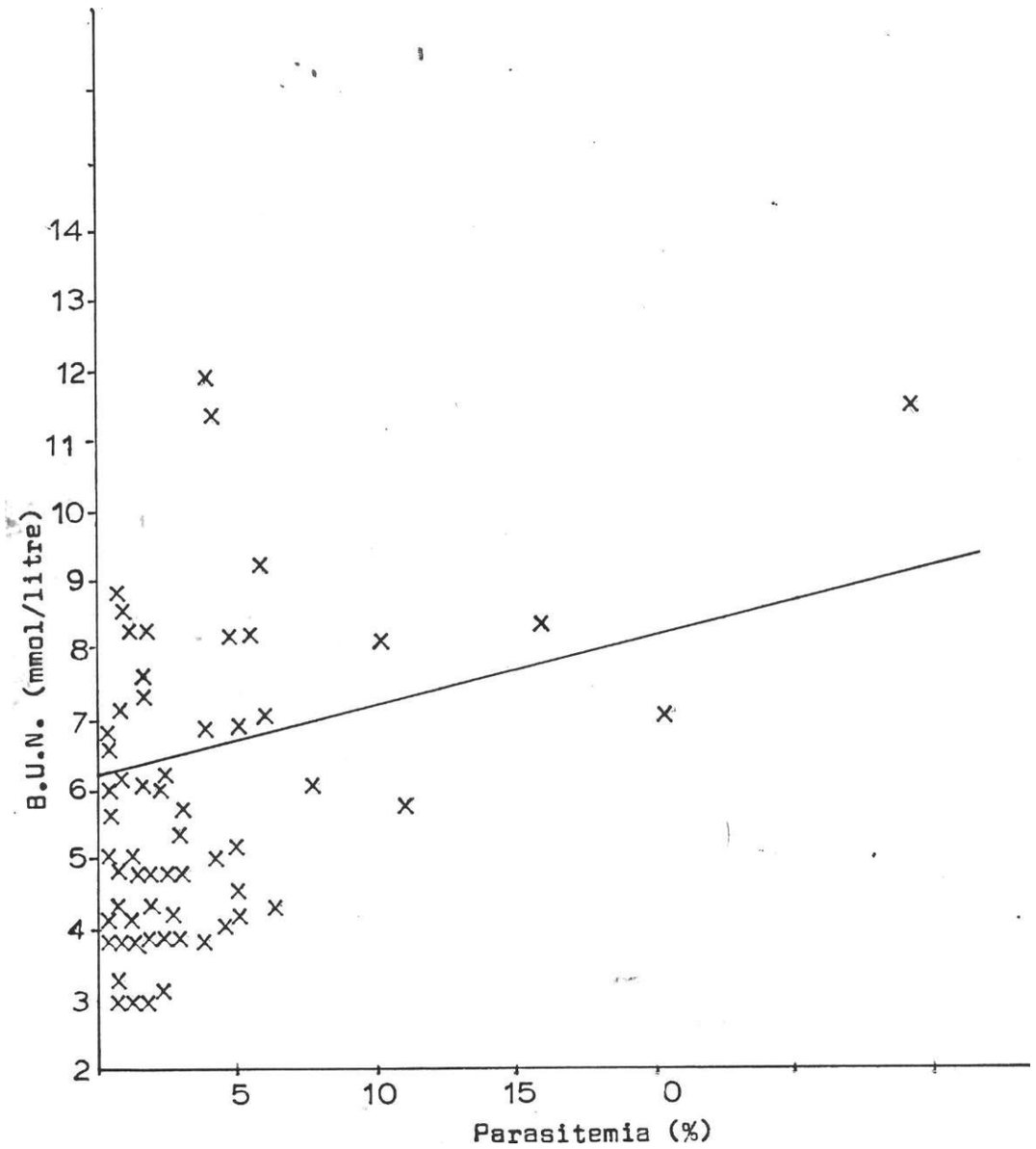


Figure 6: 5catter Diagram illustrating the relationship betmeen Parasitemia and Serum Creatinine

