# WOMEN AND TROPICAL DISEASES

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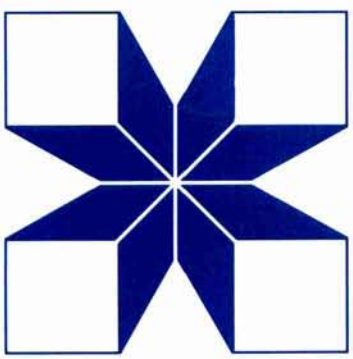

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# Women and tropical diseases

Edited by
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# Foreword

This collection resulted from a global call for papers addressing the theme of women and tropical disease research. In 1989-1990, a joint initiative was undertaken by the Special Program for Research and Training in Tropical Diseases (TDR) of the World Health Organization (WHO) and the Health Sciences Division and the Gender and Development Unit of the International Development Research Centre (IDRC). Health researchers were invited to submit papers on women and tropical diseases in a competition sponsored by the two agencies.

The papers were reviewed by an international expert panel consisting of health and social scientists from Switzerland, Australia, the United States, Sri Lanka, and Canada. They included Steering Committee members of TDR's Socioeconomic Research Program and IDRC staff. Criteria for judgement included scientific merit, relevance to gender issues, innovative ideas, research recommendations, review of the literature, and knowledge of the field. During a meeting held in September 1991 at Litchfield, Connecticut, the group chose the paper entitled "Leprosy in Women: Characteristics and Repercussions" by Marian Ulrich et al. of Instituto de Biomedicina, Caracas, Venezuela for the five thousand dollar prize that was offered. However, numerous other submissions of high quality were received from researchers in Latin America, Africa, Europe, and North America. A selection of the top ten papers, as judged by the panel, is included in this volume.

Although the general quality of the papers was excellent, the competition highlighted a gap in research on gender and tropical diseases. It is clear that there is a need for further research and for more collaborative work between biomedical and social scientists. For this reason, TDR and IDRC will sponsor a second competition in 1992 with the hope of advancing understanding of this important interdisciplinary field.

This collection of papers represents an important first step toward the stimulation of further work on gender and tropical diseases. The papers have scientific validity and interest in their own right but they also are important indicators of the current state of the literature on this subject. As such it is anticipated that they will serve to inspire further interdisciplinary research on gender and tropical diseases. It is hoped also that the collection will inspire more collaborative work and networking among researchers working in the biomedical and social sciences fields.

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# Leprosy in Women: Characteristics and Repercussions

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*Health is often measured in terms of low mortality; nevertheless, merely being alive is not a measure of the quality of life.*

H. Mendez Castellanos

## Summary

Physiological, socioeconomic, and cultural factors play important roles in the response of women to *M. leprae* and in the impact of leprosy on their lives. They appear to develop stronger immunological responses to *M. leprae* than men, as suggested by lower incidence and less severe clinical forms of disease in most areas of the world, as well as stronger reactions of cell-mediated immunity after prophylactic vaccination. Ethnic or genetic factors, pregnancy, intercurrent infection, and malnutrition might be included among the factors that modulate this response. With the introduction of multidrug therapy, leprosy control throughout the world is no longer an unrealistic goal. Active vaccination may constitute the other factor necessary for eventual eradication of the disease. Women in leprosy-endemic areas of the world, with few exceptions, suffer from marked economic and social dependency and inferiority, which can only be heightened by the social stigma associated with leprosy. Nevertheless, they bear an enormous responsibility for the health of their families, often as head of the household, and they possess a unique capacity to influence community opinion. The incorporation of women at all levels into active roles in health care programs may constitute one of the decisive factors in the success or failure of leprosy control.

## Introduction

Among tropical diseases, leprosy bears a social stigma with its roots buried deep in historical tradition. Other diseases, of which mucocutaneous and diffuse cutaneous leishmaniasis and onchocerciasis (river blindness) are examples, cause profound incapacity and disfigurement, but none is associated with the ostracism and sense of fear and repulsion inspired by leprosy throughout much of the world.

While women bear much social and cultural responsibility for maintaining the framework of the society in many developing countries and may be protected by well-intentioned legislation, their real situation is often characterized by lack of opportunity, extreme dependency, and subtle or even blatant discrimination in nearly every aspect of their lives. Many of the elements associated with social stigma, including low self-esteem and self-destructive acceptance of relegation as a second-class member of society, are reflected in the

current situation of women in many parts of the world where leprosy is endemic.

In the following pages, we will try to explore both biomedical and social aspects of leprosy among women, their status in the recent past and present, and perspectives for the future. Many of the data and observations that follow are based on our experience in Venezuela. This country clearly occupies a privileged economic position within Latin America because of the abundance of its natural resources, and our experience does not represent the more severe situations found in many under-developed and developing countries. The ethnic composition of the population is relatively uniform, with a creole mixture of Spanish, African, and native American components; small groups of African descent and of native Americans are found in the national territory but their influence is not reflected in the data relevant to leprosy. Recent studies reveal that 80% of the population lives under conditions of poverty or critical poverty; while the national birth rate has declined by 50% in the last 15 years, birth rate, morbidity, and mortality are three times as great in the 80% living in poverty (unpublished data, Foundation Center for Biological Studies of Growth and Development of the Venezuelan Population, Caracas). With regard to leprosy, the incidence of the disease has been in exponential decline since 1951.[1] The current number of active cases under treatment is about 9,100, with 12,000 under post-treatment surveillance. This represents less than 3% of the 330,000 registered active cases in the Americas in 1988.[2] The disease has been the objective of a very active control program and of basic and applied research activities for many years. The observations made during the course of these programs reflect many basic characteristics of the disease and its impact on women which we find repeated in the scientific literature from all parts of the world where leprosy represents a significant public health problem.

Social scientists and in particular medical sociologists have divided the relationships between sex and disease into two broad categories: those related to sex per se, which is a physiological attribute; and those related to gender, which refers to the sociocultural expressions of sex.[3] While the authors of this paper are all biomedical scientists, we feel that the sociocultural aspects of the problem merit rather detailed discussion, even though our analysis inevitably lacks the depth with which representatives of the social sciences are able to analyze these questions.

## Sexual Aspects of Leprosy in Women

Many of the characteristics of leprosy within areas where the disease is present in epidemic, endemic, or hypoendemic proportions reflect what appear to be true sex-related differences. This part of the discussion will be divided into aspects dealing with subclinical infection, overt disease, and response to immunological intervention.

### Subclinical infection

*Mycobacterium leprae*, contrary to popular belief, is rather highly infectious, as demonstrated by the relatively rapid development of cell-mediated immune reactivity to *M. leprae* in many health workers[4] and relatively strong reactivity to *M. leprae* antigens in household, and in a lower proportion, in non-household contacts of leprosy patients. The low

frequency of clinical disease reflects the low pathogenicity of the microorganism, in spite of high infectivity, and every clinical case of leprosy may reflect some compromise of the normal immune response. In Venezuela, 62.4% of a population of 64,559 healthy household and non-household contacts of patients with leprosy gave positive 48-hour skin test reactions to soluble antigenic extracts of *M. leprae* (Convit and Zuniga, unpublished data). This skin test measures pre-existing hypersensitivity, but is of relatively low specificity; reactivity is clearly induced in part by the active use of BCG in the leprosy control program and perhaps by contact with environmental mycobacteria or related antigens. Nevertheless, reactivity appears to be clearly related to partial or complete resistance to the development of the disease. The average reactivity of the female population of contacts to *M. leprae* soluble antigen appears to be marginally higher (44.6% with reactions of 15 mm or more) than that of males (42.6%, 15 mm or more), and this difference is particularly marked with regard to reactions equal to or greater than 30 mm.

While resistance to leprosy undoubtedly depends upon cell-mediated immunity (CMI), the antibody response to a highly specific antigen of *M. leprae*, phenolic glycolipid I (POL-I), was also significantly higher in females at every age level in a group of more than 9,000 of these healthy contacts.[5] One interpretation of these data is that subclinical infection by *M. leprae* may be more frequent in the female population; other explanations may be that females react more strongly or have higher levels of IgM, including the specific acquired PGL-I antibodies of this class. These data and many others from the literature clearly suggest that subclinical infection by *M. leprae* is much more frequent than overt infection. In this subclinical setting, females appear to develop stronger and possibly more effective immune reactions than males.

**Overt infection**

When clinical leprosy develops in the exposed population, there are many indications that the immune response has been compromised by diverse factors which will be discussed in some detail below. In the clinical setting, the prevalence, incidence, and clinical types of leprosy present in males and females show important differences. In Latin America, the prevalence of leprosy shows a ratio of about 1.8/1.0 in males and females, respectively; one country which does not show this difference is the Dominican Republic. Similar data showing a higher prevalence of leprosy in males, in a proportion of about 2:1, are reported from most areas of the world, including Southeast Asia, some areas of Africa, and other areas of the world. The principal exception to this generalization is found in some areas of Africa, where prevalence rates are similar or even higher in females.[6,7] The higher frequency of leprosy in males is less marked when measured in terms of incidence (new cases/year) for reasons which will be discussed below, but still clearly significant in most of the world. It has been suggested that this difference, while real, may reflect gender-related characteristics and environmental influence or ascertainment bias rather than true sexual differences,[6,7] a point we will come back to later.

The analysis of clinical types of leprosy also reflects significant differences between males and females. In the vast majority of studies, the frequency of multibacillary lepromatous and borderline lepromatous leprosy is reported to be higher in males than in females. This partially explains the difference in prevalence noted above; since multibacillary

leprosy persists longer even with the most effective therapy, these cases tend to show an accumulative effect in the number of prevalent cases. Figure 1 shows the clinical type of leprosy (Madrid classification) in 23,185 cases entered in the Venezuelan National Registry since 1905; the preponderance of multibacillary disease in males is very clear. The higher frequency of leprosy in males is evident at every age level, as shown in Figure 2, but this difference is smaller in children than in successive age groups. The largest number of cases in females was detected in the 15-24 year age group, while the peak in males occurred 10-20 years later, reflecting at least in part the higher frequency and longer incubation period of lepromatous leprosy.

A supervised multidrug therapy program initiated in Venezuela in 1985 illustrates many of the characteristics of clinical disease in this country in a recent period, based on epidemiological studies carried out during intake. The most relevant epidemiological data from the program are shown in Table 1 and include the following observations: predominance of cases in males; higher proportion of multibacillary (MS) cases in males (2.5 MB cases in males/1.0 in females); almost twice as many cases with Grade 2 or 3 disabilities in males, based on the 1985 WHO criteria. In the initial group of 7055 cases, 73.4% of the males and 69.3% of the females were 45 years of age or older; 2.5 and 3.3%, respectively, were younger than 15 years, partially reflecting the later onset of leprosy in the epidemiological situation of declining incidence that exists in Venezuela. Nevertheless, an active search for new cases (total 1539), initiated during the course of the program, showed only 42.9% of the males and 45.1% of the females in the 45 or older group, and 14.2 and 17.4%, respectively, younger than 15 years; in the new group there was essentially no change in the male/female proportion of total cases nor in the multibacillary/paucibacillary ratio. Age-related data clearly reflected the intensity and efficacy of case detection in this program.

The apparent enhanced immunological reactivity and greater resistance of females to clinical leprosy, as indicated by lower incidence and less severe forms of the disease, is not observed during childhood and appears to be associated with puberty and increasing estrogen and other hormone levels. Pregnancy and lactation are accompanied by alterations and instability in hormone levels, including an increase in the progesterone/estrogen ratio, which play multiple functions, some of which are immunological. Not the least of these may be a dampening of the immune response during pregnancy, so that the developing fetus is not rejected as though it were simply a partially incompatible allograft containing foreign histocompatibility antigens provided by the male.

The effects of pregnancy and lactation in leprosy have been studied in some detail in a group of 114 patients and 33 controls in Ethiopia.[8] In this study, the most interesting observations included the following: the first diagnosis of leprosy was made in two controls during pregnancy; relapse or nerve damage occurred in 12 of 25 women with "cured" tuberculoid leprosy; the disease often showed increased activity in both tuberculoid and lepromatous patients, particularly during the last trimester; erythema nodosum leprosum reactions and down-grading phenomena were frequent during pregnancy, while reversal and up-grading reactions became more frequent during lactation and the puerperium. All of these observations are compatible with a diminished and unstable immune response during pregnancy, associated with variable hormone levels. In an accompanying paper,[9] the data suggest that the compromised immune response during pregnancy may be associated with the

emergence of dapsone-resistant strains of *M. leprae*. While Fine[6] has expressed reservations about the experimental design of this study, such as the lack of appropriate non-pregnant controls, it remains one of the very few that has addressed these aspects of leprosy in women. Revision of the clinical histories of 52 Venezuelan patients (37 multibacillary, 15 paucibacillary) with one to six pregnancies showed no notable exacerbation of disease during pregnancy (Aranzazu, unpublished data), suggesting that ethnic and cultural differences may be of some importance in this respect. Dapsone resistance is very infrequent in Venezuela and clearly contributed to some of the observations made in Ethiopia.

In addition to these observations on disease activity, several other interesting questions arise with regard to leprosy, pregnancy, and lactation. Can a pregnant patient with leprosy transmit the disease to the fetus in utero? Based upon a review of the literature, the answer appears to be that the possibility exists, but it is a relatively rare occurrence. *M. leprae* has been demonstrated in the placenta of patients; anti-*M. leprae* antibodies of the IgM and TgA classes have been demonstrated in cord blood of babies born to mothers with lepromatous leprosy, and the levels of these antibodies were higher in sera taken after one month, clearly suggesting that *M. leprae* or some of its antigens cross the placenta.[10] Nevertheless, the occurrence of leprosy in infants is quite rare,[11] which is usually attributed to infection after birth and the relatively long incubation period of the disease. Until more effective treatment of leprosy became available, many leprosy control programs included the separation of children from their mothers at birth as a relatively effective measure of preventing childhood disease.

Can leprosy be transmitted by breast-feeding? Here again, the potential may exist, since large numbers of *M. leprae* have been demonstrated in studies of breast milk from mothers with leprosy.[12] Nevertheless, there is no strong evidence that this represents a significant mode of transmission of the disease, perhaps in part because the gastrointestinal route has never been considered an important portal of entry for establishing infection by *M. leprae*. In experimental models, the oral route of antigen presentation has been associated with the induction of immunological tolerance, which might be a factor in the subsequent development of leprosy.

The logical question that arises is the following: Is the higher immune response in females limited to *M. leprae*, or is it a more universal characteristic of female sexuality? While the relevant literature will not be reviewed in detail, there is considerable evidence in experimental animals and in human beings that females show stronger immunological reactivity than males.[13] This activity is expressed in higher immunoglobulin levels, more rapid rejection of allografts, and greater responses to mitogens; estrogens stimulate immunoglobulin levels, but the influence on reactions of cell-mediated immunity has been more difficult to establish and is closely related to experimental protocols. In males, testosterone appears to be immunosuppressive for both antibody and cell-mediated immune reactivity. The increased immunological activity in women appears to be expressed in forms that are clearly beneficial, such as lower mortality, longer life expectancy, greater resistance to many infections and a lower propensity to the development of immunological tolerance, but there are drawbacks as well. Morbidity, disability, and chronic disease, particularly in old age, are more frequent in females than in males; also autoimmune diseases such as lupus erythematosus and rheumatoid arthritis are much more frequent in females than in males. These observations have been made in highly industrialized countries and in developing

nations, under circumstances where women's life styles have become more similar to male patterns of activity, suggesting that true sexual differences are involved. Interestingly enough, very recent investigations suggest that disability in aged women may have a very strong psychological component based on the cultural factor of greater dependency; immunological reactivity is modulated by neuro-endocrine influences that are only beginning to be understood.

Returning to a point that was made earlier, males in many experimental models appear to develop immunological tolerance more readily than females, and the lower incidence of autoimmune disease in human males suggests that normal tolerance to self-components is less easily broken. The possibility arises that the higher incidence of leprosy in males and the higher frequency of more severe multibacillary forms may be in part predisposed by partial induction of immunological tolerance in utero and through the ingestion of *M. leprae* in breast milk, reinforced by subsequent contact with *M. leprae* and possibly by environmental mycobacteria.[14] This is not an easy hypothesis to investigate because there are still so many unanswered questions related to disease transmission. A possible relationship between genetic susceptibility to a given form of leprosy, which has been demonstrated for both tuberculoid and lepromatous forms of the disease,[15,16] and acquired immunological tolerance has not been demonstrated. One or more non-HLA genes may be responsible for natural susceptibility or resistance to leprosy per se, as has been demonstrated in experimental models in relation to a gene locus controlling innate immunity to *M. bovis* (and probably to *Leishmania donovani* and *Salmonella typhimurium*),[18] but a direct relation of the possible activity of this Bcg,Lsh,Ity locus in relation to tolerance induction has not been demonstrated to our knowledge.

Hypoendemic leprosy with declining incidence rates is characterized by several epidemiological features which include later onset of disease, an increase in multibacillary forms of leprosy, lowering of the male/female ratio of cases, and an increase in clustering and multi-case families.[19] A genetic study of 28 multi-case families in Venezuela,[16] with a total of 211 persons, 116 of whom had leprosy, demonstrated the segregation of HLA haplotypes associated with susceptibility to the lepromatous form of leprosy, though not to the disease itself. The Venezuelan study did not address questions related to the sex of the affected offspring, which would be of considerable interest. Nevertheless, the information presented in the paper can be subjected to a limited analysis of sex-related factors. In this study, the father had leprosy in ten families, the mother in ten, both parents in four, and neither parent in four families. The percentages of children with leprosy in these four groups were 49, 51, 54, and 48%, respectively; there was no significantly enhanced transmission by infected mothers in this study, though others have reported a slightly enhanced risk from infected mothers (cited in ref 7; also see below). Interestingly enough, 65% of the infected offspring of lepromatous fathers had multibacillary (MB) disease, while only 50% of the infected offspring of lepromatous mothers had MD disease.

Unpublished data (Rassi and Convit) from a retrospective study of leprosy in a colony of European immigrants to Venezuela who remained in near isolation for nearly 100 years provide additional information of exceptional interest. Forty multi-case families with a total of 278 offspring were identified. In 14 families, the father had leprosy; patients among offspring were equally divided between males (25%; 7/13 MB) and females (25%; 3/6 MB). Of 8 families in which the mother had leprosy, 52% of the male offspring developed leprosy

(3/16 MB) compared with only 22% of the females (0/6 MB). In 18 families in which neither parent had leprosy, 33% of the male children and 37% of the females developed the disease (16/29 and 9/21 MB, respectively). Several observations merit comment. In this genetically isolated group, predominance of leprosy in male offspring (2.4/1) was observed only when the female parent had the disease. The incidence in this same group was 60% higher than in the group where the male parent had leprosy, but only 12.5% had MB disease, as compared with 47.6% with MB leprosy when the male parent was infected and 50.0% MB when neither parent had leprosy. In this rather unusual situation, where leprosy was introduced into a closed, highly susceptible population, maternal leprosy was associated with a much higher incidence of disease in males, but a significantly lower incidence of multibacillary disease. A higher proportion of the male parents had multibacillary disease, so the parental form of disease does not appear to be relevant. This appears to confirm the importance of maternal factors in modulation of the disease. The postulated induction of partial tolerance suggested earlier may be relevant in the analysis of these data, as reflected in significantly higher incidence though less severe disease in male offspring of infected mothers.

### Response to immunological intervention

In Venezuela, a vaccination trial using the heat-killed *M. leprae*-BCG combined vaccine developed by Dr. Jacinto Convit[20] is being carried out in more than 29,000 volunteers with support from the WHO/UNDP/World Bank Tropical Disease Research and Training Program (TDR) and local sources (CONICIT). While the data from this study are still incomplete, Figures 3 and 4 show the comparative reactivity of males and females to soluble antigenic extract of *M. leprae* and to PPD in individuals tested at yearly intervals from 1 to 5 years after vaccination. At every interval, reactivity was higher to both antigens in females, 79% of whom were negative reactors to the former antigen at the time of entry into the trial. This evidence further suggests the higher immune response of women than men to *M. leprae*.

In summary, several lines of evidence suggest that the immunological response of women to *M. leprae* shows true physiological differences when compared with the male response. These differences include marginally higher reactions in healthy contacts, lower incidence and less severe forms of disease in nearly all parts of the world, and persistent increased cell-mediated reactivity (CMI) after active vaccination. Depression of CMI associated with pregnancy has been associated with exacerbation of disease. There is limited evidence that there may be a degree of immunomodulation by mothers with leprosy, which, depending on as yet poorly defined factors, may be favourable or unfavourable for the offspring.

## Gender-related Aspects of Leprosy in Women

We will interpret this aspect of the analysis of the impact of leprosy in women in very general terms, including socioeconomic parameters and other variables that are relevant to the entire population studied and not limited exclusively to women, but which bear an impact

on the disease with particular features in women. The point should be made at the beginning of this discussion that sociocultural and physiological features of infection are very intimately relate in many circumstances, so that the division between the two has been drawn rather arbitrarily.

In highly developed, industrialized countries, particularly in North America and Europe, the gender-related problems of women are often related to a sense of urgency in the achievement of equal opportunity in career paths and appropriate management of multiple roles including traditional activities combined with an active professional life. In the developing countries of the so-called Third World, these problems pale beside the difficulties associated with fulfilling the basic necessities of life, and much of this responsibility is borne by women. They are largely expected to fill traditional roles of housewife and mother within a situation characterized by economic deprivation and absolute dependence, often accompanied by a marked degree of violence threatening their physical integrity.[2,21]

As we stated at the beginning of this paper, *M. leprae* is rather highly infectious; most people in contact with infected patients appear to develop subclinical infections that are self-limiting. The factors which pre-dispose to active disease have never been adequately defined. The spontaneous disappearance of leprosy from northern Europe (e.g. Norway) and the failure to observe secondary transmission of the disease in much of the developed world clearly suggest that improvement of socioeconomic conditions is one of the factors associated with leprosy control and even eradication, but one that cannot be implemented merely by recognizing its importance. The basis for the relationship between lower socioeconomic development and the persistence of leprosy has been difficult to establish, and the results of descriptive studies have rarely led to the implementation of practical solutions. Perhaps the persistence of other tropical diseases is somewhat easier to understand, considering the importance of insect vectors (malaria, onchocerciasis, leishmaniasis, trypanosomiasis) or of animal reservoirs for some of these diseases. The most widely accepted modes of transmission of leprosy are by direct skin contact with a person infected with *M. leprae* or of naso-respiratory droplets. *M. leprae* remains viable for several days outside the human host, particularly in humid climates, and contact with contaminated fomites cannot be discarded as a possible source of infection; evidence for transmission by arthropods or contaminated soil is still circumstantial.

