A study of falciparum malaria in pregnancy in the Gambia

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A STUDY OF FALCIPARUM MALARIA
IN PREGNANCY IN THE GAMBIA

Michael Jon Anderson

1978
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Date
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Preface

The field research for this thesis was done in The Gambia, West Africa under the auspices of the Medical Research Council Laboratories. Although the study was an examination of malaria in pregnancy, the nature of the research emphasized a great deal more about which I feel compelled to discuss. The addition to the purely scientific effort of this thesis is a result of an exposure to the incredible magnitude of human suffering in the Third World that occurs as a consequence of so many preventable medical situations. It is something that we, with the blessings of our industrial technology, cannot morally ignore.
Acknowledgments

There are many without whom this thesis would not have been possible. At the Yale University School of Medicine, I am grateful to my thesis advisor, Dr. John M. Dwyer, my faculty advisor, Dr. Robert H. Gifford, and to the Yale University International Student Fellowship Committee. At the Medical Research Council Laboratories in The Gambia, I am indebted to Dr. R. S. Bray for the wisdom and leadership that made this thesis such a valuable experience. Finally, I am fortunate to have parents, who exposed me to the problems of others, and a wife, who so willingly gave me her dedicated support.
PART I.  The Breech Between the Rich and the Poor
What seems to us more important, more painful, more unendurable is really not what is more important, more painful, and more unendurable but merely that which for all its moans and muffled cries, its ruined lives and millions of victims, that does not threaten to come rolling up to our threshold today we consider endurable and of tolerable dimensions.

Alexander Solzhenitsyn
It can easily be said that the differences between the rich nations and the poor nations of the world are often raised as issues in international relations today. All nations, whether rich or poor, free or dictatorial, Communist or non-Communist, have certain policies and principles that determine their positions toward the question of the basic inequality of peoples of the world. The extent to which this is a preeminent concern in guiding an individual nation's foreign policy, however, seems to depend only on one factor: whether or not the nation is poor. Certainly India and her people, as representatives of the poor of the world, are more occupied with the problems of poverty than the United States of America and her people, as representatives of the rich of the world. Alexander Solzhenitsyn's thought that "everything distant which for all its moans and muffled cries... we consider endurable and of tolerable dimensions" is applicable as a possible explanation. But given the magnitude of the problem and the staggering disparity between the rich countries and the poor countries of the 1970's, it seems proper that the wealthy devote more than present levels of time, money, and effort in assistance to the countries of the underdeveloped world.

The gulf between these two groups of nations is not a small one. As an example and in an attempt to define the poverty nations, consider national per capita income. If
the level of wealth of a wealthy country were fixed at a per capita income of $500 per year, 80% of mankind is below this value. Moreover, the per capita income in the United States and Canada in this scheme is three to four times the $500 amount, while some countries, India for example, have per capita incomes one-tenth of the hypothetical $500 per year.\footnote{As further evidence of the breech, the United States with 211.9 million people, a Gross National Product of $1.4 trillion and a per capita income of $6,640 can be compared again with India with 586.1 million people, a Gross National Product of $78.9 million, and a per capita income of $130 (1974 estimates). The differences are certainly not small.}

The gulf can be examined easily in more human terms. Throughout the developing nations hunger and malnutrition are sapping energy from bodies and slowing minds. Illiteracy is stealing opportunity. Endemic unemployment is lowering pride and eliminating ambition. The population is increasing at an alarming rate. And entirely preventable diseases are killing children and adults and disabling productive workers. Symbolic of the lives of three-fourths of the human race is that over 1,000 million humans are malnourished or hungry; life expectancy is 40% of that of the Western nations; child mortality is four times what it is in the affluent world; per capita expenditures on health in some countries are less than 40¢ per year; and there are fewer than one physician per 50,000 people in some developing countries.\footnote{2}
It does not seem possible in today's political climate, which mildly encompasses the notion of the basic equality of nations, that the existent state of gross inequality can last. It must be expected that the status quo cannot remain in such an unbalanced state. The poor nations must, and will for their own survival, balance the scale. But it is disturbing that the wealthy nations of the world are giving so little effort to the formidable problems of the impoverished masses. The hope seems to be that through inactivity and the simple progression of time that order will spring from chaos. The inactivity of the wealthy nations is forfeiting the opportunity to participate in creating the greater equality of nations that is to come. Barbara Ward in *The Rich Nations and the Poor Nations* wrote of this dilemma:

Of one thing I am certain: if we continue with what is surely our greatest Western temptation, and think that in some way history owes us a solution, that we can, by pursuing our own most parochial self-interest, achieve in some miraculous way a consummation of world order, then we are heading not simply towards great disappointments, but towards disaster and tragedy as well. There has to be a new start, new policies, a new approach. Otherwise we prepare for our defeat simply by default.  

It is necessary to explore new ways of achieving the "consummation of world order." Medicine seems, as it has not in the past, to be intricately involved in the politics of social and economic development. Because so much of the developing world lies in tropical climes, the allusion to "medicine" is tropical medicine. This is not tropical
medicine primarily in the sense of "ordinary" medicine in
the tropics, i.e., treatment of heart disease, pneumonia,
or diabetes mellitus in the tropics. Nor is it tropical
medicine primarily in the sense of a well-defined group of
infections and communicable diseases which depend largely
on warm, humid climates. Both of these are too narrow and
limited in concept. This is tropical medicine, however, in
Dr. B. G. Maegraith's concept of the special circumstances
in which disease occurs in the tropics, that is amongst
poverty, dirt, a low standard of living, and a perpetually
warm climate that allows the persistence of certain disease
vectors. Tropical medicine in this context is concerned with
the availability of agricultural and veterinary products,
the overall shortage of protein, malnutrition, overpopula-
tion, conditions of sanitation, and the level of education,
as well as the diagnosis, treatment, and prevention of disease
in the tropics. Tropical medicine thus becomes a multidis-
ciplinary subject as varied and pluralistic as the conditions
and factors that are forcing the majority of mankind to con-
tinue in the unsatisfactory and squalid state in which it is
living. Indeed tropical medicine has a great role to play in
narrowing the gap between the developed and developing
nations.

As health is affected by socio-economic factors, so
does health, for better or for worse, affect socio-economic
factors. Health improvement is sometimes necessary for the
development of disease-ridden areas. Improvement in conditions of health is, at other times, needed for the successful implementation of developmental schemes. As an example of the former, onchocerciasis must be eliminated for the successful human habitation of certain areas of West Africa. As an example of the latter, schistosomiasis must be considered when constructing dams in or near areas of the schistosome snail vector. Viewed in this light, health is absolutely vital to the development and sustained utilization of socio-economic resources. It consequently becomes impossible to distinguish between medical aid and any form of economic aid. This follows directly from the notion that health is a vital factor in raising living standards and is essential to improving economic growth.

There are those who argue that the crux of the problem in the developing nations is overpopulation. Their argument is economic in that an overpopulated society diminishes food reserves as well as capital, decreasing the chances of the society saving for further investment. Because of the burdens that overpopulation provides, the economy becomes primitively subsistent without hope of improvement. Since fewer people make fewer demands, any means of decreasing the population is viewed as long-range assistance. This allows capital saving and investment. Increasing the level of health maintenance becomes problematic if, by this act, the population increases. By this logic better health care
in developing countries can be seen as a negative factor in the overall scheme of improving the plight of the Third World.

There are at least three arguments against denial of health care in order to achieve population control. First, and foremost, it is a morally unacceptable alternative. The wealthy nations are exhibiting unjustified arrogance if they assume such an omniscient attitude.

Second, improved health is, in itself, the prerequisite to reducing fertility. Many developing countries are subsistence agricultural communities. The land is tilled and worked by families that require family members as laborers. Additionally, sons and daughters are viewed by parents as security for old age. These concepts will not change quickly. But as the infant mortality rate declines from its present high level (45% before the age of five in The Gambia, for example), the population will lose the necessity of producing so many in order to retain so few. The present attitude of futility will give way to optimism. The resultant ability to plan for the continuation of human life will produce the necessity to plan for the future of those lives.

Finally, a declining birth rate is more likely to be a consequence rather than a cause of economic expansion. In the developed countries economic expansion always preceded a declining birth rate. As opportunities for education and employment improved, a large segment of the population saw
the economic advantages of a smaller family. It is interesting that this is in spite of any predominant religious views against control of family size. The chain of events, therefore, is better health leading to economic development which contributes to a lower birth rate and a reduction in population expansion. For,

without the thrust of economic growth, there is no reason why people should want smaller families. Children may die; they cannot be educated; meanwhile they work. A certain fatalism prevails. It is only when hope and expansion begin that the choice of a smaller family makes sense. 5

When examined in this light, the giving and receiving of medical aid become interdependent. It is a form of enlightened self-interest for both sides. In its most ideal and successful form, medical aid can contribute efficiently and effectively to achieving the equality of peoples that is so necessary. Medical assistance can be the first step to a more harmonious and productive world for all mankind.

There is another sense in which medical aid is beneficial to both the donor and the recipient nations: disease eradication and control. The imminent eradication of smallpox and the proposed eradication of malaria would affect beneficially not only those unfortunate people with each of these diseases, but the entire human race. Indeed the mobility of modern Western man has increased his chances of contracting communicable diseases that were once restricted to the tropics. In this age of air transit, both the speed of transportation
and the numbers of people travelling are increasing annually. In 1949, aircraft carried 20 to 40 passengers. In 1946 to 1947 a Hong Kong to London flight was a five and one half day trip with compulsory night stops. The numbers of passengers on internationally scheduled airlines has increased from seven million in 1952 to 500 million in 1975. Military movement, tourism, recurrent religious migrations, cyclical nomadic migrations, migration secondary to social or political duress, and immigration have increased the chances of Third World diseases being seen in Western world settings.

When thinking about the redistribution of disease, it is necessary to avoid thinking in the classic and narrow manner of the infected human host and the host-parasite relationship. When examining malaria in this limited sense, it is easiest to think of the malaria parasite and the *Anopheles* mosquito primarily in terms of the disease alone. It must be remembered that these agents are distributed far differently than the disease itself. Diseases are abstractions and are not concrete entities apart from mankind. A disease is not a living entity; sick people are the reality. This is important when distinguishing between endemic areas and potentially endemic areas of various communicable and vector born diseases. The combination of *Anopheles quadrimaculatus* in Central Park in New York City and more than a thousand cases of falciparum malaria in Manhattan during the 1962-1967 time period had the potential of making malaria an endemic
disease in New York City. The potential of this situation was similar to the only outbreak of malaria that has occurred in the United States since 1945. The outbreak was situated in Lake Vera, California from August 1952 to August 1953. The source of the infection was a U. S. Marine recently returned from Korea. The vectors were indigenous Anopheles punctipennis and Anopheles freeborni. Thirty-five persons were infected with Plasmodium vivax before the outbreak was controlled. All of this is illustrative of the fact that:

In this age of jet planes and soon of supersonic transport, the only way of preventing the old plagues and some new ones from spreading from continent to continent and from country to country is to help the poorest nations of the world to reach such a level of economic and technical development that it will be possible for them to combat the evil at its source.\(^\text{11}\)

In the world today malaria, filariasis, and schistosomiasis infect approximately 200 million people each. Malaria kills approximately one million people annually in Africa. In some parts of Africa, one-tenth of the population is blind secondary to onchocerciasis. If one is born to live in the African bush, one is liable to harbor four or more parasites simultaneously.\(^\text{12}\) But one must still work or the family will starve.

In Egypt today, more than one-half of the population of 38 million is infected with schistosomiasis. This is compared with the 55 million Americans alive today who will at some time in their lives develop some form of cancer.
Yet, $800 million was expended for cancer research in 1977 in the United States compared with only $40 million expended by all nations for all tropical medicine research during 1977.3 Is the Western world doing enough to bridge the gap between the rich and the poor?

To be rich and to be complacent invites the nemesis of such a condition—which is by indifference and by a narrowing of the heart to lose contact with the urgent desires of the great mass of one's fellow man. This constriction of pity can happen to individual men and women. History has always shown it. Today perhaps we see a new phenomena: rich communities succumbing to the same limitation of human understanding.14

Barbara Ward

The poor who live in the rural areas of the tropical developing countries have, with justification, been called the forgotten people. Many of them are sick, plagued by one or more chronic infections or parasitic diseases often unknown to those who live in more prosperous conditions in temperate climates. By any standard these diseases are of major world importance.15

D. S. Rowe

Something must be done both to alleviate this situation of mass suffering and to insure that the restlessness of the impoverished of the world does not give way to militancy. We are but one world.
Part I Footnotes


PART II. Medical Research in The Gambia
While conducting the experimental research of falciparum malaria and pregnancy for this thesis, certain problems and situations were encountered that can be generalized for much of the Third World. This section discusses some of these circumstances.

A description of medical research in tropical India in the late 19th century:

... swarms of flies and of 'eye-flies'—minute little insects which try to get into one's ears and eyelids—tormented me at their pleasure, while an occasional Stegomyia mosquito revenged herself on me for the death of her friends. The screws of my microscope were rusted with the sweat from my forehead and hands, and its last remaining eye-piece was cracked.¹

Ronald Ross

Men who never have had the experience of trying, in the midst of an epidemic, to remain calm and keep experimental conditions, do not realize in the security of their laboratories what one has to contend with.