-i i c<

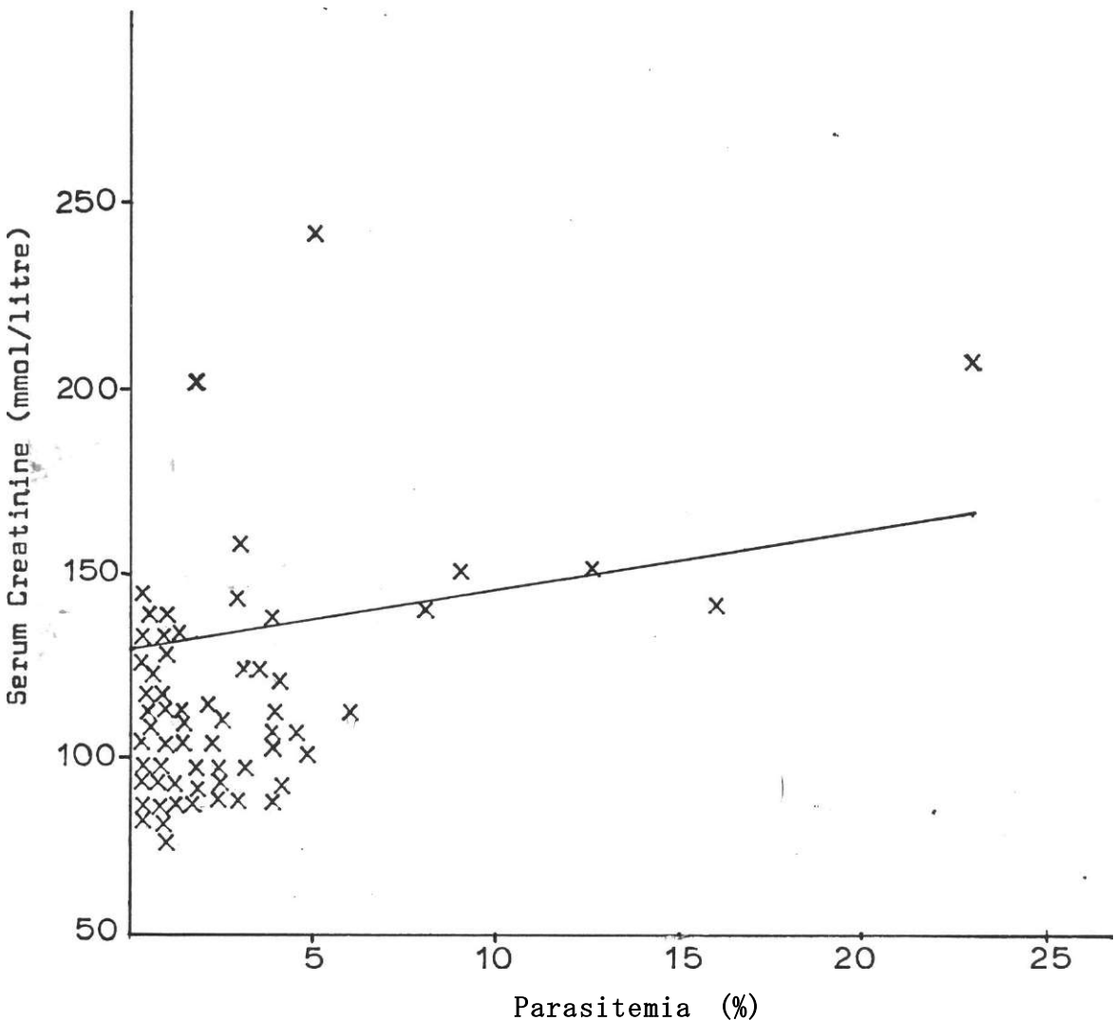
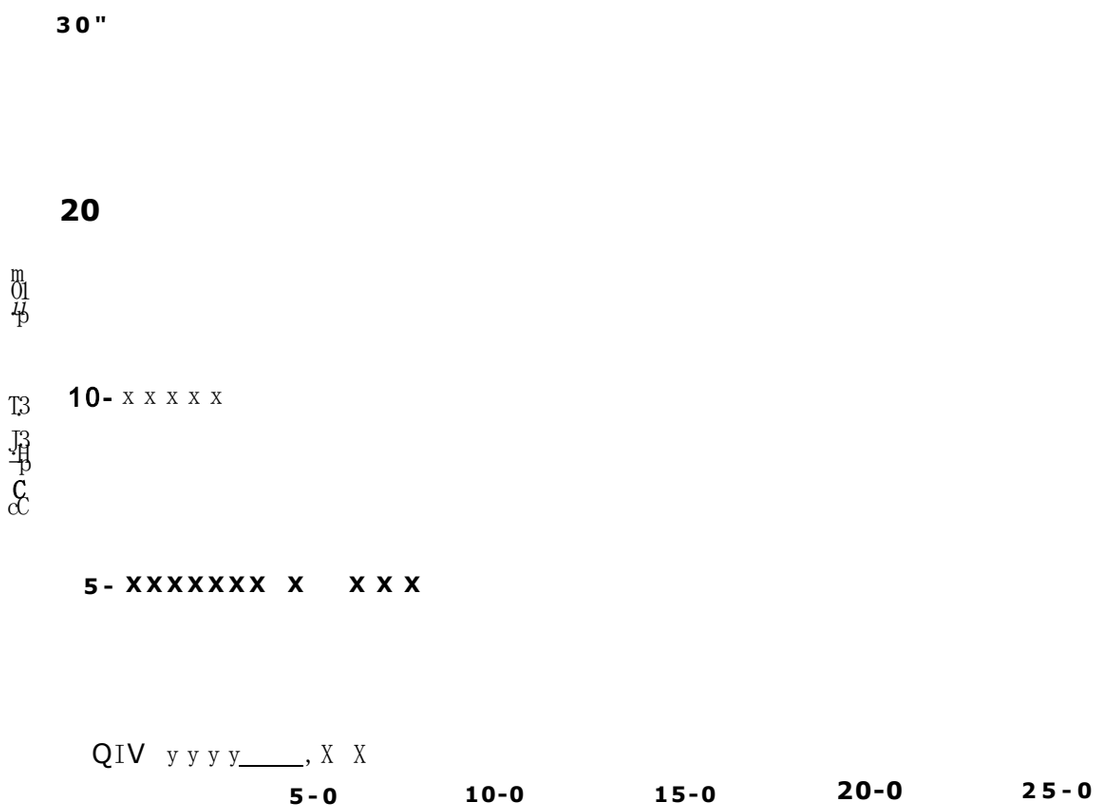


