INTRODUCTION
The English word malaria, applied generically to the fevers caused by plasmodial infections, stems directly from two Italian words mala and aria meaning bad air. Today, malaria is recognised as a disease characterised by intermittent febrile paroxysms, anaemia, and splenic enlargement caused by infection with parasites, generally assigned to the genus Plasmodium, class sporozoa. The first man who saw and described plasmodia as parasite was Laveran (1880).

Four species of malaria P. falciparum, P. vivax, P. malariae, and P. ovale, are known to infect man naturally and each produces a specific malarial disease which is named vivax malaria, falciparum malaria, ovale malaria, and malariae malaria respectively.

Malaria is caused by four species of plasmodia which have some differences in their life cycle and periodicity. Finally, the status of immunity of a patient has a direct bearing on the dose of antimalarial drug used for therapy. Thus the true value of a medicament for malaria can be determined only by observing its effect and its toxicity in a large number of experimentally infected non-immune subjects under adequate clinical and laboratory control. Only a limited number of useful anti-malarial drugs are in use which include the cinchona alkaloids, mepacrine, chloroquine, amodiaquine, primaquine, proguanil, pyrimethamine and sulphadoxin.
In the evaluation and use of these drugs, certain concept and definitions are useful. For example, drug action on schizonts, erythrocytic or exoerythrocytic is referred to as schizontocidal, on gametocytes as gametocidal; and on sporozoites as sporontocidal.

Quinine is the oldest drug available and it occupied important position in chemotherapy of malaria until World War II. During the 1930s mepacrine started to replace quinine as a blood schizontocidal drug for prophylaxis. Mepacrine was replaced by new blood schizontocidal compounds, in the late 1940s and early 1950s which were easier to use. After 2nd world war active antimalarial compounds such as the 4-aminoquinolines (chloroquine and amodiaquine) and dihydrofolate reductase inhibitors (proguanil and pyrimethamine) were introduced in 1940s or early 1950s. Chloroquine resistance was suspected in Southern Asia and confirmed in South America at the end of 1950s. *P. falciparum* was reported in 1959 in Thailand. In the following years more countries in Eastern Asia and South America became affected and in 1978 East Africa also became affected and resistance has spread to Kenya and the United Republic of Tanzania.

Foci of chloroquine resistance in the country have been identified under *P. falciparum* containment programme of NMEP in areas of Assam (District Kar, Anglong, Darrang, Kamrup and Goal Pana), U.P. (Agra, Jhansi, Mirzapur), Haryana (Gurgaon), Gujarat (Surat, Amreli), Maharashtra (Chandrapur),
Nagaland, Megalaya, Orissa (Keonjhar, Sambalpur, Kalahandi, Phulba), (Pattanayak et al., 1979; Dwivedi et al., 1979; De et al., 1979; Das et al., 1979; Chakravarty et al., 1979).

Recent studies showed that amodiaquine is more effective than chloroquine. RI resistance of *P. falciparum* to amodiaquine has been reported from Sadao, Thai, Kampuchean border, Petchabin, Northern Thailand. Therapeutic advantage of amodiaquine is no longer useful in practice in areas of very high chloroquine resistance, RII response were dramatically reduced as compared with chloroquine. There are limited areas of RIII response to amodiaquine.

Reports emanating from Thailand, Philippine, Tanzania show that the latest antimalarial which is believed to be most patent drug viz. mefloquine is tending to became ineffective in the control of multiple resistant strain of *P. falciparum* as well as those resistant to fansidar, (W.H.O., 1973) shows the efficacy of some medium and long acting sulfonamides that were introduced in 1937 (Diaz-de-leon). Compounds which have been tested against sensitive and chloroquine resistant cases of *P. falciparum* are sulfamethoxy pyridazine and sulfadimethoxine, sulfadoxine and sulfalene. Only a few trials have been carried out with sulfamethoxypyridazine and sulfadimethoxine. Activity of sulphones against *P. knowlesi* was described (Coggeshall et al., 1938) but avian model do not respond to sulphonamide (Manwell et al., 1941). But some years later in 1944 both sulphonamides and sulphones were
proved to be definitely active against *P. gallinaceum* in chicks (Coatney et al., 1944). High activity of sulphonamides against *P. berghei* was observed by Hill (1950). In Thailand 11 of 18 patients were cured with single dose 1000-1500 mg of sulfadoxine (Harinasuta et al., 1967).

For the treatment of highly drug resistant strains of *P. falciparum* which do not respond to chloroquine plus tetracycline or mefloquine also, it has been suggested by WHO to employ the combination of mefloquine with fansidar, which is hoped to lead to the ultimate control of malignant falciparum strains tending to show mefloquine resistance.

Regarding immune-dependence of antimalarial chemotherapy there is much indirect evidence to link the effectiveness of chemotherapy with the immune status of the host. Drugs which may be used prophylactically curatively or as suppressive may effect on the levels of immunity.