### Economic factors

Zuniga[22] has reported the incidence and prevalence of leprosy in Venezuela in relation to the economic level after grouping the federal entities into areas of high, intermediate, and low development. The criteria used for establishing these levels were percentage employed, nutritional status, education, mortality from 1 to 4 years, and availability of health services. As can be seen in Table 2, prevalence is more than six times higher in areas of low economic development than in the highest level, and the incidence of new cases for the year 1981 was almost twice as high. While other factors such as climate and humidity would have to be considered for a more complete analysis, the relation to economic development seems very clear.

Most cases of leprosy among 6806 women in the National Registry in Venezuela are associated with deficient standards of living with regard to economic status (79%), cultural

level (78%), nutrition (75%), hygiene (66%), and living quarters (73%). These parameters are clearly very closely related, but a detailed analysis of each in relation to disease is not within our range of competence; in addition, the data in this classification are rather soft in terms of quantitative bases for their analysis. Few analytical epidemiological and sociological studies have been made to assess these factors. We will limit the following discussion to a few rather specific examples of the possible relationship of socioeconomic and cultural expressions of sex on the characteristics of leprosy in women.

### Nutrition

Any factor which compromises immunological reactivity might be expected to enhance susceptibility to leprosy. In developing countries, one of the more obvious factors is inadequate nutrition, influenced by economic considerations and by cultural tradition in food habits. This subject has recently been reviewed[23] and will not be discussed in detail here. Nevertheless, women may be particularly susceptible to iron deficiency, subsequent anaemia, and enhanced susceptibility to disease. As mentioned above, women appear to be particularly vulnerable during pregnancy, at least in part because of physiological changes due to hormonal instability, but inadequate nutrition may also play a significant role. In social terms, pregnancy often begins at an early age and is frequent in developing countries.

### Occupation

Occupation apparently has not been shown to constitute a significant risk factor in developing leprosy. Nevertheless, the suggestion has been made, based on experimental models, that sunlight may produce systemic immunological tolerance by damage to antigen-presenting Langerhans cells in the skin, and that this might be a factor in increasing the incidence or influencing the clinical type of leprosy.[24] Presumably this would be reflected more strongly in agricultural or other outdoor occupations, which are activities that are very culture-dependent with regard to the most affected sex. Skin colour and the extent of body coverage by clothing would also be relevant factors in this context.

### Intercurrent infection

Infectious disease is a greater cause of morbidity and mortality in developing countries than in industrialized nations. Intercurrent infection is a frequent cause of depressed immunity through a variety of mechanisms and may cause increased susceptibility to leprosy. A number of viruses, of which measles is the best known example, produce transient depression of cell-mediated immunity and might be considered as risk factors in the development of leprosy. It is quite surprising that the presence of parasitic infection has not received more attention as a possible risk factor, since there is a growing body of evidence showing the interrelationships between high levels of the immunological mediator interleukin 4, high levels of immunoglobulins, and partial suppression of cell-mediated immunity. Duncan[14] has proposed that giardiasis, which produces a malabsorption syndrome in children, may be related to the initial establishment of *M. leprae* in their tissues. Gender-related patterns of parasitic infections and other diseases have been reported recently.[25-27] While

many show similar patterns of higher incidence and more severe disease in males, the authors emphasize that both biological and behavioral differences play important roles in determining these patterns.

Acquired human immunodeficiency may be of particular interest with regard to the importance of intercurrent infections, and particularly those that suppress cell-mediated immunity. In Latin America, AIDS, while of limited importance in leprosy-endemic regions with the possible exception of Brazil, is more frequent in males than females and might be expected to have a greater impact on the eventual susceptibility of the male population to all infections, including leprosy. In central Africa, on the other hand, the heterosexual nature of the infection and spread of the human immunodeficiency virus might be expected to have a significant impact on the epidemiology of leprosy, with a substantial increase in the proportion of cases among women and among young children. Nevertheless, early studies do not seem to substantiate this postulated trend.[28]

### Deformity and productivity loss

The epidemiology of deformity and incapacity in leprosy has received very little attention, but there are some data which demonstrate significant differences in the frequency and types of deformities which predominate in each sex. Among 7055 patients included in a program of supervised multidrug chemotherapy in Venezuela mentioned earlier, 17.5% of the males and 10.2% of the females had Grade II or III incapacity, based on WHO criteria. Differences in the predominant types of deformity appear to be related to the traditional cultural roles played by each group. Women in Latin America and other Third World areas, particularly in rural, economically deprived environments, usually fulfil traditional roles of housewife and mother; they suffer a high frequency of deformities of the hands (e.g. because of burns), while men more frequently suffer deformities of the feet.

Productivity loss due to deformity in leprosy has been studied in India in a random sample of 550 patients with deformity and 550 adult family members as controls.[29] Statistical analysis by logistic and log-linear regression showed that the absence of deformity would increase the probability of gainful employment and increase annual earnings substantially. Some of the gender-related data in this paper are shown in Table 3. These data reflect the vastly inferior economic situation of women (patients and controls) in the population studied, although the authors make the quite extraordinary statement that "Among control subjects, males enjoyed a modest advantage over females in employment and earnings...." This difference is much greater among the leprosy patients, where the impact of intensified attention to the prevention of deformities would have important repercussions in the economy.

### Social customs

Social structure and customs of the society exert an important force on the epidemiology and sociology of leprosy. In several societies, declining incidence of leprosy has been associated with an increase in the male/female ratio, attributed to the fact that males have greater exposure due to household and community contacts; while women are largely limited to household contact.[19] Women with leprosy are less likely to have the opportunity to

marry; when they do marry, they often seek to limit the number of children that they bear because of fears that their disease will worsen during pregnancy. In many cultures, complete physical examinations are not easily carried out in women because of extreme modesty and unwillingness to undress completely; it has been suggested that the examination of women patients by women doctors might in part overcome this cultural inhibition and increase the levels of detection of early or limited indeterminate/tuberculoid disease in women.
Case-holding and compliance with treatment: These activities represent extremely important aspects of leprosy control. We might expect women to play particularly important roles in these activities because of their nurturing role, particularly influential in children and adolescents. The relevant data are clearly contradictory. In most studies, compliance seems to be no greater in women than in men, though there is limited evidence that it is higher in young people. In some cultures, such as parts of India, men make essentially all the major decisions related to health care and the natural role that women might be expected to play is clearly subordinated to this cultural pattern.[30]

In the previously cited supervised multidrug program in Venezuela, the therapeutic scheme involves supervised administration of rifampin once a month and clofazimine every 15 days, as well as daily self-administered Dapsone, monitored at 3-month intervals by urine tests. The same regimen is used for paucibacillary (PB) disease (12-18 months) and multibacillary (MB) leprosy (minimum 36 months). Post-treatment surveillance at 6-month intervals for at least 10 years in the MB group and 2-5 years in the PB group to detect relapse, reinfection, and incapacity constitutes an integral part of the program.[31] Compliance, defined as receiving at least 75% of the supervised doses of medication, showed no significant differences among males and females (80.6 and 81.5%, respectively). As shown in Table 1, a majority of the cases in this study were of multibacillary leprosy, which increases the significance of the relatively high proportion of compliance in terms of the success of the program. Further studies for the reasons for noncompliance are exceptionally important for the implementation of multidrug therapy. In Nepal, compliance actually increased when treatment centres were farther from the patient's home, in part because of the fear that social stigmatization would be more likely if patients were identified through assistance in nearby centres; confidence in the quality of health care was also an important factor. Women were less mobile and showed lower compliance rates, particularly if they lacked confidence in the local health care programs.[32]

### Health education

Valencia[33] has emphasized that health education concerns that part of health care that is concerned with promoting health behaviour. Recognition of the advantages of multidrug therapy and prophylactic vaccination (where available), compliance and regularity of treatment, learning to recognize changes in disease condition and reporting those changes, particularly after terminating multidrug therapy, are examples of positive behaviours that should be important objectives of health education programs, based on previous knowledge of the psychosocial aspects of diverse cultures. Health education may be directed primarily to the patient and family, but community education is also fundamental in permitting patients of either sex to achieve economic independence and social acceptance. In the words of Valencia, "Within this proposition -- that the family is a critical factor in leprosy control -- is

the inherent and inexplicable role of women as initiators of health activities in relation to leprosy in the community. Women constitute the most basic unit in the building of an infrastructure for an efficient leprosy control program."

**Perspectives for the Future**

In the future, multidrug treatment of leprosy will surely cause profound changes in the epidemiology of the disease. At least three factors seem to be of fundamental importance in the success of this approach to leprosy control: early diagnosis; high levels of case-holding and of compliance with all aspects of treatment, especially including the unsupervised administration of Dapsone; and careful post-treatment surveillance to detect relapse, late reversal reactions or reinfection, and to prevent incapacity or deformity. The responsibilities for fulfilling these goals traditionally depend on medical and paramedical personnel, but there would seem to be an urgent need to incorporate medical sociologists, socio-epidemiologists and natural community leaders into these programs, which represent enormous investments in national and international economic resources. To mention only one aspect, what are the reasons for non-compliance with treatment? These have been analyzed in some detail in many cultural settings, but there still seems to be no clearly defined set of parameters which would allow prediction of potential defaulters, and the reasons for defaulting undoubtedly vary considerably in different ethnic and cultural situations. Greater emphasis should be placed on the role of women not only in self-compliance, but also within the family and community structure. Women in Latin America and in most cultures are traditionally concerned with nurturing, including great responsibility for family health (which, as stated above, may not be true in all cultures with regard to making major health-related decisions). They should be incorporated into a very active role in multidrug programs, based or previous studies in diverse cultures to determine their attitudes, willingness, and capacity to influence primary and community health programs.

Essentially no disease has ever been eradicated by drug therapy alone, and there is no reason to expect that leprosy will be the exception. Nor is there reason to believe that the disease will disappear in the foreseeable future by improving economic conditions in the developing countries, since much of Latin America is in deep economic crisis and much of sub-Saharan Africa and parts of Southeast Asia are in similar or worse situations. Detection of subclinical infection would be one component of successful control and eventual eradication programs, but no test is currently available with sufficient sensitivity and applicability to vast numbers of samples to fulfil that goal. Much emphasis has been placed on serological tests, but those available for widespread use do not possess the sensitivity required to show a profound impact on the detection of subclinical infection. Molecular biology may permit the development of highly specific recombinant proteins or polypeptides for use in skin tests capable of detecting infection. New advances such as the use of the polymerase chain reaction (PCR) may lead to unanticipated advances in the study of *M. leprae*; Hartskeerl et al.[34] have reported that *M. leprae* can be detected specifically with a limit approximating one microorganism using primers for a gene encoding the highly specific 36 kDa antigen. This powerful technique may eventually clarify many of the unanswered questions regarding ecological distribution and disease transmission, such as the possible

importance of fomites, presence of *M. leprae* in the soil or on the skin of healthy individuals. PCR and other molecular biology techniques may clarify sex differences in exposure in relation to subsequent development of disease.

Active vaccination would appear to be an indispensable component of any program which aspires to control and eventually eradicate leprosy, particularly in areas of the world such as the Indian subcontinent. Leprosy vaccines are still in an early stage of development and evaluation, in spite of important advances in the study of the molecular biology of *M. leprae*. Many studies have demonstrated that BCG induces variable levels of protection, closely related to the incidence of tuberculoid leprosy. The demonstration by Convit et al.[35] of the therapeutic efficacy of a mixture of heat-killed *M. leprae* and live BCG in patients with the most severe forms of leprosy, accompanied by the development of cell-mediated immune reactivity to *M. leprae*, clearly suggests the potential for immunoprophylactic use of this type of vaccine, which is being evaluated in large-scale trials in Venezuela and Malawi. When a successful vaccine becomes available, which seems inevitable, important decisions will have to be made in terms of the allocation of economic resources to multidrug therapy and to vaccination. Here again, women have the potential to play an exceptionally important role in determining the success of these programs. This would include not only patients who are willing and able to assume active roles in confronting their own disease and who often bear the responsibility as heads of the household for the health of their children and other family members, but also natural community leaders, health care personnel, sociologists, and others who understand more clearly the special circumstances related to women and disease.

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Table 1. Characteristics of 7055 cases of leprosy in the supervised multidrug therapy program in Venezuela, 1985-1990.

| Characteristics | Males | Females |
|---|---|---|
| Active cases | 4652 (65.9%) | 2403 (34.1%) |
| Clinical form | | |
| Multibacillary | 2864 (61.6%) | 1129 (47.0%) |
| Paucibacillary | 1788 (38.4%) | 1274 (53.0%) |
| Disabilities | | |
| Grades 2 and 3 | 812 (17.5%) | 244 (10.2%) |
| Coverage of diagnosed cases | 3986 (85.6%) | 1946 (81.0%) |
| Regular treatment | 80.6% | 81.5% |
| Adverse side effects | 4.0% | 1.9% |
| Reactional phenomena | 4.2% | 4.1% |

Source: Computerized Registry, Supervised Multidrug Therapy.

Table 2. The relationship between economic development and the prevalence and incidence of leprosy in Venezuela.[22]

| Level of development | Population 1981 | New cases | Prevalence (x 1000) | Incidence (x 1000) |
|---|---|---|---|---|
| Superior (25%) | 3.455 million | 68 | 0.30 | 1.97 |
| Intermediate (50%) | 7.341 million | 176 | 0.77 | 2.40 |
| Inferior (25%) | 3.807 million | 128 | 1.91 | 3.39 |

Table 3. Economic productivity of 550 leprosy patients with deformities and of matched controls in India.[29]

| | Patients | | Controls | |
|---|---|---|---|---|
| Parameter | Males | Females | Males | Females |
| Gainfully employed | 54.6% | 14.2% | 78.2% | 36.8% |
| Days worked per year | 273 | 281 | 286 | 265 |
| Estimated annual earnings | Rs 2629 | Rs 101 | Rs 4594 | Rs 400 |

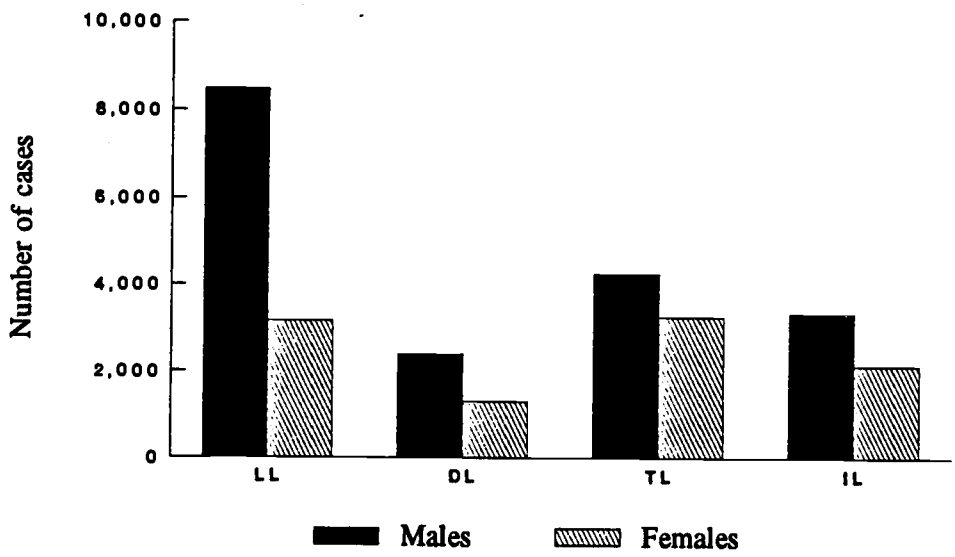


Fig. 1 Cases of leprosy by clinical type, Venezuela, 1905-1990.

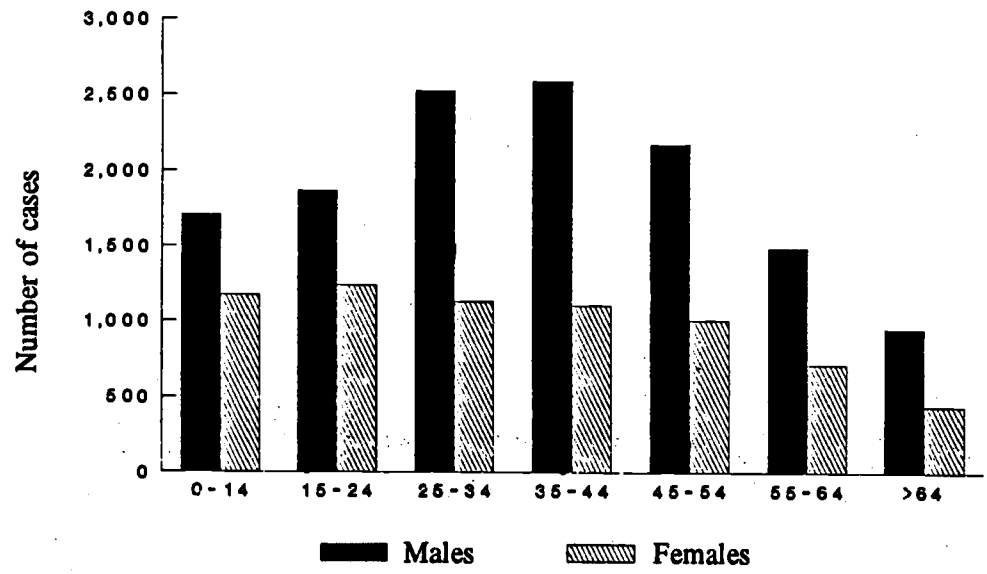


Fig. 2. Cases of leprosy by age, Venezuela, 1905-1990.

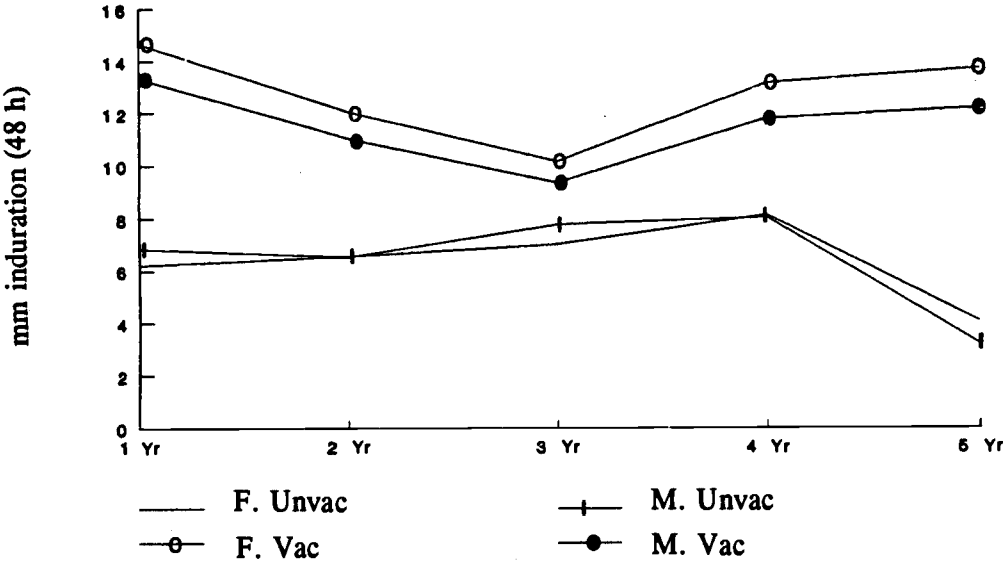


Fig. 3. Skin tests in vaccinated persons (soluble extract of *M. leprae*).

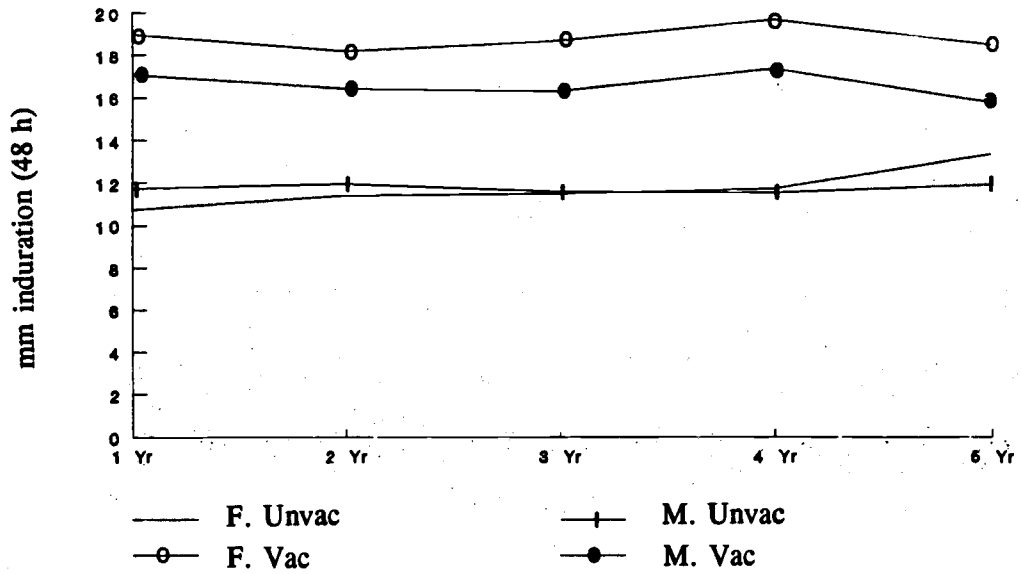


Fig. 4. Skin tests in vaccinated persons (PPD).

# Adam's Rib Awry: Women and Schistosomiasis

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*"If we continue to ignore the women's situation can we ever hope to attain Health for All, even long after the year 2000?"*

Dr. Halfdan Mahler, 1985[1]

## Summary

The present paper reviews the literature to determine if there are predisposing factors that influence the transmission, prevalence, intensity of infection, and morbidity of schistosomiasis for women. The review suggests that: (1) the higher prevalence rates observed in males, in most endemic areas, is not due to gender per se, but to the greater opportunities afforded males for exposure; (2) cultural and social biases determine occupational roles and, in some circumstances, biases against women may protect them from exposure; (3) when women assume typical "male" roles, their risk and prevalence of infection increases; (4) in Muslim societies, women's exposure to water is restricted and infection rates are usually lower; (5) morbidity does not appear to be influenced by gender; and (6) the most important impact of schistosomiasis on women is its possible disruption of maternal functions, such as pregnancy, and its role in maternal, infant, and child mortality and fetal wastage. Suggestions are made also for expanding existing research and for new studies concerning factors that may influence infection and disease in women.

