THE CLINICAL AND BIOCHEMICAL SEVERITY OF *PLASMODIUM FALCIPARUM* MALARIA IN NATAL/KWAZULU

by

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ABSTRACT

Malaria remains a major cause of morbidity and mortality in tropical Africa. The northern KwaZulu areas of the Republic of South Africa are endemic for *Plasmodium falciparum* malaria. The clinical morbidity produced by this parasite in this area has not been studied since the work of Swellengrebel and DeMeillon in the early 1930's. These workers found a high prevalence as well as a high parasite load in residents of this region prior to the institution of the present malaria control programme. Since 1984 malaria notifications have increased substantially in Natal/KwaZulu. The geographic spread and endemicity of the disease has changed in comparison to the situation prior to the introduction of the malaria control programme; transmission is now seasonal or epidemic rather than endemic.

The aim of this study was to describe the clinical severity of falciparum malaria in the endemic areas of Natal/KwaZulu, and to assess the value of surrrogate markers of infection. Fifty-nine patients were prospectively studied at a peripheral clinic during the peak malaria season in 1989; symptoms and signs of the infection, parasite load, haemoglobin values, leucocyte count, biochemical liver function tests and serum haptoglobins were recorded in all patients. The same haematological and biochemical parameters were also measured in 37 control subjects without malaria for comparative purposes.

The commonest symptoms were persistent headache(100%), rigors(98%) and myalgia(93%). None of the patients presented in coma, pulmonary oedema, hypoglycaemia or algid malaria. Splenomegaly was found in 49%, hepatomegaly in 20% and mental confusion in 5%. Mean

parasite load was 1.71% with 57% of patients having parasite loads of <1%. Anaemia of <10g/dl was significantly more frequent ($p<0.001$) in the patient group than in the control group. Leucopenia (WCC < $4.0x10^9/l$) was present in 12/50 (24%) patients compared to 2/37 (5%) controls ($p = 0.018$).

Hypoalbuminaemia was found in 64% compared to 13.5% ($p < 0.001$), hyperbilirubinaemia in 33% compared to 0% ($p < 0.001$), elevated lactate dehydrogenase (LDH) in 83% compared to 5% ($p < 0.001$) of patients and controls respectively. Serum haptoglobins were reduced in 44% of patients and 5% of controls ($p < 0.001$). AST was elevated in 15/58(26%) patients and 3/37(8%) controls ($p = 0.031$), while ALT was elevated in 2/58(3.4%) patients and 0/37(0%) controls ($p=0.254$). The best biochemical predictor of malarial infection was an elevated LDH with a sensitivity of 83%; this test may be of value as a rapid indirect indicator. Both elevated bilirubin and elevated ALT were found in malaria patients but not in any of the controls.

The results show a wide range of morbidity, without severe complications as presenting manifestations. Symptoms of infection occurred in the presence of low parasite loads; this suggests that there may be little or no immunity in this population. A greater proportion of patients had an elevated AST compared with ALT; this implies that the enzyme elevation originates from the parasitised erythrocyte rather than the hepatocyte.

In this research the statistical planning and analyses, and recommendations arising from these analyses, have been done in consultation with the Institute for Biostatistics of the Medical Research Council.

PREFACE

This study represents original work by the author and has not been submitted in any form to another university. Where use was made of the work of others it has been duly acknowledged in the text.

The research described in this dissertation was carried out in the Department of Medicine, University of Natal and Research Institute for Diseases in a Tropical Environment (RIDTE) of the Medical Research Council, under the supervision of Dr. Vinodh Gathiram.

Ethical approval to conduct this study was granted by the Ethics and Professional Standards Subcommittee of the University of Natal.

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While this work was in progress, the following papers which were relevant to this dissertation were published:

i. **PN Soni**, BL Sharp. Cerebellar ataxia in acute falciparum malaria. S Afr Med J 1992; 81: 387-8.

ii. **PN Soni**, BL Sharp, S Ngxongo, V Gathiram. Morbidity from acute falciparum malaria in Natal/KwaZulu. S Afr Med J 1992 (in press).

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CHAPTER 1

INTRODUCTION

The obligate intracellular protozoa of the genus *Plasmodium* is the cause of malaria; a disease which can have acute as well as chronic presentations. The four species of *Plasmodia* are *P. malaria* , *P. vivax*, *P. falciparum*, and *P. ovale*. It is generally agreed that malaria causes more human suffering than any other parasitic disease, and is the leading parasitic cause of morbidity and mortality in the world (Strickland 1986). More than 2.6 billion inhabitants of the tropics and subtropics are exposed to the risk of malaria infection (World Health Organisation 1985). Of the four *Plasmodium* species, *P. falciparum* is the most pathogenic. In previously non-exposed individuals who have no protective immunity the disease tends to be fulminant and death is likely to occur unless prompt treatment is given. By comparison to the other species, *P. falciparum* has the shortest incubation period and causes disease which is of the shortest duration (Bruce-Chwatt 1985).

Approximately 110 million cases of malaria occur each year, of which 90 million are in tropical Africa (World Health Organisation 1990); global deaths are estimated at approximately 1 million per year usually from falciparum infection. There is considerable underreporting of diagnosed cases and the majority of patients with malaria are not seen by trained medical practitioners (Strickland 1986).

The diseases' impact is hardest on Africa, where the climate, poverty, poor sanitation and ignorance all work in concert to provide an ideal breeding ground for the parasite. The prevalence in children exceeds 50% in many African countries, with falciparum representing between 80% and 99% of cases (Wernsdorfer 1980); on this continent falciparum malaria kills more than one million children per year . A recent study by Greenwood *et al* (1987) in a rural area of the Gambia, estimated the overall mortality rate from malaria in children under the age of 5 years, to be 10 per 1000 per year, a figure remarkably similar to that obtained by Bruce-Chwatt (1952), 35 years earlier. The problem has been aggravated by the development of resistance to a wide range of insecticides and chemotherapeutic agents by the *Anopheles* mosquito and *P. falciparum* respectively.

The annual number of malaria notifications in South Africa increased from 3.6 per 100 000 in 1957 to 30.0 per 100 000 in 1987 (Kustner 1988). The northern KwaZulu areas of Natal are endemic for falciparum malaria (Sharp *et al* 1988). This area of South Africa experienced an outbreak of falciparum malaria in late 1987 and early 1988 (Hansford and Muller 1990); clinical malaria has not been studied in this region since the work of Swellengrebel *et al* in 1931.

The malaria control programme in Natal/KwaZulu as a whole is considered to be highly effective. This is illustrated by the low case rate (range 7.0 - 26.8/100 000) between 1976 and 1983 (Kustner 1988) and the successful agricultural and industrial development of large parts of the province in contrast to the situation in the late 1920s and early 1930s (Sharp *et al* 1988).

Swellengrebel *et al* (1931) showed that there was a high prevalence of infection in this area, with 94 per cent of toddlers being parasite carriers, of whom 59 per cent were heavy ones. They concluded that there was a high level of immunity in the population which manifested among adults in three ways: (1) absence or rareness of malarial fever; (2) decrease of splenic enlargement; (3) decrease in the number of parasite carriers, all in contrast to a much suffering childhood. They concluded that "the more endemic conditions depart from the type of continuous infection, the more malaria becomes seasonal and the less chance is afforded for this state of immunity to establish itself. If malarial conditions are of the epidemic type, ie., fever years being separated by longer or shorter successions of healthy years, the chances of immunization become still less." This study is an attempt to describe the clinical features of malaria and to ascertain whether these have changed over the decades, noting the introduction of the present malaria control measures. This would assist in establishing whether the high level of semi-immunity previously described still exists in residents of this endemic region. The study described in this thesis was conducted in the northern KwaZulu areas, as this region has the highest prevalence of the disease.

CHAPTER 2

REVIEW OF LITERATURE

2.1 EPIDEMIOLOGY OF MALARIA

2.1.1 Epidemiological terminology

2.1.1.1 Malaria parasitological and clinical rates

Malaria incidence is the number of new clinical cases occurring over a given period of time in relation to the unit of population in which they occur. **Malaria prevalence** is the number of cases of infection and disease existing per defined population during a given time interval. The **malaria morbidity rate** is the number of malaria cases per 1000 or 10 000 population per year. The **malaria mortality rate** is the number of deaths due to malaria per 100 000 population per year. The **spleen rate** is the proportion of children two to nine years of age with enlarged spleens; if adults or other age groups are included then this should be specified. **Parasite rate** is the proportion of persons in a defined group on a given date with microscopically proven parasitaemia. The **transmission index** is the proportion of infants less than one year with parasitaemia (Spencer 1986).