FIGURE 7: ILLUSTRATES THE RELATIONSHIP, BETWEEN ANTIBODY TITRES AND PARASITEMIA



Hey:

Nil	> 0
Neat	+ve 5
1/10	+VB 10
1/20	+ve 20

DISCUSSION

Description of the clinical features of acute falciparum malaria are numerous but feu prospective studies have been undertaken to define the incidence and course of symptoms and signs during the primary attack and relate these to the level of parasitemia. Secondly, the relationship between parasitemia and renal function have not been critically exanined.

The clinical manifestations of acute falciparum malaria in our patients were similar to those classically described. The pattern was however unique and therefore deserve more emphasis. Ue found that 81.6% of our patients with falciparum malaria had a history of recent travel to malaria endemic areas. This agrees with what ,Dr. Rees observed in 1971. The remaining 18.4% of our patients denied any history of recent travel outside Nairobi but one of these patients gave history of blood transfusion a week prior to presentation. It seems therefore from this finding that the majority of the patients we are seeing in this hospital with malaria have 'imported-[1] malaria. Secondly it appears as if there is malaria transmission in Nairobi occuring in a small proportion of the population. Dr. Rees (7) had observed that malaria transmission in Nairobi was possible and that it seemed to be restricted to.the low lying surbubs. Earlier reports dating as far back as 1907 claimed that malaria transmission occured in Nairobi on the basis of the fact that numerous mosquitoes were found during the rainy seasons coinciding with epidemics of malaria (40).
Malaria transmission could indeed be occuring in Nairabi. However, it is an unstable malaria in that transmission stops at about 56 F (15 C) and the temperature in Nairobi ranges between ⋘0° F and B0° F.

71% of our patients complained of headaches, a non specific symptom that occur in many other diseases. This differs from what Brooks et al (41) found in Vietnam where 100% of their patients complained of headaches.

It is however difficult to logically compare the two results for various reasans:-

B. Their sample was much smaller consisting of twenty six soldiers.

b. Their sample consisted of male patients only.

c. Their study was conducted during the war when the tension alone could be the cause of the headaches.