## Introduction

It is generally conceded that, in most instances, males have higher infections rates of parasitic and infectious disease,[2,3] than do females. Chen and Mott[4] have noted with regard to *Schistosoma mansoni* that, "Among the infected subjects in rural endemic areas, males usually have higher infection rates compared with those of females." This assumption, however, has not been formally documented for the disease as a whole, nor have factors which may influence this gender unbalance been reviewed critically. The role of women in the epidemiology of this disease warrants additional scrutiny and several questions remain to be resolved: (1) Are males really more susceptible to disease than females, or is their opportunity for infection greater? (2) Do cultural and social factors protect females or do they predispose them to infection? (3) Are males more intensely infected and more subject to disease and morbidity than their female counterparts? (4) Are there physiologic and morphologic traits associated with gender that may exacerbate or diminish disease?

The present paper, therefore, reviews the literature to determine if there are sexual differences with respect to factors influencing the transmission, prevalence, intensity of infections, and morbidity of schistosomiasis.

## Factors Influencing Prevalence and Intensity of Infection

Schistosomiasis is not a single disease, but a disease complex incorporating several species of parasites that differ from one another in geographic distribution, choice of snail hosts, clinical manifestations, and in the morbidity they produce. Prevalence rates for males and females from selected but representative surveys are presented in Table 1. In as much as the studies differed in the nature and size of the samples employed, parasite species, and diagnostic techniques, they cannot be validly compared. However, gender ratios can be noted and trends compared for the various geographic areas and for the different parasite species.

### Water usage

Although the epidemiology of each of the schistosomes differs to some extent, the transmission of infection for all species is dependent on human water contact and the extent and duration of this contact in association with domestic and occupational activities.[23] The amount of body surface exposed to water, and thus to cercarial contact, during the pursuit of these activities is another factor influencing transmission.

Water-related activities may be gender influenced, are generally different for males and females, and may be modified by age and cultural traditions. Children may contribute to adult activities of both sexes, but appear to be at greatest risk as a consequence of playing and swimming in water. In reviewing the determinants of maternal health in Africa, Uyanga noted that, "Schistosomiasis poses a particular risk to women in some African societies because of their multiple water-related activities: water drawing, clothes washing, bathing children and wetland rice cultivation. The health consequences may include anaemia and weight loss."[24] However, Haddock[25] has commented that, based on studies done in Puerto Rico, "Boys traditionally have more freedom than girls to enjoy water contact such as swimming and fishing". A similar observation was made by Kvale[20] who studied an area in Brazil and remarked that, "adolescent girls and women in low-income countries usually wash clothes in local water bodies, adolescent boys and young men swim and bathe for recreation in the reservoir, canal, and river more than females." In numerous studies it has been confirmed that farming, fishing, basket weaving, ablution, and other religious rites are more often associated with males; whereas, water gathering, washing of utensils, and laundering appear more often as female activities.[7,26,27] In St. Lucia (Table 1C), higher prevalence rates in women in some communities may have been associated with clothes washing. Dalton[27] reported that, in St. Lucia, this task accounted for 21.5% of all water contacts, but 52% of total time individuals were exposed to water. In this area, the peak of cercarial density occurred during the period of most intense clothes washing. However, in certain societies women tend to wash in the early hours of the day and thus are not exposed to the period of maximum cercarial density, which usually occurs between one and three o'clock in the afternoon for *S. mansoni* and *S. haematobium*, and after sunset in endemic regions of *S. japonicum*. Yokogawa[6] noted that males were predominantly infected in the Katayama

Districts because the snail hosts were found in marshes rather than rice fields, where only men would go for fishing or cutting grass. Pesigan et al.[7] in the Philippines, reported the highest prevalence of infection in farmers and tuba gatherers, both male dominated activities, while Farooq and his associates,[26] in Egypt, found fisherman, farmers, and farm labourers, again male dominated occupations, to have the highest prevalence. In the Egyptian study, overall prevalence rates for males and females were about equal (Table 1); however, when female farm workers were compared with males in non-agricultural occupations, their prevalence was considerably higher (43.0% and 25.1%, respectively), but lower than male farmers. Another study in Upper Egypt[28] demonstrated that farmers were again the group at highest risk and in 2403 individuals examined, males had the greater prevalence (41.1% to 17.6%). The lower rates in females were attributed to diminished water contact, an observation confirmed by Kloos et al.[29] in their study of water contact behaviour in two Upper Egyptian villages. Moreover, it was noted that most women did their laundry in flat pans and all used soap which killed the cercariae.

In Africa, in most instances, fishing is a male occupation and associated with a high risk of infection.[26,30] If culture dictates a change in occupational roles, as in the Mende villages in Sierra Leone, and fishing becomes a female task during the dry season, then females will have higher prevalence rates than do males.[31] Bradley et al.[32] also noted a markedly higher prevalence rate of *S. haematobium* in males in the Lango district of Uganda, and attributed the differences to the fact that men fish all year, whereas women fish only at the end of the dry season and then only in dry years. Age may also influence the extent and longevity of water contact, and infection appears to be correlated with frequency of contact.[33] Okahara[5] noted that in rural Japan "As the female grows older (over 20 years old) the rate of infection increases. This may be due to the fact that with marriage, she becomes the worker of the family, helping with farming and taking care of household duties, and has more chances of getting infected". In Brazil, Kvale[20] noted that between the ages of 10 and 24, males had almost double the infection rate of females; whereas, in younger and older groups the rates were almost equal. This phenomenon was thought to be associated with a longer period of time spent in the water by males of this particular age cohort.

**Social and cultural attributes**

It is generally acknowledged that in the developing world, where schistosomiasis is endemic, women are often discriminated against with respect to economic opportunities, education, and health care.[34-37] Occupational tasks and associated risk of infection, as previously noted, are frequently controlled by societal dictates and are frequently gender oriented. Religious practices, such as ablution and wadu (ritual washing), are required of male Muslims several times a day. Wadu is performed only by males and entails washing three times all exposed parts of the body or approximately 25% of the total body surface.[38] Ablution pools of some Mosques have, at times, become contaminated with host snails and may serve as sites of transmission.[39] Such practices may contribute to higher male prevalence rates in Muslim communities. The high gender prevalence ratio (4.49) noted in the studies of Ruwan Sanyi village, Nigeria, were attributed to cultural traits of the inhabitants (Hausas, Fulanis, and Maguzawas) who are rather strict Muslims who markedly restrict the activity of their women.[40] Consequently, water-related activities, such as swimming and bathing by

females are severely limited. Cultural restriction begins early, as the young girls are marriageable at about 12 years of age, and effectively removes the cohort most frequently exposed to uninhibited water activity. In fact, "Bilharzia is regarded exclusively by the villagers as a male disorder, and many equate haematuria in males to menstruation." In communities having both Muslim and Christian populations, the latter have significantly less infection.[18,26]

In the Egypt 49 study,[26] it was observed that swimming was predominately a male activity (25.7% of males, 6.8% of females), and that swimmers had twice the infection rate of non-swimmers. Although the infection rate among both sexes of swimmers was the same for *S. mansoni* and mixed infections, males showed a greater rate of infection with *S. haematobium*. No explanation was offered for the *S. haematobium* difference; however, it is of interest to note that the body surface of males (1.8 $m^2$) is somewhat larger than females (1.6 $m^2$) as calculated for St. Lucian adults.[23]

Information concerning the relevance of education to the prevalence of schistosomiasis is scarce. The Egypt 49 study[26] collected educational data and demonstrated that female subjects were less well educated than their male counterparts. Thus, while 95.5% of the adult females in the project sample were unable to read or write, only 65.5% of the males were so handicapped. Likewise, 4.5% of males, but only 0.5% of the females, had obtained a primary school education. Among agricultural workers, however, higher prevalence rates were detected in literate individuals than in illiterates (60.6% to 47.3%). When all other occupations were considered, the trend was reversed with literate individuals having somewhat fewer infections (22.9% to 26.7%). If all occupations are considered, literate adults had higher infection rates than individuals with just a primary education. Children who attended school, however, had lower rates of infection than did those who did not. It would appear, therefore, that females might be at higher risk as a consequence of being educationally deprived; however, overall males and females were equal in prevalence. Jordan[21] noted that in St. Lucia, health education reduced the number of women using the river for laundering. When health education was coupled with alternative laundry and sanitary facilities and, also, provided a suitable environment for social intercourse; women's acceptance of these facilities was generally favourable.

Recent studies[41,42] suggest that understanding the behavioral patterns and attitudes of women in pursuit of their daily activities may be the key to improving water usage and sanitation associated with the transmission of water-borne disease. They assume, moreover, that the woman in the household is the determining influence on the health related activities of other household members and that she will largely govern the acceptance or rejection of behavioral change and/or introduced technical innovations. This common sense approach to understanding why improvements in water supply and sanitation may not be accompanied by a reduction in disease prevalence, has had limited application in schistosomiasis projects.

In an effort to ascertain attitudes toward schistosomiasis control, questionnaires were administered to 271 women and 168 men in several rural communities in Zimbabwe.[43] The questionnaire sought to test the knowledge of the inhabitants concerning the disease and its transmission and the uses of the plant molluscicide *Phytolacca dodecandra*. Although more women were aware of the plant as a floor polishing agent, because of their social position males were three times more aware of the other uses of the plant, i.e. as a medicine, emetic, lightning protector, and flea protector. The authors of a recent social survey in Zambia,[44]

attempting to elicit information on disease awareness and other health related attitudes, noted that in rural Zambian communities an individual's opinions often reflect the opinion of the family, kin, or clan. Moreover, "women in rural areas depend very much on their husbands or male relatives for decisions." In both of these studies, more women were interviewed than men, since men were away due to occupational duties. These studies demonstrate the difficulty in assessing women's attitudes toward health and disease in many rural areas of the Third World. Similarly, the authors of a study[41] designed to elicit household practices of Egyptian village women noted that, "most women initially tended to give what they believed to be expected answers instead of actual practice."

Inherent social attitudes may result in females resorting to activities directed against their own gender. Thus, in a study of child health in a self-help settlement in Cairo, Egypt, it was observed that a subtle male preference was expressed in many aspects of childrearing.[45] This preference resulted in marked nutritional differences between the sexes and greater survival of male children during the second and third years of life. Not only were males better nourished, but they were more apt to receive medical treatment for minor diarrhoeal episodes than were females. It has been shown by Chandiwana,[46] that a positive correlation existed between malnutrition and schistosome infection in Zimbabwean children. No correlation could not be demonstrated, however, with intensity of infection.

**Intensity of infection and general morbidity**

As a consequence of a long series of population-based epidemiological studies, it has been observed that: (1) mean prevalence and intensity of infection are correlated with one another and tend to increase in parallel; and (2) morbidity and disease are directly related and roughly proportional to the intensity of infection both in the individual and in the community.[47] Unfortunately, only a few studies could be found in which the intensity of infection and/or morbidity were compared with respect to gender. Forsyth and MacDonald[48] compared, by radiography, urological complications found in Tanzanian school children. Although the sample was small (68 boys and 21 girls), and perhaps unrepresentative, boys showed greater prevalence of deformed ureters and deformed bladders. In a subsequent longitudinal study in a community in Zanzibar, Forsyth[49] reported that both prevalence and intensity of infection were similar in primary schoolchildren, but were higher in males in other age groups (>10 years). Abnormal urograms were twice as frequent in males than in females and males also exhibited a higher percentage of hydronephroses, calcified bladders, and deformed ureters. Males were also found to have higher intensities of *S. haematobium* infection in studies conducted by Wilkins[50] and Pugh and Gilles.[40] A higher intensity of infection with *S. mansoni* has been reported by Dias et al.[19] in Brazilian males and in Ethiopian boys by Hiatt and Gebre-Nedhin.[18] On the other hand, Lehman et al.[51] noted a higher prevalence in females, but an almost identical intensity of infection in both sexes in their study in Northeastern Brazil. Intensity of infection, however, was found to be greater in Kenyan females by Siongok et al.[52] It is of interest to note that in Northern Kwazulu, South Africa, where *S. haematobium, S. mansoni*, and *S. mattheei* all occur, Schutte and his associates[53] could find no correlation between the prevalence, intensity, or morbidity of infections and sex. Several studies on *S. japonicum*[54-56] show that in most cases, but not all, intensity of infection is greater in males than females.

## Morbidity associated with physiologic and morphologic traits

A limited number of animal studies suggest that the sex of the host may influence susceptibility to schistosomiasis and consequently in most animal studies the experimental subjects are either one sex or another, but most frequently male. This bias may be a direct result of the early observations of Goble et al.[57] and of Purnell[58] who observed that female mice and hamsters were somehow more resistant to schistosome infections, harboured fewer worms, and exhibited less morbidity than did males. These studies have not been followed up and the extent of sex to the exclusion of other factors remains to be resolved. The recent analysis of Tavares-Neto and Prata,[59] on the occurrence of hepatosplenomegaly in Brazilian families, is of more interest because the data suggest that this type of morbidity may be inherited and maternally controlled. The occurrence of this severe type of morbidity in the filial generation was significantly correlated with the occurrence of the disease in the mother. This type of severe morbidity was five times as likely to occur in the offspring if the mother was infected than if the father was infected.

### *Sex hormones*

In a recent review on the effects of sex hormones on the course of parasitic infections, Alexander and Stimson[60] noted that, "Sex hormones clearly play an influential role, both directly and indirectly, in the regulation of the immune response, and so, by implication, they should also influence the control of parasitic infections." Unfortunately, they were not able to cite specific evidence to support this hypothesis and sex hormones which may favour a particular gender with one type of infection may favour the other sex in another type of infection. In general, male steroids appear to depress both cell-mediated and humeral immune mechanisms; whereas, female hormones enhance humeral responses and depress cell-mediated activity. Evasion of the immune system by schistosomes relies to a great extent on molecular mimicry and by acquisition of host antigens,[61-63] consequently modulation of effector systems by hormones may have little direct impact on these organisms.

On the other hand, Tiboldi[64-65] has studied the ovaries in acute murine schistosomiasis and noted atrophy of the corpus luteum and nuclear alterations of the interstitial cells. There was also a decrease in the mean serum level of progesterone. This pathology could be reversed, however, as a consequence of treatment with niridazole.[66] Eggs were not present in the ovaries and although the basis for the pathology was not proven, it was thought to be associated with changes in hormone levels. Estradiol levels have been found elevated in individuals with hepatosplenomegaly, and schistosomal cirrhosis may cause retention of estrogens and cause pituitary inhibition.[67-68]

### *Infections of the genital system*

Infections of the female genital system are by no means rare,[4,69-71] impose a distinct burden on the health and well-being of women, and, by definition, are gender unique. Genital organs appear more frequently involved in *S. haematobium* infections than in those caused by *S. mansoni* or *S. japonicum*, perhaps due to the localization of this species in the

vesical plexus. Involvement of the female genital organs appears not to be common[72] and only mentioned in passing in the recent review on *S. japonicum* by Chen and Mott.[79] In *S. haematobium* infections, the external organs such as the vagina, vulva, and cervix are more frequently infected than internal genitalia, such as the uterus and fallopian tubes.[74] Disease of the female genital tract may result in chronic back and abdominal pain, disturbed menstruation, menorrhagia, salpingitis, endometritis, endometriosis, oophoritis, and papillomas of the vulva, vagina, and cervix.[74-81] Wright et al.[80] reviewed the histopathology of genital tract infection in Malawi from 1976 to 1980 and concluded that schistosomiasis was "a significant cause of gynaecological morbidity, particularly when infection involved the lower genital tract..." The distribution of lesions associated with genital schistosomiasis is given in Table 2.

*Pregnancy and schistosomiasis*

It is in their roles as mothers that women are most impacted upon by the prevailing level of public health and by the discriminatory attributes of many Third World cultures. This discrimination appears to impinge on three age groups: (1) very young females who may get a smaller proportion of available food and receive less prompt medical attention; (2) childbearing women; and (3) the indigent elderly.[37] In many Third World countries, including those with endemic schistosomiasis, childbearing has the highest risk of death, and maternal mortality rates are significantly greater than in the developed world.[36-37] Likewise, infant and child mortality rates are higher than in the developed countries. It may also be that the pregnant condition is the most vulnerable to schistosomiasis, as it is with other diseases, and the state where this parasitic disease most affects the well-being of women. It is reasonable to assume that the debilitating nature of chronic schistosomiasis, encompassing hepatosplenomegaly, anaemia, genital involvement, and obstructive uropathy, might contribute significantly to the morbidity and mortality associated with pregnancy; consequently contributing not only to fetal wastage, but to infant and child mortality. Moreover, it is well recognized that the immune system is depressed during pregnancy. Much of the recent literature on the effects of schistosome infection on the pregnant woman has been reviewed by McNeeley and Magu.[81] They cite numerous references in which ectopic pregnancies, miscarriages, abortions, sterility, and infertility were attributable to schistosome infections.

Involvement of the placenta has been reported on numerous occasions in women infected with both *S. mansoni* and *S. haematobium*,[81] but apparently is uncommon with *S. japonicum*. Cort and Meleney[82] noted an experimental infection reported by Narabayashi, but no references to human infections were cited in the recent review by Chen and Mott.[73] The only cases of human congenital schistosomiasis are those reported by Narabayashi in the Japanese literature. Cort[83] later cited this report and noted that of 22 newborn babies examined, three were found infected with *S. japonicum*. Animal studies, however, support the concept that *S. japonicum* infections may be congenitally acquired.[84]

In several studies, the transplacental transfer of antibodies (IgG, IgM) has been detected in neonates[85-87] and was found to persist for up to 6 months. Similarly, when uninfected children of schistosome-infected mothers were skin tested with *S. mansoni* antigens, they were found to be sensitized.[88] Circulating antigens, also, have been detected in

the sera of newborns.[89] The milk of infected mothers may contain both schistosomal antibodies and antigens and these may be transferred to nursing infants.[90] However, the role of maternally transferred antigens and antibodies in either the protection or sensitization of children born to infected mothers requires further resolution. Experimental studies employing murine models have produced mixed results with regard to these phenomena; however, recent studies by Lenzi et al.[91] suggest that congenital and nursing transfer of immunologic substances may alter the development of schistosomal infections and lessen the host response to eggs deposited in the tissues.

Chemotherapy and treatment of the pregnant women has always been a major concern of the physician and public health worker. The highly toxic antimonials used in the past, as well as niridazole and hycanthone, which in animals are known mutagens, carcinogens and teratogens, are obviously contraindicated. Metrifonate, frequently used for the treatment of *S. haematobium*, is not recommended during pregnancy or during lactation. It has been shown to be teratogenic in a variety of laboratory animals and to be mutagenic for bacteria, mammalian cells, and mice.[92] A case of neonatal deformity and death as a consequence of its use has been reported.[93] Oxamniquine is not known at present to be either a carcinogen or a teratogen, but could be mutagenic as other nitroquinaline derivatives have this property. Foster,[94] who recently reviewed the clinical history of this drug, recommends against its use in pregnancy until more information is available. Praziquantel has not been shown to be either teratogenic or mutagenic, but it has been found to be excreted in minute amounts in the milk of lactating women.[95-97] Although there appear to be no contradictions to the use of this drug,[97] most physicians are cautious in using it for pregnant or lactating women.[98]

## Conclusions

Several pertinent points with respect to schistosomiasis and its impact on women were revealed in the present review: (1) gender per se does not influence infection and males, in most endemic areas, have higher infection rates as a consequence of opportunity for exposure; (2) cultural and social biases largely determine occupational roles and, in some circumstances, biases against women may actually serve to protect them against the opportunity for exposure; (3) when women assume typically "male" occupations, such as fishing, both their risk and prevalence of infection increase; (4) in Muslim societies, religious restrictions tend to decrease women's exposure to water and usually result in lower infection rates; (5) general morbidity does not appear to be influenced by gender, and the more severe morbidity observed in males in several studies can be attributed to the intensity of infection associated with their opportunity, frequency, and longevity for water contact; and (6) the most important impact that schistosomiasis makes on women is its effect on her maternal functions, such as pregnancy, and its possible role in increasing fetal wastage and infant and child mortality.

Several avenues for additional or new research are suggested. Animal studies suggesting that gender influences susceptibility to infection need to be repeated and expanded, particularly with respect to suppression of the immune response by sex hormones and its effect on infection. More studies are needed in which intensity of infection and morbidity are compared by gender. Existing studies are limited both in number and in the

number of individuals studied. The concept of a genetic disposition toward susceptibility to infection, the intensity of infection, and, more important, the acquisition of morbidity has scarcely been explored and warrants more effort. In particular, the suggestive evidence that morbidity may be influenced by maternal factors. (not a sentence) The contribution of infections of the female genital system to overall morbidity in women, to fertility, and to abortions, stillbirths, and fetal wastage, requires additional investigation. Maternal, infant, and child mortality continue to be the bane of all developing countries. Consequently, the contribution that schistosomiasis may make in exacerbating these conditions and its effects on the pregnant women deserve special attention. In this vein, the effect of the passive transfer of antigens and immunoglobulins from infective mothers to their newborn children remains a fertile area for immunologic investigations.