Dr. Martin Arrowsmith
in Arrowsmith
by Sinclair Lewis
The Gambia, the smallest country in Africa, is about four-fifths the size of Connecticut,\textsuperscript{2} with a population of 400,000 (1973 estimate).\textsuperscript{3} Approximately 300 miles long and 30 miles wide, it has been described as two footpaths alongside the Gambia River, the primary topographical feature of the country. The river is navigable the entire length of the country, with ocean-going vessels able to travel 175 miles inland. The climate is tropical with the rainy season lasting from June to mid-October and the dry season from November through May. The Gambia is predominantly savanna, surrounded on three sides by the Republic of Senegal. It is a stable country and has been democratic since its independence from Great Britain in 1965. Its British traditions are in juxtaposition to Senegal's French traditions. Regardless of historical and political differences, their African tribal compositions are similar: Mandingo, Fula, Wollof, Jola and Serahuli. The Gambia is primarily an agricultural country, with groundnuts (peanuts) the chief crop and major export item. Fish comprise a part of the daily diet and some cattle are raised for local consumption. Great Britain is The Gambia's major trading partner and chief source of economic aid. Per capita income in 1968 was $46.\textsuperscript{4} Educational opportunities are minimal. Children must pay tuition to enter secondary schools, which are only available in urban areas. The Gambia has neither a university nor a medical school.
The Gambia has a national health care plan, of which the organization of delivery is hierarchical. There are two hospitals in The Gambia, one in the capital, Banjul, and the other 207 miles upcountry in Bansang. The total number of hospital beds is 350. The next level of care is the health center, of which there are 11 in the country, with an average size of 15 beds. Eleven dispensaries comprise the third level and act as organizational centers for the many subdispensaries and clinics. Physicians who work in the health plan are either Europeans (generally British) or Gambians, who have trained abroad in the United Kingdom or, more frequently, in the Soviet Union. Physicians are stationed permanently only in hospitals, but travel regularly to scheduled clinics at health care centers or dispensaries. Nurses are also Europeans or Gambians trained abroad or in one of the small Gambian schools of nursing located at hospitals or health centers. Gambian-trained nurses and dresser-dispensers staff the health centers, dispensaries, subdispensaries, and clinics.

Health educational facilities and medical supplies are limited. It is recognized by the Gambian government that the two primary limiting factors in raising the level of health and health care of the country are a lack of financial resources and a dearth of qualified health professionals. Symptomatic of these problems is a 45% mortality rate amongst
rural children (12% amongst children living in Banjul) before age five.6

The confrontation between Western medicine and tribal medicine in The Gambia, much of which is described in a socio-medical study by Barbara Thompson,7 creates a difficult situation. When considering the attitudes that encompass tribal medicine, it is necessary to remember that Gambian ideas and practices reflect both an Islamic and a tribal identity. For instance, the villagers' concept of illness is that everything is ultimately the "will of Allah." But superimposed on this Islamic concept is the notion that "bad satans" are responsible for the more serious illnesses and many protracted and recurrent illnesses. European medicine in such cases is considered useless, since the specific influence which caused the satan to invade the patient must be found in order to effect a cure. As an example, a Mandingan teenage girl suffering from dysmenorrhea had lived in a Jola village during childhood. She was said to have been affected while under Jola influence and could be cured only by Jola therapy.

Delirium is a bad omen indicative of a devil being inside the sufferer. Since survivors of such illnesses are said to be mentally abnormal and unable to fulfill their proper function in society, all action to help the patient is often abandoned. Moreover, as a result of a fear of tampering with the "will of Allah," people are often alarmed when attempts are made to save a person from imminent and
obvious death. A physician who tried to revive a baby with respiration assistance was discouraged from continuing by the parents. Despite his efforts and to the relief of the parents, the child died. The death was believed to be a consequence of the "will of Allah." Because of this attitude, it is not uncommon for a patient to be withdrawn from the care of Medical Research Council Laboratories (MRC), or for help not to be sought at a time when therapy is most vital.

There are numerous other tribal concepts on the origins of disease. Large trees are not allowed to grow near village huts, because they are believed to contain bad "djinns" (spirits) which are capable of causing disease. "Night arrows," shot by supernatural beings in darkness, are thought to fly through the air towards light, causing boils and carbuncles if they should strike the body. Therefore, people are considered foolish who sit at night in a lighted hut with open doors and windows. Clinical malaria is sometimes attributed to a "hot wind"; tsetse flies are believed to cause paralysis; spider urine is thought to cause pneumonia. If a woman sits on an anthill, the villagers believe she will be sterile or her pregnancies will result in difficult labor, abortions, or stillbirths. If a man tells a lie while on an oath to the Koran to tell the truth, the belief is that his sons will develop serious mental illnesses.
Witch doctors and soothsayers are the local general practitioners and specialists in the treatment of illnesses in The Gambia. Although the two groups function interchangeably, witch doctors exorcise spirits and destroy "bad satans," while soothsayers are herbalists and fortune tellers. Often these professions are passed to sons by fathers. The success of certain soothsayers and witch doctors in areas of specialization has built a cadre of "specialists" around the village of Keneba. This cadre includes several surgeons, an orthopedic surgeon, an eye specialist, a gynecologist, and a psychiatrist. Witch doctors and soothsayers usually prescribe "nasos" and "jujus." A "naso" is any part of the Koran written with a mixture of soot and water on a board. The scripture is washed off with water and is used as an oral medication or rinse. A "juju" is a piece of the Koran wrapped with other items and enclosed in a small leather case. The "juju" is worn around the arm, waist, neck or leg. Therapy is usually accomplished with the liberal use of the spittle of the soothsayer or witch doctor and the recitation of the appropriate blessings or prayers. Additionally, therapy can be obtained to affect others. For instance, if a husband is acting aggressively toward his wife, she can obtain a medication to place in his waterpot in order to calm him.

European medicine is regarded by rural Gambians as coming from kind "djinns" with special powers and knowledge. The Gambians believe that European medical personnel perform
strange acts often resulting in miraculous cures. "Pain-goes" (injections) are considered the most advantageous form of treatment offered by European medicine, while pills and elixirs are second and third best. Unless treatment with pills and elixirs is carefully supervised, the medications are often given to other people, sold, or forgotten by the rural Gambians. In general, the villagers prefer local treatment to European medicine, but occasionally a soothsayer or witch doctor refers patients to the European "djinns" and basks in the glory of any improvement in the patient's condition. The villagers' faith in their own methods of medical treatment and their allegiance to local practitioners is preeminent.

Despite this, education is making advances. An example is the occasion in a maternal health care clinic in the village of Brikama, when a woman, with symptoms of fever, nausea, and headache, requested that her blood be examined for malarial parasites.

There are advantages that the Gambian tribal and Islamic outlook bring to modern medical care. The concept that there is a will above one's own makes it easier for the patient and family to discontinue care in terminal diseases. A male patient with the diagnosis of an advanced hepatoma and consequent liver failure, left the MRC Inpatient Ward voluntarily after a frank discussion with the resident staff.
Heroically futile medical efforts are seldom seen in a situation such as The Gambia.

The cooperation of the government of the country in which medical research is being conducted presupposes that of the local population. This has been a concern for many years. In 1897, Ross wrote to Manson,

Owing to the paucity of cases, I have asked Surgeon General Harvey for permission to travel to more malarious places. He says sanction of the government of India must be obtained! Just fancy! -- that will take some weeks.8

Permission from Third World governments to begin new research in their countries is seldom given unless the work is associated with indigenous institutions. Utilization of national universities, medical schools, and research institutions and the involvement of local scientists, physicians, nurses, and technicians enhance the immediate gains to the developing country economically and educationally.

The predilection of many rural populations towards their own local medicine (as well as their lack of understanding of modern medicine) emphasizes the problem of finding cooperative villages or districts that will allow medical research involving members of their own population. This ever-present problem is not new. In the 1880's, Ross found it necessary to bribe patients in India in order to obtain consent for a fingerprick.9 His frustration in the matter was evident in a letter to Manson,
The bazaar people won't come to me though I offer what is enormous payment to them. I offer 2 and 3 rupees for a single fingerprick and much more if I find crescents—they think it is witchcraft.\textsuperscript{10}

And finally, Ross wrote in another letter to Manson,

Alas for your hope that I shall have a plentiful supply of mosquitoes and cases here! None of either (or very few); the cold weather is in, and the people here (Bhils) so savage and superstitious that they won't allow experiments to be made on them. I had a very slight case of tertian two days ago, and some small dappled-winged \textit{Anopheles} insects. The fool flatly refused experiments.\textsuperscript{11}

There are obvious difficulties in giving money or gifts in exchange for permission to perform medical procedures. In addition to being a less than ideal situation (the patient does not develop an understanding of why such procedures are being performed), payment can become very expensive to the researcher, since cost per procedure usually increases over time.

There are various ways to develop an atmosphere of cooperation between the villagers and the researchers. In The Gambia, the two most important villagers are the administrative head of the village, or "alkalo," and the hereditary head, or "sate-tio." Whenever the MRC could gain the acceptance of these two individuals, cooperation of the entire village was the usual result. One way of achieving this acceptance was through the exchange of services. For instance, the MRC often provided the village with general
clinical services, while researching specific diseases. Additionally, the villagers were loaned tractors to plow fields and haul crops to the market. Sometimes aid was given for the maintenance or construction of a water well. Because of the length of most research projects and prescience that there will be more projects in the future, establishment of a long-lasting relationship with certain villages is optimal. The villagers and village leaders must know that the medical research community is in the country to help the indigenous population and that they will not be abandoned after a short-term project.

Equal in importance to this long-term relationship is the composition of the medical research team in the field. Individuals, intimately familiar with local languages, culture, and religion, are needed to answer questions and allay the fears of the villagers. The MRC employs Gambian laboratory technicians to fulfill this role. In one clinic, a Mandingan-speaking technician was able to refute claims that a previous fingerprick had caused generalized paralysis and that the MRC was selling blood collected from these fingerpricks to the United Kingdom. The technician's diplomacy created order out of relative chaos. M. J. Colbourne commented on this aspect:

The practical difficulty of collecting blood films should not be overlooked. It needs considerable tact on the part of the technician. . . Co-operation may depend largely on medico-religious beliefs; in Sarawak the Dayaks like to see a free
flow of blood, as it is said to indicate good health. The Chinese, on the other hand, consider blood to have an essential value of its own and grudge the loss of even a few drops.12

The ease with which work can be accomplished by medical researchers in the Third World is facilitated by a reliable reputation. The MRC's reputation is an instant attraction in village clinics throughout The Gambia. It has been earned through a sincere concern for the Gambian people and through the achievement of a delicate balance between clinical concerns and research concerns. The balance is difficult for at least two major reasons. First, the MRC must budget limited financial resources in each area. The MRC's primary purpose in The Gambia is to conduct medical research; yet, medical research without clinical services is an impossibility in such a setting. Because the vast majority of villagers are ill with at least one treatable parasitic or infectious disease, humanitarian concerns make it difficult not to treat them. Still, practicalities dictate turning away patients not in need of immediate treatment and capable of receiving help elsewhere, as well as those patients with a disease that the MRC is incapable of treating. Patients needing immediate treatment within the capabilities of the MRC are accepted. Finally, patients with diseases currently being researched are treated regardless of severity of illness.
Although it can be ideal to study a disease in its natural setting, researchers must be aware of possible problems. The researcher, as well as medical entities being studied, is profoundly influenced by environmental variables. Realizing this dilemma, Ross wrote again to Manson in 1897,

"I am having all sorts of petty difficulties at first. Cases of malaria can scarcely be obtained though I hunt the hospitals every morning. It is of course the healthy season. ... Dappled-wings are very scarce and have to be picked out from thousands of greys, and then bite very badly."

Seasonal diseases must be investigated during particular times of the year and are subject to changes in incidences and severity as a result of annual variations in the climate. In The Gambia in 1977, the rains began late, ended early, and produced fewer inches of rainfall than usual. As a consequence, because of the dependence on rain for growth and development of the Anopheles mosquito, malaria in The Gambia was less severe than in other years. For the indigenous population this was a blessing. Paradoxically, for the people conducting research of malaria for the purpose of helping the Gambians and the many others infected with malaria, the lower incidence of the disease in any one year is a hindrance. Moreover, just as there can be too little rain for the study of malaria, there can be too much rain which is destructive to Anopheles larvae. Inclement weather poses an additional problem by its effect on the movements of people. On rainy
days the number of patients seen in most rural health clinics in The Gambia is fewer than on sunny, dry days. There are no environmental factors which affect the parasite, the vector, or the patient which do not affect the research of malaria in its natural setting.