2.1.1.2 Endemicity

Malaria is defined as **endemic** when there is a measurable incidence both of cases and of natural transmission over a succession of years (Molineaux 1988). The degree of endemicity of malaria is determined by examination of a statistically significant population sample and has been

assessed and classified as follows (World Health Organisation 1951; Metselaar and van Thiel 1959):

1. **Hypoendemic** - spleen rate or parasite rate of 0% to 10% in children 2 to 9 years old.

2. **Mesoendemic** - spleen rate or parasite rate of 11% to 50% in children 2 to 9 years old.

3. **Hyperendemic** - spleen rate or parasite rate consistently over 50% in children 2 to 9 years old.

4. **Holoendemic** - spleen rate or parasite rate of more than 75% in children 2 to 9 years old; the adult spleen rate is low and the parasitaemia rate in infants is high.

Epidemics are defined by an incidence of new cases clearly in excess of the expected (Molineaux 1988). Any transmission in a previously malaria-free area is obviously in excess of the expected and constitutes an epidemic by the above definition with the proviso that, traditionally, small epidemics are usually called outbreaks. An increase in transmission in areas where the level of transmission is usually low, either naturally or under the impact of control activities, may or may not be labelled 'epidemic' depending on the magnitude of the excess of cases and on the rate at which the excess develops, as well as on the availability and interpretation of previous data from which to calculate the 'expected'. Possible precipitating factors of malaria epidemics include (Molineaux 1988): (*i*) an increase in vectorial capacity, (*ii*) immigration of infective persons, (*iii*) immigration of non-immunes, and (*iv*) drug resistance. Actual epidemics are commonly caused by a combination of several of the factors.

2.1.1.3 **Malaria** stability

Malaria situations are extremely diverse with respect to resistance to change. At one extreme, the prevalence of infection is extremely high and only little affected even by relatively large natural or man-made changes in the factors that influence transmission (eg. vector density). At the other extreme, the prevalence of infection varies widely and is very sensitive to even relatively small natural or man-made changes in the factors of transmission. Stability increases with the endemicity level.

Stable endemic malaria is present when there is a high degree of natural transmission with little change from season to season; epidemics are unlikely. Stable malaria is present in many countries in sub-Saharan Africa. In **unstable malaria** the incidence of malaria varies considerably from year to year, collective immunity is low and epidemics are likely. This pattern is typical of marginal areas of malaria distribution with relatively short transmission seasons eg. northern Natal.

2.1.2 Africa south of the Sahara

The prevalence of malaria has remained unchanged in most malarious areas and *P. falciparum* is the predominant species, being present alone or with another species in about 85% of malaria infections. Of a population of about 421 million, 373 million live in malarious areas; 37 million live in hypoendemic areas, 112 million inhabit mesoendemic zones and 224 million live in areas where malaria is hyperendemic to holoendemic (Spencer 1986). Transmission is particularly intense in rural areas of west Africa where the risk of infection is exceedingly high; it has been

shown that in the Gambia, children under the age of 7 years experienced about one clinical episode of malaria per year (Greenwood *et al* 1987).

2.1.3 Epidemiology of malaria in northern Natal

Malaria remains prevalent within the borders of Natal province, in spite of the current measures aimed at controlling the disease. During the eight year period 1976-1983 an average of 644 cases of malaria was reported annually in Natal (range 208-1324 cases per annum) (Fig. 1)(Sharp 1991). During the following five years (1984-1988) this increased to 3846 cases per annum (range 2193-7530 per annum).

The geographic spread and endemicity of the disease have changed somewhat in comparison to the situation prior to the introduction of the malaria control programme, when the 3 northern districts of Ingwavuma, Ubombo and Hlabisa (Figure 2) were classified as endemic malaria areas, with seasonal epidemics occurring to the south and inland of these districts (Sharp 1991); the highest prevalence of infected carriers being in infants and toddlers and the prevalence decreasing with age. In fact the severity of the disease was such, that "toddlers were infected without exception" (Swellengrebel *et al* 1931). Sharp (1991) has shown that although very little transmission of the disease occurs outside these three districts, which lie in the KwaZulu area of Natal, the disease pattern here has changed significantly and the transmission of malaria is now epidemic.

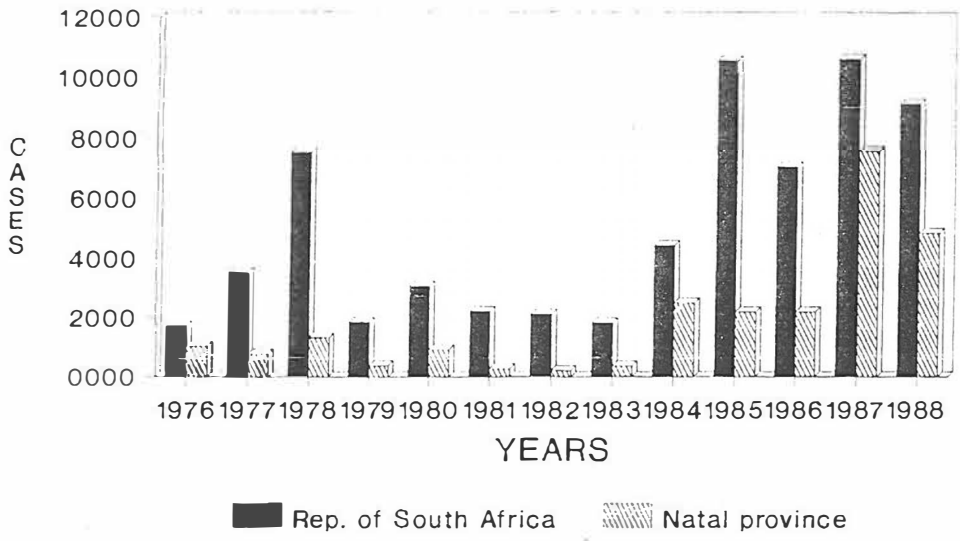

FIGURE 1: Comparative annual malaria case totals for the Republic of South Africa and Natal province for the years 1976 - 1988 (Source: B.L. Sharp 1991).

The monthly totals for those persons reporting to hospitals, clinics, and general practitioners with malaria may be used to determine the malaria transmission season. The disease shows a distinct seasonality with transmission starting in early summer and reaching a peak during the months of April and May and the detection of infected patients virtually ceasing in July (Sharp *et al* 1988). Recent findings, derived from official notifications (KwaZulu Health and Department of National health and Population Development), show that the numbers of infected individuals in the different age categories are representative of the population structure, implying that the whole population is at risk, a situation seen during epidemic malaria (Sharp *et al* 1988). This change is considered to be a direct result of the longstanding successful control programme. The endemic malaria area is consequently now considered to lie to the north in Mozambique where no formal malaria control programme has been in effect for more than 10 years.

These patients presenting to hospitals, clinics and general practitioners would mainly be non-immunes who as a result of infection developed clinical symptoms. These findings are in keeping with what is expected from an area that encompasses the most southern distribution in Africa of a mainly tropical disease.

2.2 THE MALARIA CONTROL PROGRAMME IN NATAL

In 1928-29 a large number of employees of the sugar mills and plantations of Natal were afflicted with malaria. Of an estimated 6 000 Europeans at risk, 7 died; of 20 000 Asians, 151 and of 215 000 blacks, 2 600 died (Nethercott 1974). At the invitation of the government, Professor Swellengrebel of the University of Amsterdam visited Natal in 1930 to investigate the

malaria situation in the Union of South Africa (Swellengrebel *et al* 1931). As a result of his report, intensive anti-malaria measures were implemented.

The control programme was intended to include all the malaria areas of the province with the exception of the 3 northern districts, Ingwavuma, Ubombo and Hlabisa. These were excluded on the recommendation of Swellengrebel (1931), because they were highly endemic areas and it was feared that the natural immunity of the population would diminish if a control policy was introduced.

