SOME BIOCHEMICAL CHANGES IN CHILDREN WITH ACUTE FALCIPARUM MALARIA

BY

DR. STELLA N. ABWAO, MB. ChB. (NAIROBI)

A dissertation submitted in part fulfillment for the degree of Master of Medicine (Paediatrics) at the University of Nairobi.

1988

D E C L A R A T I O N

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

Signed ----------

DR. S. N. ABWAO. M.B. Ch.B (NAIROBI)

This dissertation has been submitted for examination with our approval.

Signed ----------

DR. D.A.O. ORINDA M.SC. Ph.D (LONDON)
Department of Human Pathology
University of Nairobi.

Signed ----------

PROFESSOR H.O. PAMBA B.A. M.Sc. Ph.D (LONDON)
Department of Medical Microbiology
University of Nairobi.

Signed ----------

DR. D.W. KINUTHIA M.B. Ch.B M.MeD Paed. (NAIROBI
Department of Paediatrics
University of Nairobi.

C O N T E N T S

LIST OF TABLES AND FIGURES

ABBREVIATIONS

Na^+	- Sodium
K^+	- Potassium
BUN	- Blood urea nitrogen
ALT	- Alanine transaminase
AST	- Aspartate transaminase
ADH	- Anti-diuretic hormone
HB	- Haemoglobin
K.N.H.	- Kenyatta National Hospital
P.E.W.	- Paediatric Emergency Ward
P.F.C.	- Paediatric Filter Clinic
P.D.U.	- Paediatric Demonstration Unit
g/dl	- Grammes per decilitre
mmol/l	- Millimoles per litre
µmol/l	- Micromoles per litre
ml	- Millilitre
S.D.	- Standard deviation

S U M M A R Y

One hundred children with acute falciparum malaria attending Kenyatta National Hospital and 75 controls matched for age and sex, were the subjects of the study. Seventy five patients were compared with 75 available controls. Of the 75 patients compared, 25 (33.3%) were within the 6 - 12 month age group. An overall majority 67 (90.7%) were under the age of 5 years. The study was conducted in the Paediatric Emergency Ward (P.E.W.) of K.N.H.

From each subject of the study, venous blood was obtained and analysed for various biochemical parameters. Electrolytes, sodium and potassium, blood urea nitrogen, alanine and aspartate transaminases (ALT and AST) and blood glucose concentrations were compared between the two groups. Total bilirubin for a few patients, who were jaundiced and non jaundiced and for their controls was determined.

It was found that the malaria patients had significantly lower sodium levels than the controls, with 16% being hyponatraemic. There was no statistical difference in potassium levels. The BUN concentrations, ALT and AST levels were significantly raised in the malaria patients, with greater elevation in ALT than AST levels. All the differences noted above were statistically significant ($P<0.05$). The jaundiced patients had a higher elevation in ALT, AST and higher parasite counts but lower haemoglobin levels ($P<0.05$). Blood glucose levels for the patients with malaria were mostly in the fasting range. The patient levels were much lower than for the controls and this was highly significant ($P<0.001$). Two patients (2%) were found to be hypoglycaemic.

No significant correlation existed between parasite count and sodium, potassium, BUN, ALT and AST levels. Parasite count was inversely correlated to blood glucose level, with hypoglycaemia being associated with high parasite count ($r=0.594$). This was found to be highly significant ($p<0.001$) statistically.

An attempt to correlate biochemical changes and overall outcome was difficult to do from this particular study. It was concluded that some significant biochemical changes do occur in children with acute falciparum malaria with exception as regards potassium levels. Hypoglycaemia is likely to occur with increased parasite counts and should be anticipated.

I N T R O D U C T I O N

Malaria is a serious and complex disease in childhood with a broad clinical spectrum. It is highly prevalent in East Africa, being endemic in many parts of Kenya. Endemic areas largely include the Coast, Nyanza and Western Provinces and parts of Eastern Province (Machakos and Kitui Districts) (1). Plasmodium falciparum malaria is by far the commonest type found, forming 80 - 85% of cases. However, all four types of malaria parasites have been observed in Kenya (1).

Falciparum malaria infection of indigenous children in highly endemic areas during the first five years of life can cause severe and potentially fatal illness. In the first six months of life, the manifestations are usually mild with low grade parasitaemia. This is probably due to passive immunity acquired from immune mothers (2). The parasite rate (proportion of the population in which malarial parasites are found) increase with age from 0 - 10% during the first three months of life to 80 - 90% by one year of age and the rate persists at a high level during early childhood. (3,4). The attacks of malaria are frequent upto the age of five years. The mortality rate in hyperendemic areas is highest in the first two years of life (2), and 10% of all infants will die from falciparum malaria (1). In areas of low endemicity where the immunity of indigenous population is low, severe infection occurs in all age groups including adults (2).

Several pathophysiologic changes are known to occur during the acute phase of falciparum malaria. One of the most important effects of P. falciparum infection is capillary endothelial damage which causes increased vascular permeability leading to an impairment in microcirculation. Haemodynamic changes, haematologic change and immunologic response are among the pathophysiologic mechanisms in the pathogenesis of renal involvement. (5). In falciparum malaria renal involvement therefore varies widely from mild glomerular changes,

glomerulonephritis and haemoglobinuna to acute renal failure (6,7). Haemodynamic alteration evidenced by hypovolaemia, hypotension and dehydration occur with severe falciparum malaria (2).

Acute renal failure which can complicate falciparum malaria is more common with heavy parasitaemia which is associated more with impaired microcirculation and reduction in renal blood flow. Renal failure is catabolic in type with a rapid rise in blood urea nitrogen (BUN) concentration and uraemic symptoms. Acute renal failure also occurs due to acute intravascular haemolysis. This may be induced by the malarial infection or by antimalarial drugs in association with or without glucose - 6 - phosphate deficiency. There is usually subsequent renal ischaemia although tubular obstruction by haemoglobin casts may also be a contributing factor (6).

The clinical picture is usually that of a reversible dysfunction which only in a minority of cases progresses to established acute tubular necrosis (2). Acute renal failure as a complication of falciparum malaria is relatively unusual in infants and small children (2). However, renal impairment when it occurs, is a sensitive prognostic indicator of severe falciparum malaria (2).

Hepatic involvement is also common in falciparum malaria. Falciparum malaria inhibits liver function even in the absence of clinical evidence of hepatic insufficiency and even with low parasitaemia (8). The pathogenesis of hepatic dysfunction may be multifactorial but is not clearly delineated. Increased levels of transaminases, serum aspartate transaminase (AST : SGOT) and alanine transaminase (ALT : SGPT) are common (9, 10) in the acute malaria attack. The ALT/AST ratio is also increased (8).

Increased levels occur with or without hepatomegaly (9).

Plasma bilirubin levels are also increased and jaundice is common particularly in severe falciparum malaria. The jaundice is mild with an indirect Van den Bergh reaction. Haemolysis is the main cause of jaundice (10). Normal liver function tests are usually restored on termination of the acute acute attack with antimalarial therapy (10).

Hypoglycaemia is another important manifestation of falciparium malaria also particularly common in severe disease. Hypoglycaemia results from a combination of reduced glucose supply and increased demand (2). Severe cases of hypoglycaemia are characterized by high parasitaemia and high mortality (2). The overall incidence of hypoglycaemia is not known, but is likely to be high (11). It is increasingly recognised in African children with severe infection (12, 13). Diagnosis poses obvious difficulties since changes in level of consciousness, convulsions or deepening coma are usually attributed to cerebral malaria rather than to hypoglycaemia or both. Hypoglycaemia in this context may be unsuspected and remain untreated in those with neurological signs which could be misinterpreted as cerebral malaria. It should be suspected in any child with malaria who is comatose or convulsing.

It is important to note that falciparum malaria per se contributes to a large number, approximately 10-20%, of admissions for acute illness in the Paediatric Emergency Ward (P.E.W.) of K.N.H.. Of these malaria cases, approximately 10% will succumb to the illness. Malaria also contributes 10-15% of total deaths in this area.

Malaria is therefore an important cause of morbidity and mortality in our enviroment. It is a disease associated with various pathophysiological and biochemical changes which may contribute to the adverse overall outcome of the population affected, particularly susceptible children.

It is important to determine whether clinically significant biochemical changes do occur in children presenting with acute falciparum malaria. It is with all these factors in mind that the author was prompted to undertake the study with the following aim and objectives:-

AIM

To study some biochemical changes occuring in children with acute falciparum malaria.