Although we have established that headaches is a common symptom of malaria, we are still not clear whether malaria is the commonest cause of headaches in this hospital. Dr. Rees (7) criticised the diagnosis of clinical.malaria which was based mainly on fever and headaches when he found that only 1.3% of these patients actually had malaria. It would therefore be important to establish what proportion of patients with headache have malaria.

Joint aches occured in 33.8% of our patients. Brooks (M) found joint aches in 31% of his malaria patients in Vietnam. Just like headaches, there are very many causes of joint aches in this hospital. Some of these include rheumatic fever, brucellosis osteoarthritis and various viral fevers.

Dizziness, another non-specific symptom occured in 33.0% of the patients. It is a symptom that is commonly associated with anaemia here. It also occurs in acute anxiety neurosis and severe depression. It would be important to know what proportion of dizziness is atributed to malaria.

Uomittinp and diarrhoea occured in 16% and 15% respectively. Nausea, vomitting and diarrhoea are reported to be very common symptoms of falciparum malaria (9) (11). This does not seem from our findings to be true here. This would therefore mean that patients presenting with diarrhoea and vomitting should be investigated for ether diseases as well as for malaria.

Epistaxi occured in 3% of the patients. This particular , symptom deserves special mention because in most cases of epistaxi maleric is never suspected. The two patients who presented with 《epistexi had hyperparasitemia and coultergram showed low platelet count. The blood urea nitrogen were within normal limits for both patients.

DIC LUES suspected as the cause of' bleeding. It is said that approximately 5% of patients with cerebral malaria develop significant bleeding (9). Our patients did not have cerebral malaria but since thrombocytopenia is also a feature of uncomplicated falciparum malaria, it is difficult to conclude that DIG occured in these patients on the basis of thrombocytopenia alone.

, The other causes of **epistaxis** like raised artenial pressure, trauma, inflammation, overdose of anticoagulants and nasal tumors heamorrhagic diseases should be considered.

Fever occured in 92% of our patients. Brooks et al found fever in 120% of their patients which compares closely with our * finding here. But like headaches, fever is a non-specific sign and is a manifestation of various other conditions. It is as yet not clear which is the commcnest cause of fever in our hospital among adult patients. A study should be done in future to answer this very vital question.

19% had jaundice which was clinically detectable. This figure is close to being accurate as most of these patients had high . parasitemia which is stated to be associated with increased destruction of RBCs (2). However, viral h&patisis drug ingestion and liver cirrhosis were not ruled out in these patients.

12% of our patients had splenomegally. The spleen enlarges in Plasmodium falciparum malaria and may be enormous weighing SOOgm in the acute stage. This occurs mainly in the non-immune (8). Brooke et al (41) found splenomegally in 65% of his patients. This big difference is probably because his patients were non-immune. But splenomegally in our:environment can be due to various other conditions and our figure of 12% may not be very accurate.

However if a patiant with mal-ria is found to hcve a tendar splenomegally, thEn it is most likely due to malaria.

It is important to follow the course of splenomegally closely in these patients and to:limit their physical activity during its presence because several instances^of traumatic and spontaneous rupture of the spleen have been reported C*2,[t]+3).

Possession of one or more of the following features is sufficient for a diagnosis of severe falciparum malaria (9).

a. Hyperparasi^emi?:- a density of asexual forms of Plasmodium falciparum in the peripheral blood smear exceeding 5% of erythrocytes.

b. Cerebral malaria:- U$_n$nrcusable coma attributed solely to Plasmodium falciparum malaria.

c. Severe anaemia: Defined as a haematocrit of less than 20% or heamoglobin of less then 7.1gm/dl.

d. Jaundice:- Detectable clinically or defined by'serum bilirubin concentration of more than 50 umol/litre

e. Fluid, electrolyte, or acid ba^e disturbances requiring intravenous therapy.

f. Renal failure defined as urine output of less than [i]4[p]0mls in 2*t hours and a serum creatinine of more than 2Sumol/litre, failing tc improve after rehydration.

g. Hyperthemia - defined as rectal body temperature above 39° C.

h. Complicating or associated infections such as aspirations bronchopneumonia.

i. Pulmoary edema

j. Hypoglycemia:- defined as a blood glucose concentration nf less than 2.2mmol/litre

k. Circulatory collapse

1. Bleeding or blood clotting disturbances

m. Vomiting of oral treatment

n. haemoglobinuria

No studies have been dona here before to ″show the relationship betuiean parasitemia and clinical, manifestation of Plasmodium falcip'c-rum mBl.c?ri3» But. stucliBs ricriE ElsGuihprc hsvc shown thst parasitemia above 2.5″- (100,000 parasites/mm″') results in deeth rates of about 2Q; end that cerebral malaria occurs when 5?£ or more of the erythrocytes are infected. It has also been stated more recently that patients with parasitemia between 5-1CK are at increased rjsk of developing all dangerous manifestations of falciparum malaria.