Anti-larval measures using oil and Paris green (copper acetoarsenite) were introduced in 1932 and continued to be the main means of control until 1946. In 1934, pyrethrum was introduced as an intra-domiciliary knockdown insecticide. In 1946 the use of pyrethrum was discontinued and was replaced by DDT, both for house spraying and larviciding. This continued until 1953, when these measures were gradually extended to include the 3 northern districts, beginning with the spraying of all habitations within a three mile radius of mission stations and police camps. Anti-larval measure were abandoned in 1956. In the same year, malaria became a notifiable disease in the Union of South Africa. Total coverage of all homes with a residual insecticide was achieved for the first time in the northern districts of Natal in October 1958.

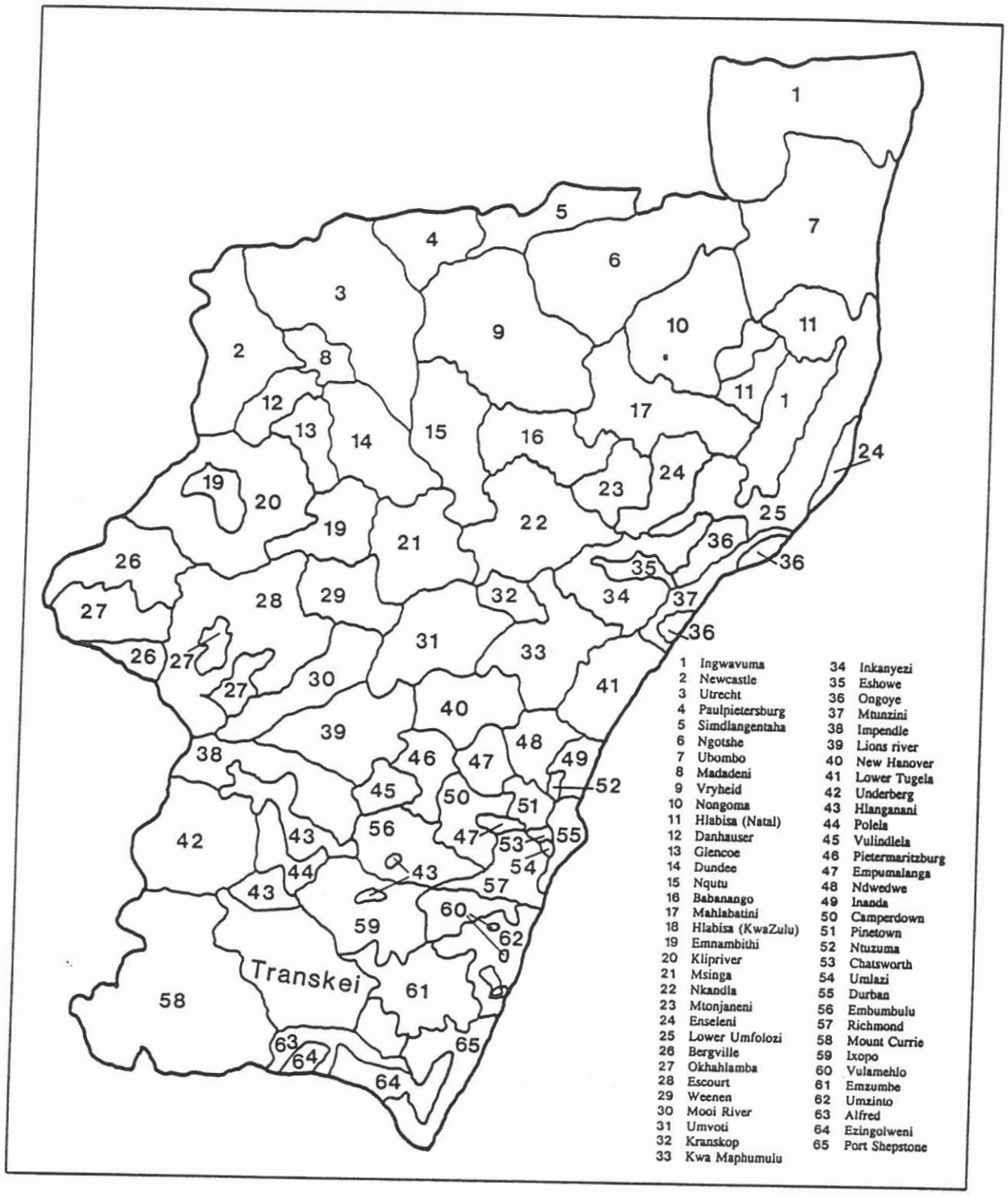

FIGURE 2: The province of Natal showing the 65 magisterial districts.

2.3 NATURALLY-ACQUIRED IMMUNITY TO MALARIA

The relationship between the parasite and the immune response of the host to it is one of the main determinants of the distribution of malaria (Bruce-Chwatt 1985). In general, persons repeatedly exposed to malaria in endemic areas develop a degree of immunity; they become semi-immune. The immune response depends on humoral immunity and cell-mediated immunity; however, no clear picture of the mechanisms of naturally-acquired immunity to malaria has yet emerged (Day and Marsh 1991). The acquisition of immunity aids in recovery from the initial malaria infection; subsequent infections increase the level of immunity. The severity of clinical manifestations, parasitaemia, the number of patent parasitaemic episodes from one inoculation and the production of gametocytes are all reduced by immunity (Spencer 1986).

The immunity which develops is species- and strain- and stage-specific (McGregor 1986). It is also dependent upon the presence of repeated infection. Loss of immunity results from loss of exposure. Thus, persons leaving endemic areas may develop symptoms after some months. Severe malaria may occur in previously immune adults who return to a malarious area after living for some time in a non-endemic one.

Naturally-acquired immunity to falciparum malaria has been shown to be closely related to the development of antibodies to circumsporozoite (CS) proteins (Hoffman *et al* 1986; Day and Marsh 1991). Levels of CS antibody have been shown to increase with age in malaria-endemic areas in Africa (Campbell *et al* 1987). Antibodies to malaria sporozoites have also been shown

to be lower in patients with cerebral malaria than in patients with acute uncomplicated malaria (Tapchaisri *et al* 1985).

2.4 CLINICAL MALARIA

The immune status of populations in areas of unstable malaria develops differently to that where there is stable transmission (World Health Organisation 1988). As a consequence:

* the general population is non-immune;
* most cases of disease occur in young adults, predominantly in males, upon taking up occupations requiring forest work;
* severe and complicated infections are seen in adults. Pregnant women, especially primiparae, are at extremely high risk of serious and fatal infections;
* symptoms of malaria may begin before parasitaemia is microscopically detectable. The presence of parasitaemia, even at a very low level, usually implies clinical illness.

The classical clinical picture of symptomatic malaria is well-known. Assessment of the clinical symptoms, particularly the presence of fever, forms the basis of malaria diagnosis at the village level and also at the first referral level in many areas. The World Health Organisation and UNICEF currently recommend treatment of clinical malaria by village health workers (Greenwood *et al* 1988). However, fever alone is a very imprecise means of diagnosis and investigations conducted in tropical Africa showed that only about 46% of patients so diagnosed were actually suffering from the disease. On the other hand, some 15% of patients clinically

diagnosed as suffering from fevers due to diseases other than malaria were in fact proven to have clinically manifest plasmodial infections (Baudon *et al* 1985).

There is no clinical parameter which used on its own would permit a reliable diagnosis of malaria and, at present, microscopic detection of parasites appears to be the most reliable method for making a definitive diagnosis. Because of the protean manifestations of the disease the differential diagnosis of malaria in the tropics includes diseases such as typhoid fever, meningitis, encephalitis, metabolic disturbances, viral hepatitis, leptospirosis, septicaemias, and many other multisystem diseases (Gilles 1988).

Light microscopy is not available in many areas and health workers require guidelines to improve the clinical diagnosis of malaria. Furthermore, to prevent mortality it is essential to establish criteria that would ensure the appropriate treatment as well as timeous referral of patients suffering from severe and complicated forms of the disease. A definition of severe malaria to be used by health workers who have different grades of clinical competence, as established by the World Health Organisation, may facilitate the diagnostic and referral procedure (Warrell *et al* 1990).