OBJECTIVES

1. To determine blood urea nitrogen (BUN) and serum electrolytes sodium (Na^+) and potassium (K^+) in children with acute falciparum malaria in comparison with controls.

2. To determine random blood glucose concentration and liver function tests, namely AST, ALT and serum bilirubin of the same groups.

3. To determine any relationship between biochemical changes and degree of parasitaemia in the patients with malaria.

MATERIALS AND METHODS

ETHICAL CONSIDERATION

Written consent was obtained from the K.N.H. Ethical committee and informed verbal consent from the patients' parents or guardian.

STUDY AREA AND PERIOD

The study was conducted in the Paediatric Emergency Ward (P.E.W.) of K.N.H. Patients comprised of those presenting to P.E.W. via Paediatric Filter Clinic (P.F.C.) with clinical features of acute malaria and confirmed by positive blood smear for malaria parasites. Controls were selected from the Paediatric Demonstration Unit (P.D.U.)/well baby clinic and Paediatric Outpatient Surgical Clinic, the latter with minor surgical conditions. The study was undertaken between June 1987 and January 1988.

SAMPLING METHODS

The first two patients fulfilling selection criteria were entered into the study each day from Monday to Friday between 9.00 a.m. and 2.00 p.m, to achieve a sample size of 100 patients and 100 controls. (However, 75 controls were obtained in this case).

INCLUSION CRITERIA

1. Patients in whom a clinical diagnosis was made on the basis of all or a combination of details found on PROFORMA I (see appendix I).

2. Patients with a positive blood smear for malaria parasites.

3. Age between six months and twelve years.

EXCLUSION CRITERIA

1. Patients with clinical evidence and history of pre-existing or existing renal or hepatic disease.
2. Patients who had received antimalarial treatment in the preceding two weeks.
3. Malnourished patients with marasmus, kwashiokor, and marasmic-kwashiorkor.

PATIENTS AND CONTROLS

Patients were selected from the Paediatric Filter Clinic (P.F.C.) by the author, medical officer and/or the Registered Clinical Officer (Paediatrics). Patients satisfied the selection criteria delineated. Blood smear for malarial parasites was obtained by the finger prick method and positive cases were referred to P.E.W. for study. The control group was obtained either from the P.D.U or the Surgical Outpatient Clinic. Controls comprised of children attending P.D.U. as part of the normal child health follow up, but with no problem. The controls from the clinic were attending with uncomplicated surgical conditions (such as hernias, undescended testes, lipomas etc).

A follow up of some of the children with acute falciparum malaria was done retrospectively by tracing the notes of 25 patients and determining their outcome. The outcome was determined in terms of death or survival, number of admission days, days of fever, days of blood smear positivity for malarial parasites and the type of antimalarial therapy administered.

LABORATORY METHODS

A total of 7 mls of Venous Blood was obtained by venepuncture. One ml. was obtained for haemoglobin estimation, white blood cell count and peripheral film. This amount was emptied.

into a sequetrene bottle. Haemoglobin and white blood cell count was determined using the automatic Coulter Counter Model S (16). Duplicate thick and thin films from this sample were made and delivered to the parasitology department for parasite count. Parasite count was determined by examination under a light microscope after staining the film with 4% Giemsa stain. Asexual parasites (trophozoites) were counted against 100 white blood cells (W.B.C.) on thick smears. Calculation of number of parasites per ml. of blood was then determined by multiplication of number of parasites per hundred W.B.C. with the total number of W.B.C.s (17).

Five mls of blood were emptied into a plain biochemistry bottle for BUN, electrolytes and liver function tests (L.F.T.S.). Na^+ and K^+ were determined using flame photometry (18). BUN, AST, ALT and total bilirubin were determined using manual kit methods. This is based on colorimetric methods determined at appropriate wavelengths (19,20,21).

Random blood glucose was determined using a glucometer strip and a drop of blood from a sample obtained in a fluoride bottle. All specimens were delivered to their respective laboratories within one hour of collection. Samples for analysis of Na^+, K^+, BUN, ALT, AST, and bilirubin were centrifuged and the serum separated and stored at-20^{o}C in a freezer. Analysis was thereafter done in several batches.

STATISTICS

Statistical analysis included range, mean, standard deviation, p value from the student - t - test (unpaired), and correlation coefficient.

RESULTS

The study comprised of 100 patients and 75 controls. Controls were matched for age and sex. Some of the patients were found to be underweight but this was comparably similar with controls. Only 75 patients were included for comparative study against 75 controls.

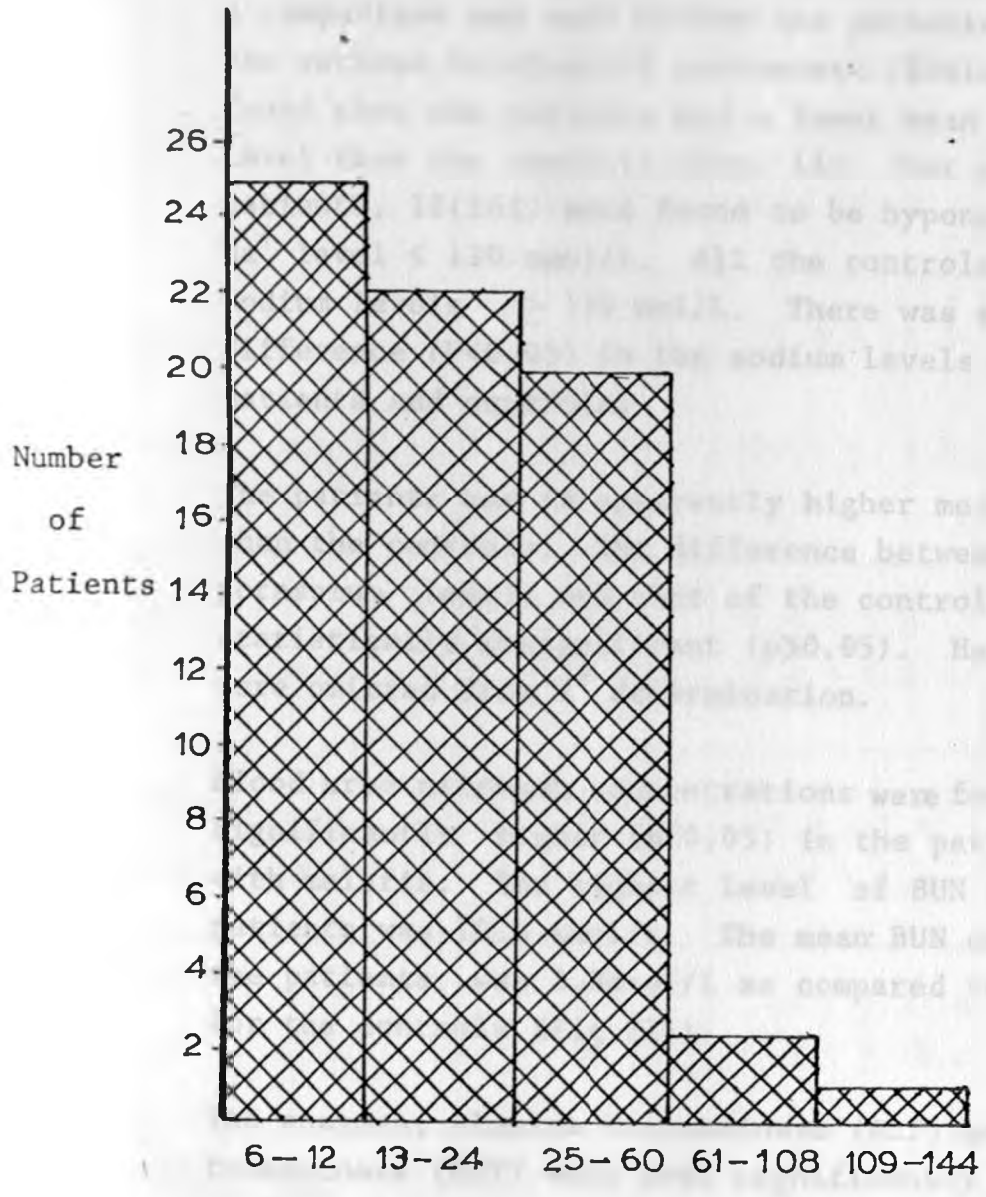
Table 1: Distribution of 75 Patients by Age and Sex

AGE MONTHS	S E X MALE n = 39	FEMALE n = 36	TOTAL PATIENTS n= 75
6 - 12	13	12	25 (33.3%)
13 - 24	13	19	22 (29.4%)
25 - 60	9	11	20 (28.0%)
61 - 108	3	3	6 (8.0%)
109 - 144	1	0	1 (1.3%)

Of the 75 patients compared, 39 were males (52%) and 36 were females (48%). Most of the patients were within the 6 - 12 month age group (33.3%), followed by 13 - 24 month age group. Very few patients were above age 5 years. This is easily demonstrated in figure I overleaf.