The mean parasitemia in our patients was 2.£', 9(1.8‴. of the. patients had parasitemia less than 5' while only 9.24 had hyperparasitemia. 68ˆ of those who had parasitemia of less than 5% had severe falciparum malaria according to the LLJHP criteria stated above. It is apparent from this finding that majority of our patients show severe manifestation at low parasitemias. This is not unusual because whereas high parasitemia can be equated with severity of malaria, the reverse is not true particularly in non immune individuals (9).

In Plasmodium falciparum infection, the paras!tejwithdraw® to the internal organs as it matures and therefore the density of parasitemia may wax and wane cyclically. Secondly, the low parasitemia in some patients with severe manifestations could be due to the indiscriminate use of antimalarial drugs which may suppress the parasitemia while the clinical features lag behind. 4

This second reason is a remote possibility because although history of having ingested any antimalarials was one of our exclusion criteria, some patients who had ingested any drugs would deny it in order to receive ″proper″ attention.

9.8* of the patients had hyperparasitemia. All these patients had severe manifestation. This finriinq agrees with the observation **by** Field and Niven that there is a correlation between the density of parasitemia and the severity of illness (44). Only one patient with hypeˆparasitemia had impaired level of consciousness. The ether patients were fully conscious. The patient who was in Grade I level of consciousness and therefore did not fit into the classification of cerebral malaria according to the WHO. The patient had 23″’ parasitemia, the highest recorded in this study.

Most fatal cases of mrlaria have evidence of central ˆnervous system disease, hours or even days prior to death (11). For purposes of clinical research, cerebral malaria has been defined as a state of unarousable coma a-ttributahle solely to falciparum malaria (5). However, in practice any degree of impaired conaciousness cculd indicate central nervcus system involvement and a potentially fatal outcome. Only three patients (4%) hod imp ired level of consciousness. Of these, two had parasitemia below 5% and one above 5%. Lne was in Grade II level of consciousness (unconscious but responsive to painful stimuli). The other two patients were in grade I (drowsy hut responsive to vocal commands). None of the three fit. in the definaticn of cerebral malaria.

The serum creatinine and BUN were found to be higher in malaria patients as compared to the controls and both parameters showed significant positive correlations with parasitemia. The mean serum creatinine in malaria patients was 110.5+79. 3m’ml/l itre. The highest serum creatinine recorded’, in our patients was 205mmol/litre which is lower than the figure quoted by WHO for renal failure complicating malaria.

Antibody titres were determined in 30 patients but did not show any correlation with parasitemia. Protective anti-plnsmodium antibodies have been reported in both experimental animal model systems and human following a natural malaria infection. The immunity confered is specific for sporozoite or blood storage forms (stage specific).

Evidence far the protective activity relies on th In . re experiments indicating inhibition of the paresite, cr merozoite neutralization. The relevance of these in vitro findings to the in vivo situation is unclear. It is presumed that the in vitro tests reflect the in vivo capacity of malaria specific antibodies to inhibit invasion of erythrocytes or enhance the clearance of parasitized erythrocytes. However, correlation between anti-plesmadi&l antibodies and clinical immunity remains unsettled.
t

Studies conducted in children in Tanzania foiled to demonstrate a direct relationship between antisporozaite antibedy levels and both splenic enlargement and parasitemia (US) Furthermore, work carried out in Kenya recently shewed no correlation between sporozoite specific antibodies in adults end parasitemia (ˆ7). The data obtained in our study support these observations.