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Table 1. Comparison of male to female prevalence rates in selected surveys for schistosomiasis.

| Country | Sample size | Age groups | Parasite* | M/F prev. ratio** | Reference |
|---|---|---|---|---|---|
| **Asia** | | | | | |
| Japan (1953) | 453 | All | SJ | 1.23 | Okahara 1962[5] |
| (1955) | 293 | All | SJ | 1.59 | |
| (1957) | 161 | All | SJ | 1.44 | |
| Japan (1969)*** | 243 | All | SJ | 1.97 | Yokogawa et al. 1969[6] |
| Philippines (Palo 1953-54) | 2909 | 14-70+ years | SJ | 1.07 | Pesigan et al. 1958[7] |
| Indonesia (1972) | 1417 | All | SJ | 0.96 | Clarke et al. 1974[8] |
| **Africa** | | | | | |
| Ethiopia (Awash Valley 1772-73) | 2508 | Adults | SM | 0.69-1.89 | Kloos and Lemma 1977[9] |
| Equatorial Guinea (1982) | 1364 | All | SI | 1.23 | Simarro et al. 1990[10] |
| Zimbabwe (198?) | 297 | All | SM | 0.51 | Chandiwama 1983[11] |
| | | | SH | 1.24 | |
| Egypt (Nile Delta 1983) | 15,058 | All | SM | 1.26 | Cline et al. 1989[12] |
| | 14,748 | All | SH | 1.75 | |
| Sudan (Rahad Zone 1986) | 17,748 | 7-15 years | SM | 1.88 | Ferwick 1986[13] |
| | | | SH | 1.97 | |
| Tanzania (Pemba Island 1986)**** | 24,462 | 5-19 years | SH | 1.14 | Savioli et al. 1989[14] |

| Country | Sample size | Age groups | Parasite* | M/F prev. ratio** | Reference |
|---|---|---|---|---|---|
| Nigeria (Ruwan Sanyi 1971) | 305 | 5-15 years | SH | 4.49 | Bell and Howells 1973[15] |
| Nigeria (1988) | 1,000 | All | SM-SH | 2.52 | Audu 1988[16] |
| Zambia (1970-71) | 6,115 | 0-4 years<br>5-14 years<br>Adults | SH | 0.92<br>0.91<br>1.00 | Anon. 1974[17] |
| Ethiopia (1976) | 272 | 7-16 years | SM | 1.07 | Hiatt and Gebre-Medhin 1977[18] |
| **Neotropics** | | | | | |
| Brazil (1980) | 3,407 | All | SM | 1.91 | Dias et al. 1898[19] |
| Brazil (Cera 1978-79) | 1,135 | All | SM | 1.53 | Kvale 1981[20] |
| St Lucia (Richfond Valley, North 1868) | 1,059 | 15+ years | SM | 0.69-0.9 | Jordan 1985[21] |
| Puerto Rico (1953) | 8,955 | 5-18 years | SM | 1.54 | White et al. 1957[22] |

* SM *Schistosoma mansoni*; SH *S. haematobium*; SJ *S. japonicum*; SI *S. intercalatum*.

** Ratio represents male prevalence divided by female prevalence.

*** Prevalence determined by immunologic test.

**** Prevalence determined by chemical method for gross haematuria.

Table 2. Distribution of gynaecological lesions associated with schistosomiasis (after Wright et al.[80]).

| Area | Ref | Vulva | Vagina | Cervix | Corpus Endometrium | Tube | Ovary | Total |
|---|---|---|---|---|---|---|---|---|
| South Africa | 72 | -- | 7 | 16 | 8 | 27 | 7 | 65 |
| South Africa | 00 | 15 | 5 | 120 | 6 | 12 | 7 | 165 |
| South Africa | 00 | 10 | 8 | 102 | -- | 15 | 3 | 138 |
| Egypt | 00 | 9 | 25 | 34 | 5 | 7 | 4 | 84 |
| Malawi | 77 | 16 | 17 | 106 | 4 | 28 | 17 | 188* |

* These lesions were from 176 cases accounting for multifocal infection in 11 cases.

# Women and Malaria

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## Abstract

This paper reviews the factors which make non-immune pregnant women particularly vulnerable to falciparum malaria and examines the problems of adequately protecting them in relation to current control strategies. Women are most at risk in areas of high and continuous transmission, particularly during their first pregnancy, and also under conditions of unstable malaria which do not permit immunity to develop.

Chemoprophylaxis is recommended for pregnant women in holo and hyperendemic areas in Africa and Papua New Guinea. Chloroquine is safe, but drug resistance problems are beginning to limit its utility. Distribution is a formidable problem in rural areas with poorly developed health care infrastructure, and research studies reveal widespread ignorance and lack of motivation.

In countries in which primary health care systems are relatively well developed, the assumption is made that women and men have equal access to medical facilities. The preponderance of reported cases among adolescent and adult males in some areas has been attributed solely to the well known greater occupational risks in some traditionally male activities. Two recent studies, however, suggest that underprivileged women, weighed down by domestic chores, do not readily attend clinics at some distance from home, and therefore are liable to be missed in passive surveillance. It is essential that services within the village should be strengthened. Constraints and problems, and lacunae in existing knowledge are discussed.

## Introduction

Malaria is a disease of poverty. It is one of Freire's "myriad diseases of poverty... known in the terminology of the oppressor as tropical diseases."[1] By and large the rich and powerful live in sanitary surroundings with easy access to medical facilities, while the poor live in crowded urban slums and in remote rural areas which favour transmission. Because ignorance, apathy, lack of means or access to medication often prevent them from seeking help early enough, the most serious manifestations of tropical diseases are invariably seen among the underprivileged. Among these, women in their role as child bearers are, along with their young children, particularly vulnerable to malaria. This review briefly examines the physiological, social, and behavioural factors that may enhance or reduce their vulnerability, and considers the problems of adequately protecting them in relation to current control strategies in countries in various stages of transition from eradication to control.

## Malaria in Pregnancy

Women are not intrinsically more susceptible to malaria than men. In the West African savannah, females had lower parasite rates for *P. falciparum* and *P. malariae* than males from the age of 5 years onward, but IgM levels and antibody titres against *P. falciparum* in the passive haemaglutination test were actually higher,[2] suggesting that antibody responses in females were stronger, as has also been observed in animal studies with other antigens. However, during pregnancy immunity status alters and there is an increased susceptibility to *P. falciparum* malaria. In the absence of treatment, morbidity and mortality rates are high in women with no or low levels of immunity. Mortality due to cerebral malaria in pregnancy is 40%, which is twice the mortality in all other patients. Pregnant women are also likely to develop hypoglycaemia and pulmonary oedema,[3] and chronic malaria often causes severe anaemia of pregnancy complicated by folate deficiency. In partially immune pregnant women, frequency and density of malaria increases progressively and peaks during mid-pregnancy, especially in primigravidae. In non-immunes, malaria during pregnancy causes abortions, stillbirths, and delivery of low birth-weight babies. In Zambia, 13/14 patients aborted in the 1st trimester, 8/19 in the 2nd trimester, and 50% went into premature labour.[4]

Where malaria is epidemiologically stable, congenital malaria with clinical manifestations in infants is rare, and there is evidence that passive transfer of maternal antibodies as well as malarial parasites takes place across the placenta.[5] McGregor considered that passive immunity mitigates clinical disease though it does not suppress parasitaemia in infants.[6] In a longitudinal study of 104 infants in a hyperendemic area in Papua New Guinea there were four cases of congenital infection with *P. falciparum*. There were only three clinical cases in 5- to 8-week- old infants in the presence of detectable maternal IgG, and 67% of such infections were asymptomatic with scanty parasitaemia. Seventy-three percent of heavy infections developed in infants without detectable antimalarial IgG. Maternal IgG disappeared between the ages of 4 and 7 months.[7] In a study in Kenya, infants from mothers with a history of antimalarial chemoprophylaxis had significantly lower IFA antibody titres than other infants.[8] The implications in terms of protectivity, however, are not clear. In a recent analytical review, Brabin[9] came to the conclusion that passive immunity plays a less significant role in the relative insusceptibility of young infants than their own active immune responses to high inoculation rates. The rapid development of splenomegaly seen during the first 3 months of life in holoendemic areas may be associated with tolerance to high parasitaemia. Other contributory factors have been suggested, which include persistence of foetal haemoglobin and the low level of PABA in milk.

## Gender Related Risk of Contracting Malaria

Individuals may vary considerably in their attractiveness to vector mosquitoes. Factors affecting this include rate of $CO_2$ emission from the skin, its temperature and colour, and amino-acids in sweat, but there is no clearcut preference for either sex. What has been shown by a number of workers is that adults, who have a larger surface area of skin, are

more attractive than children, who are smaller. This was first demonstrated in the classic study by Muirhead-Thomson[10] who collected mosquitoes on each member of a Jamaican family sleeping in the same house. In another elegant study Boreham et al.[11] analyzed bloodmeals of mosquitoes, including *Anopheles gambiae*, captured inside bed-nets under which mother-child pairs with different haptoglobin types slept. The results showed that the mothers were fed on much more than the babies. Do mothers then actually protect infants sleeping with them by diverting potentially infective mosquito bites to themselves? Not necessarily. It has been shown that close proximity to an attractive bait, such as a buffalo, in some circumstances actually increases the number of *An. flavirostris* captured on man.[12] The interesting studies of Scott and his co-workers[13] on mosquitoes attracted to birds are relevant here. Olfactometer studies showed that nestling house sparrows were significantly less attractive than adult birds. But nestlings of passerine birds are frequently bitten by colicine vectors of flaviviruses and play an important role in maintenance cycles in nature. The hypothesis is put forward that mosquitoes are attracted to the nest primarily because of the incubating adult. Because the nestlings are less well protected by feathers or avoidance behaviour than adults, mosquitoes feed more easily on them. Something similar could be happening in the case of human infants sleeping with their mothers. This is not to suggest that this traditional practice should be abandoned, particularly in an era which is rediscovering the importance of closer physical contact between mothers and babies, including premature babies. Rather, both mothers and babies should be protected from mosquito bites, preferably under pyrethroid impregnated bed nets.

Behavioural differences between the sexes may often significantly influence the chances of being bitten by malaria vectors. In a study carried out in a South Indian village in the 1960s no differences were observed in the behaviour of small girls and small boys. The more active among them received fewer mosquito bites while playing outdoors. The girls wore long skirts, but these rapidly rose to expose their limbs as they slept and there were no significant differences between catches on individual children, although one little girl who was a particularly restless sleeper and threw off her covers attracted more mosquitoes than any other child in the study. Girls over 10 were usually with their mothers in the kitchen during the early hours of the evening, where the smoke from the cooking fires, while causing respiratory ailments, would have protected them from mosquito bite. Men and boys over 10 sat outside on the *tinai* or porch in the early evening, and most often slept outdoors, even in cold weather, complaining of the bedbugs indoors. They also spent nights in the fields before harvest, guarding the crops. The women and children slept indoors.[14] However, some 25 years later, rural women sleep outdoors more often in hot weather, though not as often as men (unpublished data, CRME).

Epidemiologists are familiar with behaviour patterns like these, which can lead to differential risk of infection in areas where local malaria vectors are predominantly exophilic and exophagic. Temporary migration into forest in search of work exposes people to a greater risk of contracting malaria. Thus in Thailand gem mining, which is traditionally a male occupation, exposes a large section of adolescent and adult males to the bites of forest breeding vectors, including *An. dirus* and *An. minimus*. In 1979, death rates from malaria among males between the ages of 15 and 64 years ranged from 9 to 17 per 100,000, while among females of the same age they were distinctly lower (5 to 8 per 100,000). There was little sex difference in malaria death rates in children below 15 and persons over 65, who

normally remain within the village.[15] Similarly, in India there was increased morbidity among adult males,[16] who engage in lumber operations, slash and burn cultivation, policing, hunting, poaching, or insurgency, often living in flimsy, makeshift shelters. Men are generally more mobile and may also contract malaria in urban centres where they have gone for work, and fishermen may visit coastal villages and towns where malaria is endemic. However, these generalizations are not universally true. Frequently, whole families move into cleared forest during the agricultural season, and much of the work may be done by women. Similarly, fishermen in southern India sometimes take their families with them on long trips along the coast, and mixed illegal fishing parties of men and women frequently entered the jungle below the malarious Sathanur Dam and developed malaria after returning to their villages.

## Women and Control

### Objectives of control

The ultimate objective of the global malaria control strategy is still eradication, but this is no longer perceived as a target which can be achieved within a definite time frame. The World Health Organization in 1969 defined four alternative immediate objectives for control,[17] between which countries could choose depending on resources available and technical and other constraints, with the option of scaling up when additional funds and/or better technology becomes available. These alternative targets were: (1) reduction of mortality; (2) reduction of mortality and morbidity; (3) reduction of mortality, morbidity, and the prevalence of the disease to an acceptable and sustainable level; and (4) elimination. The first three of these strategies are specifically targeted toward protection of especially vulnerable groups, which include pregnant women and children, and the fourth implies total protection.

### Women in hyper-holoendemic areas

Pregnant women and young infants are most at risk in areas of heavy and continuous transmission of *falciparum* malaria. In most of Africa south of the Sahara, the basic reproduction rate of malaria is so high that at present the only feasible targets for achievement are numbers 1 and 2 defined above. Because of the danger of rapid evolution and spread of drug resistant strains of *P. falciparum*, chemoprophylaxis is recommended only for pregnant women, especially in their first pregnancy.[18] Chloroquine is the drug of choice because of its total lack of teratogenic effect on the foetus; however, chloroquine resistance is already widespread and second line drugs such as Maloprim (pyrimethamine + dapsone)[19] and Fansidar (sulfadoxine and pyrimethamine)[20] have also been used. In a study of pregnant women attending mobile antenatal clinics in an area of year-round malaria transmission in Papua New Guinea, primigravidae were given curative treatment with chloroquine, while all received 300 mg base chloroquine weekly as prophylaxis. Though this failed to suppress new infections or to clear persistent parasitaemia, a missed clinic visit resulted in doubling the risk of infection, so clearly chloroquine was achieving partial control. Persistent parasitaemias were treated with Fansidar.[20]

Apart from the problem of drug resistance, formidable problems of distribution and motivation remain to be solved. Thus, in spite of governmental efforts to promote chemoprophylaxis during pregnancy as part of primary health care in countries of tropical Africa, use of antimalarials is low, particularly in rural areas where access to antenatal clinics is difficult. In Guinea a survey revealed that lack of access and misconceptions about the effect of antimalarials on the foetus were the main problems.[21] In a community based control programme in Saradidi, Kenya, 90% of women interviewed knew that headache, fever, vomiting, lack of appetite, and death were associated with malaria,[22] but consumption of chloroquine was low. Antimalarial prophylaxis was available free of charge to pregnant women through a voluntary village health helper chosen by the community. Yet only 29% of the women attending antenatal clinics were taking the drug. Some of those who were not on prophylaxis were interviewed. Of those who were not in their first pregnancy 23% had experienced miscarriage or stillbirth at least once, and 29% gave malaria as the cause. Reasons for not taking antimalarials included lack of awareness that the service was available (53%), fear of itching (10%), the village health helper had no drug or advised against it (17%), "not sick" or "laziness" (14%), and "bad for pregnancy" (2%).[23] However, women over 30 took the drug more often than younger women. Greenwood and his colleagues in The Gambia were able to administer prophylaxis through traditional birth attendants during 87% of all pregnancies which occurred in 16 study villages over a 3 year period.[19] These authors had earlier shown that illiterate village health workers could be trained to give antimalarial prophylaxis and record data using specially designed report forms. Their records correlated well with evidence of drug in urine samples.[24]

The extent to which antimalarial prophylaxis or curative treatment can reduce the risks to mothers and babies will depend on the prevalence and causes of anaemia. In a series of severely anaemic pregnant women in Zambia, 84% had *P. falciparum* malaria, 35% showed nutritional iron deficiency, sickle cell anaemia and AIDS accounted for 3%, and 62% were folate deficient, mostly related to malaria haemolysis.[25] In such situations, antimalarial therapy is essential. Except in cases of proved iron deficiency anaemia, adminstration of parental iron is contraindicated, because it has been shown to be followed by increased frequency and intensity of malaria.[26] Women attending antenatal clinics in Kenya who were receiving regular prophylaxis with chloroquine had significantly lower parasite rates and higher haemoglobin levels than those not on chemoprophylaxis.[27] In The Gambia, primigravidae who had received Maloprim had lower parasite rates and significantly higher packed cell volumes than those receiving placebo, and the birth weight of their babies also increased. In multigravidae, chemoprophylaxis reduced parasitaemia but did not have a beneficial effect on haemoglobin levels and there was much less effect on birth weight.[19]

### Women in meso-hyperendemic areas

Outside tropical Africa and Papua New Guinea, malaria transmission is less intense, although there are some areas which can be classified as hyperendemic. In these, and under conditions of unstable malaria which do not permit immunity to develop, pregnant women are potentially at risk. In Thailand, malaria is a major cause of maternal mortality[28] but there

is little comparable information from elsewhere. Wherever there is ready availability of antimalarials and relatively well developed primary health care infrastructure the assumption seems to be that women are receiving treatment along with everyone else who needs it. This assumption needs to be examined in the context of changing control strategies.

Almost all countries outside tropical Africa originally had eradication programmes. A few achieved their goals; the majority have reverted to control, with achievement target number 3, reduction in prevalence of the disease and alleviation of suffering. Active surveillance for cases followed by curative treatment was a method designed for eradication programmes. Malaria surveillance workers have now been retrained as multipurpose workers or diverted to other types of work. Although some form of active surveillance continues in several countries, there are increasing doubts about its utility. In a study of the performance of various surveillance and monitoring services in Thailand[29] it was found that 39% of all cases in a zone of high incidence of malaria were detected by all services, the rest being mostly asymptomatic parasitaemias. Only 18% were detected by the local health services, and about half the people sought medicare in hospitals and clinics outside the village. Two zones were compared, one with low and the other with high malaria incidence. In the former, active case detection accounted for 19% of bloodsmears collected but only 2% of the cases detected, while in the latter, corresponding figures were 46% and 16%, respectively. The malaria clinics were extremely effective, accounting for 16% and 19% of bloodsmears, but contributing 57% and 56% of the cases. A hospital in the zone of low incidence was also efficient, collecting 35% of bloodsmears and detecting 30% of the cases. Village volunteers collected 18% and 14% of bloodsmears, which yielded 8% and 14% respectively of the total cases. Active surveillance is clearly inefficient and largely responsible for overloading of laboratories with negative slides, which is a common feature in Thailand as it is in India and other countries of the region.

On the basis of cost-effectiveness it might be considered desirable to rely mainly or entirely on malaria clinics, hospitals, and primary health centres for surveillance and monitoring of malaria. However, the excellent study just described has one defect; it did not analyze malaria cases by sex. Ettling et al.[30] found that young males between 16 and 30 years of age accounted for 56% of all cases detected in malaria clinics in Thailand. By contrast sero-epidemiological findings from a sample of over 500 villages showed similar exposure rates among males and females up to 30 years old. There was under-representation of women and children of all ages in clinics. Village volunteers and rural health posts also reported detecting mainly male cases. A very similar situation has been reported from the state of Orissa in India.[31] The age and sex composition of cases from passive case detection at 39 PHCs was analyzed. Women between the ages of 20 and 49 and young children from 0 to 9 years were severely under-represented, while there was over-representation of adult males. Sex selection was not a factor operating against representation of young children since baby girls were only slightly less represented than baby boys. There was a strong correlation between the proportion of small children and of women of 25 to 39 years, suggesting that mothers primarily came because their children were sick, but took the opportunity to get themselves examined also. Such epidemiological similarities between very different and geographically widely separated cultures suggests that the underlying behavioural patterns are widespread and basic. Underprivileged women are generally loaded with household chores and the care of young children and are therefore less likely than men to attend clinics or

hospitals at a distance from their homes unless forced to do so by serious illness. This could go, and clearly has gone, unnoticed because of the masking effect of the well-known greater occupational risk of malaria for adult males.

What is happening to the missing women and children? Are they receiving antimalarials through the village volunteers, drug distribution centres, or their equivalents in various countries? No answers are forthcoming. Ettling[30] suggested making treatment available within the village by means of mobile malaria clinics run by teams of microscopist and assistant, with portable equipment, travelling on motorcycles to a fixed schedule. While this would be an ideal solution, it is an expensive model which might be difficult to organize and implement in many developing countries. What is clear is the importance of strengthening the existing agencies within the village, particularly in areas which may be cut off for months at a time by floods, bad roads, or unsettled conditions. Health volunteers and services provided by them, such as the drug distribution centres, are continuously available to village women.

Latin America provides an example of what can be achieved by volunteer workers. More than 20 countries in Central and South America, Mexico, and the Caribbean have passive malaria case detection networks made up of unpaid community volunteer workers, which were established in the late 1950s. In many countries they are the principal means of malaria surveillance and antimalarial drug treatment used by the national malaria service. In a project to improve the functioning of the volunteer collaborator network in Guatemala, illiterate workers were successfully employed. They were selected by informal community poll and trained in their homes. Some residents who initially lacked faith in illiterate workers gained confidence in their performance during the 1 year evaluation period.[32]

Elsewhere in the world, although national health policy emphasizes primary health care, stressing community participation and the transfer of simple skills to health volunteers, it has proved difficult to implement. In India, non-governmental organizations, the best known being that of the Drs. Arole in Jamkhed,[33] have shown how well the three tier system can work, with the community health worker, sometimes illiterate, at the lowest level and, a centre of specialization at the highest. However, within the government system, although more than 30,000 village health guides were trained and preliminary evaluations were encouraging, the programme has not been a success. For this, Dr. Shanti Ghosh[34] puts the blame squarely on the medical fraternity, who distrust the village level worker. Rajagopalan and Das[35] are presumably expressing the PHC doctor's point of view when they say "Taking advantage of the remoteness of the area and the ignorance of the people, many VHGs resort to private practice with the drugs supplied from the PHC.... The PHC medical officer can do very little to rectify the situation as he is not involved in the selection of the VHG, nor has any disciplinary authority over them." The situation is further complicated by the rivalry that often exists between the community health workers and the first-level government health worker,[36] i.e. the multiple purpose worker, with the latter having direct access to the PHC medical officer. The drug distribution centre is a casualty of this rivalry and distrust. Thus the number of drug distribution centres functioning in widely separated rural areas with a high incidence of *P. falciparum* malaria decreased between 1985 and 1989, and one young doctor in an area prone to floods which cut off access to remote villages, candidly admitted to the author that he did not support his DDCs because they "did not work."

Ghosh[34] believes that without suitable training and motivation there is a lack of

empathy between PHC staff and the community. The team leader, the PHC medical officer, does not understand the problems rural women face, nor why they do not utilize his services, and therefore does not appreciate the importance of the village based volunteer. Unfortunately, reorientation of medical education toward community medicine is proceeding extremely slowly in India because of lack of commitment in many medical colleges.[37]

On the other hand, the defects in the functioning of the VHG scheme should not be minimized. In India, health guides are paid a small honorarium each month. In some places the author visited they were not paid regularly and were sullen and uncooperative. None were satisfied with the amount they received and all wished to become regular government servants. The unpaid volunteer model as in Latin America, might work better. The method of selection of volunteers also needs scrutiny. Ideally they should be selected by and be answerable to the community and not the doctor or any other external agency, but can it be ensured that powerful factions within the village do not overrule the weakest among the community who need the service most? Women, because of their low status, may often have little say in selection of volunteer workers. It might be desirable to have several trained volunteers in one village, one per 20 families or so. Undoubtedly, in view of the large number of individuals involved, some of the existing VHGs have exploited the communities they were intended to serve, but so in some cases have the MPWs; and the solution to this problem is not to condemn the system, but to generate awareness so that the community knows that it is entitled to free service.