FIGURE I.

DISTRIBUTION OF 75 PATIENTS IN AGE GROUPS



A comparison was made between the patients and controls for the various biochemical parameters (Table II). It was found that the patients had a lower mean serum sodium level than the controls (Fig. II). Out of the 75 patients, 12(16%) were found to be hyponatraemic, with Na^+ level < 130 mmol/l. All the controls had serum sodium levels $\geq$ 130 mml/L. There was significant difference ($P<0.05$) in the sodium levels between the patients and controls.

The patients had an apparently higher mean potassium level than the controls. The difference between the patient potassium levels and that of the controls was however statistically insignificant ($p>0.05$). Haemolysed samples were omitted from K^+ determination.

Blood urea nitrogen concentrations were found to be significantly higher ($p<0.05$) in the patients with malaria. The highest level of BUN in these patients was 10.5 mmol/L. The mean BUN concentration for the patients was 3.8mmol/l as compared to 2.1 mmol/l for the controls (Fig III).

The enzymes, alanine transaminase (ALT) and aspartate transminase (AST) were both significantly raised ($p<0.05$) in malaria patients. In these patients, it was found that ALT levels were more markedly elevated than AST levels. The mean ALT level for the patients was 46.1 U/L as compared to 19.1 U/L for the controls. AST levels were lower with a patient mean of 12.2 U/L and 4.5 U/L for the controls.

Blood glucose concentrations were found to be generally lower in the patients. Two patients were found to be hypoglycaemic with a blood glucose concentration < 2.2mmol/l. The majority of patients had blood glucose levels between 3-5.5mmol/l. The control group had levels

TABLE II SOME BIOCHEMICAL PARAMETERS IN MALARIA PATIENTS AND CONTROLS

	PARAMETER	RANGE	MEAN S.D.	P. VALUE
PATIENTS n = 75	Na^+ mmol/L	120-150	132.5 ± 16.1	p<0.05
CONTROLS n = 75		130-148	139.4 ± 6.7	
PATIENTS	K^+ mmol/l	3.0-5.0	3.9 ± 0.8	p>0.05
CONTROLS		3.2-4.8	3.6 ± 0.6	
PATIENTS	BUN mmol/l	1.3-10.5	3.8 ± 1.9	p<0.05
CONTROLS		0.6-5.4	2.1 ± 1.4	
PATIENTS	ALT U/L	7-184	46.1 ± 37.8	p<0.05
CONTROLS		3- 83	19.1 ± 15.3	
PATIENTS	AST U/L	0-64	12.2 ± 13.1	p<0.05
CONTROLS		0-25	4.5 ± 4.3	
PATIENTS	BLOOD GLUCOSE mmol/l	1.3-7.0	4.1 ± 1.1	p<0.001
CONTROL		3.7-8.3	5.4 ± 1.1	
PATIENTS	PARASITE COUNT NO./ML	590-328,650	19064 ± 67713	

FIGURE II : MEAN Na^+ LEVELS

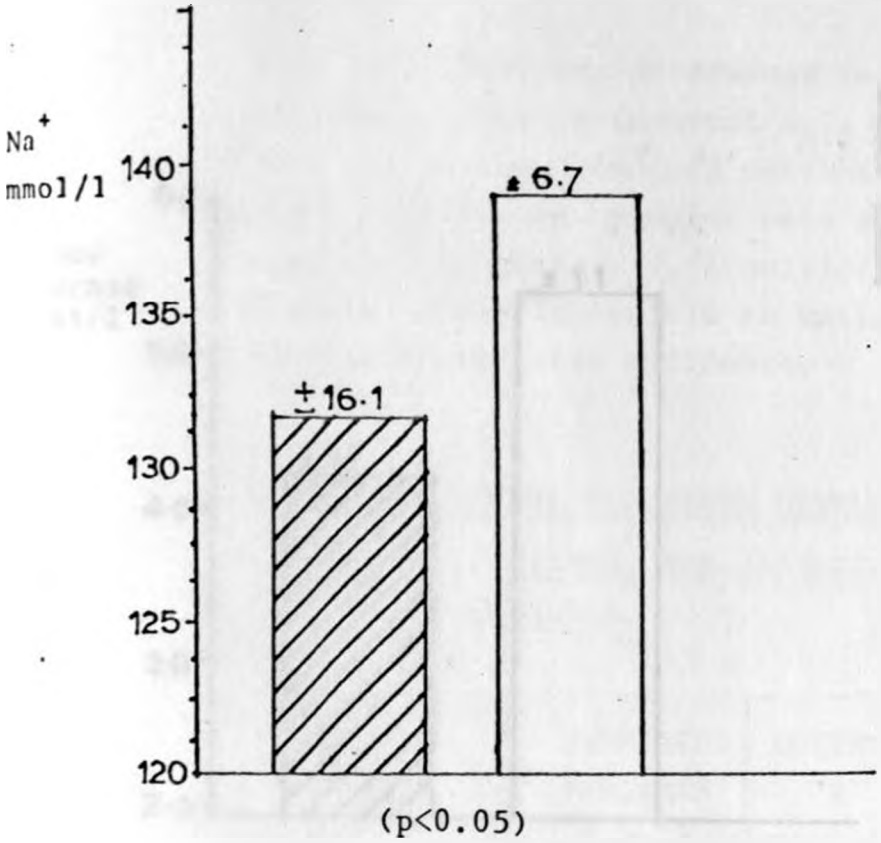
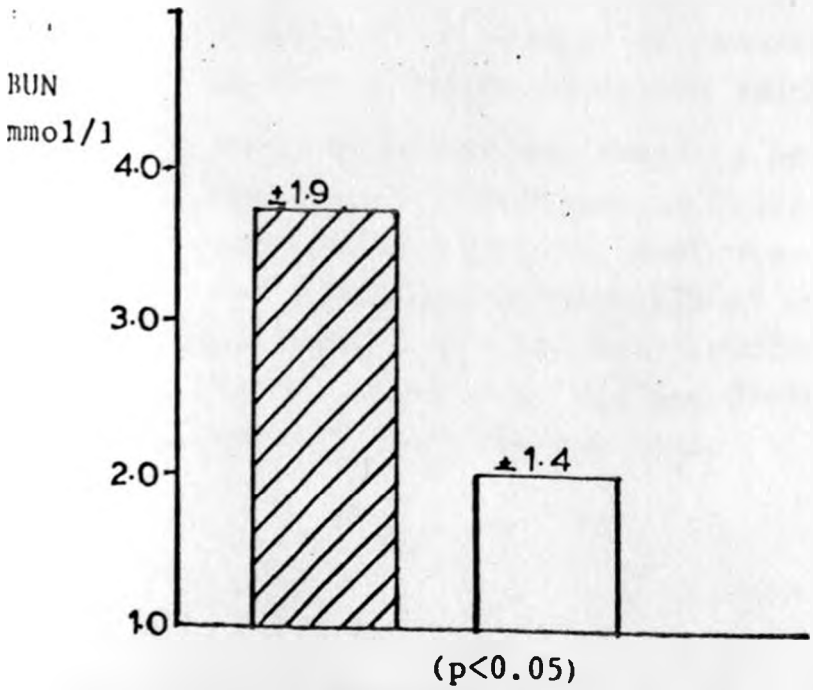