As modern medicine becomes more prevalent in developing countries, the problem of finding untreated patients with specific diseases will increase. The beneficial treatment of pregnant Gambian women with antimalarials given by German missionary physicians eliminated that group of women from a malaria and pregnancy study and necessitated travel farther inland for the population survey. Indiscriminate and undocumented use of unprescribed antimalarials within the population near Banjul eliminated this segment of the population from the study, also. Ross encountered the same problem in 1836 in India when he had difficulty finding patients with malaria who were not "soaked with quinine." Third World populations often carry more than one infectious or parasitic disease per patient, complicating the biologic setting of the disease of interest. Widespread and uneven distribution of treatments for these diseases complicates the situation further. These problems suggest the necessity for baseline studies of patient populations unaffected by modern medical treatments to be compared with additional studies of similar patient populations as they are affected by modern medical techniques, diagnosis, and therapy.
Modern medicine, which deals in specifics and exact information as often as possible, is often frustrated by the attitudes and values which are common in rural Third World villages. For example, it is impossible to obtain the exact ages of patients in rural Gambia. This is not surprising when confronted with an elderly male or female; the situation is the same, however, for babies who are less than a month old. Exact age is unimportant to the villagers. Moreover, ensuring that patients return to a clinic for follow-up is difficult at best. If the patient feels better, the likelihood is that he or she will not return. It was estimated by one permanent MRC staff person that the return rate for follow-up was 30%. This raises another problem. If return is absolutely necessary, it is difficult to find the patient, since towns lack street names and numbers. Additionally, the name of the patient given at the MRC clinic may be a different name than the one known to the villagers. In order to find the patient, it is necessary to get his or her name, compound (village subsection), village, and parents' names.

There is an inclination on the part of Western-trained medical persons to believe that these daily problems result from a lack of patient motivation. This is not the correct explanation in The Gambia. The above examples simply reflect our cultural differences.

It cannot be assumed that the technological advances of the modern industrial age will be present in a Third World
country. A more realistic assumption is that complete self-sufficiency in all aspects of the medical research effort will be necessary. This includes transportation, accommodations, laboratory facilities, and (often) electricity and water. In order to travel upcountry in The Gambia with a medical laboratory capability, the MRC at one time had used a self-sufficient houseboat. As roads became more accessible, electricity and water more common, and the upkeep on the houseboat more expensive, the MRC changed from houseboat to land transportation and now utilizes mobile trailers for living accommodations and laboratory space. Communication between medical researchers stationed inland and those near population centers cannot be assumed either. Indeed, the most rapid communication between MRC at Bansang and the MRC at Fajara, near Banjul, was overland message traffic. Additionally, repair facilities often have to be generated by the laboratory. This includes repair of laboratory equipment, such as -70°C freezers and high speed centrifuges, as well as vehicles and living accommodations. Although the laboratory facilities at MRC in Fajara were excellent, in the laboratories upcountry water and electricity failed occasionally; insects were sometimes troublesome at night; improvised solutions to practical problems were often necessary.
There are many problems, but few are insurmountable. Indeed, developing solutions to unique medical situations and cultural conflicts can lead to rewarding and exciting experiences and (it is hoped) beneficial results for a majority of mankind.
Part II Footnotes


3. Ibid., p. 1040.


6. Ibid.


9. Ibid., p. 139.

10. Ibid., p. 164.

11. Ibid., p. 250.


14. Ibid., p. 139.
PART III. Malaria
Malarial fever is important not only because of the misery which it inflicts upon mankind, but because of the serious opposition which it has always given to the march of civilization in the tropics. Unlike many diseases, it is essentially endemic, a local malady, and one which unfortunately haunts more especially the fertile, well-watered, and luxuriant tracts—precisely those which are of the greatest value to man... No wild deserts, no savage races, no geographical difficulties have proved so inimical to civilization as this disease. We may also say that it has withheld an entire continent from humanity—the immense and fertile tracts of Africa; what we call the Dark Continent should be called the Malarious Continent.

Sir Ronald Ross
The preceding quotation, written 75 years ago, is still true today. By causing extensive morbidity and mortality, malaria is in serious opposition to the march of civilization in many countries of the world. Approximately one million children die of malaria every year in Africa south of the Sahara. Additionally, an average of 15 to 30 per cent of rural health workers' time in this part of Africa is occupied with the diagnosis of acute cases of malaria. This situation is typical of other areas of the world, also. In India in 1952, 100 million cases of malaria were reported. As a result of a World Health Organization eradication program, this case load decreased to the 60,000 cases that were reported in 1962. Due to several factors, however, the reported case load has increased from the 1962 low to 5.3 million cases reported in 1975. In 1975-1976 global incidence of malaria was 120 million cases per year. Today, there are 500 million people living in areas where malaria is endemic and where antimalarial measures are limited or nonexistent.

Regardless of the amount of human suffering involved, the severity of the debilitating effect that this incidence has on the economy of endemic malarious areas cannot be overestimated. Ceylon (Sri Lanka) is a prime example. When the death rate in Ceylon dropped from 20 per 1,000 in 1946 to 14 per 1,000 in 1947 following the commencement of the World Health Organization's malaria eradication program in that
country, there were predictions of famine and impoverishment as a result of overpopulation. These hypothetical consequences were refuted by the observed effects of malaria control on the economy. Prior to 1947 malaria in Ceylon was regarded as a "relatively unimportant" cause of death, but as a foremost cause of illness. The number of cases of malaria in a year was equivalent to half the population of Ceylon. With the introduction of control measures, the incidence of malaria decreased dramatically. This not only created a healthier and more productive indigenous population, but it opened up a large portion of the island for human habitation. Before malaria control measures were instituted, approximately three-fifths of the population was crowded into the one-fifth of the island's area that was only little or rarely affected by malaria. Malaria control allowed a more uniform population distribution without the hardship of malaria morbidity. The result of this redistribution was an increase in cultivated acreage from 927,078 acres in 1946 to 1,411,700 acres in 1960, and an increase in rice production from 246,000 tons in 1946 to 630,000 tons in 1961. The control of malaria in Ceylon was closely associated with an increase in the quality of life as well as the quantity of human resources.

Similar conclusions were reached by the Pan American Health Organization in an analysis of the affect of malaria on economic development in a malarious region in Paraguay.
The study compared the lives of the same individuals and families under two conditions: malarious and nonmalarious. The collected data indicated that malaria morbidity affected a family's production of crops by: lowering crop production for export; lowering crop production for internal consumption; increasing the percentage of manioc and decreasing the percentage of garden produce in the diet; reducing the amount of land cleared for planting; causing an inability to plant crops during the appropriate season; causing a loss of new crops. The influence of malaria morbidity operated almost entirely through its incapacitating effect on the labor force by decreasing the time spent on the job and by lowering the laborers' efficiency when working.

Billions of individuals have been afflicted with malaria. Because of paleontological evidence of fossilized mosquitoes and the abundance of *Plasmodium* infections in all the primates of the modern world, "one takes no great liberty with historical truth in assuming that prehistoric man, at least in some of the warmer regions, must have experienced malarial chills and fever." Man's attempt to master malaria must date from that time, also.

There are references that show that malaria was a prevalent disease in Mesopotamia, India, and South China during pre-Grecian times. Ancient Jewish notions in the Talmud support the existence of malaria, while ancient India referred to malaria as the "King of Diseases." One of the
four Vedas of the Hindus, the Arthavana, mentions this disease as occurring primarily in the autumn, with symptoms described as alternating hot and cold fevers, occurring daily or every third day. There is even a description of a "splenic belly" associated with the "King of Diseases": an "enlarged spleen which distends the left side, is as hard as stone, and is arched like the back of a turtle."

Hippocrates of Cos (460-377 BC) can be regarded as the world's first malariologist. He was the first to clearly define the intermittent fevers of malaria (quotidian, tertian, and quartan fevers) as distinct from continuous fevers. His description of malaria included headache and chills, exacerbations and relapses of the disease, and the relation of the distribution of malarial fever to seasonal and topographical changes. Recognizing the association between malaria and marshes, Hippocrates wrote in *Airs Waters Places*,

> Should there be rivers in the land, which drain off from the ground the stagnant water and the rain water, these will be healthy and bright. But if there be no rivers, and the water that the people drink be marshy, stagnant, and fenny, the physique of the people must show protruding bellies and enlarged spleens.

Hippocrates thought that drinking from stagnant bodies of water was included in the etiology of the disease now known as malaria.

Roman medical literature includes several descriptions of malaria. It is clear from these accounts that the Romans thought that marshes and swamps were the source of
the disease. Marcus Terentius Varro (116-27BC) wrote in Rerum Rusticarum (I.12.ii.),

Note also if there be any swampy ground... because certain minute animals, invisible to the eye, breed there and borne by the air, reach the inside of the body by way of the mouth and nose, and cause diseases which are difficult to be rid of.17

"Roman airs" were well-known in many parts of the world by the 17th century. There existed a well-established belief in the etiological relationship between swamps and intermittent fevers. Malaria was thought to be caused by noxious emanations which originated in swamps and invaded man from the outside. Some thought that the miasma entered man in contaminated water; others held the opinion that the offending substance was in the air that accompanied stagnant water. By 1830 the theories of the etiology of malaria could be listed in four categories: 1) the chemical compounds in marshy areas; 2) moisture; 3) decomposition products of animal and vegetable matter; 4) living, invisible organisms. The fourth theory followed new advances in medicine, bacteriology, and the development of the microscope.

In 1878 Charles Louis Alphonse Laveran, a French Army surgeon stationed in North Africa, began a study of post-mortem tissue and blood smears taken from malarious patients. He found the pigmented bodies associated with malaria that had been described by others. Laveran suspected
the parasitic nature of malaria

when on November 6, 1880, while examining
one of the spherical pigmented elements
in a preparation of fresh blood, he
noticed with joy at the periphery motile
filaments of the animated nature of which
there was no room for doubt.

By 1887, three of the species of *Plasmodium* infective to
man, *falciparum*, *vivax*, and *malariae*, had been described.
In 1922, the fourth, *ovale*, was identified.

Laveran's malaria parasite theory was widely accepted
by 1895. The question of the mode of infection, however, had
not been answered. Insects have been thought to be vectors
of disease by many cultures in man's history. Occasionally
the mosquito was linked with malaria, but most often the con¬
jecture was that insects in general (and mosquitoes as a
representative insect) were capable of propagating and causing
disease in man. The insect theory existed as such until 1877-
1879, when Patrick Manson, the father of medical entomology,
traced the development of microfilariae (*Wuchereria bancrofti*)
in a mosquito. Manson proved for the first time in medical
history that an insect was the intermediate host to a para¬
site of man. Similarly, he theorized that the mosquito was
the agent of infection for man.

Joseph Bancroft, in 1899 in Australia, and G. C. Low,
in 1900 in England, were responsible for showing that certain
species of mosquitoes infected man with Bancroft's filariasis
via the act of blood-sucking. Ronald Ross and G. B. Grassi
proved the same theory with certain species of the *Anopheles* genus and malaria.

Ronald Ross began his investigation of malaria and mosquitoes as a surgeon in the Indian Medical Service in May 1895. The investigation led to the discovery of the ontogeny of the malaria parasite in an *Anopheles* mosquito as well as the reinfection of a bird by a malaria-infected *Anopheles* mosquito. With this background Ross was able to make the well-founded conjecture that

malaria is conveyed from a diseased person or bird to a healthy one by the proper species of mosquito, and is inoculated by its bite.\(^1\)

Relying on Ross's work, G. B. Grassi proved Ross's theory of human malaria in November 1898. This was confirmed by Ross himself in Sierra Leone in 1899.

Two other major discoveries contributed to our knowledge of the malaria parasite. In 1891 D. L. Romanowsky developed a stain that enabled accurate study of the erythrocytic stage of the parasite in blood smears. Completion of our present knowledge of the cycle of the malaria parasite was accomplished in 1948 by P. C. C. Garnham, H. E. Shortt, R. S. Bray, and others, when they discovered the pre-erythrocytic stage in man. Man's knowledge of the vector, parasite, pathology, and treatment of malaria has increased to such a degree that worldwide control and eradication of this disease is becoming a possibility.
More than 100 species of malaria parasites are capable of infecting mammals, birds and reptiles. The vector in each case is an Anopheles female.

The life cycle of the human malaria parasite consists of two phases: the exogenous sexual phase (or invertebrate phase, termed sporogony, occurring in the mosquito), and the endogenous asexual phase (or vertebrate phase, termed schizogony, occurring in man). Sporogony begins with the ingestion of blood containing the mature sexual form of the parasite (microgametocytes and macrogametocytes). Within minutes after reaching the mosquito's stomach, the microgametocyte begins the process of exflagellation of which the outcome is the production of approximately eight actively motile flagellar microgametes. Meanwhile, the macrogametocyte has undergone less obvious changes in which it has matured by rounding up in preparation for fertilization by the microgametocyte. Fertilization occurs amid the gut contents of the insect with the fusion of the male and female nuclear chromatin and the elongation of the zygote into a motile ookinete or traveling vermicule. The ookinete forces its way through the brush border of an epithelial cell in the mid-gut, traverses the cell, and lodges on the other side. At this point the ookinete secretes a thin cyst wall, undergoes progressive vacuolization, and develops into a growing oocyst. Between 48 and 72 hours after ingestion of the blood meal, the diploid nucleus of the oocyst undergoes
meiotic division followed by mitotic divisions in which the haploid number of chromosomes is produced and remains throughout the parasite's cycle until the reformation of the zygote. The nuclei of the oocyst formed by these mitotic divisions arrange themselves so that each is associated with a filam¬
tous, cytoplasmic strand. These structures develop into sporozoites which differentiate and gather in an entangled mass in the interior of the oocyst. The cyst bursts and liberates more than a thousand Plasmodium sporozoites into the hemocèle. These sporozoites migrate to the salivary gland of the mosquito where they remain in a dormant state until injection into the human host. The duration of the exogenous phase of development (the extrinsic incubation period) of the Plasmodium parasites infective to man varies with the species and the ambient temperature and humidity. Under ideal climatic conditions, the extrinsic incubation period is from seven to 14 days for P. falciparum and P. vivax, 14 to 21 days for P. ovale, and 21 days or more for P. malariae.