**An active role for women**

So far in this review women have been treated as victims, passively waiting to be protected from the ravages of malaria. This is only part of the reality. There is a network of women health professionals, from research scientists, doctors, and technicians, down to the VHGs and the *anganwadi* (courtyard) workers, actively involved in the control effort. Among the early workers there is Ms. M. Maryon, who collaborated with Schute to produce the classic "Laboratory technique for the study of malaria."[38] Her successors have been many and their contributions varied in the field and the laboratory.

One area in which women will increasingly play a pivotal role is that of personal protection against the bites of malaria vectors. Mosquito nets have always been used to reduce man-vector contact, but in village houses they quickly develop holes and cease to afford protection, often as a result of being gnawed by rats. Moreover, a bed net will only protect the individual or individuals sleeping under it, while the mosquitoes will merely be diverted to other sleepers outside. An important development in recent years has been the introduction of the use of bed nets impregnated with synthetic pyrethroids, which both repel vectors and, over long periods of time, kill those which alight on them. Thus even a torn net can continue to protect the individual sleeping under it as well as contribute to the protection of others sleeping nearby by killing potentially infective vectors. The very low mammalian toxicity of pyrethroids makes this an ideal method for community use, and some large-scale trials have been carried out. In China widespread use of bed nets over a number of years resulted in a striking reduction in vector density and malaria incidence. On the other hand, in Africa it was not always possible to show a reduction in parasite rates, but sporozoite rates and high parasitaemias were significantly reduced.[39] This might be a desirable outcome since

it would lead to reduced morbidity due to malaria without affecting the normal build-up of immunity. The method has its limitations; people may be bitten during the first part of the night when they are not normally under bed nets, and bed nets may not be acceptable in regions or seasons when night temperatures are high. In such cases impregnated curtains of cheap local materials might be effective. However, it is clear that this technique has tremendous potential for use at the community level and is likely to be used on an increasingly large scale in future. Mobilization of the support of the women of the community will be an important factor in the success of such a programme. It is they who will bring the family bed nets to the health centres to be dipped in pyrethroid suspension, it is they who will put them on mattresses to dry, and see that the children stay under them at night. It is they who will decide whether the nets are to be washed and at what intervals, and when they need to be retreated with pyrethroid because mosquitoes are beginning to bite again. Similarly, if mosquito repellent creams, soaps, or smokes are used on a large scale in integrated control programmes of the future, it will be the responsibility of the women to see that they are used properly by the family, and that children in particular wash repellent applications off their skins before reapplication. The involvement of women in any type of community vector control activity is important for successful implementation, but it is most essential here.

**Research Needs**

1. Community based studies with special emphasis on women are urgently required in India to quantitate morbidity and mortality due to malaria at the periphery of the primary health care system. It is notoriously difficult to establish a reliable diagnosis of malaria in severe cases resulting in death in remote rural areas. The presence of research personnel inevitably results in improved medical facilities in a village making it impossible to assess what would have happened in their absence. This difficulty could be overcome by carrying out longitudinal studies of how many clinical attacks of malaria an individual may suffer annually in some index villages, while obtaining information from a larger number of others, as has been done in The Gambia through a "village reporter" system combined with a postmortem questionnaire technique, to identify the probable cause of death and serious illness.[40] Simultaneously, the PHC serving the area should be involved in clinical diagnosis and parasitological confirmation of serious cases brought in for treatment.

2. Concurrently surveys should be carried out to determine attitudes to the disease and it's treatment. Do rural women resort to self medication for themselves and their children, to traditional practitioners, to drug distribution agencies within the village, or to PHCs and hospitals? Are they utilizing the medical facilities provided by the government, and if not, why not? To what extent are they aware of the special risks malaria has for them?

As discussed earlier, where such questions have already been asked the answers that have been obtained are often disturbing. For example, Etterling et al.[41] have found that 91% of villagers in one area in Thailand preferred not to attend malaria clinics when suffering from fever, and yet malaria clinics treat over 60% of all reported cases in that country! This type of information from various countries and situations is essential if effective drug distribution and treatment is to be provided through governmental programmes.

3. Lack of awareness of medical facilities available is a recurrent theme in studies in rural areas. In Saradidi, Kenya, more than half the pregnant women who were not on antimalarial prophylaxis did not know that chloroquine was available from volunteer workers free of charge[23] and tribals in Koraput, Orissa, did not know that they were entitled to receive the drug without payment.[35] It is necessary therefore to follow up attitude surveys with systematic health education campaigns to see whether a significant improvement can be brought about by these means alone.

4. Finally, it is necessary to carry out a survey of women's attitudes towards community health workers and first-level government health workers whom they can contact within the village. Do they prefer to deal with a woman, do they have faith in the ANM, the village teacher, the *anganwadi* worker who is now the nodal point within the village for all maternal and child welfare schemes, or the female basic health worker? In tribal India where traditional healers are influential, can they be trained and recruited as village volunteers? This has been achieved on a pilot scale in Thailand. The successful integration of malaria control into primary health care will depend on the answers to these basic questions.

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# Leprosy

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## Summary

Pregnancy in women with leprosy is hazardous. First appearance of leprosy, reactivation of the disease, and relapse in cured patients is likely to occur particularly in the third trimester. Leprosy reactions caused by variation in cell-mediated and humeral immunity are triggered by pregnancy: type 1 (reversal) reaction post-partum; type 2 reaction (erythema nodosum leprosum) peaks in late pregnancy. Both types of reaction continue long into lactation. Relapse, reaction, and nerve damage, especially "silent neuritis," with subsequent deformity and disability, occur not only in women on apparently effective treatment but also in those who have received multidrug therapy and are released from treatment (RFT). The mechanisms of early and late reaction and neuritis need urgent research to prevent disability. Pregnancy is not only a trigger factor for reaction but an ideal in vivo model for research.

Up to 20% of children born to mothers with leprosy may develop leprosy by puberty. Women with cured leprosy could play an important role in screening for, and detection of, both early leprosy in children and late post-MDT nerve damage.

## Introduction

For many in industrialized countries leprosy is a disease of biblical times that has largely died out leaving a handful of deformed, fingerless, blind beggars, supported by Lepra and other leprosy mission agencies. This misconception is one of the greatest disservices to effective understanding, treatment, and prevention of leprosy. Because of the stigmata of the disease, many hide their affliction, coming only for treatment once clinical signs are obvious. It is, therefore, difficult to ascertain the exact number affected. It is estimated that leprosy affects 10 to 12 million people, one-third of whom are women of reproductive age. The majority live in tropical or sub-tropical zones where 5.1 million people are registered patients receiving treatment, and 1.6 billion are at risk.[1]

### Leprosy - the disease

Leprosy has at least three properties of particular immunological interest: first, it is an exceedingly chronic disease. *Mycobacterium leprae*, the infecting organism, has a division time of about 12 days. The incubation period is thus about 2-10 years, although periods of up to 27 years have been recorded. Moreover, because of slow progression of the disease the period from first appearance of symptoms to initiation of treatment can be several years. Secondly, *M. leprae* are virtually non-toxic. Patients with active leprosy may harbour up to

$10^{13}$ bacilli in body tissues and have a bacteraemia of $10^5$ ml without signs or symptoms of the disease, thus remaining active and apparently healthy. The clinical signs of the disease are largely the result of the host response to the infection. Thirdly, the host-parasite relationship in leprosy is often unstable, and variations in cell-mediated immunity (CMI) and immune complex formation/deposition can cause clinical manifestations (called reactions) which are not directly related to the bacteriological progress or regression of the disease.

**Immunology**

When there is a powerful cell-mediated immune response, lesions are localized and there are very few bacilli, found chiefly in nerve: this is tuberculoid leprosy (TT). Where CMI is low, probably because of a specific defect of T-lymphocyte reactivity to *M. leprae*, the disease is diffuse and generalized: this is lepromatous leprosy (LL). Between these two polar forms of the disease lie the immunologically unstable borderline forms of the disease - borderline tuberculoid (BT), borderline lepromatous (BL), and borderline leprosy (BB) which exhibits features of both BT and BL leprosy. A spectrum of the disease has been defined in terms of bacteriological load, immunological response/status, histology, and clinical features (Fig. 1). The 5 group classification - TT, BT, BB, BL, and LL[2] is used in this paper.

**Reactions**

CMI underlies the immune response in leprosy. Reactions in leprosy are clinical phenomena caused by alterations in the immune status of the patient. There are two types of reaction: type 1 leprosy (reversal) reaction (RR) and type 2 reaction, or erythema nodosum leprosum (ENL). Many of the damaging complications of leprosy are caused by an unstable host-parasite relationship related to changes in the host's immune response potential. Diminished CMI can cause increased bacillary multiplication, progress of leprosy, and down grading of classification. Type 1 leprosy reaction is attributed to factors which alter the patient's delayed type hypersensitivity (DTH) with a shift along the classification scale.[3] Increase of CMI or DTH will tend to cause upgrading or shift toward the tuberculoid end of the leprosy scale (reversal reaction), which may involve either skin or nerve lesions with resulting neuritis, nerve damage, and bent deformity. Type 2 reaction characterized by ENL, the appearance in the skin of painful red nodules, can cause systemic illness and a variety of clinical manifestations including neuritis. Although the trigger mechanisms of the reactions are not as yet well understood, conditions causing diminution (of increase) of CMI may initiate reactions. Pregnancy is such a condition.

**Treatment**

Treatment for leprosy has been until recently dapsone monotherapy. However, with low dosage and irregular therapy together with poor patient compliance[4] and initial misclassification of leprosy,[5] dapsone resistance, both primary and secondary, has become a worldwide problem,[6,7] threatening to nullify even the limited gains made in the control of leprosy in the last 25 years.[1] Several alternative drugs are available for treating leprosy

including clofazimine and rifampicin which with dapsone form the basis of multidrug therapy (MDT) now recommended for all forms of leprosy.[8] Both rifampicin and dapsone penetrate into peripheral nerve.[9] Prednisolone is used for treatment of type I leprosy reactions[10] and thalidomide, clofazimine and prednisolone may be used for treatment of type 2 leprosy reactions.[11] Dapsone is not known to have adverse effects on mother or foetus: clofazimine,[12,13] prednisolone and thalidomide, however, can affect both and rifampicin is not recommended within the first trimester of pregnancy.

**Transmission of leprosy**

While *M. leprae* have been found in all body secretions including pus from ulcers of highly infective LL patients, the chief means of transmission is droplet with transplacental and breast milk as modes of infection of young children (reviewed Duncan 1985[14]). The most infectious people are those who are incubating leprosy, who have active lesions in the anterior nares who show no external evidence of leprosy, and the patient, labelled as having chronic quiescent leprosy, who has developed dapsone resistance, who is shedding dapsone-resistant *M. leprae* into the environment. Droplet transmission may be from mother to child during lactation and everyday child care and handling, or from other family members, father, grandparents, siblings, and close friends. Analysis of 271 registered child leprosy patients (age less than 15 years) in Ethiopia showed that 53% of the children had a relative with leprosy.[15] The younger the child, the more likelihood of the mother and other relatives having active leprosy. Poor housing, ventilation, and overcrowding are additional risk factors.

Until recently it has been almost impossible to evaluate placental transmission of *M. leprae*. Now, however, antibody tests can be used as diagnostic tools for leprosy before there are clinical signs of active disease. In a recent prospective study, cord blood IgA was significantly increased in babies of mothers with lepromatous leprosy.[16] IgA and anti-*M. leprae* antibodies were present in 30% of cord sera of babies of mothers with active lepromatous leprosy.[17] There was evidence of active production of specific IgA and IgM anti-*M. leprae* antibody during the first six months of life,[18] and the prevalence of leprosy in children under 2 years of age whose mothers had active lepromatous leprosy was 5% (2/28),[19] a figure comparable with that reported by other workers.[20,21]

**Leprosy in children**

This related and very large subject (reviewed Duncan 1985[22]) will not be dealt with in detail here. Leprosy in young children tends to be indeterminate clinically, tuberculoid histologically, and undergoes self healing without reaction.[23,24] The question of what happens to *M. leprae* in children who have serological evidence of infection but show no outward evidence of the disease, has been a subject of speculation. Do *M. leprae* go into hiding in lymph nodes, nerves, or other tissues, to be reactivated later, particularly during the hormonal upheaval of puberty? Recent review of a cohort of adolescent children of leprous mothers studied from birth showed that 13/79 (9/56 girls: 16%) had developed indeterminate leprosy at puberty.[25]

**Activation of *M. Leprae***

The immune status of the host is of the greatest importance in determining the activation of *M. leprae* hidden in immunologically privileged sites in the body. Any factor which alters the immune status of the host, decreasing CMI, must be regarded as a significant activating agent. Of these, by far the most important are the nutritional factors. Chronic protein-calorie deprivation/malnutrition causes thymic and lymphoid atrophy which results in suppression of CMI. However, the situation is frequently more complicated as viruses, in particular measles and HIV, and protozoa (especially *Giardia intestinalis (G. lamblia)* and to a lesser extent *Strongyloides stercoralis, Entamoeba histolytica*, and *Leishmania tropica*) also may cause both generalized and specific immunosuppression. Furthermore, acute gastroenteritis and diarrhoeal diseases, so prevalent in the tropics and subtropics as secondary causes of protein-calorie deprivation, themselves cause suppression of CMI.[15]

Of particular relevance to women are hormonal factors. In particular, increased levels of oestrogen as occurs at puberty and during pregnancy cause suppression off CMI. It has been noted that there is a sudden increase in numbers of girls compared with boys with leprosy at puberty (Fig.2).[15,26] When marriage occurs, as frequently happens, shortly after puberty, the combined hormonal effect of puberty and the first pregnancy may be disastrous in terms of leprosy (Fig.3).

**Maternal response to pregnancy**

In certain diseases natural remission occurs with the advance of pregnancy, followed by deterioration after delivery. In contrast, infections in which the host response is mediated by CMI tend to become overt or to progress rapidly during pregnancy, especially during the third trimester and immediately postpartum. Explanations for these observations include raised hormone levels during pregnancy, metabolic disturbances and alterations in CMI. Non-specific suppression of CMI during pregnancy is probably due to a combination of factors, serum factors, lymphocyte factors, in particular cell-mediated suppressor mechanisms (reviewed Duncan et al. 1981; 1982[27,28]), oestrogen dependent pregnancy-associated alpha 2-glycoprotein (PAG),[29] impaired phagocyte function,[30-32] and for leprosy patients specific serum suppressive factors.[33] The immunosuppression comes off at the time of delivery and by 6 weeks postpartum, lymphocyte function is restored to normal, even in lactating women. The possible clinical significance of the laboratory findings of depressed immune and phagocyte function is the activation of mycobacterial and certain viral diseases.[34]

**Historical review of causation and transmission of leprosy**

From earliest records two themes run side-by-side: leprosy was highly infectious and leprosy could result from incurring the anger of supernatural powers. In mythology, in the story of Troylus and Cresseid, Cresseid attributed her misfortunes in love to the fickleness and pranks of the gods, and thus, incurring their wrath developed leprosy.[35] In Judaio-Christian circles it was understood that leprosy was God's judgement for sin[36] and that this judgement could be extended to the third and fourth generation.[37] This thinking was not

confined to centres of Judaio-Christian teaching, as in Chinese tradition leprosy was regarded as punishment for sexual misdemeanour and was transmissible within the family to the third and fourth generations:[38-41] the children born of the fourth generation were considered healthy and could return to society.[42]

**Sexual transmission of leprosy**

The idea that leprosy was transmitted as a venereal disease was prevalent in England in the Middle Ages, and prompted some of the rules of the leper houses.[43] As Donne - did he appreciate droplet transmission - recorded:

*"By thee the silly amorous sucks his death [sic: seely]*
*By drawing in a leprous harlot's breath."*[43b]

Richter[44] maintained that leprosy was transmitted by sexual contact. In China, women with leprosy believed they could be cured of their disease if they had sexual contact with a healthy male transferring the disease to him, thus the practice of "selling leprosy" was develop. The dread of this had a great influence on promiscuous intercourse and on the general moral conduct of the people.[38-40] In Mysore, India, it was also a common belief that leprosy was a form of venereal disease.[45]

After the advent of syphilis to Europe in the sixteenth century there was some confusion between syphilis and leprosy caused in part by the similarity of the clinical picture of ulcers, sores, lymphadenopathy and destruction of nasal bones: hence the term "syphilitic leprosy" came into use. The observation that syphilis is transmitted by sexual contact may have given additional support to the theory of sexual transmission of leprosy.

**Attitudes and laws regarding leprosy, marriage, divorce, and procreation**

In the seventh century, Rothan, King of Lombards, made laws to prevent marriage of lepers.[46] A hundred years later, in 757, Pepin, King of France, passed a law in which leprosy was regarded as a cause of separation, allowing remarriage of the healthy partner.[47] In 789 Carlemagne forbade by law marriage of lepers,[48] as did the Welsh King Hoel Dha about 950 although the term "leprosy" covered various skin diseases.[47] In 1186, Pope Urban III said that subsequent leprosy allowed a betrothed couple not to marry.[49]

Scot's law, before 1057, in measures to control disease, ordered castration of carriers of hereditary disease, and to prevent spread of leprosy banished any woman sufferer from the company of men, with the penalty of burial alive with her child, should she give birth whilst suffering from leprosy.[50] The practice of castration of lepers was widely practiced in the Middle Ages.[51]

Segregation of lepers from healthy persons in the Middle Ages was followed by separation of the sexes as evidenced by the rules of leper houses, e.g. at St Julien's Hospital, thirteenth century, those admitted were to be single: if they were married they were to part by consent and vow chastity.[43] Sometimes the lepers' wives lived with them, as at the Edinburgh Greenside Hospital in 1591, where to enforce complete segregation of the lepers, one of the wives was allowed to go out to the market while the lepers took it in turns to sit and beg alms at the hospital door.[52]

In France in 1757, leprosy was a valid cause for divorce, while British regional laws forbade cohabitation if either husband or wife were a leper: a leper being considered as dead.[48,53] Icelandic law, 1776, forbade marriage of lepers.[54] Norwegian law in 1781 allowed divorce of lepers and remarriage of the healthy partner,[55] and a second law in 1790 allowed husbands whose wives were placed in the leper hospital at Bergen, to remarry, the woman declared to be civilly dead.[48] In Crete in 1874, the Bishop recommended the priests not to sanction marriages with or among lepers.[48]

In the nineteenth century, regulations regarding marriage varied with leper asylums. In South Africa, conjugal intercourse was discouraged between lepers until they were past child-bearing age, and was not permitted at all between lepers and healthy persons,[56] while in India, where marriages amongst lepers were not prolific,[57] marriage was permitted for mutual care rather than enjoyment of sexual relations.[58] Of 1600 inmates of Matunga leper asylum, Bombay, only 7 children were born in 9 years. Similarly in Hawaii only 26 children were born in 15 years to 2864 lepers.[57]

Reduced fertility amongst lepers, however, was not always the rule. In Indo-China, where the birth rate amongst lepers was high and hereditary transmission of leprosy was considered most important, a strong case was made for sterilization of leprosy patients of both sexes.[51] In Panama, at the Palo Seco asylum, marriages of lepers were allowed only after sterilization of the male on his written request.[59]

In Korea, segregation of sexes practiced in leper hospitals resulted not only in sexual perversion, but also in patients leaving the leper hospital. Some such patients forming transient attachments with those of the opposite sex joined leper camps - children born in such circumstances not only had a precarious home life, but if they remained with their parents, half of them were infected with leprosy. A system of arranged marriages and adoptions (in accordance with local customs) together with voluntary sterilization was found to be effective in providing for the needs of segregated lepers.[60] It is interesting to find in a recent textbook recommendations that infectious patients should live separately, avoid marriage may be encouraged to be sterilized.[61b]

## Leprosy and fertility

In the pre-sulphone era, leprosy was associated with sub-fertility if not frank infertility.[61-63] This was attributed to frigidity[64] and "decreasing sexual instinct" with progression of the disease.[65] Testicular atrophy[61,66] and destruction of the testicle by scarring with fibrosis, resulting in azoospermia were observed.[67] Fertility of Hawaiian leprosy patients was shown to be two-thirds that of the normal population due to decreased male fertility, while the females were not affected.[68] Forty-three of 50 women patients in a Yugoslavian study were reported as sterile largely due to irregular oligomenorrhoea associated with pre-pubertal onset of leprosy.[69] More recent studies have confirmed early observations showing only 10% of 68 female patients to be sterile[70] in contrast to 65% or 50% of males.[71,72] Infertility in male patients due to lepromatous involvement of the testicles has been reviewed recently,[73-76] and is thought to precede testicular atrophy and hypogonadism.[77]

Early reports of pre-pubertal leprosy in female patients resulted in primary amenorrhoea,[78] and post-pubertal leprosy causing menstrual irregularity progressing to

secondary amenorrhoea,[61,78,79] indicate that advanced untreated leprosy had a similar gynaecological effect as tuberculosis. In contrast a recent study recorded no significant menstrual upset: although anovulation was frequent (78%), fertility was not impaired.[70] Indeed, dapsone became known as a fertility drug in parts of Africa where gonococcal pelvic inflammatory disease was rife! Beneficial effects of dapsone were noted in Ethiopia where women receiving dapsone for leprosy had less puerperal sepsis and low grade pelvic inflammatory disease, causing irregular menstruation, than the non-leprous population of the same socio-economic group.[14]

## The Effects of Pregnancy on Leprosy

### New cases, exacerbation, relapse, and reactivation of leprosy

It has long been recognized that the clinical signs of leprosy first appear in association with pregnancy.[27,28,70,71,80-83] Pregnancy also exacerbates pre-existing leprosy (Fig 3).[27,28,70,71,80-82,84,85] It used to be thought that exacerbation of leprosy due to pregnancy occurred in lepromatous but not tuberculoid forms of the disease,[71,84] more so in untreated (18/23) compared with treated patients (5/23);[80] that the majority of cases presented after delivery either during the puerperium or later in lactation;[70,81,82] and that pregnancy terminating in abortion had little effect on leprosy although occasionally exacerbation might occur.[81]