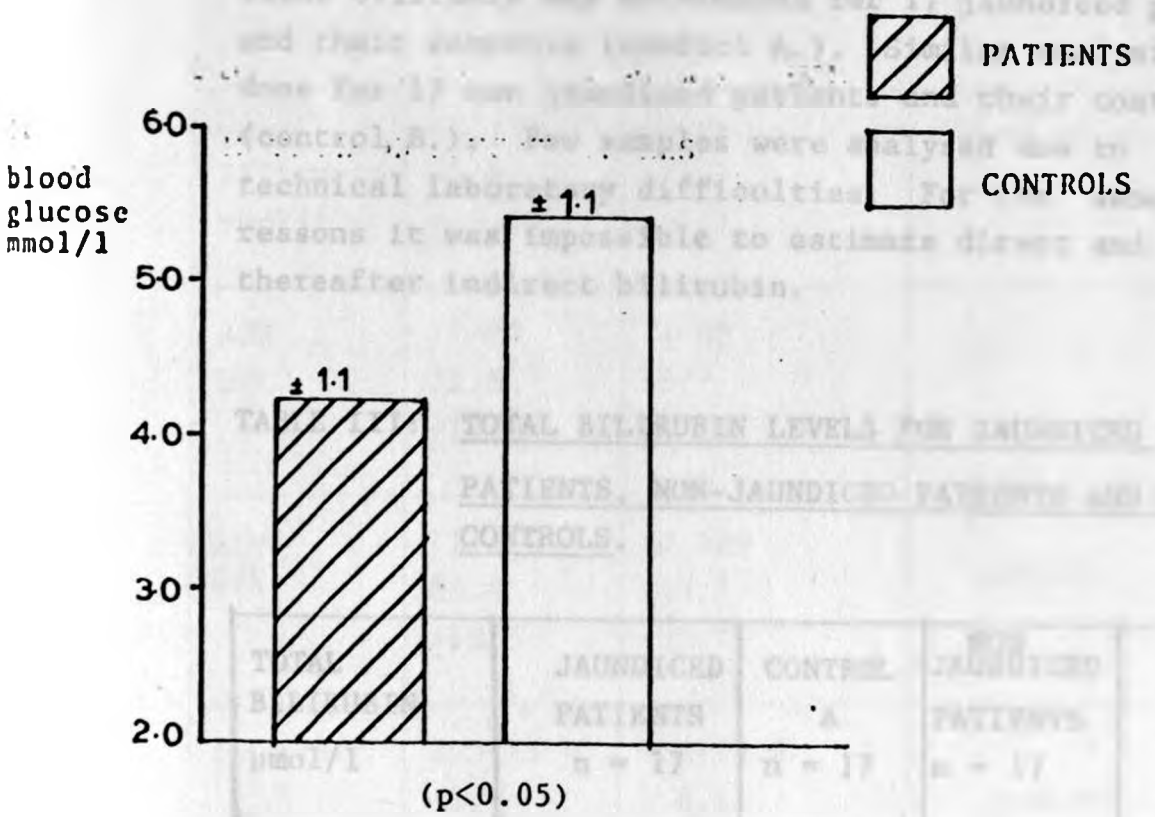
FIGURE III: MEAN BUN LEVELS



PATIENTS

CONTROLS

FIGURE IV: MEAN BLOOD GLUCOSE LEVELS



between 3.7 - 8.3 mmol/l, with a higher mean value of 5.4 mmol/l (Fig. IV). The patients had a mean blood glucose level of 4.1 mmol/l. The differences between the patients and the controls was statistically highly significant ($p<0.001$).

Total bilirubin was determined for 17 jaundiced patients and their controls (control A.). Similar analysis was done for 17 non jaundiced patients and their controls (control B.). Few samples were analysed due to technical laboratory difficulties. For the same reasons it was impossible to estimate direct and thereafter indirect bilirubin.

TABLE III: TOTAL BILIRUBIN LEVELS FOR JAUNDICED MALARIA PATIENTS, NON-JAUNDICED PATIENTS AND THEIR CONTROLS.

TOTAL BILIRUBIN µmol/l	JAUNDICED PATIENTS n = 17	CONTROL A n = 17	NON JAUNDICED PATIENTS n = 17	CONTROL B n = 17
RANGE	34-138	3-22	4-24	4-15
MEAN	46.8	8.8	13.3	7.2
S.D.	± 15	± 6.7	± 6.7	± 3.6

Control A = Controls of jaundiced patients
Control B = Control of non jaundiced patients

Total bilirubin was found to be significantly higher in the jaundiced patients ($p<0,05$), than the non jaundiced patients and than the controls. The jaundiced patients had a mean total bilirubin of 46.8 µmol/l as compared to 13.3 µmol/l for the non jaundiced patients. The non jaundiced patients did not differ significantly ($p>0.05$) from the controls.

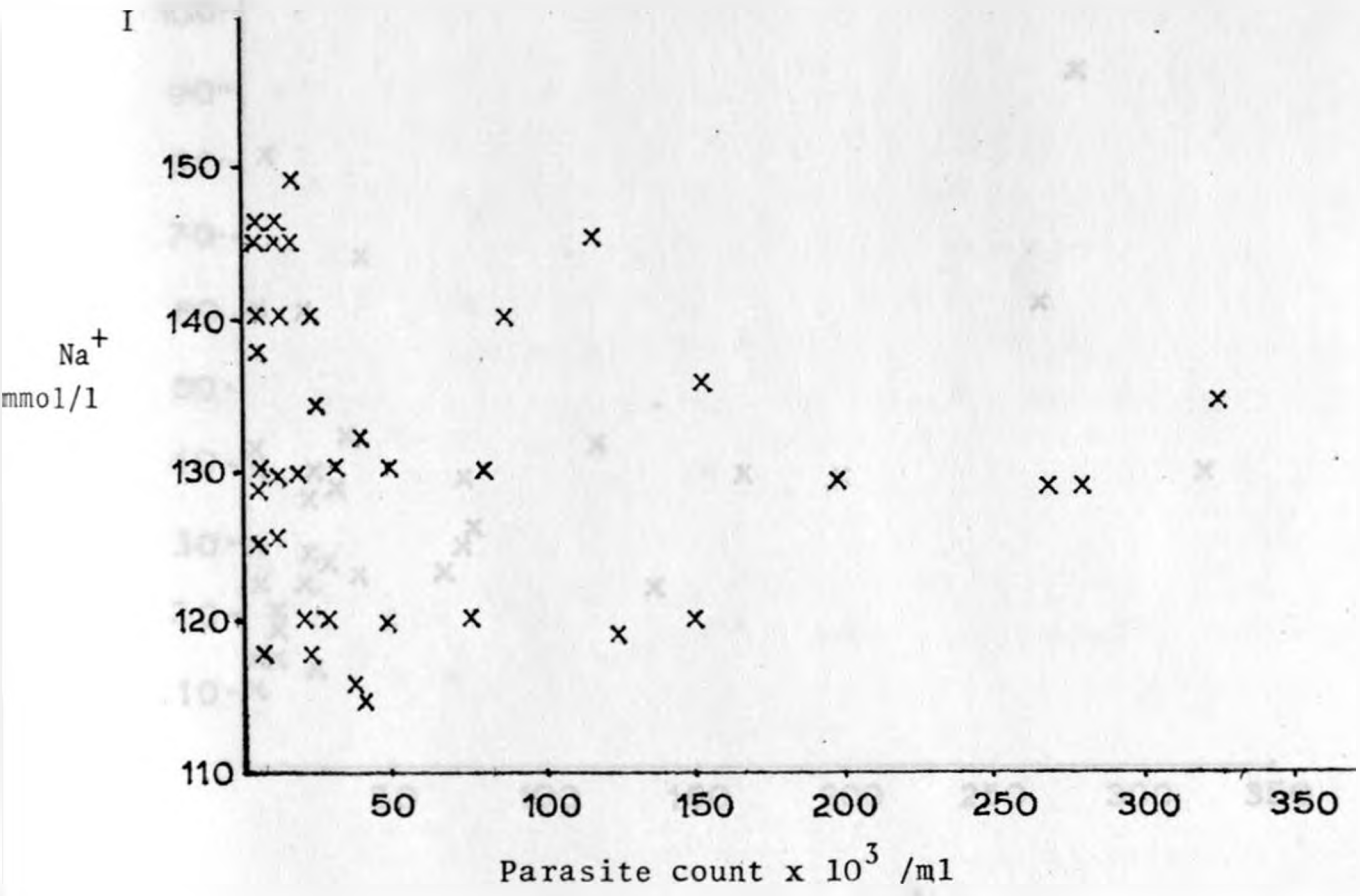
TABLE IV : COMPARISON OF VARIOUS PARAMETERS IN JAUNDICED AND NON JAUNDICED PATIENTS.