Injection of the sporozoites by the mosquito into a human begins the endogenous asexual phase termed schizogony. The sporozoites disappear from the peripheral blood in approximately 30 minutes and initiate the pre-erythrocytic (or exo-erythrocytic) cycle. The parasite next appears in the parenchymal cells of the liver. Here, each individual parasite develops into a mature schizont which bursts after six to 15
days (depending on the species of parasite), releasing from 7500 to 40,000 merozoites (again, depending on the species) into the peripheral blood. This ends pre-erythrocytic schizogony in *falciparum* malaria; in relapsing malarias, such as *vivax*, the exo-erythrocytic cycle persists in the liver parenchymal cells.

Merozoite release from the liver begins erythrocytic schizogony in which the first form is the early trophozoite, or "signet ring." Within a few hours the ring develops into an ameboid, intermediate stage, termed the trophozoite. The trophozoite continues to grow, ameboid activity slows, and the nucleus divides by mitosis. Nuclear division proceeds until a mature schizont is produced which consists of a solid body with eight to 24 nuclei, the number varying amongst the four species of *Plasmodium* that infect humans. Cytoplasmic division follows. Each portion of cytoplasm includes one of the newly formed nuclei, which eventually become merozoites. The red cell envelope collapses and the merozoites escape into the bloodstream. Those that escape destruction by the immune system quickly begin a new cycle by invading additional erythrocytes.

At this point, one of two morphologies may develop. The invading merozoite can go on to develop in the asexual cycle previously described. Or, for reasons unknown, the merozoite may commence the sexual cycle and develop into a macrogametocyte or microgametocyte. It is unknown if there
is a special type of schizont giving rise to merozoites (each of which develops into a gametocyte), or if a particular stimulus is involved that triggers the sexual development of a particular merozoite. A single schizont has the capacity to produce both sexual and asexual progeny, since inoculation of a single asexual parasite of an avian or mammalian species gives rise to infections that have both asexual and sexual forms. It is interesting that in the *vivax*, *ovale*, and *malariae* species of *Plasmodium*, both the sexual and asexual stages are visible in the peripheral blood. For reasons not known, only early trophozoites and gametocytes are usually demonstrable in falciparum malaria. The intermediate stages of development occur in the capillaries of the viscera, are seen only infrequently in the peripheral blood, and are usually associated with heavy falciparum infections. Depending on the species of *Plasmodium* infective to humans, the time required to complete one cycle of schizogony varies between 42 and 72 hours. After inoculation of the sporozoites by the mosquito, the prepatent period varies according to the species, the usual lengths being: *P. vivax*, 12 to 14 days; *P. falciparum*, 10 to 13 days; *P. ovale*, 12 to 20 days; *P. malariae*, 27 to 37 days. Gametocytes infective to mosquitoes appear in the peripheral blood within three to ten days after the onset of the primary parasitemia.

Early clinical manifestations of malaria in the human host include such nonspecific symptoms as chills, fever,
headache, myalgia, abdominal pain, nausea, and anorexia. During the early period of the illness, fever may be continuous or quotidian. After development of parasite synchrony, the fever will assume the well-known tertian characteristic of *P. falciparum*, *P. vivax*, and *P. ovale*, or the quartan characteristic of *P. malariae*. The typical clinical pattern of fever in malaria is a chill with a rise in temperature to 40° to 41°C, headache, and myalgia. After several hours of an elevated temperature, there is diffuse sweating and a fall in temperature. Sleep often follows, after which the patient awakes feeling exhausted, but well. *P. vivax*, *P. ovale*, and *P. malariae* are capable of producing severe illness, but cause dangerous complications less often than malignant tertian malaria, *P. falciparum*. Common complications of falciparum malaria are coma, acute renal failure, severe hemolytic anemia, and acute pulmonary edema. Physical examination reveals tachycardia, splenomegaly, and often hepatomegaly. Herpes simplex lesions are frequent. Laboratory results include normocytic normochronic anemia after several days' illness, normal or low blood leukocyte count, thrombocytopenia (especially in falciparum malaria), elevated erythrocyte sedimentation rate, and elevated indirect bilirubin. Definitive diagnosis is by demonstration of the parasite on a blood film.

Chronic malaria results in anemia, cachexia, and debility. This syndrome is most likely the result of repeated malaria infection of a patient immune to *Plasmodium*, occurring
predominantly in hypoendemic areas. Although the patient may be asymptomatic, he may have intermittently detectable parasitemia, anemia, elevated antimalarial antibody titers, hypergammaglobulinemia, and splenomegaly. Occasionally, the patient will suffer from the symptoms of an acute attack. Bacterial infection (of which cholera, bacillary dysentery, and pyogenic pneumonia are common) is often the cause of death in such a patient. Foci of tuberculosis often extend in patients with chronic malaria.

Immunity to malaria infections is of two kinds: natural and acquired. A natural form of immunity, conferring the advantage to the host of a less severe form of the disease, results from certain hemoglobinopathies and inherited enzyme defects such as sickle-cell trait, hemoglobin C, D, E, K, O, b-thalassemia, and glucose-6-phosphate dehydrogenase deficiency. Human erythrocytes with an absence of Duffy group antigens are resistant to \textit{Plasmodium knowlesi} infection, a simian parasite that can infect Duffy positive human erythrocytes.\textsuperscript{21} The Duffy negative determinant is present in a high proportion of Africans, but it is rare in other racial groups.\textsuperscript{22} Although susceptible to \textit{P. falciparum}, \textit{P. ovale}, and \textit{P. malariae} infections, Africans and American blacks are resistant to infection by \textit{P. vivax}.\textsuperscript{23,24} This suggests that immunity to \textit{P. vivax} is conferred by the absence of an erythrocytic receptor.

Acquired immunity is strictly strain-specific, conferring to the individual partial or total resistance to
reinfection by the same strain of the particular species of parasite. Strain, in this sense, is defined as parasites of the same species or variety that show differences in immunological or other characteristics. Parasites, derived from a single source and maintained without intermixture with parasites from other sources, constitute a strain of a species. Tolerance to the infection is the first characteristic of immunity to malaria, that is, cessation of clinical phenomena despite persistence of parasitemia. This is an example of premunition, or clinical immunity associated with a continued low-grade infection.

Acquired immunity to malaria involves both humoral and cell-mediated mechanisms. It is well established that humoral immunity is a major feature in the acquired resistance to malaria and the control of an acute infection. Protective antibody acts against the schizonts and extracellular merozoites, perhaps by blocking parasite attachment to the red cell membrane. Having no effect on the growth of intracellular parasites, the IgG fraction contains the protective antibody and inhibits the cycle of development of the parasite after schizogony. The effects are strain specific. In clinically immune subjects studied in hypoendemic areas, the rate of synthesis of IgG and IgM are increased. However, only 5% of the IgG fraction is specific for malaria parasite antigens. The malaria parasite is thought to have a mitogenic effect on the humoral immune system. With regard to the cell-mediated immunity to the
malaria parasite, there is as yet little or no direct evidence to indicate that this mechanism is an important effector of immunity. Nevertheless, because of complexities in the antigenic response to the malaria parasite, cell-mediated involvement is a well-founded speculation.

Modern medicine's arsenal of therapeutics for malaria infections includes three classes of drugs: dihydrofolate reductase inhibitors, sulfonamides and sulfones, and quinolines. The dihydrofolate reductase inhibitors include proguanil, chlorproguanil, pyrimethamine, and trimethoprim. The class has three actions: erythrocytic schizontocidal activity, tissue schizontocidal activity, and sporontocidal activity. Complete resistance by the parasite can develop after a single exposure to the drug.

The sulfonamides and sulfones are important for the treatment of falciparum malaria, but ineffective against other species.

The quinolines include blood schizontocides and tissue schizontocides. The blood schizontocides are quinine, the 9-aminoacridines (mepacrine), and the 4-aminoquinolines (chloroquine). Resistance of many strains of Plasmodium falciparum to each of these drugs is well-known. The 8-aminoquinolines (primaquine) comprise the tissue schizontocides of the quinoline group. Primaquine confers its lethal action on all sexual and erythrocytic forms of Plasmodium species infective to humans.
The resistance of certain strains of falciparum malaria to many antimalarial compounds is alarming. Thirty years of use of 4-aminoquinolines and their derivatives suggest that malaria parasites in quinine sensitive areas (Africa south of the Sahara Desert and most of the Indian subcontinent) are incapable of developing significant drug resistance. But distant spread of resistant *P. falciparum* strains is not an impossibility, since both *Anopheles stephensi* and *Anopheles gambiae* are efficient laboratory vectors.

In 1955 the Eighth World Health Assembly in Mexico City instructed the World Health Organization to coordinate a campaign aimed at worldwide eradication of malaria. This began the 1956-1968 World Malaria Eradication Program, which has been described as the "most massive public health operation ever undertaken." The campaign was based mainly on DDT insecticide coverage of dwellings in malarious areas and synchronization of neighboring national campaigns to protect against reintroduction. The extension of the program by 1968 to 80% of the population within malarious areas caused the world's malaria mortality to fall from 2.5 million per year in 1955 to less than one million in 1968.

However, the malaria eradication program encountered certain obstacles. The resistance of the malaria parasite to available drugs was a major problem. Additionally, *Anopheles* mosquitoes became increasingly resistant to DDT. This necessitated using propoxur and an organophosphorous insecticide, malathion, at five times the cost of DDT. The insects began
to show signs of developing resistance to these newer chemicals. Moreover, the inflationary rise in cost of materials and labor, combined with other worldwide economic developments, caused a contraction of financial support from multilateral and bilateral sources. As a consequence of these problems, the Twenty-Second World Health Assembly emphasized control more than eradication. In those countries where eradication was presumed to be a possibility, efforts were continued to eradicate malaria; however, in those areas where difficulties were great, the program was one of control.

Although progress has been made toward mastering malaria, much more is necessary. In spite of the morbidity, human suffering, and numbers of lives lost each year from malaria, it was said about Africa in 1954,

Into Africa—perhaps the most malarious ridden of all continents—modern methods of control by residual insecticides were introduced at a late date on a small scale. It will be only fair to admit that during the past few years there has been no radical improvement of the situation in tropical Africa.

Twenty years later, countrywide malaria eradication had not been attempted on the mainland of Africa.

There are two relatively new areas of research in maliariology (vaccination against malaria and biological control of mosquitoes) that offer some promise for the future. The enormous numbers of humans suffering from malaria demand that these areas be researched with new vigor.
Part III Footnotes

2. Ibid., p. 53.
10. Ibid., p. 386.
11. Ibid., p. 391.
15. Ibid., p. 5.
17. Ibid., p. 12.
18. Ibid., p. 32.
28. Ibid., p. 1649.
31. Ibid., p. 19.
35. Ibid., p. 10.
36. Time Magazine, September 12, 1977, p. 64.
38. Ibid., p. 15.
PART IV. A Review of Malaria in Pregnancy
From several epidemiological studies of malaria and pregnancy, it has been concluded that pregnancy affects the clinical course of malaria in both stable and unstable malarious areas. Additionally, malaria affects the health of women during pregnancy and the fetus during gestation and following parturition. It is probable that the *Plasmodium* species incidence of malaria in pregnancy depends on the relative local frequency of the different species of the parasite.\(^1\) However, falciparum malaria (as the most prevalent species in tropical regions)\(^2\) has been studied most intensely. The relationship of malaria and pregnancy raises interesting immunological questions.

Malaria's prevalence of infection and density of parasitemia in a population of pregnant women are higher than in a non-pregnant population. This has been demonstrated repeatedly in stable, or holoendemic (as defined by G. Macdonald)\(^3\) malarious areas. In Lagos, Nigeria, L. J. Bruce-Chwatt found that the mean incidence of malaria parasitemia (due primarily to *P. falciparum*) was 33% amongst a group of 551 parturient Africans.\(^4\) This was higher by 12% than the mean parasite rate of the adult indigenous population. H. M. Gilles *et al.* determined in a prospective study of 33 Nigerian women in Ibadan, that the incidence of malaria parasitemia was 34% before and 79% during pregnancy. Comparing the number of positive monthly blood films taken from
these women, 22 of 385 (5.7%) were positive before pregnancy while 44 of 198 (22.2%) were positive during pregnancy. Gilles concluded that parasitemia occurred four to 12 times more frequently during than before pregnancy. The log median parasite density during gestation was about ten times higher than before conception (1,775 parasites per cu. mm. as compared with 140 parasites per cu. mm.). The predominant parasite was \textit{P. falciparum} (\textit{P. malariae} occurred once singly). In a study comparing 153 pregnant with 123 nonpregnant Tanzanian women, H. F. Kortmann found that the parasite rate more than doubled, the parasite density and spleen rate were elevated, and the number of attacks of clinical malaria was greatly increased in the pregnant group. Other studies have resulted in similar determinations.