For experimental studies choice of host plays a very important role. Excellent review of taxonomy and detailed description of the various types of rodent malaria have been published by Carter and Diggs (1977) and Killick-Kendrick (1978). Other aspects are reviewed by Killick-Kendrick and Peters (1978). Rodent malaria models for chemotherapeutic studies have proven to be extremely valuable in assessing the activity of established and potentially new antimalarial compounds. Peters (1970, 1974, 1980), Peters and Howells
Numerous species and subspecies of rodent malarias that have been isolated are divided into two main series, the berghei group and the vinckei group. The group used for the majority of chemotherapy research the berghei group containing *P. berghei* (KBG-173) isolated by Vincke and Lips (1948), *P. yoelii* 17X (Landau and Kili-Kendrick, 1966) and *Plasmodium yoelli nigeriensis* N67 (Killick-Kendrick, 1973) and the other subspecies the Vinckei group contains *P. vinckei* and *P. chabaudi*.

Experimental studies carried out in CDRI showed that strains of *P. berghei* resistant to pyrimethamine and chloroquine could be obtained by treatment with sub-curative and interrupted doses of drugs in weanling rats (Agarwal et al., 1979; Puri et al., 1979). Subsequent studies have shown that resistance to single drug like mefloquine, primaquine and sulphanilamide could be built in strains of *P. berghei* (Kazim et al., 1980) strain resistant to these drugs have been developed elsewhere also (Peters, 1970). *P. yoelii nigeriensis* naturally resistant to chloroquine is reported by Peters (1970).

At CDRI chemotherapeutic response of *P. yoelii nigeriensis* to antimalarial drug was reported by Pandey et al., (1982).
Very little information on *P. yoelii nigeriensis* is available with regards to its host parasite response, chemotherapy and its drug resistance susceptibility. *P. yoelii nigeriensis* can serve as a valuable test model for experimental malaria such as (1) chemotherapeutic studies against blood stages (2) Studies on gametocytocid activity (3) Strains of this parasite resistant to antimalarial drugs are developed. (4) The information is 100% fatal in Swiss mice accompanied with higher level of parasitaemia.

Efforts have been made to study malaria parasites in laboratory animals. The rhesus monkey, *M. mulata* is the most widely used since it is susceptible to infection with all the Asian monkey malaria parasites as well as the African parasites *P. gonderi*. In this host, the parasitaemia often reaches very high levels and, frequently, monkey dies of overwhelming infection.

*Plasmodium knowlesi* is almost always fatal when the infection is induced via the inoculation of parasitized blood.

Efforts to infect man with the malaria parasites of non-human primates have been of special interest. *P. knowlesi* was the first seen to be infectious to man. The infection was induced by inoculation of parasitized blood (Knowles and Dasgupta, 1932). A considerable amount of study has been made on the transmission of *P. cynomolgi B* to man following the accidental infection of several laboratory workers in 1960 (Eyles et al., 1960).
A limited number of attempts have been made earlier to select drug resistant strain of simian malaria. Hawking and Perry (1948) selected a proguanil resistant line of *P. cynomolgi* which exhibited 100 fold resistance to this drug. The resistance was stable after mosquito passage of the parasite. Schmidt *et al.* (1949) also reported successful selection of proguainl resistant strain of *P. cynomolgi* which showed 2000-fold resistance to proguanil, HCl in three successive passages by subcurative therapy. Subsequent work done by Jaswant Singh *et al.* (1952) showed that a strain of *P. knowlesi* showing 2400-fold resistance to proguanil was developed after 5 serial passages in rhesus monkey. The resistance was stable after drug free passage. The strain also developed cross resistance to pyrimethamine and the level of resistance was 1600-fold. In another study, Jaswant Singh *et al.* (1953) reported successful selection of pyrimethamine resistant strain of *P. cynomolgi* which exhibited 12-fold level of resistance. The strain also developed cross resistance to proguanil and bromoguanide. The antimalarial drugs which are used for the treatment of human malaria are also effective in the treatment of malaria infections in non-human primates. Very little experimental work has been done on the drug resistance in strains of primate malaria.

Present thesis deals with chemotherapeutic and drug resistance studies with long acting antimalarials and sulfa
drugs particularly with *P. knowlesi* and *P. yoelii nigeriensis*. The present study provides comprehensive data on chemotherapy and drug resistance to malaria specially.

1. Evaluation and comparison of different criteria for assessing antimalarial activity i.e. suppression of parasitaemia, mean survival time and determination of minimum effective dose (MED).

2. Testing of long acting nature of antimalarials in Swiss mice.

3. Efficacy of single dose treatment with sulfa drugs against *P. yoelii nigeriensis*.

4. Selection of sulphadoxine plus pyrimethamine (fansidar) plus mefloquine resistant strain of *P. yoelii nigeriensis*.

5. Challenge and rechallenge of chloroquine, amodiaquine treated monkeys with *P. knowlesi* for evaluation of immune status of host.

6. Efforts have also been made to carry out cross chemotherapeutic studies of these strains in order to find out the sensitivity/resistance of resistant strains to other drugs.