Employing an immunofluorescence staining technique, antibodies to blood stage antigens were screened in the malaria patients. The major antigen detected is expressed in the membrane of infected erythrocytes with early ring or trophozoite stages of the parasite. It hes a molecular weight of 15:,CC0 and is design-ted Pf 155 antigen. Antibodies directed against Pf 155 have been reported to confer protection and are found in immune populations in melaria-holoendemic areas C+B). The results in the 3P melria patients examined indicate no correlation between the Pf 155 antibodies and parasitemia.

Overall, malaria specific antibody level were very low indicating that the patients examined were non-immune Secondly most of our patients had severe disease with parasitemia less than *5':t.* Nan immune subjects are known to get severe manifestations with low parasitemia (9). It seems very likely therefore that majority of our petients were non-immune.

CONCLUSION

Majority of patients presenting in thfs hospital with , **Plasmodium** falciparum malaria show severe manifestations even at low level of parasitemia. On the other hand, these patients seem to be resistant to developing cerebral malaria end ether pernicous complications even **at** higher levels of parasitemia.

3oth 3U¥i and serum creatinine correlate with parasitemia positively but no relationship is demonstrable? between the antibody titre and parasitemia.

RECCMFfcND -TIEN 5

1. Further studies to specifically look at the relationship between Parasitemia and the complications of malaria should be done.

?. Future research should focus on the evolution of malaria antibody isotypes levels and direct relationship with protective immunity. The precise role of cell-m.pdiated mechanisms in cerebral malaria also reruires elucidation.