During an epidemic of falciparum malaria in Ceylon (an unstable malarious area with a nonimmune population) in 1935, G. A. Wickramsuriya concluded that pregnancy aggravated the clinical course of malaria. The mortality rate amongst pregnant women was twice (13%) that observed in women of childbearing age who were not pregnant. Cerebral malaria in Colombo was more common amongst pregnant women than other adults of the city. A. M. Smith determined that pregnancy can lead to a relapse of vivax malaria. J. B. Lawson in \textit{Obstetrics and Gynecology in the Tropics} stated that a patient immune to malaria loses the ability to limit parasitemia during pregnancy. As a consequence, parasite rates
and densities, as well as febrile attacks caused by malaria, are more common during pregnancy.\textsuperscript{9}

In a vicious circle, as pregnancy increases malaria's prevalence and parasite density, malaria has profound effects on pregnancy. The consequences of a malaria infection on gestation include maternal pathology, adverse results to the outcome of pregnancy, and poor prognostic indicators for both the fetus \textit{in utero} and the newly born infant. Additionally, malaria during pregnancy may have more long lasting consequences throughout the subsequent lifetime of the product of such a gestation.

The most important influences of this disease on maternal health are caused by the increased frequency and severity of the malaria attacks during pregnancy and the anemia secondary to infection.\textsuperscript{10} With regard to the first issue, it is known that high fever during pregnancy is a cause of premature uterine contraction and abortion. Malaria is no exception. Because of the increased incidence and severity of symptomatic malaria infection during gestation, there is a higher incidence of abortions and premature labor.\textsuperscript{11} However, while pyrexia plays a relatively minor role in causing abortion or premature labor in an immune population, it is a major cause of such incidents in a non-immune population.\textsuperscript{12,13} Cerebral malaria, as a more common complication to falciparum infections in a nonimmune pregnant versus a nonimmune nonpregnant group, can cause pyrexia, convulsions, coma and death.
A number of studies of immune populations have correlated an increased incidence of anemia during pregnancy with malaria infections. Gilles et al. determined in Lagos that, whereas one out of 19 pregnant women protected with antimalarial prophylaxis developed anemia (PCV < 28%), 24 out of 38 unprotected pregnant women became anemic. The findings regarding anemia (hemoglobin < 7.0 gm/100 ml) in H. F. Kortmann's study were similar. Additionally, Kortmann correlated more severe and frequent occurrences of anemia in primiparous as opposed to multiparous women. Gilles et al. determined that the development of anemia was invariably between the 16th and 24th weeks of pregnancy and was in all instances hemolytic with a superimposed megaloblastic component. Severe hemolysis causes excessive bone-marrow activity that exhausts the available supply of folic acid. In a study in Nigeria, Fleming et al. determined that the two most important causes of maternal anemia during gravidity, hemolysis secondary to malaria infection and folate deficiency, were almost entirely prevented by antimalarial chemoprophylaxis. There is agreement that the severity of anemia that develops in a malaria infection during pregnancy is not correlated with the degree of parasite density. Moreover, the chronology of events is not consistent. Anemia may develop before the demonstration of parasitemia; parasitemia may precede the development of anemia; anemia may occur weeks after clearance of parasitemia. The explanation of this is
speculation that there is an immune causation to the anemia common to malaria infections. Anemia secondary to malaria during pregnancy is also a common cause of abortion and premature labor.

It is well known that the maternal side of the placenta has a peculiar ability to accumulate the Plasmodium falciparum organism. In 1915 in Panama, H. C. Clark concluded from a study of placental blood films in aestivo-autumnal malaria that the placenta had a capability of localizing the falciparum parasite in its intervillous space. In a study in Sierra Leone in 1925 by Blacklock and Gordon, 55 of 150 (36%) placentas examined were infected with P. falciparum. The authors determined that the parasites were delimited by the syncytiotrophoblastic layer and remained within the maternal intervillous space of the placentas. A heavy infestation of all morphologies of the asexual parasite was seen, but the sexual forms were lacking. Since only young trophozoites are seen in the peripheral blood during the course of the usual P. falciparum infection and gametocytes are associated with heavy falciparum infections, it is of interest that the parasite presented with such a distribution of developmental stages. The authors surmised that the lack of gametocytes indicated an unfavorable condition or a degree of host immunity that otherwise was ineffective in preventing parasitic growth. In 1952, L. J. Bruce-Chwatt published a study of 323 Nigerian
placentas (77, or 23.8%, of which were infected with P. falciparum) in which he described the intensity of the host's cellular response to a placental falciparum infection as including a large number of active macrophages, lymphocytes and polymorphonuclear cells. In his 1958 study of 392 Nigerian placentas, D. S. H. Cannon concluded that prevalence of falciparum placental infection is inversely related to parity. He indicated that this relationship could be due to an increase in age of the mother of which the result is an increase in immunity to infection.

Speculation of the placenta's capability to accumulate P. falciparum parasites has centered on two issues. First, the physical characteristics of the intervillous space have been noted. A large endothelial surface, sluggish movement of blood in a cavernous space, a large number of red blood cells, a temperature equal to body core temperature, and a low oxygen tension have all been noted as possibly providing an ideal milieu for P. falciparum growth. Second, it is common to explain this phenomenon as an unidentified immunosuppression occurring during pregnancy and affecting the falciparum parasite's local habitat within the placenta.

The proportion of mothers who at the same time showed parasites in both peripheral blood and placenta has differed grossly amongst these studies. Differing percentages include Blacklock and Gordon (Sierra Leone, 1925) 20%, Schwetz and
Peel (Belgian Congo, 1934) 74%,
Garnham (Kenya, 1938) 59%,
Bruce-Chwatt (Nigeria, 1952) 43%,
and Archibald (Nigeria, 1958) 79%.
Speculation to explain these proportional differences was that a more effective state of immunity existed in those with only placental infections as compared with those with both placental and peripheral evidence of infection. This was suggested by Blacklock and Gordon and Archibald.

G. Covell commented on the concept that *Plasmodium* parasitic infection of the placenta is rare amongst nonimmune women in malarious areas. Only ten of the 135 articles citing malaria infections in nonimmune pregnant populations from 1873 to 1950 included examination of the placentas. Presumably this omission led to the thought that placental infection in nonimmunes is rare, since such evidence as is available says it is not uncommon.

It is of particular interest to consider the incidence of congenital malaria relative to the incidence of placental malaria infections. In a review of congenital malaria, G. Covell noted that literature discussing this subject falls into one of two categories. The first contains observations made on indigenous populations of malarious regions possessing a high degree of immunity. The second consists of case reports, the majority of which refer to nonimmune subjects. With regard to the former, as Table 1 summarizes, the incidence of placental malaria and *Plasmodium* parasitemia
<table>
<thead>
<tr>
<th>Author</th>
<th>Locality</th>
<th>No. of Infants</th>
<th>% of Infants Infected</th>
<th>% of Placentas Infected</th>
<th>% of Mothers Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark 1915</td>
<td>Panama</td>
<td>400</td>
<td>0.25</td>
<td>4.75</td>
<td>2.0</td>
</tr>
<tr>
<td>Blacklock &amp; Gordon 1925</td>
<td>Sierra Leone</td>
<td>173</td>
<td>0</td>
<td>38</td>
<td>5.2</td>
</tr>
<tr>
<td>Van Den Branden 1927</td>
<td>Belgian Congo</td>
<td>55</td>
<td>0</td>
<td>1.8</td>
<td>56</td>
</tr>
<tr>
<td>Lombert 1931</td>
<td>Belgian Congo</td>
<td>50</td>
<td>2.0</td>
<td>50</td>
<td>56</td>
</tr>
<tr>
<td>Schwetz &amp; Peel 1934</td>
<td>Belgian Congo</td>
<td>56</td>
<td>3.6</td>
<td>74</td>
<td>68</td>
</tr>
<tr>
<td>Garnham 1938</td>
<td>Kenya</td>
<td>404</td>
<td>0</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>Garnham 1949</td>
<td>Kenya</td>
<td>146</td>
<td>0</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Butler 1930</td>
<td>Gold Coast</td>
<td>328</td>
<td>--</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Walton 1947</td>
<td>Sierra Leone</td>
<td>2,154</td>
<td>0.32</td>
<td>4.8</td>
<td>5.5</td>
</tr>
<tr>
<td>Bruce-Chwatt 1950</td>
<td>Nigeria</td>
<td>543</td>
<td>0.18</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Perves 1943</td>
<td>French Cameroons</td>
<td>661</td>
<td>9.6</td>
<td>--</td>
<td>44</td>
</tr>
<tr>
<td>Deless &amp; Lavergne 1936</td>
<td>Indo-China</td>
<td>887</td>
<td>0.3</td>
<td>--</td>
<td>1.1</td>
</tr>
</tbody>
</table>
is far greater than the incidence of congenital malaria. The observation total of Table 1 is 5,324 of which 0.03% infants were infected. Among the nonimmune population, there is evidence that congenital malaria is more common than in the immune population.34

The explanation for the lack of occasion of congenital malaria has usually concerned the placental barrier. Most researchers have invoked the theory that the placenta is impermeable to maternofetal passage of cells other than the transfer that occurs secondary to placental trauma. Yet in macroscopical and histological examinations of placentas of cases of congenital malaria in the 1934-1935 epidemic of Ceylon (Sri Lanka), G. A. Wickramasuriya found no evidence of placental damage.35 P. C. C. Garnham suggested that in addition to the cellular impermeability of the trophoblastic layer of the placenta, red cell surface stickiness conferred by P. falciparum parasitization inhibited passage to the fetal circulation.36 B. M. Das Gupta determined that Plasmodium knowlesi infections of pregnant rhesus monkeys are similar to Plasmodium infections of humans.37 Maternal blood in the placentae was massively infected with parasites while fetal blood was free. Whatever the mechanism, it is generally agreed that congenital malaria infections are rare occurrences.

Regardless of the rarity of congenital malaria, maternal Plasmodium species infections during pregnancy are not without adverse effects on the fetus. Blacklock and
Gordon (1925) were the first to suggest that placental malaria infections were associated with unfavorable neonatal conditions that increased infant morbidity and mortality within the first week after birth.\textsuperscript{38} L. J. Bruce-Chwatt (1952) was unable to correlate neonatal mortality with malaria infection of the placenta, but showed that such an infection was related to births of underweight babies.\textsuperscript{39} Since Bruce-Chwatt's study in Nigeria, a number of analyses, summarized in Table 2,\textsuperscript{40} have corroborated his results. In each of the studies, malaria infection of the placenta was associated with a decreased birth weight. Archibald (1958), Cannon (1958), and Jelliffe (1968) showed that this relationship was true regardless of parity.\textsuperscript{41,42,43} In all groupings of equivalent parity, summarized in Cannon's study in Table 3,\textsuperscript{44} the mean birthweight of products of parasitized placentas was less than nonparasitized placentas. Additionally, as previously mentioned, there is an inverse relationship between parity and percentage of positive placentas.

The studies cited heretofore have concluded that placental infections of women in endemic malarious areas are associated with low mean birthweights. E. F. Jelliffe demonstrated the same relationship in a population of lower immunity in an area of decreased malaria endemicity.\textsuperscript{45} In a study that compared an immune population with a population of decreased malaria immunity in Nigeria, H. M. Archibald concluded that placental malaria infection in nonimmunes results
<table>
<thead>
<tr>
<th>Study</th>
<th>Total # of Placenta Examined</th>
<th>Positive</th>
<th>% Premature</th>
<th>Mean B.W. (gm)</th>
<th>Diff. in Mean B.W. (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td>%</td>
<td>Placenta  -</td>
<td>Placenta  +</td>
</tr>
<tr>
<td>Bruce-Chwatt</td>
<td>310</td>
<td>73</td>
<td>23.5</td>
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<tr>
<td>(1952)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Archibald</td>
<td>463</td>
<td>68</td>
<td>14.7</td>
<td>16.5</td>
<td>29.4</td>
</tr>
<tr>
<td>(1956)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Archibald</td>
<td>440</td>
<td>62</td>
<td>14.1</td>
<td>8.2</td>
<td>21.0</td>
</tr>
<tr>
<td>(1958)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannon</td>
<td>392</td>
<td>130</td>
<td>33.2</td>
<td>12.2</td>
<td>36.9</td>
</tr>
<tr>
<td>(1958)</td>
<td></td>
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<tr>
<td>Spitz</td>
<td>516</td>
<td>136</td>
<td>23.6</td>
<td>27.0</td>
<td>41.2</td>
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<td>(1959)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>McLaren &amp; Ward</td>
<td>400</td>
<td>86</td>
<td>21.5</td>
<td>7.3</td>
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<tr>
<td>(1962)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Jelliffe</td>
<td>570</td>
<td>92</td>
<td>16.1</td>
<td>10.0</td>
<td>19.6</td>
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<tr>
<td>Para</td>
<td>Infected Placentas</td>
<td>Non-Infected Placentas</td>
<td>Positive Placentas</td>
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</tr>
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<td>-----------------------</td>
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<tr>
<td></td>
<td>No.</td>
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<td>%</td>
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<td>Premature #</td>
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<tr>
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<td>9</td>
<td>2</td>
<td>22.2</td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>130</td>
<td>48</td>
<td>37.0</td>
<td>262</td>
<td>32</td>
</tr>
</tbody>
</table>
in an even lower mean birth weight. E. F. Jelliffe determined that the effects of *P. falciparum* were more severe in lowering birthweight than *P. malariae* placental infections. Finally, J. D. MacGregor and J. G. Avery, and D. Morley et al. showed in malarious areas that the mean birth weight of babies of women receiving antimalarial prophylactic treatment during gestation was higher than of women receiving placebo or nothing.