2.5 BIOCHEMISTRY AND HAEMATOLOGY

Today, discussion of advances in the diagnosis of malaria is conducted in the languages of molecular biology and immunology. The measurement of various biochemical and immunological parameters may be used as indirect indicators of many diseases but their

application to the diagnosis of malaria has not been adequately explored (World Health Organisation 1988). If such cheap and reliable tests could be developed they would be a valuable diagnostic tool in areas where the provision of reliable microscopic facilities is not possible. An ideal diagnostic test - sensitive, specific, reproducible, inexpensive, and rapid and simple to perform - has yet to be developed (Bruce-Chwatt 1987).

Malaria, especially due to *P. falciparum* is a disease in which clinical and biochemical changes are produced by parasite-induced blood destruction as well as cytokine release. These changes are usually quantitatively related to the degree of blood destruction. In addition, liver function is almost always disturbed during the acute phases of infection (World Health Organisation 1988). Pathological changes in hepatic function are usually manifest in acute malaria even when parasitaemia is low or moderate. Major disturbances of renal function are seen in severe and complicated malaria and malarial nephropathy, but rarely in non-complicated falciparum malaria. However, a mild proteinuria is very common in acute malaria. Immune processes, in conjunction with hepatic dysfunction, often leads to a significant decrease of the albumin/globulin ratio.

Tests for urobilin, albumin and haptoglobin degradation products in urine as well as for lactate dehydrogenase, transaminases and haptoglobin levels in blood may be potential indirect indicators of acute malaria (World Health Organisation 1988). Haptoglobin is an alpha-2 globulin which binds free haemoglobin. Low serum levels are therefore found in haemolytic conditions. Hypohaptoglobinaemia has recently been shown to be a valuable epidemiological and clinical indicator for malaria (Rougemont *et al* 1988, Trape *et al* 1985). Serum bilirubin often shows a

moderate increase in malaria, but bilirubinuria is rare except in complicated malaria with major hepatic involvement. Similar changes are also observed in patients suffering from viral hepatitis when bilirubin values are usually high in both blood and urine.

Anaemia is a common feature of malaria and the degree of anaemia is often far in excess to that accounted for by the removal of infected cells alone (Pasvol 1986). Leucopenia is also a frequent accompanying characteristic with leucocytosis suggesting a complication or an unrelated disease (Reiley and Barrett 1971).

2.6 SOUTH AFRICAN STUDIES ON CLINICAL MALARIA

Swellengrebel (1931) commented that:

> "It is a generally accepted idea that in an area of high malarial endemicity, the adult indigenous population acquires a certain degree of immunity by being exposed to ever recurrent infections from early childhood onward. This state of immunity shows itself among adults in three ways: (1) absence or rareness of malarial fever; (2) decrease of splenic enlargement; (3) decrease in the number of parasite carriers, all in contrast with a too much suffering childhood. The more endemic conditions depart from the type of continuous infection, the more malaria becomes seasonal and the less chance is afforded for this state of immunity to establish itself. If malarial conditions are of the epidemic type, i.e., fever years being separated by longer or shorter successions of healthy years, the chances for immunisation become still less."

He observed in the African population that:

> "... as far as the distribution of crescents is concerned in relation to age. The highest percentage of crescent-carriers and the most prolific crescent-carriers are to be found among the young children, ... the infections in early age are much heavier in our observations, the 'toddler-age' is infected, almost without exception, and the parasite rate amongst adults decreases....."

These early observations are typical of an area where the level of naturally-acquired immunity to malaria is high. Two other studies (Eales 1972; Jairam *et al* 1990) describing the clinical illness were both retrospective studies at teaching hospitals; both studied mainly immigrants visiting South Africa or locals returning from an endemic area.

2.7 CHLOROQUINE-RESISTANT MALARIA

Reports of resistance to P. falciparum parasites to chloroquine, first observed in 1960-61 in Brazil and Colombia (Bruce-Chwatt 1980), were of great consequence since together with quinine these are the most valuable drugs for the treatment of acute malaria. Further reports on drug resistance came from Thailand, Malaysia, Cambodia, Philippines, Indonesia, Viet-Nam, Laos, Burma and other areas of south-east Asia. Chloroquine-resistant *P. falciparum* malaria was first reported from Africa in 1979 and has since spread throughout most of southern Africa (Spracklen and Whittaker 1984).

Resistance of *P. falciparum* to chloroquine was first detected in Natal in 1985 (Herbst *et al* 1985) and studies completed by Freese *et al* (1988) found 94% of the isolates tested to be resistant, with only 74% being inhibited at $>=32$ pmol/ul of chloroquine, indicating RIII resistance (World Health Organisation 1984). In February 1988, the authorities responsible for malaria control in Natal changed to using pyrimethamine-sulphadoxine (Fansidar/Roche) for the treatment of the asexual stages of P. falciparum infection, coupled with the use of primaquine as a gametocytocide (Dr. M. Short, personal communication).

CHAPTER 3

PATIENTS AND METHODS

The epidemiology and pattern of transmission of falciparum malaria in northern Natal has changed from one of intense transmission in the earlier decades of this century, to seasonal transmission in the last few decades. This is largely a result of the successful control measures implemented during the 1950s (Nethercott 1974). Consequent to the lack of repeated exposure to infection, the degree of acquired immunity to the parasite is likely to have decreased. Furthermore, the annual number of malaria notifications in this region has increased in the latter half of the 1980s; chloroquine resistance has also been documented during this period (Herbst *et al* 1985; Freese *et al* 1988).

The objective of this dissertation was to determine whether changes in epidemiological patterns have had an impact on the clinical features of falciparum malaria infection on the local population in northern Natal. To achieve this objective we studied the effects of the disease on a group of confirmed patients presenting to a primary health care facility for medical attention.

The second objective was to assess the value of haematological and biochemical parameters as rapid indirect indicators of *P. falciparum* infection. For this part of the study a control group of healthy volunteers from the study area was also studied for comparison.

This was a cross-sectional study conducted during March and April (1989), which is the peak season for malaria in this region. It was a field study performed in the Ingwavuma district of northern KwaZulu (district 1 in Figure 2). The patients were studied at the Ndumu clinic, which is close to the Mozambican border. This is a primary health care centre and a point of first contact for the population in this district. It is staffed by nurses and paramedics with no full-time medically-qualified staff.

3.1.1 PATIENTS

All patients in the study were diagnosed by passive detection, i.e. they presented themselves for medical attention as a result of symptoms. Actively-detected patients are those in whom a diagnosis of malaria is made as a result of routine blood-smear examination performed during mass blood screening.

A research team travelled to the Medical Research Council field station in Jozini for periods of one week at a time during the peak malaria season. This team consisted of a medical research officer (the author), Dr. Brian Sharp (researcher at the Research Institute for Diseases in a Tropical Environment), a nursing sister, and a technologist. From there the team travelled daily to Ndumu Clinic, which is approximately 75 kilometres from the field station.

The nursing staff at the clinic referred suspected malaria patients to us for detection of asexual forms of *P. falciparum* on thin blood smears. Microscopic examination was carried out using a compound microscope and a combination of lenses which provided a total linear magnification of 1000 for oil immersion microscopy. The microscope was powered by a

generator and the slides were stained with Giemsa. A total of 59 patients of > =5 years of age with confirmed *P. falciparum* infection was obtained by sequential sampling and included in this study. Patients under 5 years were excluded because of the difficulty of obtaining adequate amounts of blood for haematological and biochemical analysis. Informed consent was obtained from all patients, and from the guardians in the case of minors.

A history of relevant symptoms was obtained from each patient. Thereafter a thorough clinical examination was performed; special emphasis was placed on clinical signs of malaria. Guidelines set out (Characteristics of severe malaria and their identification at different levels of the health services) by the WHO Malaria Action Programme (1986) (Warrell *et al* 1990) were closely adhered to when making the clinical assessment. Appendix 1 is an example of a clinical data sheet. In the majority of patients, the duration of the illness was not recorded; in those in whom it was available, it was thought to be unreliable as many patients were unsure of the duration.

In each patient thin blood smears were quantitatively examined to estimate the parasite load. In addition, urine samples from the patients were tested for the presence of blood and protein using dipstix (*Ames*) and blood glucose was measured on a fingerprick specimen using a glucometer (Ames). Blood samples were drawn by venepuncture for later haematological and biochemical analysis.