In a recent prospective study, however, reactivation/relapse was recorded in 55/119 (46%) pregnancies in association with pregnancy or the first 12 months of lactation (Fig 4). This was assessed by carrying out routine skin smears for bacteriological index (BI) and morphological index (MI) together with biopsies in early and late pregnancy and postpartum. In 43/55 (78%) the deterioration occurred during the second half of pregnancy or the first three months of lactation, most commonly (31 cases: 56%) during the third trimester when CMI would be maximally suppressed.[28] A few patients continued to relapse well into the second year of lactation.[27] Patients of all classifications from "cured" tuberculoid to active lepromatous were affected:[27,28] 8/25 TT and BT "cured" patients who had stopped dapsone treatment relapsed with active leprosy; while among patients receiving treatment, 7/18 (38%) TI and BT, 18/41 (44%) BL, and 22/35 (63%) LL patients had exacerbation of the disease. Despite apparently active chemotherapy, 20% of patients receiving treatment showed transient worsening of their leprosy daring late pregnancy, while 38% showed significant and apparently progressive deterioration probably caused by the emergence of the dapsone-resistant leprosy.[26,28] This figure (38%) may be related to the proportion of new cases (50%) in Ethiopia showing primary low grade dapsone resistance.[87] The phenomenon of downgrading was observed particularly during pregnancy as might be expected in any condition where CMI is suppressed.[27,28,86,88]

### Reversal (type 1) reaction (RR)

As RR is due to an increase in CMI or DTH it is not surprising that it occurs immediately after delivery (Fig 4).[28,82,85,89] In the Ethiopian study during pregnancy and the first year of lactation, 40 women were diagnosed as having RR: in 20 (50%) the first

occurrence was during the first six months of lactation. The classical appearance of RR, erythema, and oedema of skin lesions, was not a prominent feature except in those who also relapsed with active leprosy or who had very recently started treatment.[28] The picture described by Rose and McDougall (1975) may reflect the natural evolution of the disease in untreated patients.[82] Reaction in skin and nerve was a feature of pregnancy and early lactation, whereas reaction in nerve alone was a feature of the lactation period, moreover RR was seen coincidentally with ENL in association with pregnancy.[28] While the peak incidence of new cases of RR occurred immediately after delivery, new and recurrent episodes involving nerves also occurred late in lactation.[28] This suggested that residual Schwann cells in the nerve trunks contain small numbers of bacilli which previously are unrecognized,[28] but with the recovery of CMI were recognized and attacked. Alternatively late reaction may be caused by the release of sensitized lymphocytes which can be trapped in the spleen for prolonged periods.[9]

**ENL (type 2) reaction**

In contrast to type 1 reaction which has hitherto received little attention as being a complication of pregnancy, ENL has long been recognized as a problem of pregnancy and lactation (Fig.4) and frequently associated, if not confused with exacerbation of leprosy[81,83] Severe ENL in three cases was attributed to exacerbation of leprosy with bacteraemia.[71] A similar observation, namely of ENL in pregnancy in 10/14 new bacilliferous lepromatous patients compared with 0/20 lepromatous patients responding to bent, was recorded more recently.[92] The peak incidence of ENL in the third trimester of pregnancy coincided with the peak of relapse.[28,93] Others recorded onset of severe ENL in 7/11 women in the first trimester of pregnancy, for them an indication for termination of pregnancy.[88]

In a prospective study, 30/79 patients (38%) developed ENL in association with pregnancy and lactation (Fig.3) (10/45 BL, 22%; 20/34 LL, 59%), 11 during the first trimester when there is inversion of the T and B lymphocyte ratio. However, a high proportion of women, 15% at any time, suffer from ENL in skin or nerve for 18 months continuously from the third trimester of pregnancy to 15 months postpartum.[93] Thus ENL overlaps the period of exacerbation of leprosy during the third trimester. Unlike ENL in non-pregnant patients which may occur for a considerable time before loss of nerve function is observed, in pregnant and lactating women early significant loss of nerve function occurs in 75% of patients who have ENL. As with RR, ENL is more common in the shin during pregnancy and in nerve during lactation.[93]

**Leprosy neuritis in pregnancy and lactation**

Nerve damage in leprosy may be caused by slow multiplication of *M. leprae* within Schwann cells or more acutely by intra-neural type 1 and type 2 reactions of which type 1 reaction is the most important (Fig 3). Leprosy neuritis in association with pregnancy until recently received scant attention, only a few cases having been recorded, although patients with established nerve damage attribute the onset of neuritis which caused it to a preceding pregnancy or abortion.[14] In a recent study 51/115 (45%) women with leprosy developed nerve damage with loss of sensory and/or motor function in association with any pregnancy

or lactation.[94] All leprosy patients, including those who are considered to be "cured" and have stopped treatment, and those who are incubating the disease, were at risk. In many cases neuritis was accompanied by reaction and/or exacerbation of leprosy (Fig 4): this was particularly the case when neuritis was associated with nerve pain or tenderness, (overt neuritis). However, "silent neuritis"[94] (nerve damage without nerve pain or tenderness: also called "quiet nerve paralysis"[1]) preceded by the complaint of "rheumatism" and the clinical finding of enlarged peripheral nerves, occurred more frequently than overt neuritis. This insidious "silent" neuritis with toss of sensory and motor function during lactation is a particularly dangerous and little recognized risk of pregnancy. A prospective study with serial nerve biopsies is necessary to elucidate the pathogenesis of leprosy neuritis in pregnancy.[94] Leprosy neuritis occurs even in the best supervised women and unless treated immediately will result in permanent deformity.

**Symptomatology of exacerbation and reactions during pregnancy and lactation**

Since the classical descriptions of leprosy in the 19th century, symptomatology in leprosy has been largely overlooked, although the pain associated with reactions in leprosy is well documented. In pregnant lepromatous women *des arthralgies* have been recorded as being a feature of ENL.[71] In Zaire, *anatisme*, generalized vague pains, was a problem of pregnancy accompanying exacerbation of pre-existing but apparently quiescent leprosy. In Ethiopia the symptom *qurtimat* (limb pains or "rheumatism") was found to precede or accompany exacerbation of the infection or overt relapse and neuritis, especially the insidious silent neuritis of lactation. It was rare for *qurtimat* to occur without some objective evidence of nerve damage or relapse.[95]

**Late nerve damage in leprous mothers released from treatment**

One hundred and eight women, 87 with leprosy and 21 healthy controls who had been studied prospectively during and after pregnancy from 1975-78,[27,28,93,94] were reviewed with their children aged 13-15 years during an 8-week period in 1990 when those with leprosy deemed "cured" had been released from treatment (RFT): 49 had completed dapsone monotherapy; 2 MDT for pauci-bacillary leprosy (PB); 33 MDT for 2 years or more for multibacillary leprosy (MB); 3 clofazimine monotherapy for dapsone resistant leprosy; and 4 had incomplete records (Table 1). Of 87 mothers with leprosy, 59 (68%) had clinical evidence of nerve damage following RFT (Table 2): 31 (36%) had 39 episodes of neuritis with new sensory or motor loss; 36 (41%) had varying degrees of stocking and glove anaesthesia (this was not confined to MB patients); and 5 (6%) had tender nerves. It was notable that 15/31 (48%) patients had their new post-MDT/RFT nerve damage in association with pregnancy, 14 postpartum, and that the majority (32/39 episodes: 82%) appeared to be "silent" neuritis or 'quiet nerve paralysis' confirming an earlier report.[94] The mechanism of late nerve damage is uncertain. As 48% episodes were in association with pregnancy it is likely to be the result of late RR in nerve possibly associated with rest "persister" *M. leprae* or particulate *M. leprae* antigen. Whether or not stocking and glove anaesthesia is the late end result of intraneural fibrosis or an on-going generalized intraneural RR must be a matter for prospective research. In addition 8/87 (9%) relapsed with new leprosy, 5 post partum,

and 3/21 (14%) healthy controls developed new leprosy and started on treatment; 35/87 (40%) had the warning symptom of *qurtimat* ['rheumatism'] (Table 1).[123] These figures are in contrast to those obtained at an interim assessment in 1984 when 76 mothers with leprosy were reassessed having just stopped dapsone monotherapy or having just started MDT (MB): 36/76 (47%) had improved leprosy status; 34/76 (45%) "no change"/stable leprosy status; and only 6/76 (8%) were worse (Melsom R, Duncan ME unpublished observations). Clearly pregnancy in RFT women was a hazardous undertaking in terms of leprosy - detailed analysis showed that while BL patients treated with dapsone monotherapy were most at risk, all MB patients whether BL positive or negative at start of MDT treatment had a high risk of late nerve damage.[96] These data were obtained by retrospective review of patients records (where pregnancy was not always recorded), from interviews with patients (who could not always clearly recall details of pregnancies/birth dates of children who died, were stillborn, or abortions), and a full clinical assessment of patients. It is possible that the association of pregnancy and neuritis might have been even higher had these women been assessed prospectively with concurrent recording of all obstetric data. Even amongst those recorded as having "no problem" a significant percentage had increased neuropathic destruction of hands and feet, some requiring surgery. The results of this review show that nerve damage in leprous women occur after RFT even in those treated with MDT especially in relation to childbirth. Most of the women in the study are still of child bearing age and could be expected to deteriorate further with subsequent pregnancies. Further research is urgently needed.

## The Effect of Leprosy on Pregnancy and Childbirth

Pregnancy in women with all classifications of leprosy is remarkably uncomplicated with no increased incidence of pregnancy associated hypertension, antepartum haemorrhage, or other major complication of pregnancy.[63,69,71,83,84,97,98] Although anaemia is common in LL patients, it was not a feature of pregnant women receiving regular antenatal care[97] nor was there increased incidence of abortion[71,96] or multiple pregnancy.[14]

### Placental function, birth weight, and placenta weight

Zambacho (1897) observed that many of the children born to mothers with leprosy looked like "old men" or even "abortions at term" at the time of birth; these children were unduly susceptible to intercurrent disease.[64] Recent reports from Vietnam[71] and the USA[92] respectively record 19/64 (30%) and 8/35 (23%) "prematurity," more so in women with lepromatous leprosy. However it is impossible to assess whether what is reported[71,92] is true "prematurity" or "dysmaturity," namely infants born "small for gestational age." There are scattered reports throughout the older literature of low birth weights in babies born to leprous mothers, but it is only recently that birth weight, placental weight, and placental coefficients have been correlated with the classification of the mothers' leprosy.[98,99]

Babies of mothers with leprosy weigh less than those of healthy mothers, placental weights and coefficients following the same trend with the highest weights recorded in healthy mothers and the lowest in women with LL leprosy. The cause of the reduced foetal-

placental weight is thought to be related to the immune status of the mother. Foetal distress or Apgar scores of less than 4 at 1 minute after birth were recorded in 20% of the babies of BL or LL mothers, and respiratory problems were a significant cause of neonatal mortality in babies of lepromatous mothers.[98]

Further evidence of impaired placental function is shown by the urinary oestrogen excretion (oestriol) which is lower in leprous women than controls and the incidence of subnormal oestriol which is greater in leprosy patients than in controls. These findings are most marked in LL women, 59% of whom show subnormal oestriols. Oestriol values are unaffected by dapsone treatment as there is no significant difference between mean oestriol excretion in women with cured BT and TT leprosy who have stopped treatment and in women with active BT and TT leprosy continuing on treatment,[100] are reduced by clofazimine.[101] Impaired placental function detected clinically as intrauterine growth retardation (IUGR) is most marked in babies of mothers with LL and BL leprosy and may be detected as early as 16 weeks of gestation.[14] The diminished placental function reflected in reduced oestrogen excretion, low birth, and small placenta weight is not associated with the severity of the mother's leprosy in terms of BI and MI, as it was noted that the smallest babies and the lowest oestriol assays were seen in women with chronic LL who were BI O.

**The placenta in leprosy**

Studies of placentae from leprous women have been relatively few and largely limited to morphological and bacteriological investigation either of single, or very few, placentae.[63,80,92,102-108] Only two substantial studies are recorded[109,110] in which 104 and 27 placentae respectively from leprous mothers were examined. Positive findings were limited to the finding of granular lepromatous lesions in the villous tissue of one placenta[111] but positive bacteriological findings i.e. demonstration of *M. leprae* were reported in 66/172 placentae examined in these accumulated series. In a recent study 81 placentae from women with leprosy and 17 placentae from healthy controls were subjected to a detailed macroscopic, light microscopic, ultrastructural, immunopathological, microbiological, and biochemical study. Placental morphology and immunohistology were normal, and there was no morphological evidence of infection of the placenta due to *M. leprae*. No acid-fast bacilli (AFB) or acid-fast bacillary granules were seen on light microscopy of any of the placentae from leprous women, although homogenates from 2/7 placentae from women with very active lepromatous leprosy contained AFB in very small numbers. The small placental size of women with leprosy, most marked in LL women, appears to be due to a decrease in placental cell size, rather than to a reduced number of cells in the placenta.[111]

**Breast milk of women with leprosy**

Maternal milk may be a possible source of infection for babies. While high counts of *M.leprae* in breast milk have been recorded from a few patients with active untreated lepromatous leprosy,[113,114] a larger study failed to corroborate this.[20] In a recent study *M. leprae* were isolated from the milk of 9/14 untreated LL women, and 1 out of 3 LL women on treatment - a patient treated for 8 years who was almost certainly developing dapsone resistance.[115] Using a PEG precipitation technique, non-cultivatable AFB were isolated from

the milk of 9/12 LL patients, some bacilli being found intracellularly in macrophages.[116] No bacillary counts were recorded, nor whether the mothers were receiving any treatment, although dapsone-resistant leprosy had become a major problem.[117] In another study, milk from nine Ethiopian mothers with active lepromatous leprosy was examined and found negative for AFB by concentration methods.[19] These negative results may reflect the use of a less sensitive technique[116] or, alternatively, may be because most of the Ethiopian patients were relapsing with rather localized lesions. Heavy breast milk infection may well require advanced disease involving the nipple and milk ducts.[19]

**Neonatal and infant mortality**

It is well recognized that the low birth weight infant in a tropical or sub-tropical country is at increased risk. The child has impaired growth in terms of weight, length, and head circumference. The children of BL and LL mothers are unusually susceptible to common childhood infections which run a more severe course than in the child of a healthy or BT mother. Neonatal mortality is increased due to respiratory difficulties and these contribute to a significantly higher infant mortality rate in babies born to LL and BL mothers.[118] Feeding problems are especially significant in babies of BL and LL mothers. The cause of failure to thrive in children under the age of 6 months who are fully breast fed is hard to evaluate, especially when the mothers have a plentiful supply of milk and none have troublesome neuritis or ENL. A number of children with feeding problems have been observed to have *G. intestinalis*. These childrens' feeding problems and weight improve dramatically when giardiasis is treated.[14,118] Giardiasis has an increased prevalence in lower socioeconomic groups, especially in young children[119] and the immunologically compromised.[120,121] Chronic giardiasis may cause a reversible malabsorption syndrome which may include milk tolerance,[122] as was observed in many of the children in the Ethiopian study.[118]

**The low birth weight baby as a health risk to its mother**

In most developing countries there is no form of state pension or social security. In the traditional family children would be expected to care for their aging, sick, and physically handicapped parents. In some developing countries the mortality of children under the age of 5 may be as high as 50%. Where infection with HIV and AIDS is a serious problem, the already high mortality of early childhood may be expected to rise much higher. The woman with leprosy has to plan for 2-3 surviving children to care for her in ill health and old age. Unless her children are well cared for half of them may die in early childhood while almost 20% will develop leprosy themselves by adulthood, thus she may be condemned to having 5,6 or more pregnancies to achieve her goal. With each successive pregnancy she runs the risk of her leprosy deteriorating, of developing dapsone resistance (if she is receiving monotherapy), of increasing sensory and motor nerve damage, neuropathic hand and feet, and ultimately leading the life of a street beggar (Fig 3). This tragic picture can only be stopped by a combination of well planned health education together with the highest standard of clinical supervision during pregnancy, prolonged lactation, and at regular intervals during

the reproductive life, even after she would normally be released from surveillance after completion of MDT.

### Health education and general recommendations regarding care of women with leprosy during pregnancy and lactation

The importance of health education of women with leprosy of child bearing age cannot be overstressed.[27,28,94,123] Pregnancies should be postponed until leprosy is fully controlled by chemotherapy[28] and there should be increased surveillance during pregnancy and lactation.[27,28,94] Women who are not already receiving MDT should do so as soon as pregnancy is confirmed. In countries which cannot afford MDT, supplementary chemotherapy in effective dosage should be given to pregnant women. This would aim both to prevent the emergence of dapsone-resistant leprosy and also lessen the risk of infecting the baby before and after delivery. If rifampicin is not available clofazimine for a minimum of 1 year from the beginning of the second trimester would be the most suitable supplementary drug having the additional advantage of reducing the amount of ENL occurring during pregnancy and lactation. If available, rifampicin should be given, supervised, once monthly for 1 year from the second trimester during the attendance at antenatal/postnatal/child health clinics. Mothers should be encouraged to limit their families by whatever means are locally acceptable. There is no evidence that termination of pregnancy is of any benefit to the mother. Each pregnancy whether full term or terminated prematurely carries the same risk to the mother's leprosy. Women with both overt and silent neuritis particularly need supervision and follow-up with home visits if necessary, should the patient default from the clinic. Children of mothers with leprosy, especially BL and LL mothers, require special care and monitoring in utero and after birth, with, if necessary, supervised supplementary feeding from 6 months of age to improve their chance of survival, thus, in turn, enabling their mothers to achieve their desired family size with fewer pregnancies. Prophylactic administration of antileprotic drugs to the baby is probably not only unnecessary, as the drugs commonly used all pass the placenta and milk barrier, but is also less valuable than adequately treating and watching the mother during pregnancy and lactation, and observing the child regularly during the first few years of life, and again at puberty.

## Research Priorities

### The problems

This review has highlighted serious risks for women with leprosy all in association with child bearing, pregnancy/lactation:

(a) Relapse/reactivation/transient exacerbation maximally in late pregnancy;
(b) ENL in the first and third trimester continuing with nerve damage post partum;
(c) Reversal reaction maximally post partum, even after MDT/RFT;
(d) Neuritis affecting almost 50% of women in any pregnancy/lactation, in most cases as:

(d) "Silent" neuritis with new motor and sensory loss, even after MDT/RFT;
(e) Stocking and glove anaesthesia even in PB women and post MDT/RFT;
(f) A high prevalence of early indeterminate leprosy in adolescent children born to mothers with leprosy.

**Further considerations**

(a) While MDT is of inestimable value as a major public health tool to reduce both the pool of infection and the risk of drug resistance in the community in areas of endemic leprosy, it can never replace the need for prolonged patient surveillance in the prevention of (late) nerve damage and subsequent deformity. Indeed it has been suggested that there is a higher reaction rate in new patients on MDT than in those treated initially with dapsone monotherapy (Currie H and Ato Msgana, personal observations) - this needs to be evaluated in a prospective study if considered ethical to do so.

(b) Although *M. leprae* are killed off very rapidly with MDT there is no evidence to suggest that destroyed bacilli, a potential source of both soluble and particulate antigen, are cleared more quickly from the body and from nerve in particular. There is evidence that immunotherapy improves phagocytic function of macrophages,[124] whether this would reduce late nerve damage by hastening removal of particulate antigen needs to be assessed clinically.

(c) There has been essentially no new understanding of mechanisms of reaction since the classic studies of the dapsone monotherapy era,[3,124-127] although pregnancy has been shown to be a trigger factor.[28] Leprosy reactions occur where there is are changes in CMI, T and B cell ratio and in phagocyte function all of which are known to occur in pregnancy. The pregnant woman is thus the ideal in vivo study model for investigating afresh the mechanisms of reaction in order to prevent subsequent deformity. "Evaluation of lymphocyte transformation (LTT) in pregnant women classified as BT/RFT increased our understanding of some of the hitherto 'bizarre' results observed in some BT and BL women in reaction" (Bjune G).[93] Studies of the effect of pregnancy in laboratory animals, possibly mangabey monkeys, would allow more nerve biopsies than can be done in humans.

(d) The mechanism of nerve damage in new MDT, and post-MDT patients needs research for both "silent neuritis" and glove and stocking anaesthesia. We know very little about the reactive phase of leprosy which is closely associated with the pathogenesis of nerve damage.[129]

(e) The possible protective role of corticosteroids, effective for treatment of leprosy neuritis, (or other anti-inflammatory drug) could be assessed in a prospective study of the prevention of late, post-MDT nerve damage.

(f) Neville recently suggested that the community based rehabilitation worker (CBRW) might be used for continuing care of post-MDT patients,[128] which is beyond the possibilities of most leprosy control programs.[130] In Ethiopia, women have proved themselves invaluable in health care as shown by two very different examples: (1) illiterate women who have had surgical treatment for vesica-vaginal fistula (VVF) and know the social ostracism associated with the condition, have become not only health educationalists, but are trained in the surgical and medical care and rehabilitation of these outcasts at the Addis Ababa Fistula Hospital; (2) community nurse midwives trained in the diagnosis and treatment of STD and

pelvic inflammatory disease are far superior to fully qualified doctors in their patient care, and research abilities (personal observation). Women with leprosy (post MDT, with/without deformity) could play an important role in the community both in detection/screening/school surveys for early leprosy and for health education and detection of late post-MDT nerve damage, possibly supervised by community nurse midwives.

## Research

**To assess as a long-term prospective study (at least 10 years), in different groups of patients, reaction and neuritis in MDT patients.**

*Patients* (1) women of reproductive age - to allow study of ongoing pregnancy-immunosuppression/recovery effect; (2) non-child bearing women of the same age (infertile/sterilized); (3) women on the "pill"; (4) men of the same age; (groups 2, 3, and 4 being controls).

*Personnel* A team including diagnosticians; clinicians and nursing staff; leprosy control officers; community health midwives; physiotherapy staff; laboratory staff at different levels - doing routine diagnostic BI and MI, serologic studies, study of macrophages and subsets of lymphocytes, *M. leprae* antigenic components; cell biologists and histopathologists; data bank managers and statisticians.

*Projects*

*The effect of different regimes on subsequent development/nondevelopment of reaction and early/late nerve damage.* MDT; MDT with corticosteroids; MDT with immunotherapy; dapsone for 6 months to be followed by (if considered ethical).

Baseline investigation: general medical examination; leprosy examination, skin, nerves, lymph nodes; BI and MI with biopsy if possible of skin and nerve (a few); skin testing with lepromin and PPD; chest x-ray if PPD positive; assessment of nerve damage, voluntary muscle testing (VMT), graded sensory skin testing (STG), light touch/thermal testing for glove and stocking anaesthesia.

Assessment frequency: at start of treatment and 6 month intervals except in pregnancy when 3 monthly assessments would be made. Smaller studies could be initiated in collaboration with the larger study at an early stage, incorporating patients already identified, investigating:

*The mechanism of reversal reaction in BT and BL patients just starting treatment, using the model of Barnetson et al. 1975[27] and the groups 1 to 5.*

Additional investigations including LTT using as antigens *M. leprae* whole, *M. leprae* sonicated (crude preparation) and antigenic fractions obtained by Western blot;[131] storage of

serum, lymphocytes and crude buffy coat layer at -70°C for subsequent testing; tests would be made for well controlled patients studied before, during, and after reaction; biopsies of skin, nerve, lymph nodes;

*The mechanism and cause of nerve damage.* A well constructed small study using patients from first project above with reaction in nerve.