Poor fetal nutrition has been discussed as a reason for the correlation between *Plasmodium* infected placentas and low mean infant birth weight. K. A. Harrison and P. A. Ibeziako noted that, as malaria during pregnancy is associated with maternal anemia, maternal anemia during pregnancy (Hct < 30%) is associated with lower mean fetal birthweight. If, at the end of gestation, maternal anemia remained uncorrected, each 2% drop in maternal hematocrit below 30% resulted in a mean reduction of fetal birthweight of 100 grams. P. C. C. Garnham noted that the intervillous space of the parasitized placenta contained an almost solid mass of reticuloendothelial cells and speculated that, as a consequence, fetal nutrition was less than adequate. D. S. McLaren and P. G. Ward examined this hypothesis in Tanganyika (Tanzania) by comparing various physiological parameters of infants of parasitized mothers with infants of non-parasitized mothers. There was no significant difference in hemoglobin, hematocrit, mean
corpuscular hemoglobin concentration, plasma vitamin A, or plasma protein of the two populations of infants.\textsuperscript{52}

To emphasize the importance of the effect on infants of maternal malaria during pregnancy, prematurity (as defined by the World Health Organization, a birthweight less than 2500 grams) is the most common cause of neonatal death in Nigeria.\textsuperscript{53} Moreover, in a five year study in the United States, P. M. Fitzhardinge and E. M. Steven correlated low infant birthweight with a 25\% incidence of minimal cerebral dysfunction and electroencephalogram abnormalities, 26\% to 33\% incidence of speech defects, and 36\% to 50\% incidence of school failure.\textsuperscript{54} Therefore, in addition to suffering from a high infant mortality, it is possible that malarious countries may be burdened substantially by an educational disadvantage.

Interesting aspects of the host's immune response and malaria's immunopathological effects are emphasized in the relationship of malaria and pregnancy. Malaria and pregnancy are interrelated in affecting the host's immune system.

Acquired immunity to malaria is often slow to develop, allowing persistent low grade parasitemia. The mechanism that allows malaria parasites to evade the consequences of immunization is a central problem to understanding malaria immunity. The host responds humorally to infection with \textit{Plasmodium} parasites by considerably increasing serum levels of IgG and IgM. In clinically immune African subjects, the rate of IgG
production is seven times greater than normal European individuals. IgG synthesis declines by one-third in immune African patients after institution of malarial prophylactic therapy. By the 24th month of life, a malarious infant has significantly higher levels of immunoglobulin (IgG and IgM) than nonmalarious children. B. M. Greenwood and R. M. Vick demonstrated a lymphocytic mitogen factor in sera and red cell lysate obtained from Nigerian children infected with *P. falciparum*. It is yet unknown if this has any part in the production of the hypergammaglobulinemia characteristic of this infection.

Within a population of one to 20 year old individuals in an endemic malarious area, mean IgG levels were elevated significantly in association with parasitemia in the one to two year age group (34% elevation among those with parasitemia) and insignificantly in the 15 to 20 year group (3% elevation in those with parasitemia). In a Tanzanian group of individuals over 30 years of age, A. Voller et al. showed that, whereas mean IgM levels varied with malarial antibody titer, mean IgG levels did not vary significantly. Regardless, by passive transferral of immunity, S. Cohen et al. demonstrated a powerful antiparasitic effect in the IgG fraction of immune individuals that was not evident with the IgM fraction, serum free of IgG, or IgG from nonimmune subjects. They concluded that the protective fraction of antibody to *Plasmodium* infections is within the IgG fraction.
In addition to the presence of a humoral mitogen, a suppression of the host's humoral immune response to other foreign antigens encountered during the course of a malaria infection is evident. It has been demonstrated that antigenic challenge of a rat during a *Plasmodium berghei yoellii* infection resulted in a diminished humoral response and an unaltered cell-mediated immune response.\(^6^1\) Moreover, the humoral response of a group of malarious Gambian children to tetanus toxoid was shown to be diminished when compared to the response of a non-malarious group of Gambian children.\(^6^2\) This obviously further complicates the issue of malaria's immunopathological effect.

The maternal-fetal immunological relationship has been studied in great detail in an attempt to explain why the fetus is an unrejected homograft. Although there is little evidence of a measurable defective maternal immune response, certain infections do occur with abnormal frequency during pregnancy, possibly indicating a reduced immunological capacity of the pregnant woman. Certainly there are a number of changing physiological parameters during gestation that would emphasize the possibility of immunosuppression during gravidism. A factor in this category is the increased production of glucocorticoids which achieve maximum blood-levels late in pregnancy. Substances with immunosuppressive capabilities present in maternal serum during gestation, such as the newly described pregnancy-associated serum glycoprotein,\(^6^3\) also support the theory of reduced maternal immunity during pregnancy.
Evidence of pregnancy's effect on the maternal immune system includes diminished cell mediated immunity. Lowered lymphocytic reactivity to tuberculin purified protein derivative and phytohemagglutinin stimulation begins early in gestation and may diminish to approximately one-half the activity of the nonpregnant state.\textsuperscript{64,65} It is interesting that there is no evidence to support a depression of antibody formation in normal pregnant humans and animals.\textsuperscript{66,67}

An additional effect of pregnancy on the immune system includes stimulation of the reticuloendothelial system. T. Nicol and B. Vernon-Roberts noted two peaks of reticuloendothelial activity in the course of rat and mouse pregnancies: one at the time of implantation and the other towards the end of pregnancy before parturition.\textsuperscript{68} They pointed out that this follows the level of murine plasma estrogen during pregnancy which peaks early, falls to a low level, and peaks again late in gestation. It has been demonstrated in humans that the reticuloendothelial activity increases steadily throughout pregnancy and falls rapidly to a low level at parturition. This, also, follows the pattern of blood estrogen levels during parturition.\textsuperscript{69} Finally, Nicol \textit{et al.} discovered that estrogen, administered to a rat in a dosage 100 times that achieved during the estrous cycle, stimulated the reticuloendothelial system and generally raised murine defenses, as indicated by an increase in phagocytic activity, elevation of serum IgG to approximately three times the normal level, and protection against lethal doses of virulent bacteria.\textsuperscript{70}
Estrogen levels during the course of a normal human pregnancy increase at least 1000 fold over maximum levels achieved during the estrous cycle. In assessing possible reasons for the increased prevalence of malaria infections during pregnancy, investigators have examined the maternal immune response. S. Cohen and I. A. McGregor determined that a three-month pregnant Gambian subject, unprotected with antimalarial prophylactics in a hyperendemic malarious area, synthesized considerably less IgG (84 mg/kg/day) than seven other unprotected Gambians (139-203 mg/kg/day). McGregor also showed that mean values of IgG and IgA were considerably less in pregnant Gambians than in nonpregnant counterparts. Levels of IgG fell progressively throughout pregnancy, reaching their lowest level in the last ten-week period. Additionally, McGregor demonstrated with small numbers of subjects that the immune response (as evidenced by fluorescent antibody titers) of a pregnant Gambian was less than that of a nonpregnant Gambian when both were challenged with a naturally occurring malaria infection. H. F. Kortmann found no difference in fluorescent antibody titers in pregnant and nonpregnant populations of Tanzanians. It is of interest that the fetus does not react immunologically to a maternal placental malaria infection with a response of increased IgM production. Moreover, S-antigens, found in association with a large percentage of Plasmodium falciparum infections, have never been found in fetal sera.
The present study of examination of large numbers of thick blood films and fluorescent antibody titers of pregnant and nonpregnant female members of a falciparum malaria immune population was undertaken to answer the following questions:

1. In a comparison of parity-matched pregnant and nonpregnant women, does the pregnant state confer an absolute disadvantage in prevalence of falciparum malaria infection and \textit{P. falciparum} density?

2. At what stage in pregnancy is a woman most susceptible to a falciparum malaria infection?

3. Can the disadvantage (if one exists) during pregnancy regarding falciparum malaria infection be correlated with a change in fluorescent antibody titers as compared with the nonpregnant state?
Part IV Footnotes

10. Ibid.
11. Ibid.
69. Ibid.
73. McGregor, I. A. et al., Clinical and Experimental Immunology 7:51, 1970.
PART V. Materials and Methods
Thick blood films stained with Giemsa stain and obtained by fingerprick of 1,000 pregnant and 1,000 non-pregnant rural Gambian women were examined for *Plasmodium falciparum* parasites. Sera from 300 pregnant and 300 non-pregnant women were collected by fingerprick in 2 ml Carroway tubes from rural Gambian women in Mansakonko for determination of falciparum malarial fluorescent antibody titers by the indirect fluorescent antibody technique. Name, parity, and week of pregnancy were noted within the pregnant group. The age of the last child, as well as name and parity, were noted within the nonpregnant group. The population of women was comprised of patients of the Antenatal Health Care Clinics and Infant Health Care Clinics of two health centers, Brikama and Mansakonko, and one hospital, Bansang, in The Gambia in 1977 during the peak period of annual rains in September and October. This coincides with the peak of the malaria transmission. Clinic days were on alternating Fridays in Mansakonko and on consecutive days of the week at the other two clinics (Monday and Tuesday in Bansang and Tuesday and Wednesday in Brikama). The clinics were part of the Gambian health care system and were run by government-employed nurses, who cared for maternal and child health by immunization, health and nutrition education, regular care for children under five years, maternity services, and planned parenthood. Each woman brought a health record card to each of the clinics.
with pertinent clinical data (including week of pregnancy as determined by the Gambian nurse midwife) and treatment data (including records of prescribed antimalarials). Women treated with antimalarials within eight weeks of a clinic visit were not chosen for this survey. Women were confident of their parity, but determination of gravida was not possible. Pregnant women for this survey were seen in the Antenatal Health Care Clinics and nonpregnant women, as they brought their children for care, were seen in the Infant Health Care Clinics. An equivalent number of pregnant and nonpregnant women were seen from each town: 250, 300 and 450 in each group of pregnant and nonpregnant women in Brikama, Mansakonko and Bansang respectively.

The randomness and completeness of the patient sample was good. The Mansakonko Health Center, for example, serves a population of 38,000 people. In 1976, 1,533 patients were seen in the antenatal clinic and 2,033 patients were seen in the infant health care clinic. Considering that the population of The Gambia increased either 2.4% or 4.6% (conflicting figures from two surveys) during 1963 to 1973, and that it is estimated to be growing presently at the same rate, 912 to 1748 infants were born in the area of the Mansakonko Health Care Center during 1976.1 The number of patients seen in the two clinics is roughly equivalent to the number of estimated candidate patients.
Distances involved were Banjul to Brikama—22 miles, Banjul to Mansakonko—114 miles, Banjul to Bansang—207 miles. Ten clinic days were spent in Brikama, eight days in Mansakonko, and five days in Bansang. Total mileage traveled via MRC land transportation for the purpose of the survey was approximately 5,050 miles.

In examination of thick blood films, the number of *Plasmodium falciparum* parasites was counted per 5000 white blood cells. Average white cell counts of 50 pregnant and 50 nonpregnant women were determined. Average *P. falciparum* parasite density and prevalence of falciparum malaria infection of the 1,000 pregnant women were compared with the 1,000 nonpregnant women. Average *P. falciparum* parasite density and the prevalence of falciparum malaria infections were compared between groups of equivalent parity in the pregnant and nonpregnant state. In each case, nonpregnant women were age corrected for comparison with pregnant women by subtracting the sum of the average age of the last child of the nonpregnant women and the average time remaining in pregnancy of the pregnant woman from the average time between children in The Gambia. Within the total pregnant group, *P. falciparum* parasite density and falciparum malaria infection prevalence was determined for less than or equal to 24 weeks gravidism, 25 weeks to 32 weeks gravidism, and 33 weeks to 40 weeks gravidism. Density and prevalence were determined, also, for the same bands of gravidism in the primiparous group, the
para one plus para two group, and the equal to or greater than para three group.

Falciparum malaria fluorescent antibody titers for 300 pregnant and 300 nonpregnant women seen in Mansakonko were determined by an indirect fluorescent antibody technique. *Plasmodium falciparum* schizont antigen placed in 12 wells per slide was obtained from culture of *P. falciparum* trophozoites taken from a Gambian infected with falciparum malaria. Antigen slides were stored at -20°C and were placed in a dessicator jar for ten to 20 minutes before use. Sera, from the individual collections of whole blood from the 600 Gambian women, were separated by centrifugation, stored at -20°C, and allowed to thaw before use. Microtiter plates, eight wells by 12 wells, were used for titration. Neat serum was diluted ten-fold with phosphate buffered saline (PBS) and, thereafter, diluted two-fold to 1:20480. Antigen slides were placed in one-third normal HCl for five minutes after dessication, washed in PBS, and dried with light blotting. The dilutions of sera were added to the slide wells. The slides were placed in a moist chamber for one half hour, after which they were washed under a PBS flow and subsequently in PBS-filled Cotlin jars. The wells were dried with light blotting and 1:20 PBS-diluted fluorescein tagged rabbit anti-human IgG was added to each well. The slide was placed in a moist chamber for one half hour, after which the wells were washed in PBS and allowed to remain in PBS-filled Cotlin jars for up to
one hour prior to microscopic examination. Each well of the slide was examined using the 10X lens of a Leitz transmitted dark field ultraviolet microscope. The last positive titer was recorded.