All patients were treated by the KwaZulu health authorities with sulphadoxine-pyrimethamine (Fansidar/Roche) 3 tablets stat for adults and adjusted according to weight for minors.

Patients with greater severity of illness were referred to Mosvold Hospital, a district hospital in this area, for inpatient management.

3.1.2 CONTROLS

Thirty-seven volunteers aged 5 years and above served as controls. This group consisted of healthy subjects living in the same endemic area and were studied during the same malaria season. They had not suffered from malaria during this season, and their blood smears were negative for *Plasmodium spp*. Blood was drawn after informed consent for biochemical and haematological measurements.

3.2 PROCESSING OF BLOOD SAMPLES

Haemoglobin (Hb) estimation and white cell count were performed using a Cell-Dyne analyzer. Serum was separated from cells and stored in small aliquots at -20°C for analysis at the biochemistry laboratory at King Edward VIII Hospital, Durban. All serum samples were analyzed for liver function tests using an autoanalyser (Beckman Instruments Inc., Brea, CA, USA); serum haptoglobin levels were also measured, using a commercially available kit (Beckman Array Protein System, CA, USA) by the principles of rate nephelometry.

3.3 DATA STORAGE AND ANALYSIS

D-Base IIIplus was used for data storage and Statsgraphics employed for data analysis. Statistical assistance was provided by the Institute of Biostatistics of the Medical Research Council. The Student's t-test was used for comparison of means and the chi-squared test for comparison of categoric data. Where the expected cell sizes were less than five in the 2x2 case, the Fischer's exact test was used.

3.4 ETHICAL APPROVAL

This was granted by the Ethics and Professional Standards Subcommittee of the University of Natal.

CHAPTER 4

RESULTS

4.1 DEMOGRAPHIC DATA

Of the 59 patients studied, 33 were female and 26 male. Their mean age was 22 years with a range 5 to 60 years. The control population consisted of 27 females and 10 males, with a mean age of 26 years, range 5-60 years.

4.2 SYMPTOMS AND SIGNS

Figure 3 shows the frequency of occurrence of symptoms. Persistent headache, rigors and myalgia were the most common symptoms; these were present in 100%, 98%, and 93% of patients respectively.

Seventy-three per cent of patients complained of fever and their mean temperature was 38.5°C, with a range of 36.8°C to 40.5°C. Mild jaundice was detected in 2 patients. The mean pulse rate was 102/minute; there was no patient with algid malaria, although systolic blood pressure was less than 100mmHg in 21(35.6%) patients.

Splenomegaly, ranging from 1 cm. to 8 cm.(mean 2.4cm.), was found in 29(49%) patients. Hepatomegaly was detectable in 12(20.3%) patients; the mean increase in liver size was 2 cm. with a range from 1 to 4 cm. 54% of patients were found to be dull or drowsy and 3 patients (5%) were confused. None of the patients presented with hypoglycaemia and the

mean blood sugar was 6.4 mmol/l, ranging from 3.6 to 11.4 mmol/l. No patient presented to the clinic in coma or pulmonary oedema.

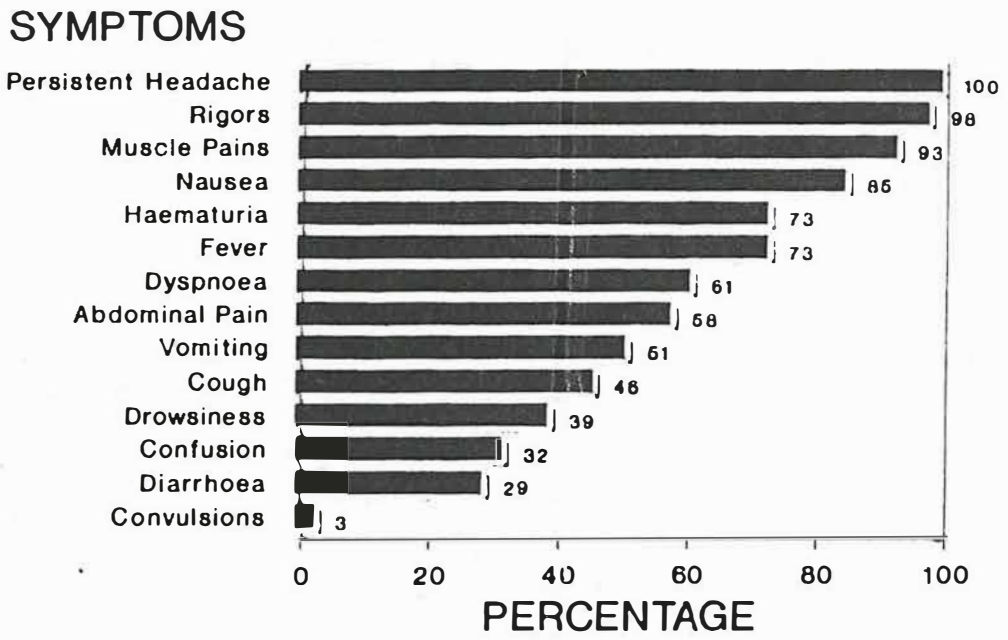

FIGURE 3: Bar graph of symptoms in 59 patients with *P. falciparum* malaria.

Proteinuria was detected in 95% of patients, however in the majority (81.3%) this was mild (trace to +). Haematuria was detected in 59%; in 14 of them this was severe (+ + + +).

I observed three patients with cerebellar signs and acute falciparum malaria. All three patients had severe gait and truncal ataxia. One patient had to be ferried to the field station in a wheelbarrow as he was unable to walk. Another was unable to walk unaided through a

doorway because of his ataxia (Soni and Sharp 1992). A third patient was also noticed to have nystagmus and suffered a grand mal seizure while being examined. All patients had ring forms of the parasite in their blood films, together with fever and other manifestations of acute *P. falciparum* infection. Only the first patient had taken Chloroquine, and this was in prophylactic doses only. Unfortunately, it was not possible to perform any special investigations on these patients and follow-up, except for the first patient who recovered completely, is unavailable for the latter two patients.

4.3 PARASITE LOAD

The median parasite load was 0.64% (of erythrocytes infected) on thin smear with a range of 0.01 to 10.74%. The majority of patients (57%) had parasite counts of $<1\%$. Five (8.5%) patients had hyperparasitaemia ie. $>5\%$ of erythrocytes infected. Plate 1 shows a blood film of a patient with a heavy infection showing the asexual forms of the parasite (trophozoites).

4.4 HAEMATOLOGY

Haemoglobin was measured in 50 patients and the mean was 10.8g/dl (range 6.9 to 16.9g/dl). The mean for the control group was 12.1 (range 8 to 14.6g/dl). This difference was statistically significant ($p = 0.0019$). 35/50 patients compared to 16/37 controls had a Hb of <12g/dl ($p=0.012$). From Figure 4 it is apparent that a significantly ($p < 0.001$; chi-squared $= 13.47$) more severe anaemia (under 10g/dl) occurred in patients (40%) than in controls (5%). There was no correlation between the parasite load and haemoglobin ($R = -0.004$).