PLATE 1: SHOWS THICK FILM WITH HIGH PARASITEMIA

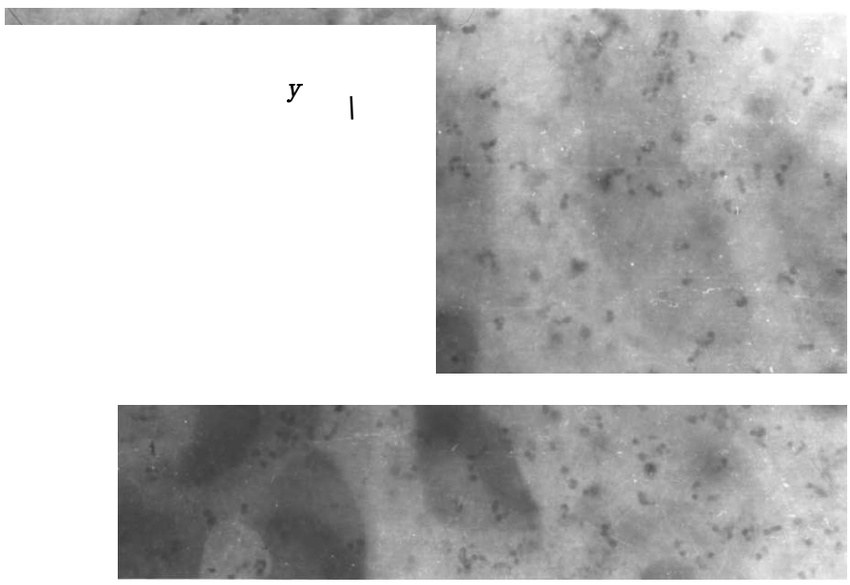


PLATE 2: SHOWS THICK FILM UIITH MODERATE PARASITEMIA

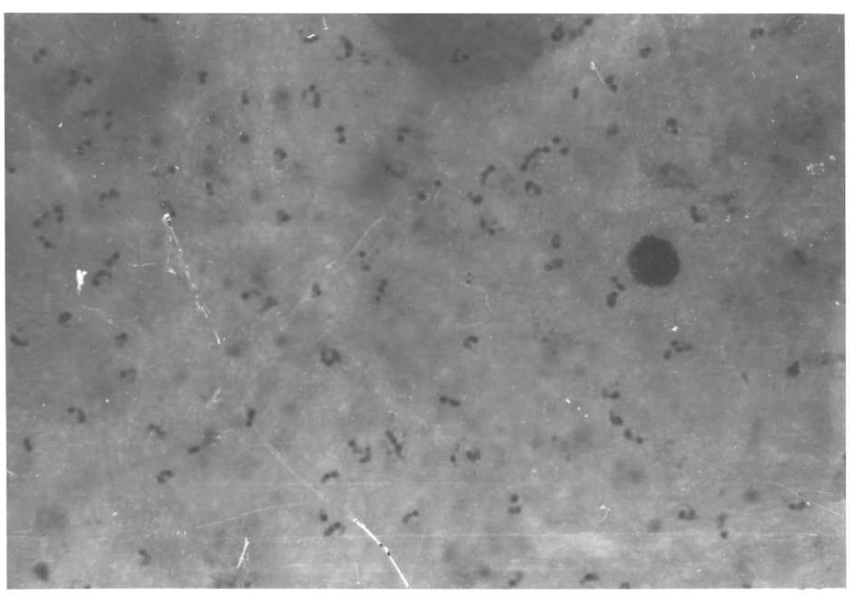


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PLATE 3: SHOWS THICK FILM WITH MODERATE PARASITEMIA

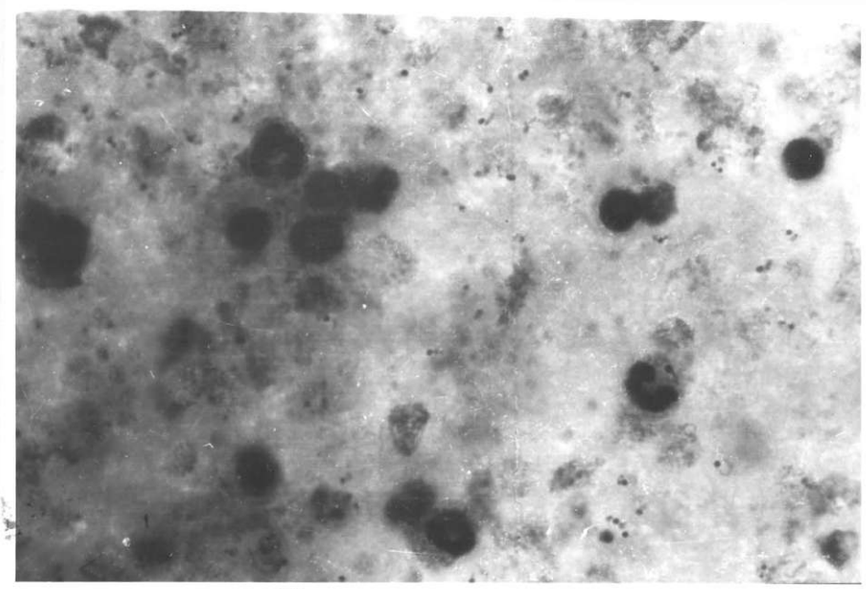
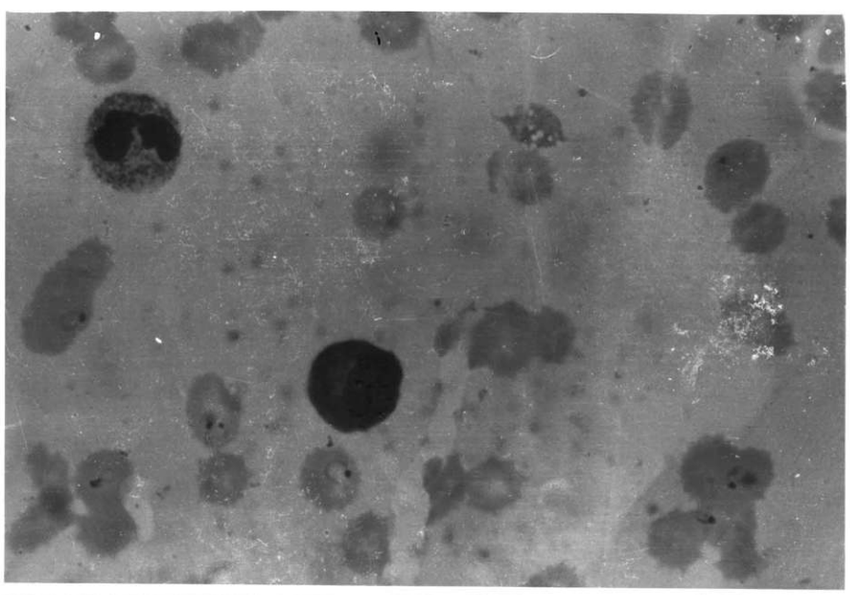


PLATE 4: THIN FILM SHOWING DOUBLE INFECTION BY PLASMODIUM FALCIPARUM



ACKrvCˆL FDGEf'-˜r-:T5

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