Additional investigations including nerve conduction studies, serial nerve biopsy for histopathology and EM studies, some nerve biopsies to be snap frozen and stored for subsequent study with polymerase chain reaction (PCR)[132] - this could be especially helpful in late nerve damage and glove and stocking anaesthesia; Control groups should include non-pregnant women, women on the pill (exogenous oestrogen), and men.

**To assess the potential of women with cured RFT leprosy for prolonged follow up of RFT patients whether MDT or after dapsone monotherapy**

*Personnel* Successfully treated women with full sensation in their hands would be taught clinical assessment of nerves, SST, and VMT.

**To assess the potential of women with cured RFT leprosy to screen children for early indeterminate leprosy "examination for skin diseases"**

Women without deformity would be most acceptable, and could be taught simple diagnosis and treatment. All suspect cases would be referred. As the role of these women became established they would then become health educators.

*Possible location for such studies* Certain criteria would have to be fulfilled: (a) Leprosy endemic area; (b) High birth rate to allow studies of reaction and nerve damage in pregnant women; Africa or South America would be better than India; (c) Absence of/very low prevalence of other major infections affecting pregnant women e.g. malaria; Addis Ababa, Ethiopian highland at an altitude above the malarial zone would be suitable; (d) Low prevalence of HIV infection. While HIV does not have a significant effect on leprosy in highly endemic areas it could affect the overall mortality of study patients and long term follow up. Much of sub-Saharan Africa would be excluded: Ethiopia, 6 years behind, has only 2-3% HIV positive urban antenatal patients. The prevalence of HIV in rural areas should be lower, as in rural Malawi at Karonga.[133]

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Table 1. Problems encountered in women with leprosy released from control.

| | | | Treatment | | | | |
|---|---|---|---|---|---|---|---|
| | | Control (NL) | DDS mono | MDT (MB) | MDT (PB) | DDS res clofaz | Total leprosy |
| Clinical features | | No[*] | No[*] | No[*] | No[*] | No[*] | No[*] |
| No studied RFT | | 21 | 49 | 33 | 2 | 3 | 87** |
| Problems with leprosy | No | 10 | 40 | 27 | 2 | 3 | 72 |
| | (%) | 48 | 77 | 82 | 100 | 100 | 83 |
| Qurtimat "rheumatism" | No | 9 | 20[6*] | 12[1*] | 1 | 2 | 35[7*] |
| | (%) | 43 | 41 | 36 | | | 40 |
| Acute reaction ENL/RR | No | | 1 | 4 | | | 5 |
| | (%) | | 2 | 12 | | | 6 |
| Neuritis | No | | 19[9**] | 10[5*] | 2[1*] | | 31[14*] |
| | (%) | | 39 | 30 | 100 | | 36 |
| New case/Relapse confirmed MDT | No | 3 | 6[3*] | 1[1*] | 1[1*] | | 8[5*] |
| | (%) | 14 | 12 | 3 | | | 9 |
| Leprosy problems related to pregnancy/post partum | | | | | | | |
| Total | No | | 16[15*] | 8[8*] | 1[1*] | | 25[24*] |
| | (%) | | 33 | 24 | | | 29 |

NL = non-leprous mothers; DDS mono = dapsone monotherapy; MDT(MB) = at least 2 years MDT; MDT(PB) = 6 months MDT; DDS res clofaz = dapsone resistant treated with clofazimine.

[*] problem occurred for the first time post partum.

** 2 mothers who were RTF having completed DDS-monotherapy relapsed after the interim assessment in 1984, and then treated with MDT(MB) and RTF a second time, are counted as 4 women RTF. A third mother BL/RTF, relapsed as BT(nerve) was treated MDT(PB) and again RTF, relapsed again as MB(nerve) was treated MDT(MB) and RTF a third time is counted as 3 women RTF.

Table 2. Neuritis in women with leprosy released from control.

| | | | Treatment | | | | |
|---|---|---|---|---|---|---|---|
| | | Control (NL) | DDS mono | MDT (MB) | MDT (PB) | DDS res clofaz | Total leprosy |
| Neuritis | | No[*] | No[*] | No[*] | No[*] | No[*] | No[*] |
| Patients | | | 19[9**] | 10[5*] | 2[1*] | | 31[15**] |
| | | | 39 | 30 | 100 | | 36 |
| Episodes | No | | 21[9**] | 15[6*] | 3[1*] | | 39[16*] |
| Overt neuritis | No | | 3[1***] | 3 | 1 | 2 | 7[1***] |
| | (%) | | 6 | 9 | | | 8 |
| "Silent" neuritis | No | | 18[8*] | 12[*] | 2[1*] | | 32[15*] |
| | (%) | | 37 | 36 | | | 37 |
| Tender nerves without the loss of function | No | 3 | 4# | | 1 | | 5 |
| | (%) | 14 | 8 | | | | 6 |
| Stocking/glove anaesthesia | No | | 18 | 15 | | 3 | 36 |
| | (%) | | 37 | 45 | | 100 | 41 |
| Total no studied | | 21 | 49 | 33 | 2 | 3 | 87 |

NL = non-leprous mothers; DDS mono = dapsone monotherapy; MDT(MB) = at least 2 years MDT; MDT(PB) = 6 months MDT; DDS res clofaz = dapsone resistant treated with clofazimine.

[*] neuritis occurred for the first time post partum.

** neuritis occurred during pregnancy in one mother, post partum in the rest.

*** neuritis occurred during pregnancy.

# one patient required emergency nerve release.

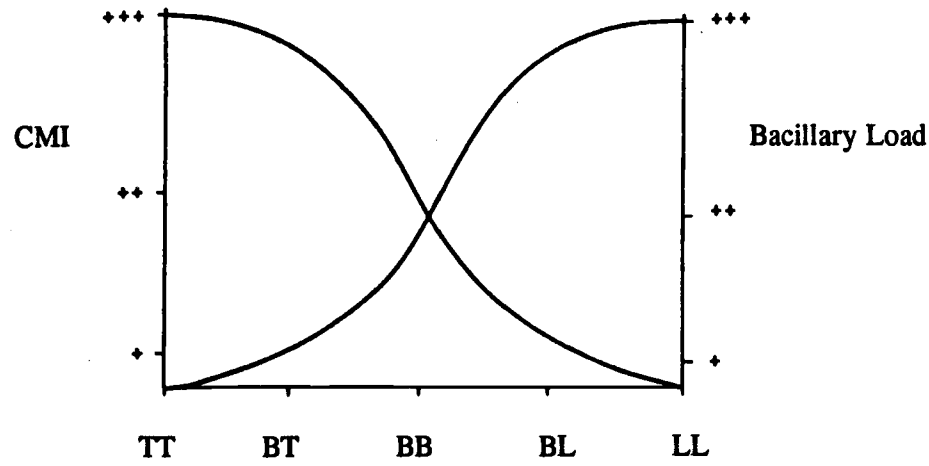


Fig. 1. The spectrum of leprosy in terms of cell mediated immunity (CMI) and bicillary load. TT - tuberculoid leprosy, BT - borderline tuberculoid leprosy, BB - borderline leprosy, BL - borderline lepromatous leprosy, LL - lepromatous leprosy. Pregnancy causes a shift toward LL, child birth a shift toward TT.

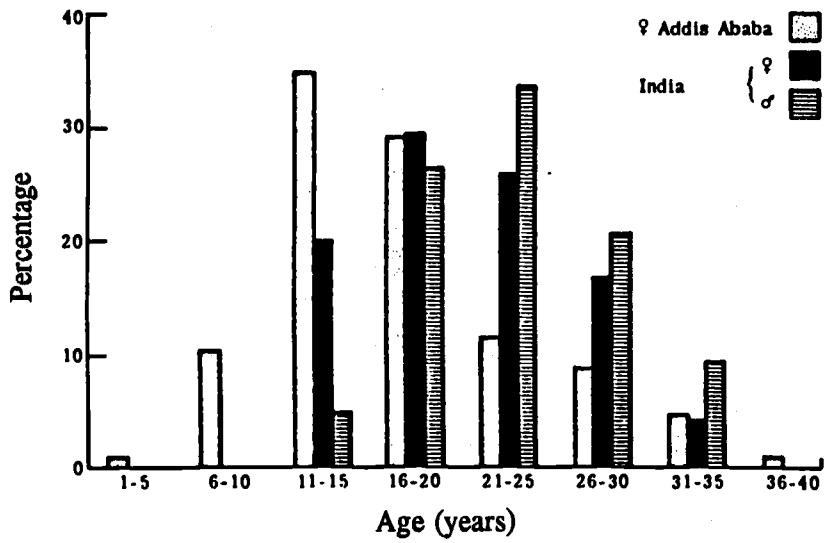


Fig. 2. Probable age of onset of leprosy as percentage of a group. Very small numbers occur in early childhood increasing sharply with onset of puberty.

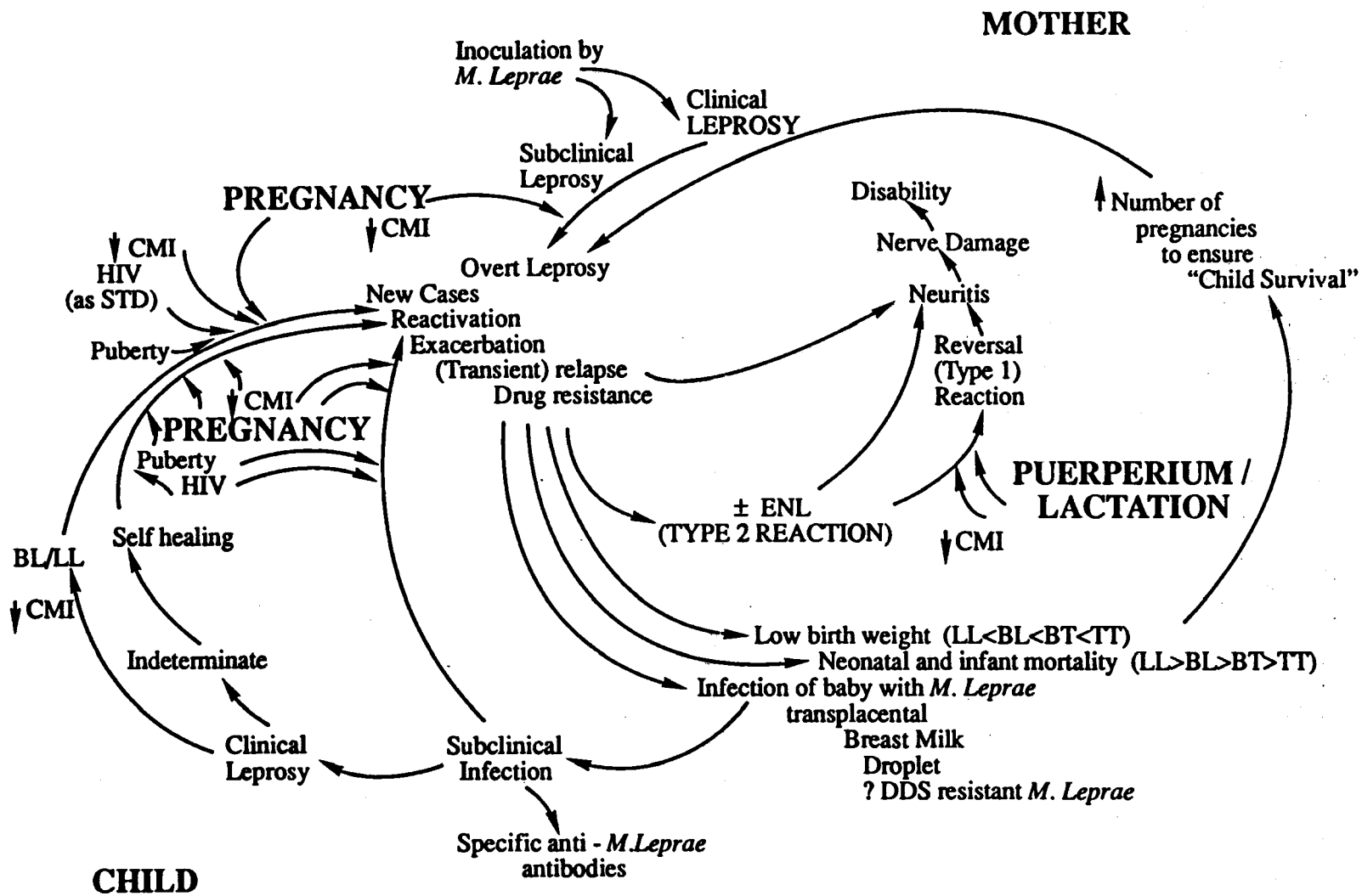


Fig. 3. The effect of puberty, pregnancy, and puerperium/lactation on the evolution of leprosy. Puerperium = the first 6 weeks after childbirth.

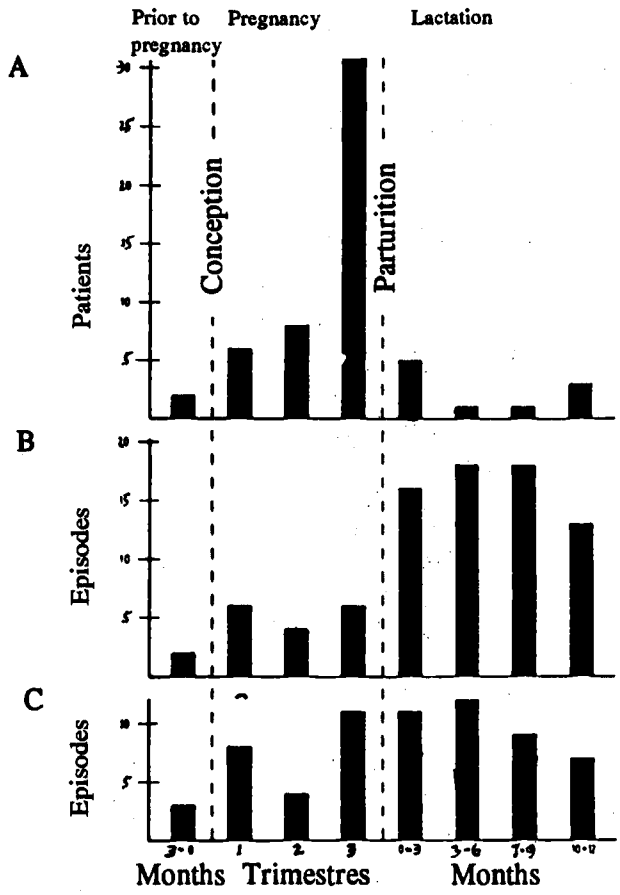


Fig. 4. The time of occurrence, prior to conception and during pregnancy and lactation of: (a) first evidence of relapse/development of dapsome resistance; (b) reversal reaction; (c) ENL. The incidence is expressed as a percentage of the patients studied in each 3-month period.

# Does Schistosomiasis Infection Impair the Health of Women?

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**Summary**

A group of experts working for the World Health Organization recently wrote: "Of all the parasitic infections that affect man, schistosomiasis is one of the most widespread. In terms of socioeconomic and public health importance in tropical and subtropical areas, it is second only to malaria" (WHO 1985: 16,20). This quote reflects a long-standing and widespread perception among biomedical practitioners and research workers that schistosomiasis presents a major public health problem (Lapage 1966; Weir 1969; Inhorn and Brown 1990).[1] It also draws attention to the widespread belief that "man" includes women.

This paper suggests both perceptions are incorrect. It does not provide an analysis of the historical, cultural, and economic forces that have shaped our biomedical ("scientific") understanding of schistosomiasis. It shows, however, that there is insufficient and inadequate information to gauge the impact of schistosomal infection on health and that the dearth of information is particularly acute for women. It is necessary to explore the behavioural, social, and economic aspects of infection from an anthropological perspective (and to blend these with biomedical information) to develop a holistic picture of the impact of schistosomal infection on health and well-being.

The paper is divided into three sections. Section one reviews the biomedical, economic, and sociological literature on schistosomiasis. This is not an exhaustive review, but some of the most important findings and approaches are highlighted to show that research workers have adopted a narrow conception of health and well-being in these three spheres of work. It is suggested that it will not be possible to gauge the impact of schistosomal infection on the health and well-being of women (with any degree of confidence) until broader conceptions of health, illness, and sickness are accepted. This entails interdisciplinary research; therefore methodological innovations and flexibility are necessary from research workers in the biological and social sciences.

The second section shows how interdisciplinary research can be carried out with

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[1]Schistosomiasis (or bilharziasis) is the broad descriptive term given to a group of chronic parasitic infections caused by schistosomes. The majority of human infections are caused by three species of schistosome: *Schistosoma mansoni, S. haematobium*, and *S. japonicum*. These schistosomes have similar life-cycles that involve an aquatic snail intermediate host, the human definitive host, and their mutual presence in a common environment where transmission occurs: typically irrigated fields, irrigation and drainage channels, rivers, ponds, and ditches. The biology and ecology of human schistosomes has been reviewed by Sturrock (1987).

reference to schistosomal infection and behaviour. To the best of my knowledge, the work I carried out in Gezira Province, Sudan is the only piece of interdisciplinary research that examines the effects of schistosomal infection on female behaviour (Parker 1989). This work shows, among other things, that it is possible for a single investigator to collect biomedical, ethnographic, and continuous observational data. It is unusual to blend these types of data in a single study and the methods and results are, therefore, discussed at length. The third and final section of this paper briefly comments on "the state of the art" in the study of schistosomiasis.

## An Inadequate Literature

The study of schistosomiasis has been dominated by pathologists, hospital-based clinicians, clinical epidemiologists, and physiologists. The literature is enormous and immensely rich but the subjects participating in this research tend to be men or children rather than women. Moreover, the questions raised by this type of research inevitably reflect biomedical conceptions of health, illness, and sickness. Jordan and Webbe (1982), Mahmoud (1985), Rollinson and Simpson (1987), and Chen and Mott (1989) have written and/or edited a number of articles that review this literature from a biomedical point of view. This section does not seek to match these reviews. Instead, some of the most important results and approaches are noted to show why biomedical research cannot, singlehandedly, address the question of whether schistosomal infection impairs health and well-being. Unfortunately, there is very little research examining the economic and social aspects of schistosomal infection and, as will be demonstrated, the research undertaken in these spheres is rather superficial.

### Biomedical aspects of infection

#### *Pathological and clinical aspects of infection*

Pathologists and hospital-based clinicians have studied the nature, development, and outcome of infection by *S. japonicum, S. mansoni*, and/or *S. haematobium*.[2] These investigators have focused on individual patients exhibiting (or having exhibited) symptoms and signs of infection and, inevitably, they have not addressed the issue of how many carriers are asymptomatic in a population. They have shown that when symptoms do arise, these vary from one species to another but, it is possible for all three species to lead to disability,[3] disease, and even death.

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[2]Biomedical research has tended to focus on *S. mansoni* and *S. haematobium* rather than *S.japonicum* and the literature reviewed in this paper reflects this bias.

[3]Hospital-based clinicians generally assess disability in terms of a patient's reported symptoms. These include fatigue, abdominal pain, and diarrhoea for infection by *S. mansoni* and *S.japonicum* and blood in the urine for infection by *S. haematobium*.

It is unclear why some carriers become symptomatic while others do not, but autopsy studies suggest that the damage caused by schistosomes is related to the reaction of host tissues to eggs laid by female worms and the number of schistosome eggs in the tissue. Cheever et al. (1968, 1975, 1977) and Kamel et al. (1978), for example, have established a clear relationship between the presence of schistosomal disease and worm burden for *S. mansoni* and *S. haematobium*. These studies have also shown that while the extent of disease is related to worm burden, worm burden, in turn, is related to the excretion of eggs in faeces (for *S. mansoni*) and urine (for *S. haematobium*). These observations suggest that excretion of eggs in the faeces and urine may be a useful measure of intensity of infection in living persons.

Some clinical hospital-based studies also support these findings. Salih et al. (1979), for example, reported a significant relationship between "heavy" infestations of schistosomes (as measured by egg output) and schistosomal disease.

Nevertheless, since both post-mortem and hospital-based clinical studies only deal with symptomatic cases, it is difficult to use this type of information to gauge whether infection by schistosomes presents a major public health problem. Cheever's research team have emphasized this limitation themselves. They examined a rural disease in a city hospital without knowledge of the past or present residence of the patients or other epidemiological data. Not surprisingly, therefore, they express great caution in applying the results of their studies to infected populations.

An additional problem with the pathological and clinical literature is that women have rarely featured in this type of research. It is thus not clear whether it is valid to extrapolate the findings generated from male subjects to women. The few pathological and clinical studies that have concentrated on women, have concerned themselves with female reproductive organs. Some of the more interesting findings include the following: first, the presence of *S. haematobium* eggs in the female genital organs is not uncommon (WHO 1985); second, Wright et al. (1982) suggested that gynaecological complications from infection by *S. haematobium* were a significant cause of female morbidity in women; and third, el Mahgoub's research (1982) among women suggests that pelvic schistosomiasis, although usually asymptomatic, may cause infertility (but, no other investigators have shown this association).

*Physiological aspects of infection*

There is no research examining the relationship between infection, intensity of infection, and the physiological aspects of disability among women. However, physiologists have assessed the effects of *S. mansoni* on the work capacity of men in controlled laboratory conditions (Omer and Ahmed 1974; Collins et al. 1976; Awad el Karim et al. 1980, 1981; van Ee et al. 1984) and selected field situations (Awad el Karim et al. 1987). These studies have been solely concerned with the physiological performance of active working subjects and the main findings may be summarized as follows.

Collins et al. (1976), van Ee et al. (1984) and Awad el Karim et al. (1981, 1987) asked their subjects to perform, among other things, submaximal exercise tests on bicycle ergometers to estimate work capacity. The data generated by these four studies suggested that infection did not impair standard parameters of physiological function.

Awad el Karimm et al. (1980) and Omer and Ahmed (1974) also conducted exercise tests using a bicycle ergometer and step-test, respectively. These two studies suggested that infection significantly impaired physiological performance. Awad el Karim et al. (1980) found that heavily infected canal cleaners (>2000 eggs/g) suffered a 16-18% impairment of maximal physical working capacity compared with lightly infected (<1000 eggs/g) and uninfected villagers. Differences between lightly infected and uninfected individuals could not be detected, and it was concluded that *S. mansoni* only impairs physical working capacity when there is a high intensity of infection, as assessed by egg load.