PARAMETER	JAUNDICED PATIENT n = 17	NON-JAUNDICED n = 17	P VALUE
TOTAL Bilirubin µmol/l	20-138 46.8 ±15.0	7-27 13.3 ±6.7	p<0.05
AST U/L	7-89 22.6 ±18.5	2-48 13.7 ±17.0	p<0.05
ALT U/L	12-184 65.8 ±48.5	10-120 43.7 ±27.2	p<0.05
HB.g/dl	5.5-11.4 8.7 ±1.6	5.7-13.8 8.2 ±2.6	p<0.05
PARASITE COUNT NO./ML.	1400-283,050 48,578 81385	590-68,600 15,139 19,436	p<0.05

For all the parameters shown, there was significant difference ($p<0.05$) between the two groups. The jaundiced patients had lower haemoglobin levels and higher mean ALT and AST levels and higher mean parasite counts.

For the 100 patients with acute falciparium malaria studied, any relationship between parasite count and each of the different parameters was sought. (This was done excluding total bilirubin due to the reasons already mentioned).

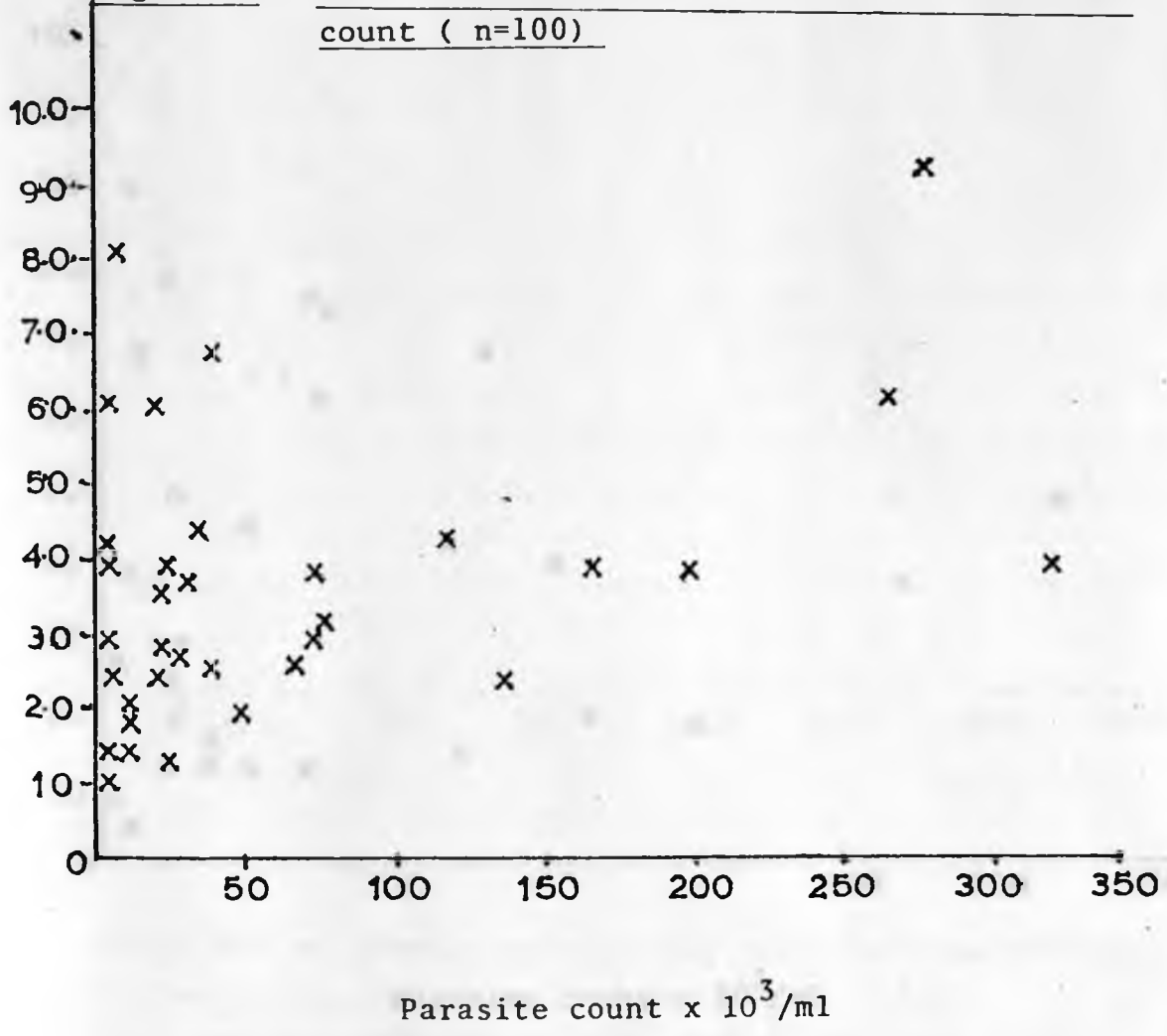
Figure V: Relationship between sodium and parasite count (n = 100)



No statistically significant correlation was found between sodium levels and parasite count ($r = 0.172$)

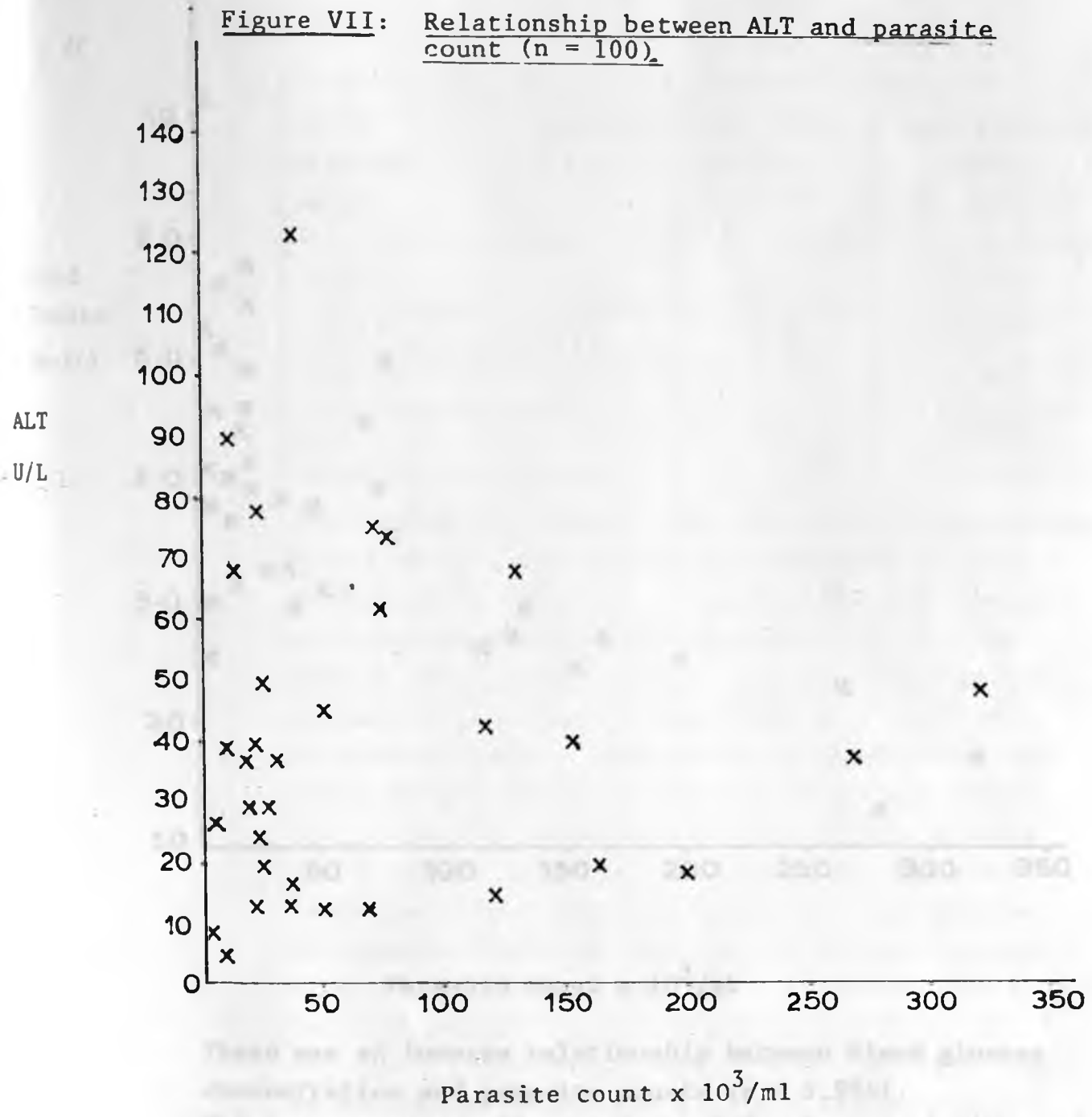
There was also no correlation found ($r = 0.0136$) between parasite count and potassium levels. Potassium levels varied irrespective of how high the parasite count was. The levels of K^+ did not differ from those of the controls as determined earlier on.