There was no statistical difference ($p = 0.267$) between the mean leucocyte count in the patient group (6.1×10^9/l) and the control group (6.7×10^9/l). The leucocyte count in the

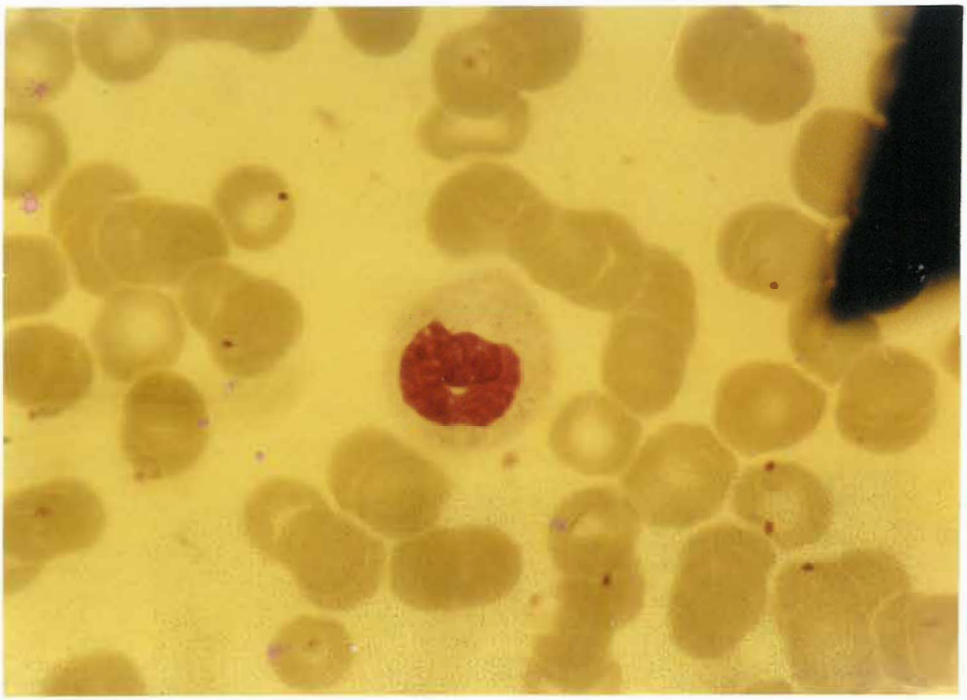

PLATE 1: Photomicrograph of a thin smear of blood in a patient with heavy infection showing trophozoites (ring forms) of *P. falciparum* (X 1000). Some erythrocytes are infected with more than one ring form.

patients had a wide scatter with a range of 2.3 to 20x10⁹/l. Leucopenia (WCC < 4.0x10⁹/l) occurred significantly more frequently in patients (12/50) than controls(2/37)(p=0.018).

Leucocytosis (WCC > 11.0x10⁹/l) was found in 4/50 patients and none of the control population.

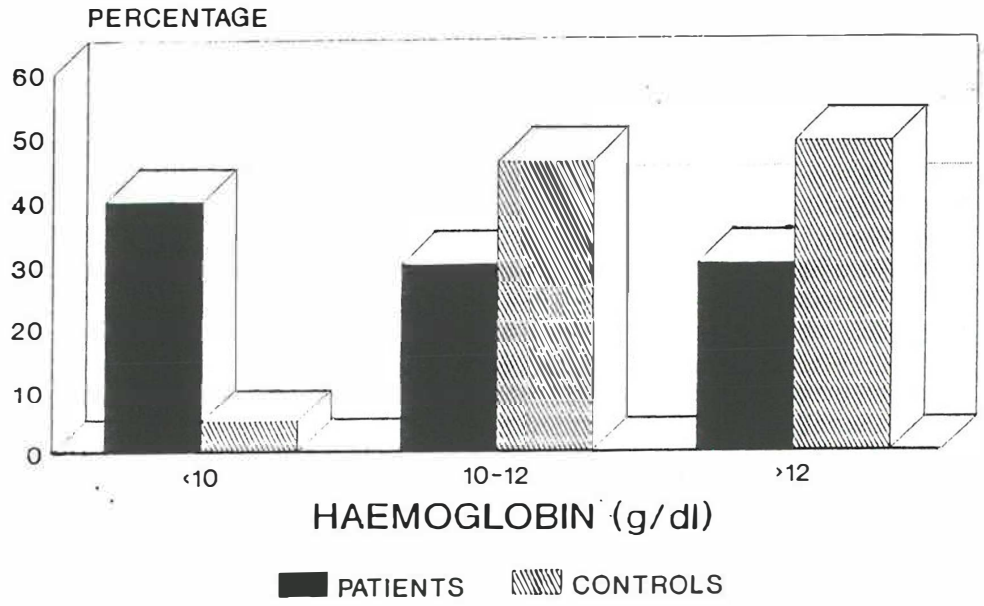

FIGURE 4: Haemoglobin values in 50 patients and 37 control subjects.

4.5 BIOCHEMISTRY

Table I shows the results of biochemical liver function tests in 58 patients and the 37 control subjects. Abbreviations and normal values used in this table are the following:

AST : Aspartate transaminase; Normal 10-42 IU/l

ALT : Alanine transaminase; Normal 10-60 IU/l

LDH : Lactate dehydrogenase; Normal 266-500 IU/l

Albumin : Normal 35-50 g/l

Bilirubin : Normal 0-17 umol/l

No. reduced and no. elevated in Table I refers to below and above the normal range respectively.

More patients had hypoalbuminaemia, hyperbilirubinaemia, and increased LDH and AST enzymes than control subjects (Table I); the difference was statistically significant. However, only 2 patients and no controls had an elevated ALT. There was no correlation between parasite load and bilirubin ($R = 0.186$), AST ($R = 0.051$), LDH ($R = 0.196$) or ALT ($R = 0.013$). Of the 19 patients who had elevated bilrubin levels, 12 had a direct (conjugated) bilirubin result which was greater than the total bilirubin. It is unclear whether this was due to a faulty reading on the autoanalyser or a printer malfunction; it was therefore not possible to investigate unconjugated hyperbilirubinaemia as a measure of haemolysis.

4.6 HAPTOGLOBINS

The normal values for serum haptoglobins is 0.13 to 1.63 g/l. 26 of 59 (44%) patients had reduced levels of haptoglobins (< 0.13 g/l), including 6 patients in whom the level was too low to be measured; a decrease in haptoglobin levels was seen in only 2 of 37 controls (5%). This difference was highly significant ($p < 0.001$).

Table I: Biochemical liver function tests in 58 patients with *P. falciparum* malaria and 37 control subjects.

TEST	PATIENTS (n = 58)	CONTROLS (n = 37)	p VALUE
Albumin (g/l)			
Mean (range)	32 (20-45)	39 (29-46)	<0.001
No. reduced (%)	37 (64)	5 (13.5)	<0.001
Bilirubin (umol/l)			
Mean (range)	16 (6-47)	6 (3-12)	<0.001
No. elevated (%)	19 (33)	0 (0)	<0.001
AST (IU/l)			
Mean (range)	37 (10-139)	26 (10-51)	0.001
No. elevated (%)	15 (26)	3 (8)	0.031
ALT (IU/l)			
Mean (range)	21 (7-67)	12 (7-20)	<0.001
No. elevated (%)	2 (3.5)	0 (0)	0.254
LDH (IU/L)			
Mean (Range)	791 (273-2257)	400 (217-692)	<0.001
No. elevated (%)	48 (83)	2 (5)	<0.001

CHAPTER 5

DISCUSSION OF RESULTS

This study differs from other clinical studies in the Republic of South Africa (Eales 1972; Jairam *et al* 1990) in two ways. Firstly it was performed at a primary health care centre rather than a tertiary referral hospital; and secondly it reflects the morbidity of *P. falciparum* malaria in residents of the region (indigenous malaria) rather than immigrants or South Africans returning from travels elsewhere in Africa. Both the above studies (Eales 1972; Jairam *et al* 1990) were retrospective; these were descriptions of imported malaria in white patients and neither described any cases of indigenous malaria. In the study by Jairam *et al* (1990) the 3 regions where the patients most often contracted malaria were Botswana, Malawi and Zimbabwe; none of their patients were thought to have contracted the disease in South Africa. In Eales's study (1972) at Grootte Schuur Hospital, only 2 of 47 patients had contracted malaria in South Africa during holiday visits to the Kruger National Park.

5.1 CLINICAL

It is apparent from the results described in Chapter 4 that none of the patients presented with severe complications of falciparum malaria, such as coma, pulmonary oedema, hypoglycaemia or algid malaria. Symptomatic infection in the presence of low parasite loads in most patients suggests that there may be little or no immunity to *P. falciparum* in this population. Field (1949) showed that poor outcome was directly related to high parasite density; he commented that the

parasite density was "the most reliable indication of severity in all but very few cases"; however the reverse was not true. This implies that the level of parasitaemia is not the only factor determining malaria mortality and morbidity. Another important factor is the degree of immunity which the individual possesses to the parasite.