*P. falciparum* fluorescent antibody titers of 300 pregnant women seen in Mansakonko were compared with the *P. falciparum* fluorescent antibody titers of 300 nonpregnant women seen in the same health center. The ratio of number of pregnant women with a titer of 1:640 or greater to the number of pregnant women with a titer of 1:320 or lower was compared with the same ratio in the nonpregnant group of women. This same ratio of titers was determined for the primiparous, para one and para two, and para three or greater parity groups of pregnant women and the para one, para two and para three, and para four or greater parity groups of nonpregnant women. The greater than or equal to 640 to less than or equal to 320 ratio was also determined for the less than or equal to 24 weeks, 25 weeks to 32 weeks, and 33 weeks to 40 weeks of gravidism within the group of 300 pregnant women. This ratio was determined, also, for the parasitized and nonparasitized women in each of the pregnant and nonpregnant groups.

Results were graphed and analyzed.
Part V Footnotes

PART VI. Results
The prevalence of falciparum malaria within the pregnant group was 41.3%. There were two patients with *P. falciparum* and *P. malariae* mixed infections that were included in the positively infected group. There were eight patients with *P. malariae* infections and one patient with a *P. ovale* infection which were excluded from the positive group. The geometric mean density of *P. falciparum* parasites (log $(n+1)$) per 5000 WBCs was 0.92 ± a standard error of the mean of 0.08. The mean white blood count of 50 randomly selected pregnant Gambians was 6742 ± a standard error of the mean of 278. Parity was inversely related to the prevalence of falciparum malaria infection and geometric mean density of parasites per 5000 WBCs. The para 2 group was the one exception to this inverse relationship. A complete presentation of results is in Table 4 and Figure 1.

The prevalence of falciparum malaria within the non-pregnant group was 35.3%. There were two patients with *P. falciparum* and *P. ovale* mixed infections that were included in the positively infected group. There were five patients with *P. malariae* infections and one patient with a *P. ovale* infection which were excluded from the positive group. The geometric mean density of *P. falciparum* parasites (log $(n+1)$) per 5000 WBCs was 0.58 ± a standard error of the mean of 0.06. The mean white blood count of 50 randomly selected nonpregnant Gambian women was 5982 ± a standard error of the mean of 293. Parity
was inversely related to the prevalence of falciparum malaria infection and geometric mean density of parasites per 5000 WBCs. A complete presentation of results is in Table 5 and Figure 2.

The prevalence of infection and geometric mean of parasite density was higher in the pregnant than in the non-pregnant group. Both of these values were higher in primiparous women than in para 1 nonpregnant women, para 1 pregnant women than in para 2 nonpregnant women, and so on. The one exception to this generalization was the comparison of prevalence of infection of the para 2 pregnant women with the para 3 nonpregnant women.

Correcting the age of the nonpregnant group to their pregnant equivalents by subtracting the sum of the average age of the last child of the nonpregnant group (9.41 months) plus the average time remaining in pregnancy of the pregnant group (12 weeks) from the average number of years between successive children in The Gambia (2.5 years)^1 gave an age correction factor of 17.59 months. Application of this value to Figure 2 yielded age corrected values for the nonpregnant group. The prevalence of infection and geometric mean density was higher in the pregnant than in the age-corrected nonpregnant group. Comparing both of these values in the respective categories of parity showed that each of the pregnant parities was higher than the nonpregnant parities. Again the one exception to this generalization was the prevalence of infection of the
### TABLE 4

**Pregnant Group**

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Number Infected</th>
<th>% Prevalence</th>
<th>Mean Density log(n+1)</th>
<th>2 x S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primip</td>
<td>255</td>
<td>151</td>
<td>59.2</td>
<td>1.59</td>
<td>0.19</td>
</tr>
<tr>
<td>Para 1</td>
<td>171</td>
<td>75</td>
<td>43.9</td>
<td>0.98</td>
<td>0.21</td>
</tr>
<tr>
<td>Para 2</td>
<td>189</td>
<td>59</td>
<td>31.2</td>
<td>0.62</td>
<td>0.16</td>
</tr>
<tr>
<td>Para 3</td>
<td>123</td>
<td>47</td>
<td>38.2</td>
<td>0.74</td>
<td>0.20</td>
</tr>
<tr>
<td>&gt;Para 4</td>
<td>262</td>
<td>81</td>
<td>30.9</td>
<td>0.53</td>
<td>0.11</td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>413</td>
<td>41.3</td>
<td>0.92</td>
<td>0.08</td>
</tr>
</tbody>
</table>

### TABLE 5

**Nonpregnant Group**

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Number Infected</th>
<th>% Prevalence</th>
<th>Mean Density log(n+1)</th>
<th>2 x S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Para 1</td>
<td>320</td>
<td>146</td>
<td>45.6</td>
<td>0.81</td>
<td>0.12</td>
</tr>
<tr>
<td>Para 2</td>
<td>176</td>
<td>65</td>
<td>36.9</td>
<td>0.61</td>
<td>0.15</td>
</tr>
<tr>
<td>Para 3</td>
<td>172</td>
<td>54</td>
<td>31.4</td>
<td>0.47</td>
<td>0.13</td>
</tr>
<tr>
<td>Para 4</td>
<td>142</td>
<td>42</td>
<td>29.6</td>
<td>0.41</td>
<td>0.13</td>
</tr>
<tr>
<td>&gt;Para 5</td>
<td>190</td>
<td>46</td>
<td>24.2</td>
<td>0.38</td>
<td>0.11</td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>353</td>
<td>35.3</td>
<td>0.58</td>
<td>0.06</td>
</tr>
</tbody>
</table>
FIG. 1 PREGNANT GROUP

- ○ Mean Parasite Density
- △ Prevalence

PREVALENCE (%) vs. MEAN PARASITE DENSITY log (n+1) per 5000 WBC

PRIMIP  P1  P2  P3  P4  P5  P6  P7  P8
para 2 pregnant group compared with that of the para 3 nonpregnant group. A complete presentation of these results is Figure 3 and Figure 4.

There were 57 nonpregnant women with children less than one month of age of which 18 were infected (31.6% prevalence of infection) and the geometric mean parasite density was 0.56 ± a standard error of the mean of 0.27. Both of these values were lower than the same values for the pregnant group.

Women in the less than or equal to 24 week period of pregnancy had a higher prevalence of infection and geometric mean density of parasites than women in the 25 week to 32 week period. These values for the latter group of women were higher than for the women in the 33 week to 40 week period of pregnancy. This data is presented in Table 6 and Figure 5. Primiparous women had a higher prevalence and geometric mean density of infection in each of the periods of pregnancy than para 1 and para 2 women. Prevalence and geometric mean parasite density of the latter group were higher in each of the periods of pregnancy than the greater than or equal to para 3 group. Figures 6 and 7 and Tables 7 through 9 are complete presentations of this data.

The ratio of the sum of the number of pregnant sera with titers greater than or equal to 620 to the number of pregnant sera with titers less than or equal to 320 was 0.572. The same ratio within the nonpregnant group was 0.936. The
### TABLE 6

**All Pregnant Women in Weeks of Gestation**

<table>
<thead>
<tr>
<th>Weeks Pregnant</th>
<th>Total</th>
<th>Number Infected</th>
<th>% Prevalence</th>
<th>Mean Density log (n+1)</th>
<th>2 x S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 24</td>
<td>276</td>
<td>139</td>
<td>50.4</td>
<td>1.22</td>
<td>0.17</td>
</tr>
<tr>
<td>25-32</td>
<td>450</td>
<td>176</td>
<td>39.1</td>
<td>0.85</td>
<td>0.12</td>
</tr>
<tr>
<td>33-40</td>
<td>274</td>
<td>98</td>
<td>35.8</td>
<td>0.73</td>
<td>0.14</td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>413</td>
<td>41.3</td>
<td>0.92</td>
<td>0.08</td>
</tr>
</tbody>
</table>

### TABLE 7

**Primips in Weeks of Gestation**

<table>
<thead>
<tr>
<th>Weeks Pregnant</th>
<th>Total</th>
<th>Number Infected</th>
<th>% Prevalence</th>
<th>Mean Density log (n+1)</th>
<th>2 x S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 24</td>
<td>89</td>
<td>59</td>
<td>66.3</td>
<td>1.93</td>
<td>0.32</td>
</tr>
<tr>
<td>25-32</td>
<td>105</td>
<td>60</td>
<td>57.1</td>
<td>1.53</td>
<td>0.30</td>
</tr>
<tr>
<td>33-40</td>
<td>61</td>
<td>32</td>
<td>52.4</td>
<td>1.21</td>
<td>0.38</td>
</tr>
<tr>
<td>Total</td>
<td>255</td>
<td>151</td>
<td>59.2</td>
<td>1.59</td>
<td>0.19</td>
</tr>
</tbody>
</table>

### TABLE 8

**Para 1 and Para 2 in Weeks of Gestation**

<table>
<thead>
<tr>
<th>Weeks Pregnant</th>
<th>Total</th>
<th>Number Infected</th>
<th>% Prevalence</th>
<th>Mean Density log (n+1)</th>
<th>2 x S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 24</td>
<td>83</td>
<td>40</td>
<td>48.2</td>
<td>1.04</td>
<td>0.30</td>
</tr>
<tr>
<td>25-32</td>
<td>170</td>
<td>60</td>
<td>35.3</td>
<td>0.70</td>
<td>0.18</td>
</tr>
<tr>
<td>33-40</td>
<td>107</td>
<td>34</td>
<td>31.8</td>
<td>0.73</td>
<td>0.24</td>
</tr>
<tr>
<td>Total</td>
<td>360</td>
<td>134</td>
<td>37.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE 9

Para 3 in Weeks of Gestation

<table>
<thead>
<tr>
<th>Weeks Pregnant</th>
<th>Total</th>
<th>Number Infected</th>
<th>% Prevalence</th>
<th>Mean Density log (n+1)</th>
<th>2 x S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 24</td>
<td>104</td>
<td>40</td>
<td>38.5</td>
<td>0.76</td>
<td>0.22</td>
</tr>
<tr>
<td>25-32</td>
<td>176</td>
<td>56</td>
<td>31.8</td>
<td>0.59</td>
<td>0.15</td>
</tr>
<tr>
<td>33-40</td>
<td>106</td>
<td>32</td>
<td>30.2</td>
<td>0.44</td>
<td>0.16</td>
</tr>
<tr>
<td>Total</td>
<td>386</td>
<td>128</td>
<td>33.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The value of this ratio for parity grouped pregnant women compared with similar parity grouped nonpregnant was lower in every case but one. The value of this ratio was roughly the same for all parity groups of nonpregnant women. Within the pregnant group, the ratio of titers \( \frac{\text{number} \geq 640}{\text{number} < 320} \) was less for the less than or equal to 24 week group than for the 25 week to 32 week group, which in turn was less than the 33 week to 40 week group. These results are presented in Tables 10 through 12 and Figures 3 and 9. The ratio \( \frac{\text{number} \geq 640}{\text{number} < 320} \) for parasitized pregnant women was .595; for nonparasitized pregnant women .552; for parasitized and nonparasitized nonpregnant women 1.15 and .862 respectively. Results are presented in Tables 13 and 14 and Figure 10.
### TABLE 10

Pregnant (300 Women): Parity Vs. Titer

<table>
<thead>
<tr>
<th>Titer</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
<th>160</th>
<th>320</th>
<th>640</th>
<th>1280</th>
<th>2560</th>
<th>5120</th>
<th>10240</th>
<th>20480</th>
<th>total ≥ 640</th>
<th>total &lt; 320</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primip</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>10</td>
<td>8</td>
<td>9</td>
<td>14</td>
<td>9</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>33/36 = .916</td>
<td></td>
</tr>
<tr>
<td>P1+P2</td>
<td>0</td>
<td>6</td>
<td>8</td>
<td>16</td>
<td>20</td>
<td>31</td>
<td>15</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>31/80 = .389</td>
<td></td>
</tr>
<tr>
<td>P3</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>17</td>
<td>25</td>
<td>24</td>
<td>17</td>
<td>14</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>45/75 = .600</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>9</td>
<td>20</td>
<td>43</td>
<td>53</td>
<td>64</td>
<td>46</td>
<td>31</td>
<td>14</td>
<td>11</td>
<td>5</td>
<td>2</td>
<td>109/191 = .570</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 11

NONPREGNANT (300 Women): Parity Vs. Titer

<table>
<thead>
<tr>
<th>Titer</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
<th>160</th>
<th>320</th>
<th>640</th>
<th>1280</th>
<th>2560</th>
<th>5120</th>
<th>10240</th>
<th>20480</th>
<th>total ≥ 640</th>
<th>total &lt; 320</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>11</td>
<td>15</td>
<td>22</td>
<td>20</td>
<td>1</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>47/53 = .869</td>
<td></td>
</tr>
<tr>
<td>P2+P3</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>10</td>
<td>15</td>
<td>22</td>
<td>22</td>
<td>19</td>
<td>12</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>59/57 = 1.035</td>
<td></td>
</tr>
<tr>
<td>P4</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>17</td>
<td>17</td>
<td>18</td>
<td>8</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>39/45 = .866</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>2</td>
<td>15</td>
<td>27</td>
<td>47</td>
<td>61</td>
<td>60</td>
<td>41</td>
<td>27</td>
<td>13</td>
<td>4</td>
<td>0</td>
<td>145/155 = .936</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 12