Figure VI : Relationship between BUN and parasite count (n=100)



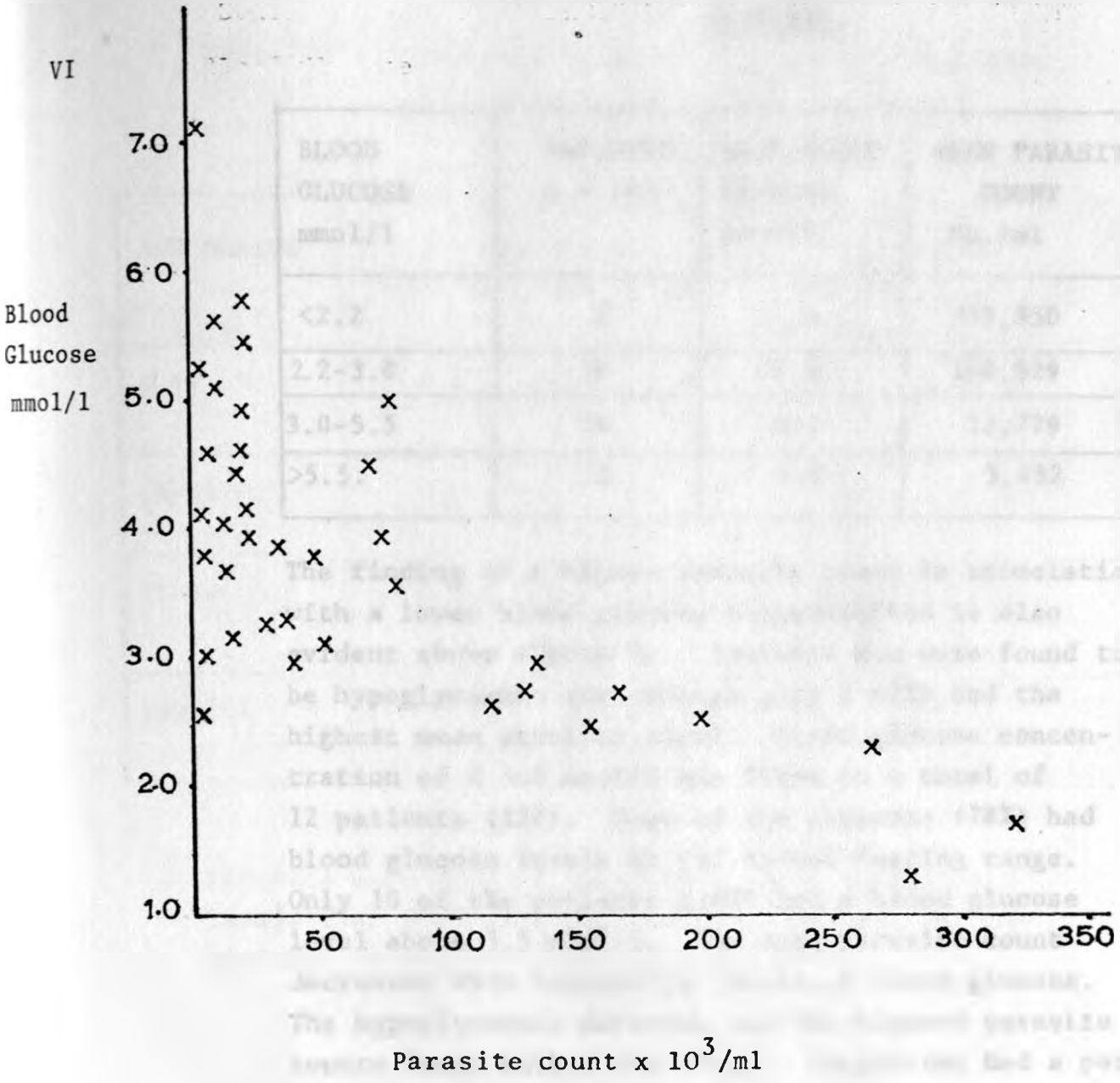
There was a tendancy towards a higher BUN concentration with a higher parasite count for some of the patients. A positive correlation ($r = 0.217$) though found, this was statistically insignificant ($p>0.05$)

Figure VII: Relationship between ALT and parasite count (n = 100).



No relationship was found between a higher parasite count and higher ALT level. Despite the patients having a much higher ALT level was not statistically related to higher parasite counts (r = 0.136). Similar to ALT again there was no correlation (r = 0.005) between AST and higher parasite counts.

Figure VIII : Relationship between blood glucose and parasite count. (n = 100)



There was an inverse relationship between blood glucose concentration and parasite counts ($r = 0.594$).
This was statistically highly significant ($p < 0.001$).

TABLE V : INTER RELATIONSHIP BETWEEN BLOOD GLUCOSE LEVELS AND PARASITE COUNT AND NUMBER OF PATIENTS.

BLOOD GLUCOSE mmol/l	PATIENTS n = 100	MEAN BLOOD GLUCOSE mmol/l	MEAN PARASITE COUNT No./ml
<2.2	2	1.6	305,850
2.2-3.0	10	2.6	118,529
3.0-5.5	78	4.1	12,779
>5.5.	10	6.0	3,452

The finding of a higher parasite count in association with a lower blood glucose concentration is also evident above (Table V). Patients who were found to be hypoglycaemic even though only 2 (2%), had the highest mean parasite count. Blood glucose concentration of < 3.0 mmol/l was found in a total of 12 patients (12%). Most of the patients (78%) had blood glucose levels in the normal fasting range. Only 10 of the patients (10%) had a blood glucose level above 5.5 mmol/l. The mean parasite count decreased with increasing levels of blood glucose. The hypoglycaemic patients had the highest parasite counts found within the study. One patient had a parasite count of 283,050/ml with blood glucose level of 1.3 mmol/l. The other patient had a parasite count of 328,650/ml with a blood glucose concentration of 2.0 mmol/l. Both these patients were found clinically to be anarousably comatose.

Parasite counts found within the study varied between 590 parasites of 328, 650 parasites per ml. with a mean parasite count of 33,575/ml.

Table IV : Haemoglobin levels for malaria patients and controls at various age groups

AGE MONTHS	PATIENTS Mean HB g/dl ± SD	CONTROLS Mean HB g/dl ± SD
6-12	8.6 ± 1.8	11.0 ± 1.1
13-24	8.0 ± 2.0	10.8 ± 1.2
25-60	7.8 ± 0.9	13.2 ± 0.5
109-144	7.2	13.2

Patients were found to have lower mean haemoglobin levels than the controls. This was evident for the patients in all the different age groups.

Some inferences were made as regards biochemical changes and overall outcome of the patients. A small number of patients 25 out of 100 were studied in this respect. It was apparent that the patients with higher parasite counts stayed the longest in the ward, with a mean stay of 7 days. Those with hypoglycaemia stayed upto 12 days. Hyponatraemia was common to those who were admitted and stayed for more than 3 days. (Range of stay was between 2 - 12 days). Fever was found to subside over a longer time and blood smears for trophozoites remained positive for more than 3 days in those with greater changes in biochemical parameters.

All the patients who were still positive for malaria parasites on blood smears were given quinine or metakelfin as alternative antimalarial therapy after the initial course of chloroquine. Those with hypoglycaemia were infused with 50% dextrose and 5% dextrose thereafter. No death was recorded for the 25 patients.

DISCUSSION

Several pathophysiologic changes known to occur in malaria result in a spectrum of renal manifestations. Renal changes may well have an effect on electrolyte and water balance but the exact mechanisms are not clearly delineated. Disturbances in renal microcirculation are responsible for acute renal failure. Massive intravascular haemolysis causes haemoglobinuria with or without renal failure. Immunologic reaction to the parasite may lead to mild glomerular changes. In addition to this, renal pathological changes noted by Sitprija et al (1978) (6), may also contribute. These renal changes are predominantly those of diffuse degeneration rather than inflammation (8). They are confined mainly to the tubules. Necrosis and degeneration appear more severe in the distal rather than the proximal convoluted tubules. Proximal tubular epithelial cells show cloudy swelling and vacuolization. Haemoglobin and granular casts are usually present in the lumen of both proximal and distal tubules and the collecting ducts. During the recovery phase dilatation of the distal convoluted tubules with regeneration of the epithelial cells is observed (6).