The majority of patients in this study (57%) had less than 1% of erythrocytes infected, yet were sufficiently symptomatic to warrant seeking medical attention; the median parasite load was also low (0.64%). This was certainly not the case in the study area in 1931 (Swellengrebel *et al* 1931). The picture described by Swellengrebel *et al* is similar to those of other hyperendemic areas such as Gambia (McGregor 1964), Kenya (Garnham 1948), Liberia (Miller 1958) and the Sudan Savanna of West Africa (Molineaux and Gramiccia 1980). Garnham (1948) found that the most striking feature of the disease in children was the failure to find any apparent deterioration in general health, both in the initial and in the continuing malaria infection. He commented that "with the exception of occasional attacks of slight fever the children were well" and noted that it was remarkable how little fever accompanied the infection; only 10% of the total cases could be classified as severe. All children in his study were infected by the age of one year.

McGregor and Smith (1952) found that malarial pyrexia ceased to be common around the fourth year of life and that the number of parasites per 100 fields of thick blood films was maximal in very young children (under 1 year) and declined progressively in the older age groups. Miller (1958) in Liberia found that the clinical threshold counts for *P. falciparum* in adults ranged from

30 to 4550/mm^3 and the mean count for all attacks was 1644/mm^3. The clinical threshold is the parasite density which produces symptoms (Molineaux 1988); it rises as immunity is acquired.

The difference in the clinical picture produced by infection with the same parasite in the same region over a period of time, and in different parts of the same continent, is probably related to differences in epidemiology and immunity. The epidemiological pattern of malaria within a community can vary from country to country and, within countries, from area to area. Macdonald (1957) drew attention to the two extremes in which the infection may be present and appropriately termed them unstable and stable. The unstable form occurs when endemicity is normally low but where transmission may become intense for brief periods. Characteristically the resultant malaria shows substantial seasonal swings in incidence and a capacity swiftly to become epidemic given suitable conditions. It is in this form that malaria exacts its greatest toll in terms of illness and mortality and its effects are easily discernible at all ages within the community. Stable malaria, on the other hand, occurs when endemicity is high and where inhabitants are exposed to multiple infections in the course of each year. In such circumstances the epidemiological presentation remains remarkably constant year after year over long periods of time and its effects are most noticable in the young child section of the population. Macdonald considered that a major result of the epidemiological characteristics of malaria in any area was the degree of communal immunity possessed by the population. Where malaria is unstable communal immunity is low, save perhaps in periods immediately following an epidemic episode; where it is stable communal immunity is high.

The results of this study are in contrast to what is expected for a highly endemic, stable malaria area. Rather, the findings presented here are more representative of a population subjected to epidemic malaria, with little or no immunity to infection. Epidemiologic observations (Sharp *et al* 1988; Sharp 1991) in this area are consistent with this. This change from an endemic situation in the 1930s to an epidemic one presently is probably the direct result of an effective malaria control programme of long standing.

The common symptoms in the patients were all non-specific, many of which occur in other infections such as typhoid fever. This small study shows that the presence of a combination of common symptoms may be useful to field workers in selecting individuals for examination of blood smears in mass screening programmes. However, this needs to be validated by testing these symptoms in patients presenting to a clinic for attention for these complaints during the peak malaria season, using the positive blood slide as a gold standard. Respiratory and gastro-intestinal symptoms were commonly found (Figure 3). The presence of a soft splenomegaly in almost half the patients is a useful clue to diagnosis. Fever, headache, rigors and splenomegaly commonly observed in this study were also frequent presenting features in the two previous South African studies (Eales 1972; Jairam *et al* 1990). Similar results have been reported from other southern African countries (Table II), like Zimbabwe (Basset *et al* 1991; Stein and Gelfand 1985; Schmitz and Gelfand 1976) and Tanzania (Mkawagile and Kihamia 1986). These observations also concur with that of Goldstein (1968) in his study of non-immune American soldiers in Vietnam (Table II).

Jaundice is common in adult patients, particularly those with severe falciparum malaria, but is uncommon in African children (Warrell and Francis 1991). Apart from jaundice, signs of hepatic dysfunction are unusual; clinical signs of liver failure are never seen unless there is concomitant viral hepatitis (White and Warrell 1988). Tender enlargement of the liver and spleen is a common finding in all human malarias, especially in young children and non-immune adults.

Table II: Commonest symptoms with *P. falciparum* infection reported in different studies.

Commonest symptoms (%)	Country	Reference
Headache(86), weakness(79), fever(73)	Zimbabwe	Basset
Fever(93), headache(44), vomiting(40)	Zimbabwe	Stein & Gelfand
Headache(73), vomiting(39), abdominal pain(38)	Zimbabwe	Schmitz & Gelfand
Fever(90), headache(95), myo-arthralgia (90)	Tanzania	Mkawagile & Kihamia
Fever(100), headache(100), myalgia(75)	Vietnam	Goldstein
Fever(88), headache(72), rigors(51)	RSA	Jairam
Fever(90), headache(70), rigors(68)	RSA	Eales
Headache(100), rigors(98), myalgia(93)	KwaZulu	Soni

Proteinuria and haematuria were also common. Mild proteinuria may occur with any febrile illness. In malaria the deposition of immune complexes on the glomerular basement membrane may result in an acute nephritis with resultant haematuria and proteinuria. Haematuria may also be a result of *Schistosoma haematobium* infection of the bladder. This was not investigated in our patients, though it is well documented that adjacent districts in Northern KwaZulu have a high prevalence of *S. haematobium* infection (Schutte *et al* 1981).

Cerebral malaria has a multitude of neurological manifestations, including confusion, delirium, psychoses, convulsions, coma, meningism, involuntary movements and other focal neurological phenomena. Cerebellar signs have been described by several workers during different stages of the disease. A delayed cerebellar syndrome following successful treatment of falciparum malaria has been described by De Silva *et al* (1988) and Senanayake (1987). It is uncertain whether this is a consequence of chloroquine therapy or a sequelae of the infection. Hangasekera and De Sylva (1976) also described two patients with an acute cerebellar syndrome occurring during an acute attack of falciparum malaria.

Several questions arise from the previous reports of cerebellar involvement in falciparum malaria. The first one is whether this clinical picture is a delayed syndrome following therapy of the infection or whether it arises during the acute attack. In our patients, it was believed to be the latter rather than the former (Soni and Sharp 1992). The second question is whether this clinical entity occurs outside of Sri Lanka, as all previous case reports have originated from Sri

Lanka. It has been suggested by Senanayake (1987) that if this picture is confined to Sri Lanka, then a mutant strain of falciparum may be responsible. However, this seems less likely if a similar condition is seen as far away as South Africa.

The possible pathogenic mechanisms for this syndrome remain undetermined. The possibility of a drug effect is unlikely, as no common drug was given to all three of our patients. Direct invasion of the central nervous system by the organism might damage the cerebellar system by causing vascular occlusion, haemorrhage or inflammation. This could be likely in our patients as all were ill and toxic during the episode of cerebellar disease. Vascular occlusion may be the result of adhesion of infected cells to endothelium, which is mediated by ICAM-I and Tumour necrosis factor. However, it seems unlikely to be the mechanism responsible in those patients previously reported with a delayed cerebellar syndrome where there was a delay of 21-26 days between the fever and the ataxia, which occurred weeks after treatment of the acute infection. In those cases an immune-mediated mechanism would probably be more likely. The possibility of the malarial episode in some way activating a dormant neurotropic virus which subsequently produces the cerebellar damage cannot be excluded (Senanayake 1987).

5.2 HAEMATOLOGY

Anaemia is a prominent feature of the infection. The combination of haematuria and anaemia suggests red cell destruction as the primary cause of the anaemia; however no correlation was observed between malaria parasite density and haemoglobin level. This observation concurs with the results of Olweny *et al* (1985). The mechanisms of anaemia are both multifactorial and

complex; including destruction of the red cell by the parasite, immune mediated haemolysis, non-immune mediated haemolysis, disseminated intravascular haemolysis, dyserythropoiesis and a reduction in serum iron and transferrin (Pasvol 1986; Phillips *et al* 1986).

Leucopenia has been reported in 30% (Goldstein 1968) and 33% (Reiley and O'Neill 1971) of American soldiers in Vietnam suffering from acute *P. falciparum* infections and occurred with a similar frequency (24%) in our patients. Typhoid fever, which is also endemic to this study area, can also produce a leucopenia. Thus a low white cell count in the presence of a febrile illness is a less sensitive indicator of malaria. Leucocytosis was also uncommon in the above studies (Goldstein 1968; Reiley and O'Neill 1971) of uncomplicated malaria and its occurrence should raise the possibility of another disease.