**Pregnant (300 Women): In Weeks of Gestation Vs. Titer**

<table>
<thead>
<tr>
<th>Titer</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
<th>160</th>
<th>320</th>
<th>640</th>
<th>1280</th>
<th>2560</th>
<th>5120</th>
<th>10240</th>
<th>20480</th>
<th>Total</th>
<th>( \geq 640 ) ( \leq 320 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( &lt; 24W )</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td>13</td>
<td>18</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>21/53 = .395</td>
<td></td>
</tr>
<tr>
<td>( 25-32W )</td>
<td>0</td>
<td>4</td>
<td>9</td>
<td>26</td>
<td>29</td>
<td>35</td>
<td>24</td>
<td>16</td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>57/105 = .542</td>
<td></td>
</tr>
<tr>
<td>( 33-40W )</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>11</td>
<td>11</td>
<td>12</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>31/33 = .939</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>9</td>
<td>20</td>
<td>43</td>
<td>53</td>
<td>64</td>
<td>46</td>
<td>31</td>
<td>14</td>
<td>11</td>
<td>5</td>
<td>2</td>
<td>109/191 = .570</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 13

**Pregnant (300 Women)**

<table>
<thead>
<tr>
<th>Titer</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
<th>160</th>
<th>320</th>
<th>640</th>
<th>1280</th>
<th>2560</th>
<th>5120</th>
<th>10240</th>
<th>20480</th>
<th>( \geq 640 \leq 320 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P^* )</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>12</td>
<td>9</td>
<td>16</td>
<td>13</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>28/47 = .595</td>
</tr>
<tr>
<td>( N-P^{**} )</td>
<td>2</td>
<td>5</td>
<td>14</td>
<td>31</td>
<td>44</td>
<td>48</td>
<td>33</td>
<td>23</td>
<td>11</td>
<td>9</td>
<td>4</td>
<td>1</td>
<td>81/144 = .562</td>
</tr>
</tbody>
</table>

*\( P^* = \) parasitized; \( N-P^{**} = \) nonparasitized*

### TABLE 14

**Nonpregnant (300 Women)**

<table>
<thead>
<tr>
<th>Titer</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
<th>160</th>
<th>320</th>
<th>640</th>
<th>1280</th>
<th>2560</th>
<th>5120</th>
<th>10240</th>
<th>20480</th>
<th>( \geq 640 \leq 320 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P^* )</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td>9</td>
<td>18</td>
<td>18</td>
<td>14</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>45/39 = 1.15</td>
</tr>
<tr>
<td>( N-P^{**} )</td>
<td>3</td>
<td>2</td>
<td>9</td>
<td>21</td>
<td>38</td>
<td>43</td>
<td>42</td>
<td>29</td>
<td>19</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>100/116 = .862</td>
</tr>
</tbody>
</table>

*\( P^* = \) parasitized; \( N-P^{**} = \) nonparasitized*
FIG. 3 PREGNANT, NONPREGNANT, AND NONPREGNANT AGE-CORRECTED PREVALENCE OF INFECTION

- Pregnant
- Nonpregnant
- Nonpregnant Age-Corrected

PREVALENCE (%)

PARITY

PO P1 P2 P3 P4 P5 TOTALS
FIG. 5: PREVALENCE AND MEAN PARASITE DENSITY FOR ALL PREGNANT WOMEN VS WEEKS OF GESTATION

Mean Parasite Density

Prevalence

PREVALENCE (%)
FIG. 6 PREVALENCE AND PARITY VS WEEKS OF GESTATION
FIG. 7 MEAN PARASITE DENSITY AND PARITY VS WEEKS OF GESTATION

MEAN PARASITE DENSITY log (n+1) per 5000 WBC

PRIMIPS

PARA1 + PARA2

PARA3

WEEKS OF GESTATION

WEEKS OF GESTATION
FIG. 8

CLASSIFICATION

- PREGNANT PRIMIPS
- NONPREGNANT PARA1
- PREGNANT PARA1 + PARA2
- NONPREGNANT PARA2 + PARA3
- PREGNANT ≥ PARA3
- NONPREGNANT ≥ PARA4
- TOTAL PREGNANT
- TOTAL NONPREGNANT

RATIO of \[
\frac{\text{total } \geq 640}{\text{total } < 320}
\]
Fig. 10

Classification

PREGNANT PARASITIZED
PREGNANT NONPARASITIZED
NONPREGNANT PARASITIZED
NONPREGNANT NONPARASITIZED

RATIO of \( \frac{\text{total} \geq 640}{\text{total} \leq 320} \)
Part VI Footnotes

PART VII. Discussion
The results of this study agreed with previous conclusions that the prevalence and parasite density of falciparum malaria were higher in an immune pregnant population than in an immune nonpregnant population. The state of pregnancy conferred an absolute disadvantage to the host with regard to falciparum malaria infection. This is evident in the prevalence and parasite density of the total number of pregnant women as compared with the total number of nonpregnant women (41.3%, log 0.92 and 35.3%, log 0.58 respectively). It is emphasized, also, by the comparison of pregnant women with nonpregnant women who had delivered within one month of examination (41.3%, log 0.92 and 31.6%, log 0.56). Rapid breakdown of dense parasitemia after uterine emptying is suggestive of the possibility that a mechanism of immunity was present during pregnancy that was unable to act in the presence of an antagonistic principle somehow removed with parturition. Further evidence of a disadvantaged pregnant state is that regardless of parity (with one exception), pregnant women had a higher prevalence and peripheral parasite density than their nonpregnant parity-matched counterparts. Prevalence and parasite density decreased in both pregnant and nonpregnant groups of women with increasing parity. This is consistent with an individual's immunity to malaria in hyperendemic and holoendemic areas increasing with age.
It has been suggested that falciparum malaria prevalence and parasite density increased throughout the course of gestation.¹ This study supports the idea that both parameters decrease with increasing gestational time. Additionally, the increased immunity attained with chronological age of the individual holds true when comparing specific times in gestation amongst differing groups of parity throughout pregnancy.

Immunoglobulin levels during the course of a normal pregnancy have been shown not to differ from nonpregnant individuals. Yet there are conflicting results of IgG measurement during pregnancies of individuals immune to malaria residing in hyperendemic or holoendemic areas. McGregor et al. has stated that IgG levels fall progressively throughout pregnancy in a population of 133 Gambians.² He suggested that the humoral immunological response (as evidenced by fluorescent antibody titer) to falciparum malaria is less in a pregnant immune population than in a nonpregnant immune population.³ Cohen and McGregor concluded that daily synthesis of IgG is less in a pregnant immune subject than nonpregnant immune counterparts.⁴ H. F. Kortmann found no difference in fluorescent antibody titer measurement comparing 123 pregnant with 153 nonpregnant Tanzanian women. This study concluded that IgG levels, as measured by fluorescent antibody titer to Plasmodium falciparum schizont antigen, were less (with one exception) in pregnant than in parity-matched nonpregnant immune Gambian women. This study supported the suggestion of
McGregor that a pregnant immune individual is less able to mount a humoral immune defense (as evidenced by fluorescent antibody titer) than a nonpregnant immune woman. Moreover, fluorescent antibody titers were inversely related to prevalence and parasite density throughout the course of pregnancy. This inverse relation was true, also, in the comparison of pregnant and nonpregnant immune women.

The importance of IgG in immunity to *Plasmodium* infections has been emphasized. This study demonstrated evidence that decreased levels of IgG specific for falciparum antigen could be responsible for increased *P. falciparum* prevalence and parasite density during pregnancy. J. B. Lawson suggested that fetal protein requirements withdrew protein from the maternal immunological system and, consequently, lowered maternal immunity to malaria by decreasing maternal levels of IgG. P. D. Karsden and L. J. Bruce-Chwatt suggested that patent *P. falciparum* infections develop during pregnancy as a consequence of a maternofetal IgG drain. It is also possible that the combined (albeit poorly defined) immunosuppressive properties of malaria and pregnancy decrease IgG production.

The activity of the reticuloendothelial system in the host's response to *Plasmodium* infection has been described. Inasmuch as *P. falciparum* prevalence and parasite density decline throughout the course of pregnancy regardless of parity, it is interesting to note that reticuloendothelial
activity increases throughout gestation as a result of estrogen stimulation.\(^7\)

Although not examined in this study, it is necessary to mention two additional characteristics of malaria infections during pregnancy. First, the curious ability of the placenta to accumulate *P. falciparum* parasites raises speculation of the mechanism of this phenomenon. D. L. Berliner et al. have isolated cortisol, cortisone, 11-dehydrocortisone, aldosterone, and corticosteroid metabolites in high concentrations from the placenta.\(^8\) R. E. Billingham has demonstrated local immunosuppressive effects of corticosteroids in dosages that had little effect when applied systemically.\(^9\) The suggestion is that the local immunosuppressive effects of corticosteroids in the placenta may create a favorable milieu for *P. falciparum* growth. Additionally, E. J. Jenkinson et al. demonstrated evidence for the existence of IgG Fc receptors on the surface of the exposed placental syncitiotrophoblastic layer.\(^10\) This suggests the possibility of *P. falciparum* antigen binding with the Fsβ portion of the placental-bound IgG molecule, allowing the organism to escape further immunological effects.

Finally, the low incidence of congenital malaria is interesting. The absence of fetal IgM response and S-antigen in fetal serum suggests that the placenta is a very effective barrier to maternofetal transfer of *P. falciparum* parasites.
In addition to *Plasmodium* infected monkeys as models for further study of malaria during pregnancy, *Trypanosoma musculi* infection during murine pregnancy is a possible model. A murine *T. musculi* infection, normally controlled in the nonpregnant state, is (during pregnancy) an infection that rapidly increases in parasitic density, causes retardation of embryonic development, and can cause maternal death. Rapid breakdown of dense parasitemia always follows normal delivery of litter, abortion, or surgical removal of the pregnant uterus. Since separate surgical removal of the embryo with preservation of the placenta *in situ* does not significantly influence the development of high parasitemia, it has been suggested that the presence of a growing placenta is the reason for the disturbance of the host’s immunological response.

Further study of the problems of malaria and pregnancy should include examination of reticuloendothelial activity during the course of pregnancies in a population immune to malaria as well as determinations of IgG levels during pregnancies complicated with malaria and other infections.

The importance of understanding the effects of malaria infection on the course and outcome of pregnancy is protean. Adequate comprehension of this model would lead to greater appreciation of both the immunological system during pregnancy and malaria immunopathology. Additionally, alleviation of the morbidity caused by *Plasmodium* parasitemia
during pregnancy could significantly affect the health and development of Third World countries by eliminating the high incidence of low infant birthweight. This, in turn, would reduce infant mortality and remove the possibility of an educational disadvantage secondary to retardation of fetal development. *Plasmodium* parasite infections during pregnancy is a subject that warrants a great deal of further study.
The Earth, as it appears from 100,000 miles in space:

The planet appears as a lovely blue, white and brown globe swimming in space. It looks quiet and peaceful. From this vast distance you cannot see the sprawling populations riddled with disease, badly fed, living below subsistence level, plagued by poverty, aggression and the inequalities of terrestrial life. It seems a pity to have to go so far away to see it in perspective for what it is—One World, on which mankind must learn to live peacefully and well.
Part VII Footnotes


Summary

This study examined the prevalence and parasite density of *Plasmodium falciparum* infections in a population of 1000 pregnant Gambian women compared with a population of 1000 nonpregnant Gambian women. Results supported previous studies that have determined that *Plasmodium falciparum* prevalence and parasite density are higher in an immune pregnant population in an endemic area. In addition, this study determined that this relationship is true regardless of parity.

It had been suggested that *Plasmodium falciparum* prevalence and parasite density increased with increasing gestational time. This study demonstrated that both parameters declined (again, regardless of parity) with gestational time.

Fluorescent antibody (IgG) titers of 300 Gambian pregnant women and 300 Gambian nonpregnant women to *Plasmodium falciparum* schizont antigen were determined, also. Using the ratio \( \frac{\text{total number} > 640}{\text{total number} \leq 320} \) to compare pregnant and nonpregnant groups, differing gestational times, and parasitized or nonparasitized groups, it was determined (in general) that within the pregnant group antibody titers were inversely related to *Plasmodium falciparum* prevalence and parasite density. Compared to the nonpregnant group,
the pregnant group demonstrated a decreased ability to mount a high titer antibody response during *Plasmodium falciparum* infection.

This study produced evidence that supports the theory that a decreased IgG response is at least partly involved with the increased *Plasmodium falciparum* prevalence and parasite density of an immune pregnant population within an endemic area. It is suggested that the decline of prevalence and parasite density throughout the course of gestation may be related to the increasingly estrogen-stimulated reticuloendothelial system during pregnancy.

A murine-*Trypanosoma musculi* model is suggested as a possibility for further study of issues related to *Plasmodium falciparum* infections during human pregnancy. Further studies should include examination of reticuloendothelial system activity during pregnancies of *Plasmodium falciparum* immune women in endemic malarious areas and determination of IgG levels during pregnancies complicated by malaria and other infections.
BIBLIOGRAPHY
Bibliography


Das Gupta, B. M. Malaria infection in the placenta and transmission to the foetus. Tropical Diseases Bulletin 37:184, 1940.


Youtananukorn, V., Matangkasambut, P. and Osathanondh, V.
Onset of human maternal cell-mediated immune reaction to placental antigens during the first pregnancy.
Clinical and Experimental Immunology 16:593, 1974.


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