SODIUM AND POTASSIUM

Volume depletion with azotaemia may occur during the acute phase of falciparum malaria especially in severe cases. The causes of hypovolaemia are multiple, including increased insensible loss of fluid, sweating from pyrexia, decreased fluid intake and increased capillary permeability possibly due to kinins, histamine, adenine and an uncategorized "permeability factor". Pure water depletion is however uncommon. Hypernatraemia has seldom been observed in severe malaria (6). Hyponatraemia has however been observed in cases with heavy infection (6). The causes of hyponatraemia may be multiple

but are not clearly defined. In some patients, there is evidence of increased anti diuretic hormone (ADH) activity. The electrolyte pattern is consistent with the syndrome of inappropriate ADH secretion (S I A D H). The mechanism for S I A D H is not clear but may be related to fever as has been noted in other febrile illness (6). In other patients the hyponatraemia is unexplained.

In the present study the mean patient sodium level was found to be 132.5 mmol/l which was significantly lower than the control value of 139.4 mmol/l. Hyponatraemia was found in 16% of these patients. This percentage is somewhat lower than that quoted by Sitprija et al (6) who found upto 67% of patients with falciparum malaria had hyponatraemia. The present study has found no significant correlation between hyponatraemia and high parasite count. No other studies have been done as regards sodium level and falciparum malaria.

Studies on potassium levels and their changes in acute falciparum malaria are scanty in the literature. There are some reports of hyperkalaemia due to excessive haemolysis and also that related to tubular failure (6). The present study has shown that potassium levels were not significantly raised in the patients with malaria and none of them developed hyperkalaemia.

Previous studies have shown the existence of hyperkalaemia in association with the complication of acute renal failure due to heavy infection or with acute intravascular haemolysis. Stone et al (1972) (22) studied 42 patients with falciparum malaria and acute renal failure, of whom 5 (12%) were found to have hyperkalaemia. In the present study, no patient had features of acute renal failure and there was no correlation between potassium levels and parasite counts. No previous studies have established a correlation between hyperkalamia and increased parasitaemia.

BLOOD UREA NITROGEN

The patients in this study had significantly higher mean BUN levels (3.9 mmol/1) than the controls (3.6 mmol/1). Previous studies have shown that patients with acute falciparum malaria have more markedly raised BUN levels only in association with acute renal failure (7). Stone et al found a raised BUN level in all the 42 patients studied (22). The present study had a few patients with high BUN concentration with high parasite counts, but these patients were not in acute renal failure. There was no significant correlation ($r = 0.217$) between increasing parasite counts and high BUN concentration.

ALANINE TRANSAMINASE (ALT) AND ASPARTATE TRANSAMINASE (AST)

Hepatic dysfunction has been known to occur in childhood malaria. In the pathology of malaria, the liver becomes enlarged and congested with parasitized red cells in the sinusoids and centrilobular veins. Parenchymatous and Kupfer cells are oedematous and the lobular structure is indistinct. The smaller blood vessels and sinusoidal epithelium is damaged. Liver cells around the central veins are sometimes atrophied and necrosed but this is not common (8). Severe damage to parenchymal cells is unusual unless there is gross anaemia or malnutrition in which there is already some degree of fatty change (8).

Together with the above changes, previous studies have shown that as well as an increase in ALT and AST, there is also increase in plasma bilirubin (9, 10). In a study done by Patwari et al (1979) (9) in children with P. vivax malaria, it was found that there was increased levels of ALT and AST. Sadun et al (1966) reported increased levels of the same enzymes. In the present study, both ALT and AST levels were raised significantly in the patients, with a greater increase in ALT than AST levels. This is similar to that found by Sadun et al (1966) but contrary to findings reported by Patwari et al (1979) (9). In the present study, higher parasite counts were not associated with a higher increase in ALT or AST levels. This is in keeping with what has been noted previously in that hepatic dysfunction may occur with low parasitaemia (8).

Total Bilirubin

Previous studies have shown increased levels of plasma bilirubin as noted by Woodruff (1974) and Ramachandran et al (1967) (10). As compared to the non jaundiced patients, the jaundiced patients in the present study had much higher total bilirubin levels. In addition these jaundiced patients had higher ALT, AST levels and parasite counts (Table IV).

Hypoglycaemia

Hypoglycaemia has been noted to be an important manifestation of falciparum malaria (White et al, (1983) (12). Hypoglycaemia arises due to reduced glucose supply which results from reduced hepatic gluconeogenesis and glycogenolysis. In addition to this hepatic impairment, in some cases glycogen depletion impairs the glycogenolytic and gluconeogenic response to hypoglycaemia (11). Those with severe malaria are also more susceptible to hypoglycaemia because of prolonged fasting and increased metabolic demand related to fever and the substrate requirements of large numbers of parasites (11).

Hypoglycaemia has been particularly observed in pregnant women and patients with severe disease. There are several reports of hypoglycaemia in the literature in association with falciparum malaria (Fitz-Hugh et al 1944; Devabul, 1960; Migasena (1983) (2). This includes at least four cases who had not been treated with quinine (Looareesuwan et al 1985; White et al, 1983; Fischer, 1983) (2). However, quinine has been found to be the most common cause of hypoglycaemia as found by Okitolonda et al (1987) (13). The part played by starvation in the pathogenesis of hypoglycaemia in children with severe malaria is difficult to assess. Children become hypoglycaemic more readily than adults do after a short period of starvation (12) and these children with severe malaria would have had little or no food in the day preceding

admission. Few studies have been done in children with severe malaria in isolation from quinine therapy.

In a study done by White et al (1987) (12) in Gambian children, it was found that hypoglycaemia occurred in 15 out of 47 children (32%). Nine of these children with hypoglycaemia had cerebral malaria. In the present study a much lower percentage 2% of the patients had hypoglycaemia. Both these patients were unarousably comatose on admission and had the highest parasite counts within the study. In this study blood glucose levels were obtained before any form of antimalarial treatment was instituted.

It is not clear whether hypoglycaemia contributes to the fatal outcome or any residual deficit in survivors or whether low blood sugar simply reflects a severe and usually fatal infection (12). Hypoglycaemia is an important and frequent complication irrespective of antimalarial treatment (unlike in adults). The present study affirms that children with acute falciparum malaria are likely to have low levels of blood glucose being mostly in the fasting range. The study reaffirms that hypoglycaemia occurs and is unrelated to antimalarial therapy, and that the likelihood of hypoglycaemia increases with heavy infections.

With the follow up notes of a few (25 patients) of the malaria patients, it is apparent that those with the longest stay in hospital were those with greater biochemical abnormalities especially those with hypoglycaemia and related high parasite counts. These patients also had more days of fever and blood smear positivity for malarial parasites. However, this particular study had its limitations in that samples were taken at a particular point in time.

Due to the congestion in the study area (P.E.W.) there is also a need to discharge patients at the earliest date possible. The patients are then discharged as soon as clinical improvement is noted. The number of days of admission in this respect would then become a poor indicator of patient progress. In addition to this, inadequacy and/or inaccuracy of some of the notes traced contributes to an incomplete picture.

In conclusion, the present study established that some biochemical changes do occur in children with acute falciparum malaria. Blood glucose concentration is affected by increased parasite counts. Although changes do occur in total bilirubin, ALT and AST levels, these do not relate to parasite counts and this may not warrant a search for them in all children with acute falciparum malaria. However, they may be important in the patients who are jaundiced. Hyponatraemia does occur in these patients with malaria but there is little change in potassium levels. Hyperkalaemia does not occur in those with no evidence of associated acute renal failure. BUN levels even though raised, do not also relate to parasite counts. Both BUN and K^+ levels become important in patients with acute renal failure. It is clear that hypoglycaemia is a danger and should be searched for in these children with acute falciparum malaria.

CONCLUSIONS

1. Sodium level is reduced in children in this study with acute falciparum malaria. hyponatraemia is found in 16% of the patients.

2. Potassium levels in these children do not differ from those of controls.

3. Blood urea nitrogen is increased in comparison with controls.

4. Liver enzymes ALT and AST and total bilirubin are increased in children with acute falciparum malaria and more so in the jaundiced patients.

5. Blood glucose levels are significantly lower in the children with acute falciparum malaria. The majority in this study have blood glucose levels in the normal fasting range and 2% are hypoglycaemic.