5.3 LIVER BIOCHEMISTRY

Some impairment of liver function is common in malaria (White and Warrell 1983), but true liver failure is unusual. Unfortunately, assessment of 'liver function' by measurement of blood concentrations of bilirubin and the liver-related enzymes is notoriously imprecise, particularly when there is coexisting haemolysis. The measurable consequences of hepatic dysfunction in malaria are coagulation abnormalities, hypoalbuminaemia and reduced metabolic clearance of many substances (White 1986). Serum enzyme assays such as the aminotransferases are very sensitive indicators of tissue-cell damage, particularly in the liver.

Sadun *et al* (1966) were one of the first groups of investigators to use serum enzymes to detect cell lesions in malaria. They investigated American military personnel returning from Vietnam with *P. falciparum* malaria and reported a significant increase in infected patients over values in uninfected control individuals in serum ALT levels but not in serum AST levels. The former enzyme is generally accepted as being more specific for liver lesions than the latter one.

Serum biochemical changes were also measured by Sadun *et al* (1966) in infected and non-infected indigenous Thai subjects living in an endemic area. Significant serum increases in both ALT and AST were seen in infected individuals. AST is present in erythrocytes, heart, kidney and skeletal muscle as well as liver; ALT is a more sensitive and specific indicator of hepatocellular damage than is AST (Preisig *et al* 1992). Deller *et al* (1967) found that elevated serum enzymes were associated with either liver tenderness or gastrointestinal symptoms, or both. The liver biopsy findings were abnormal in almost all the cases, whether or not the serum enzymes were increased. There was a lack of cell necrosis but increased hepatocyte nuclear and cytoplasmic activity was observed, together with Kupffer cell hyperplasia and some mononuclear infiltration.

As expected, this study showed a greater number of patients(64%) than control subjects (13.5%) with a low serum albumin. Hypoalbuminaemia is an important index of hepatic dysfunction. Lower serum albumin levels were also observed in the infected Thai patients (Sadun *et al* 1966). However, only 2 of 58(3.5%) patients in our study had an elevated serum ALT compared to 15 of 58(26%) patients who had an elevated AST. Considering the high proportion of infected

individuals who had an elevated LDH(83%), it is more likely that the enzyme elevation is secondary to destruction of the parasitised erythrocyte than hepatic involvement. LDH is found in heart, skeletal muscle, liver, kidney, brain and erythrocytes.

In most patients with falciparum malaria the plasma concentration of total bilirubin is increased, implying haemolysis. In this study it was elevated in 33% of patients compared to none in the control group. The most commonly present biochemical indicators of *P. falciparum* infection were elevated LDH(83%) and hypoalbuminaemia(64%).

5.4 HAPTOGLOBINS

Previous studies have demonstrated low levels of serum haptoglobins in regions of Africa where the prevalence of malaria is high (Trape *et al* 1985; Hill *et al* 1987). These studies suggest that in regions where malaria is endemic the prevalence of hypohaptoglobinaemia could be a useful indicator of the parasitic index; additionally it is much easier to monitor. Rougemont *et al* (1988) have demonstrated the reappearance of detectable levels of haptoglobin after antimalarial therapy. They also demonstrated a correlation between the haptoglobin index (the proportion of subjects in a given group with concentrations of less than 10%) and the parasite index and parasite load.

In the study by Trape *et al* (1985) in the Congo, the proportion of individuals with ahaptoglobinaemia reached 42.1% in those heavily infected. The present study showed that 44% of infected individuals had low levels of haptoglobins in an area with seasonal malaria transmission. Blumberg *et al* (1963) showed a decrease in serum haptoglobin level to correlate

with the fall in haemoglobin level in a group of seven patients. The results in Chapter 4 do appear to show a relationship between the fall in the haemoglobin and the serum haptoglobin. However, this could not be quantified because several patients had undetectable levels of haptoglobin. Serum haptoglobins appear to show some promise as a rapid indicator of malaria infection.

CHAPTER 6

CONCLUSIONS

Sharp (1988 and 1991) has shown that the pattern of malaria transmission in the northern areas of Natal/KwaZulu has changed from one of endemic malaria to epidemic transmission with peaks during the months of March and April. This study demonstrates that the clinical profile of *Plasmodium falciparum* infection in the region has also altered.

The clinical manifestations of falciparum malaria in the Natal/KwaZulu area prior to institution of the of the malaria control programme were similar to that seen in other malarious areas (Swellengrebel 1931). However in the present study, severe and complicated malaria, as recently defined by the World Health Organisation (Warrell *et al* 1990), was not common at presentation in this select (clinic) population. The severity of infection ranged from a flu-like illness to high fever with convulsions. It must be noted that since this study was performed at a primary care level, all the features of severe and complicated malaria could not be conclusively diagnosed, eg. renal failure, acid-base disturbances.

Parasite loads were generally low in most patients in this study. However, those patients with low parasite loads had prominent symptoms of infection; the low parasitaemia also suggests that they may be presenting early in the infection for medical attention. This would imply a much lower level of acquired immunity than that suggested by Swellengrebel *et al* in the same area in

1931. The change in clinical profile, coupled with the changing epidemiology, is a strong indicator that the malaria control programme in the region has had an impact on the disease.

The lack of naturally-acquired immunity needs to be verified by further studies, eg. by measuring levels of circumsporozoite antibodies in patients and the local population. The loss of the semi-immune status of the population has implications for epidemics of malaria infection. Local outbreaks of infection, usually following heavy rainfall, will result in considerable morbidity and mortality; all age groups will be prone to symptomatic infection, with or without complications. This was probably the basis for the high case rates in 1987 and 1988 following flooding of this area. Epidemics have been reported in areas in which malaria had been reduced to a very low level through control measures. Examples are Sri Lanka in 1965, the Gezirah, Sudan, in 1975, and the Adana plain, Turkey, in 1977 (Molineaux 1988). Typically, transmission had been controlled mainly by the spraying of residual insecticides whose effect was temporary only.

The combination of common symptoms found in our patients are a useful clue for field workers carrying out mass blood screening examinations. The World Health Organisation and UNICEF currently recommend treatment of clinical malaria by village health workers and others as the optimum strategy for the control of malaria in children (Greenwood *et al* 1988).

Valuable indirect biochemical indicators of malaria infection include an elevated LDH and reduced haptoglobin levels, which are both sensitive and may be of value in rapid diagnosis.

However, a diagnosis cannot be confirmed on these indicators alone and microscopic examination of a blood film remains the only confirmatory test. Furthermore, equipment required to measure these biochemical products is usually unavailable in areas where the disease is prevalent.

This study also shows that a greater number of patients had an elevated AST compared with ALT; this suggests that the enzyme elevation originates from the parasitised erythrocyte rather than the hepatocyte.

Finally, the comments by Najera (1986) on malaria control are fitting to conclude this dissertation:

> "Research in malaria is already producing promising results in the development of new drugs, new methods of diagnosis, and possible means of active immunisation against malaria. However, the main obstacle to malaria control has not been the lack of technology or even knowledge, but the difficulties of adapting existing knowledge to local situations and making optimal use of the resources of the health infrastructure and of community participation and intersectoral cooperation."

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APPENDIX

DATA SHEET

NAME NO.

AGE SEX DATE

RESIDENCE AREA

CLINIC/HOSPITAL

A. SYMPTOMS

FEVER RIGORS

SHORTNESS OF BREATH COUGH

INADEQUATE EXCERCISE LEVEL MUSCLE PAINS

NAUSEA/VOMITING DIARRHOEA

ABDOMINAL PAIN PERSISTENT HEADACHE

HAEMATURIA

CONFUSION, DROWSINESS, CONVULSIONS

B. SIGNS

ANAEMIA NIL/MILD/MOD/SEVERE

JAUNDICE TEMPERATURE

PULSE BP /

SPLEEN SIZE (cm) LIVER SIZE (cm)

PULM OEDEMA

LEVEL OF CONSCIOUSNESS

URINE : BLOOD PROTEIN

BLOOD SUGAR