6. Hypoglycaemia is associated with higher parasite counts and is unrelated to antimalarial therapy.

7. Haemoglobin levels are lower in children with acute falciparum malaria than in the controls.

RECOMMENDATIONS

1. Hypoglycaemia should be suspected in any child with acute falciparum malaria who is unrousable. Determination of blood glucose levels in those with severe disease would be valuable.

2. In patients with severe disease a follow up study relating biochemical changes to clinical outcome will be useful.

3. Assessment of liver function tests will be of value in jaundiced malaria patients.

4. Investigation of K^+ and BUN concentrations is recommended in patients with associated acute renal failure and in those with evidence of intravascular haemolysis.

A C K N O W L E D G E M E N T

I am greatly indebted to the following people who made this work possible. I would like to sincerely thank them all.

1. Dr. D.A.Orinda, for his guidance, constructive criticism and encouragement throughout the study and for the use of laboratory facilities provided by his department.
2. Prof. H. Pamba for his guidance and allowing the use of facilities in the parasitology department.
3. Dr. D. Kinuthia for the guidance and useful criticism and encouragement in putting this study together.
4. Dr. J.B. Were of KEMRI for the kind financial assistance enabling the purchase of biochemical kits without which the study would not have been possible.
5. Mr. J. Kangau for carrying out meticulous laboratory work, without whose help this work would have been impossible
6. Mr. P.Chitayi for the great assistance in determining parasite counts.
7. Mr. K. Kanga - for assistance in searching for various references.
8. Mr. R.Agwanda for his advice on statistical analysis
9. Last but not the least Miss Rosalind Wambui and Florence Sagala for typing this manuscript.

REFERENCES

1. Vogel L.C., Muller, AS., Odingo,R.S., Onyango, Z. and deGeus A. Health and Disease in Kenya. E.A. Lit.Bureau. Nairobi 1st Edition 305, 1974.

2. W.H.O. Malaria action programme. Severe and complicated malaria. Trans. Roy. Soc. Trop. Med. and Hyg. 80: 1-50, 1986.

3. Bruce-Chwatt, L.J., Malaria in African Infants and Children in Southern Nigeria. Annal Trop. Med. Parasitol. 46: 173-200, 1952.

4. Gilles, H.M., Fletcher, K.A., Hendrickse, R.G., Lindner, R., Reddy, S., and Allan, N., Glucose 6 - phosphate dehydrogenase deficiency, sickling and malaria in African children in South Western Nigeria. Lancet 1: 138-140, 1967.

5. Sheehy, J.W. and Reba, R.C., Complications of falciparum malaria and their treatment. Anals. Int. Med, 67: 1163-1171, 1967.

6. Sitprija, V., Vongsthongsri, M and Poshyachi, V. Renal failure in malaria, a Pathophysiologic study. Nephron 18: 807-809, 1977.

7. Sitprija, V. and Boonpucknavig, V. Renal Disease in acute P. falciparum infection in man. Kidney Int. 16:41-52, 1979

8. Manson - Bahr, P.E.C., and Apted, F.I.C., Manson's Tropical Diseases. Balliere Tindall. London. 18th Edition 42-45, 1985

9. Patwari, A., Aneja, S., Barry, A.M., and Ghosh, S. Hepatic dysfunction in childhood Malaria Arch. Dis. Child, 54: 139-141, 1979.

10. Ramachandran, S. and Renera, M.V.
Jaundice and hepatomegaly in primary malaria
J. Trop. Med. Hyg. 79: 207-210, 1976.

11. White, N.J. Warrel, D.A., Chanthavanich P., Looareesuwan, S., Warrel, M.J., Krishna, S., Williamson, D.H., and Turner, R.C., Severe hypoglycaemia and hyperinsulinaemia in falciparum malaria.
New Engl. J. Med. 309: 61-66, 1983.

12. White, N.J., Marsh, K., Turner, R.C., Berry, C.D., Williamson, D.H., and Brown, J. Hypoglycaemia in African children with severe malaria.
Lancet 1: 708-711, 1987.

13. Okitolonda, W., Delacollette, C., Malengreau, M. and Henguin J.C. High incidence of hypoglycaemia in African patients treated with intravenous quinine for severe malaria.
Br. Med.J., 295: 716-718, 1987.

14. Wolthus, F. H., Nephropathy in Malaria
Trop. Geog. Med, 20: 21-27, 1968.

15. Berger, M., Conte, N.F. and Birch, M.L., The nephrotic syndrome secondary to acute glomerulonephritis during falciparum malaria.
Annals. Int.med 67: 1171, 1967.

16. Gambino S.R.
Haemoglobinometry
American Society of Clinical Pathologists
Commission on continuing Education
Chicago IL. 1967.

17. Bruce - Chwatt, L.J. Essential Malariology
Heinmann, 2nd Edition 1986.
2nd Edition 1986.

18. Berry, J.W., Campbell, D.G. and Barnes, R.S., Improved method of flame photometry. Ind. Eng. Chem. Anal XVIIIth edition 19. 1946.

19 Reitman, S. and Frankel, S., Colorimetric manual method for determination of SGOT and SGPT at 546 nm, Amer J., Clin. Path 28:56, 1957.

20. Marsh, W.H., Fingerhut, B., and Miller, H., Automated and normal direct methods for determination of blood urea. Clin. Chemistry 11: 624, 1965.

21 Gambino, S.R., and Freda, V. I. The measurement of amniotic fluid bilirubin by method of Jendrassik and Grof. Amer. J. Clin. Path. 46: 198-203, 1966.

22. Stone, W.J., Hanchett J.E., and Knepshield, J.H., Acute Renal Insufficiency due to falciparum malaria. Arch Intrn. Med. 129:1972

23. Misagena S. Hypoglycaemia in falciparum malaria Ann. Trop. Med. Parasitol 77:323-4, 1983.

24. Looareesuwan, S. Phillips, R.E., and White N.J. Quinine and severe falciparum malaria in late pregnancey. Lancet ii: 4-8, 1985.

25. Mcmahon, AE., Kelsey, J.E., and Derauf D.E. Hepatitis of Malarial origin. A.M.A. Arch. Int. Med. 93:379-385, 1954

26. Fischer C.S.W. Acidosis and hypoglycaemia in malaria. Br. Med. J. 286: 1261, 1983.

27. Brooks, M.H., Malloy, J.P., and Bartonelli P.J., Tigertt, W.D. Sheehy, T.W., and Barry, K.G. Pathophysiology of Acute falciparum malaria Amer., J. Med. 43:735-744. 1976.

28. Sitprija, V., Vongsthongsri, M., Poshyachinda, V. and Arthachinta, S. Renal failure in malaria A Pathophysiologic Study. Nephron 18: 277-281, 1977.

APPENDIX I

PROFORMA I

Name .....

Study Number .....

Hospital Unit No. .....

Address .....

Age ..... Months

Sex .....

Code: Male = 1 Female = 2

Weight .....Kg

Height .....cm

History of residence in an endemic area

Code = yes = 1 No. = 2

If yes, Name of Place .....

History of recent travel .....

Date/Month of travel .....

History of the following: code: Yes = 1 No = 2

- Fever
- Diarrhoea
- Vomiting
- Constipation
- Headache
- Chills and rigors
- Malaise
- Joint pains
- Abdominal pain
- Convulsion
- Jaundice or contact with jaundiced person
- Pedal and/or facial swelling

CLINICAL SIGNS

Fever (raised temperature)

- Has patient fed in past 12 hours?
- Liver disease
- Renal disease
- Treatment with chloroquine?
- When?

Code: No = 1, Mild = 2, Mod = 3, Severe = 4

- Splenomegaly Size cm

- Hepatomegaly Size cm

Palpable Kidneys Rt .....Lt .....

Code: Present = 1 Absent = 2

Level of Consciousness

Code: Conscious = 1

Drowsy but rousable = 2

Unarousable = 3

CLINICAL SIGNS

Fever (raised temperature)

Pallor .....

Dehydration .....

Jaundice

Code: No = 1, Mild = 2, Mod = 3, Severe = 4

- Splenomegaly Size cm

- Hepatomegaly Size cm

Palpable Kidneys Rt .....Lt .....

Code: Present = 1 Absent = 2

Level of Consciousness

Code: Conscious = 1

Drowsy but rousable = 2

Unarousable = 3

Name .....

Study Number.....

Haemoglobin level ..... g/dl

Parasite count ..... no/ml

Blood glucose concentration ..... mmol/l

Na^+ Concentration ..... mmol/l

K^+ Concentration ..... mmol/l

AST level .....U/L

ALT Level ..... U/L

Serum bilirubin concentration ..... µmol/l