It could be argued that the results generated by this study do not conflict with the work of van Ee et al. (1984) and Awad el Karim et al. (1981, 1987) because the infected subjects participating in the latter three studies were not as heavily infected as the canal cleaners. However, this does not explain the negative findings recorded by Collins et al. (1976) and the positive findings recorded by Omer and Ahmed (1974). Although the investigators in these two studies did not record the egg loads of infected subjects, Omer and Ahmed's subjects did not have hepatic or splenic enlargement and they did not appear to be more heavily infected than those participating in the study undertaken by Collins et al. (1974).

In addition, there are a number of problems with Awad el Karim's study. First, the daily activity patterns of canal cleaners is entirely different from the control group (lightly infected and uninfected villagers). As Awad el Karim et al. (1980) and Collins (1983) acknowledge, it is possible that particular aspects of their working conditions may cause detraining of the leg muscles for work tests on a bicycle ergometer. Second, the social, cultural, and economic position of the canal cleaners differs considerably from the villagers with whom they were compared. Although they had lived in Gezira for an average of 14 years at the time of the study, many of these differences have continued; and it is significant that their monthly income was nearly half that of the villagers. Although Awad el Karim et al. (1980) assert that this difference did not affect nutritional intake they do not demonstrate it. This is especially unfortunate, because they found that heavily infected canal cleaners had a significantly lower haemoglobin level than the lightly infected and uninfected villagers. It is possible that the canal cleaners had an already depleted haemoglobin level for nutritional reasons, and that nutrition rather than infection affected maximal aerobic power output. Third, the subjects in this study were divided into "uninfected", "lightly infected," and "heavily infected" groups on the basis of a single round of stool examinations. Egg output varies over time and the analysis of single stool samples can fail to detect light infections. It is not clear whether "light" infections do not impair physiological performance because some of the uninfected subjects may have been infected but not passed eggs on the days their stools were examined.

Above all, the work of Awad el Karim and other investigators suggests that physiological tests are currently unable to contribute a great deal to our understanding of disability from schistosomal infection. It is not clear, for example, whether harnessing respirometers to infected and uninfected subjects and then asking them to cycle on stationary bicycles (when the subjects themselves have never had access to a bicycle before) generates useful results. These tests may not, after all, bear any relationship to the impact of schistosomal infection on actual working (or other) behaviour in the agricultural or domestic sector. It would be helpful to know the total time each participant spent at work (as well as

the frequency and nature of the work undertaken in the course of each day) and the extent to which test results reflected these working patterns. Without collecting broadly based information such as this, it becomes difficult to utilize these physiological data when assessing the nature of disability for those who harbour schistosome worms.

*Epidemiological aspects of infection*

Clinical epidemiologists have shown that infection with *S. japonicum, S. mansoni*, and *S. haematobium* can significantly contribute to the overall morbidity in endemic areas (WHO 1985). There is, however, considerable disagreement about the relationship between infection, intensity of infection, and the development of schistosomal disease as well as the relationship between infection, intensity of infection, and the nature and extent of disability (Mott 1987; Tanner 1989). This controversy applies to all species of schistosome.

It is thus extremely difficult to interpret epidemiological information conveying the incidence, prevalence, and/or intensity of infection. In particular, we still do not understand the extent to which variations in the prevalence and intensity of infection can explain existing morbidity patterns, and the extent to which they may also be influenced by factors such as regional differences in schistosomal strains (Nash 1982; Gryseels 1989), host susceptibility (Khattab et al. 1968; Camus et al. 1977; Pereira et al. 1979; Salam et al. 1979), nutritional factors (Akpon et al. 1975; Stephenson et al. 1986); and concomitant parasitism (Ongom and Bradley 1972; Smith et al. 1979; Sukwa et al. 1986).

The long-term significance of infections (among infected populations) is also far from clear. The majority of studies have a cross-sectional design and it is difficult to predict the outcome of schistosomal infection without knowledge of the duration of infection, the frequency of reinfection, or the age of first infection (Jordan et al. 1982).

These difficulties apply to women, men, and children. Epidemiologists have not excluded women from their investigations but the social and clinical risk factors that affect the epidemiology of schistosomal infection among women have not been thoroughly investigated (Brabin 1990 a,b). It is thus difficult to explain why the prevalence and intensity of infection is often significantly lower among females than males (at least for *S. haematobium*) in different areas.

Brabin's articles (1990 a,b) draw attention to the paucity of information on women. Her papers raise a number of serious issues but the "health of women" is essentially restricted to the study of three risk groups: pre-pregnant, pregnant, and inter-partum women. Women's health is, therefore, limited to the study of women in their reproductive years.

It is common for epidemiologists and clinicians investigating schistosomiasis and many other communicable diseases to equate women's health with the study of reproductive performance (pregnancy, childbirth, etc.) and reproductive organs. To quote Graham and Campbell: "women's health has tended to be conceptualized as a discrete, negative state; characterised by physical rather than social or mental manifestations, and by a narrow time-perspective focusing on pregnancy, delivery and the puerperium" (1990:i).

The narrow conceptualization of women's health in Brabin's articles reflects an approach that is widespread among biomedical research workers investigating schistosomiasis. It is this: health, illness, and disease are only conceptualized in biomedical terms. Health, in other words, is equated with the absence of clinical signs of infection and

illness is deemed to follow from infection - or at least from heavy infestations of schistosomes. The World Health Organization's definition of health as "a state of complete physical, mental, and social well-being" is ignored.

This is unfortunate. It is important to understand the relationship between infection, intensity of infection, disease, and disability because this will help us to address the question of whether schistosomiasis is a major public health problem. However, this will not be possible until biomedical information is placed in cultural context and this necessarily entails the acceptance of broader notions of health, illness, and sickness.

Popkin (1982) has suggested that attempts to assess the effects of schistosomal infection (and other tropical infections) on health should focus on the household rather than the individual. Herrin (1986) and Tanner (1989), among others, have supported Popkin's suggestion. This approach would presumably include women in their post-reproductive years as well as women in their child-bearing years. However, the economic and sociological research undertaken since the publication of these articles has generally ignored these suggestions. This literature is reviewed in the following section.

## Economic and social aspects of infection

### *Economic aspects of infection*

Attempts to explore the economic aspects of schistosomal infection among women have been minimal. Weisbrod et al. (1973; 1974) and Baldwin et al. (1974) investigated the effects of *S. mansoni* on labour productivity and supply among female and male plantation workers in St Lucia, as well as female workers for an urban light engineering firm. Their investigations did not reveal any significant relationships between *S. mansoni* and absenteeism, reduced daily and/or weekly earnings, or workload. The intensity of infection was low with participants being classified according to one of two egg counts: 1-19 eggs/g and over 19 eggs/g. It is possible that different results would have been obtained if egg loads had been substantially heavier.

There have been several studies examining the economic consequences of infection by *S. mansoni* and/or *S. haematobium* for men but these studies have generated a series of conflicting results. Foster (1967) and Collins et al. (1976) did not find any significant differences in output between infected and uninfected subjects at work in the fields, but Foster (1967) recorded a higher degree of absenteeism among those who were infected. Fenwick and Figenshou (1972) found the mean bonus earnings of infected workers to be significantly less than the mean bonus earnings of uninfected workers for three of the four 6-month periods they studied. Finally, Barbosa et al. (1981) recorded a 35.1% reduction in productivity among those with hepatosplenic disease, as compared to those with "light" intestinal infections.

Prescott (1979) reviewed these studies and showed that the investigators used crude methods and indicators in their work. Some of the more striking limitations include the following: first, they were generally biased toward the selection of relatively fit and healthy workers; second, the economic effects of infection were only considered for the individual and the response to an individual's sickness within and between households did not receive

any attention; third, the long-term economic consequences of infection were not adequately studied; and fourth, the economic consequences of schistosomal infection for women engaged in domestic work was not known.

These limitations aside, it is difficult to draw any conclusions from the above-mentioned studies about the economic consequences of schistosomal infection. In particular, it is not clear whether the selected indicators (absenteeism, weekly earnings, etc.) are too insensitive to detect the relationship between infection, intensity of infection, and the economic consequences of infection, or whether the results simply reflect the fact that *S. mansoni* and/or *S. haematobium* has a differential impact on economic performance within and between populations. It is, of course, unlikely that social, cultural, psychological, and economic forces do not influence the relationship between infection, intensity of infection, and economic performance but the investigators conducting these studies have failed to use local information and insights to interpret their data. Future research in this area would benefit from anthropological input because this would enable quantitative indicators of economic performance to be placed and understood in cultural context.

*Social aspects of infection*

An increasing number of research workers have investigated the social aspects of schistosomal infection (Kloos et al. 1982, 1986; Stephenson et al. 1986; Tiglao 1982; Herrin 1988; Maiga 1988). Many of these studies have been carried out with the explicit objective of improving the health education component of control programmes and/or devising ways to facilitate effective community participation in control programs. Tanner et al. (1987), Degremont et al. (1987), and Lengeler et al. (1991) have also developed a variety of techniques for examining local perceptions of *S. haematobium* and other infections endemic in parts of Tanzania. These studies attempted to record local ideas about which diseases should be prioritized for control. Research has rarely, if ever, focused on women and this sub-section raises two questions: Why is it necessary to elicit local perceptions of illness, health, and well-being from women? Is it appropriate to repeat the studies that have been done for men and children on women?

First, there is no doubt that questions which fall within the remit of "the social aspects of infection among women" overlay rather than mirror questions concerning "the social aspects of infection among men." In fact, medical anthropologists have drawn attention to the fact that social differentiation between women in the same population (let alone differentiation between women and men) often affects the articulation and expression of illness. This, in turn, has important ramifications for diagnosis and treatment (Morsy 1978; Constantinides 1985).

In addition, attention has increasingly been drawn to the impact women have within a household on the health of their children and other household members. For example, a group of experts working for the World Health Organization recently wrote: "The full participation of women in the health education process is particularly important. Their potential role in promoting the health of their families and their influence in helping to prevent schistosomiasis in their children should be stressed in the health education activities carried out in the community" (WHO 1985:47).

Without doubt, it would be helpful and interesting to address these issues with

reference to schistosomiasis. The question remains, however, whether it is sufficient to repeat the studies that have been done on male knowledge, attitudes, and practices for women. In other words, is it appropriate to add an extra set of questions to an interview schedule to explore the effects of *S. japonicum, S. mansoni*, or *S. haematobium* among women on pregnancy, childbirth, and a mother's ability to care for her children etc?

I shall address this question with reference to papers published by Tiglao (1982), Kloos et al. (1982), Lengeler et al. (1991), and Herrin (1988). These papers illustrate some of the approaches that are commonly used to examine local perceptions of schistosomal infection. In fact, a number of serious issues are raised in these papers and they include the following: is it useful to gauge the impact of schistosomal infection on health and well-being by asking an individual to rank its severity according to a pre-designed scale?

Kloos et al. (1982) and Tiglao (1982) used this approach to record the perceived severity of *S. haematobium* and *S. japonicum*, respectively. Kloos et al. (1982) asked male subjects "is bilharzia a mild or serious disease?" Tiglao asked male and female heads of households whether they thought schistosomiasis was "very serious, somewhat serious, neither serious nor not serious, somewhat not serious or not serious at all."

It is not clear how the participants in these two studies differentiated between "mild or serious" and "very serious, somewhat serious, neither serious nor not serious etc." In the case of Tiglao's research, severity could refer to any one of the following: the perceived impact of schistosomal infection for a particular organ or set of organs in the human body; the perceived impact of infection for an individual's overall state of health; or the perceived ramifications of illness for social relationships within or between households and/or extended family groups. Similarly, Kloos et al. (1982) do not say how the participants in their study interpreted the word "mild" but the word "serious" appears to refer to the perceived impact of infection for an individual's organs and/or their overall state of health.

Above all, Kloos et al. (1982) and Tiglao (1982) have ignored the work of medical anthropologists. This work has repeatedly drawn attention to the social, moral, and religious aspects of illness and affliction. It is likely that the perceived impact of schistosomal infection (if it is identified by the participants) varies within and between populations according to these influences as well as gender, age, authority, access to curative health care, etc. Future research workers investigating the social aspects of infection should address these issues. They may find that it is unhelpful to rank the perceived severity of schistosomal infection (or any other infection) because ranking bears little relationship to indigenous ways of thinking about the social consequences of infection.

Ranking played a slightly different role in the research undertaken by Lengeler et al. (1991) in northeastern Tanzania. These investigators used questionnaires, distributed through schools and party administrative systems, to identify communities at risk for urinary schistosomiasis. They asked school teachers and party officials to rank the diseases most prevalent among school children and villagers, respectively. They were also asked to rank the six most important problems in their village (e.g. health, agricultural, food, etc) and six priority diseases for control.

This approach may prove to be cheaper than epidemiological investigations as Lengeler et al. (1991) found that the priority given to *S. haematobium* was related to its prevalence in the community. Indeed, there was a "cut-off" prevalence rate, above which schistosomiasis was almost always a "top 5" priority disease, while below this limit it was often not cited.

The fact that a literate and predominantly male sector of the population perceive *S. haematobium* to be a "top 5" priority disease in a number of communities does not, of course, tell us very much about the way in which *S. haematobium* impairs health and well-being. This issue has been addressed by Herrin (1988).

Herrin used a questionnaire to explore the social consequences of infection by *S. japonicum* in the Philippines. A wide range of questions were asked and the following results were reported: the majority of infected and uninfected participants thought *S. japonicum* caused severe and recurrent pain and that people looked down on men and women infected by schistosomes. Indeed, it was thought that an individual infected by *S. japonicum* would damage the social standing of his/her family.

In addition, the majority of infected and uninfected participants felt that infection hampered a man's ability to "make progress in life" and that a mother would be less able to carry out her domestic duties. Herrin also found that perceptions of schistosomiasis varied according to infective status. That is, participants free from infection perceived the impact of schistosomal infection to be worse than participants infected by *S. japonicum*.

The prevalence and intensity of infection is not mentioned in this article and it is not clear whether the perceived consequences of schistosomal infection vary according to the age and sex of the respondents. Nevertheless, this study is one of the first attempts to incorporate a wide range of indicators to assess the impact of schistosomal infection on health and well-being. The investigator has not restricted his research to an investigation of a patient's reported symptoms or ill-defined notions of severity.

It is difficult to comment on the methodology from the limited information presented in this article but it seems that the author relied entirely on a questionnaire to elicit local perceptions of schistosomal infection. The reliance on quantitative survey methods is common in the study of schistosomiasis and other infectious diseases (Foster 1987). These methods have been widely criticised and it is likely that some of the theories and methods employed by medical anthropologists would enhance our understanding of the social aspects of schistosomal infection.

There is insufficient space in this paper to review the key debates in medical anthropology. Suffice to say that ethnographic research would enable a shift away from the "ethnic cookbook" approach that dominates the study of schistosomiasis and other infectious diseases. This approach describes the social and cultural aspects of infection in terms of discrete variables (such as religion, class, ethnicity, etc) that can be easily identified and measured. The investigator's perception of the problem is generally reflected in the selected list of variables and the results are frequently reduced to a series of simple associations. A sense of process is not conveyed in this work and the context is lost. Above all, the techniques are too insensitive to accurately describe health, sickness, and illness from the actor's point of view.

Ethnographic research methods have their problems too. But the research undertaken by Frankel (1982) in Papua New Guinea and Davison et al. (1991) in South Wales has shown that it is possible to blend qualitative (and predominantly ethnographic) methods with quantitative (and predominantly sociological and epidemiological) methods in the study of disease, illness, and health. It would be useful and interesting to apply a similar approach in research addressing the relationship between infection, intensity of infection, and perceived well-being among women.

In summary, this section has shown that research exploring the economic and social aspects of schistosomal infection has not focused on women. It would be inappropriate to repeat the type of work that has been done with men, children, and occasionally women for the following reasons: first, research exploring the economic aspects of infection has relied on single performance indicators that are rooted in the cultural traditions of the research workers rather than the participants; second, research exploring the social aspects of infection has relied on questionnaires to elicit perceptions of well-being and local, culturally specific information has not been used to formulate the questions. It is likely that the theories and methods employed by medical anthropologists would enrich our understanding of the economic and social aspects of schistosomal infection.

**Schistosomal Infection and Female Behaviour**

There is very little research examining the effects of *S. japonicum, S.mansoni* or *S. haematobium* on behaviour for women, men, or children.[4] In fact, the work I carried out in Omdurman aj Jadida, a registered village in the Gezira/Managil irrigation scheme, Sudan, is the only piece of research that examines the effects of schistosomal infection on female behaviour (Parker 1989). This section summarizes the methods and results of this research to show how anthropological fieldwork can contextualize biomedical and behavioural research and thereby develop a more holistic picture of the effects of schistosomal infection on behaviour.

Fieldwork took place between April 1985 and May 1986. During this time, I lived with an extended family of sixteen. I learnt to speak Sudanese Colloquial Arabic and, wherever possible, I behaved in ways that were considered appropriate for a single woman living in a segregated muslim village in central Sudan. Inevitably, my presence and work challenged some of their expectations but, over time, I established close relationships with a number of women in the village. Indeed, it would be true to say that I came to experience, and view, certain aspects of their daily life in their own terms. These experiences (in combination with some other research that I attempted in Gezira in 1981 and 1983) influenced the way I designed and carried out the biomedical and behavioural research. They also affected the way I analyzed and interpreted the biomedical and behavioural data that I collected.

Two major questions were addressed during this research: first, does *S. mansoni* impair daily activities among women engaged in agricultural work in the cotton fields; second, does *S. mansoni* impair daily activities among women nursing newborn infants and engaged in domestic work? The methods employed in these two studies were similar and the results strikingly dissimilar. They may be summarized as follows: both studies are characterized by small samples and a paired design. That is, the 11 most heavily infected women engaged in agricultural work were paired with 11 women free from infection but also

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[4]The literature on water contact studies is not reviewed in this section because this type of work examines human behavioural factors associated with the transmission of schistosomiasis. It does not address the question of whether schistosomal infection impairs health and well-being.

engaged in agricultural work; and the 12 most heavily infected women engaged in domestic work and nursing newborn infants were paired with 12 women free from infection but also engaged in domestic work and nursing newborn infants.[5]

Infective status aside, women were matched as closely as possible for a wide range of social, economic, and biological variables that might otherwise have affected their daily activities.[6] By pairing women so finely it was possible to minimize the role of those variables that might otherwise have affected a woman's work regime. However, it was not possible to control for the skills with which a woman carried out her daily activities, the motivation with which she completed her daily tasks, or the extent to which the presence of an observer altered her daily activities.

To detect the effects of *S. mansoni* on female activity patterns in the cotton fields and the domestic sphere, observations were conducted on a minute by minute basis. The methods and results employed in these two studies are described in turn.

### The effects of *S. mansoni* on female activities in the cotton fields

Twenty-two women (11 pairs) were observed in the cotton fields. Each woman in each pair was observed for one day by the same observer (myself), and the following information was collected in the course of each day's observation: the total time spent in the cotton fields; the type and duration of activities undertaken in the cotton fields; and the amount of cotton picked. This information was collected from each woman in the morning and the afternoon (where relevant).

To record the type and duration of activities undertaken in the cotton fields, observations were carried out on a minute by minute basis. Each period of observation lasted for 16 minutes and every period of observation was followed by a 14 minute interval. These observations took place at the following time intervals: 0730-0745, 0800-0815, 0830-0845, 0900-0915, 0930-0945, 1000-1015; and 1500-1515, 1530-1545, 1600-1615, 1630-1645, 1700-1715, 1730-1745 hours, respectively.

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[5]The cellophane faecal thick smear technique (Kato) was used to detect and quantify schistosoma ova in stool samples (WHO 1983). Egg output varies over time and the analysis of single stool samples can fail to detect light infections. I, therefore, collected a minimum of five different samples to ensure that negative results reflected an absence of infection with *S. mansoni* and a minimum of two samples from women infected with *S. mansoni* to generate a more accurate picture of their worm burden.

[6]See Parker (1989) for a detailed account of the selected pairs in these two studies. Statistical tests (including paired t-tests) subsequently revealed no significant differences between infected and uninfected women in either study for any of the selected social, economic, or anthropometric variables. The analysis of stool and urine samples did not reveal any cases of *S. haematobium*, *T. solium*, ascaris, or hookworm and the analysis of blood samples suggested that infected women did not experience the debilitating consequences of malaria with any greater or lesser frequency than uninfected women. Finally, infected and uninfected women did not report or exhibit symptoms associated with infectious hepatitis, typhoid, or meningitis - the other main infectious diseases in the area.

Every single activity undertaken by a woman during these time periods was recorded. These activities were subsequently divided into the following five activity groups: posture, while picking cotton; rest (such as lying down, sleeping); work activities associated with cotton picking (such as filling sacks with cotton); other agricultural work activities (such as collecting weeds for goats); all other activities undertaken in the cotton fields that did not directly affect a woman's daily productive output.

The analyses of these data revealed the following results:[7] first, women infected by *S. mansoni* had an arithmetic mean egg load of 1958 eggs/g and their egg loads ranged from 726 eggs/g to 3768 eggs/g. Second, every women in this study went to the fields in the morning and infective status did not, therefore, influence a woman's decision to go to the fields. Third, paired t-test analyses showed that women infected by *S. mansoni* spent significantly less time in the cotton fields in the morning than their uninfected pairs ($p$ = 0.008). They also spent significantly less observed time picking cotton ($p$ = 0.009) but they did not pick significantly less cotton ($p$ = 0.620). In other words, women infected by *S. mansoni* attempted to pick as much cotton as possible in the shortest time period feasible.

In the afternoon, this pattern was partially repeated by those women infected by *S. mansoni* who returned to the fields. They continued to spend significantly less observed time picking cotton ($p$ = 0.034) and they did not pick significantly less cotton ($p$ = 0.803). They did, however, spend significantly less observed time engaged in other important agricultural activities such as collecting weeds for goats ($p$ = 0.054).

It was also striking that more than 18% of women did not go to the fields in the afternoon. These women were all infected by *S. mansoni* and, without exception, they said they were too tired to attempt any work. In fact, Fisher's exact probability test (one-tail) showed this difference to be significant ($p$ = 0.045). It is difficult to gauge the economic implications of this finding without additional information concerning an infected woman's overall loss in productive output and the extent of intra- and inter-household compensation. Further research, with a longitudinal dimension, would certainly help to establish the relationship between infection by *S. mansoni*, intensity of infection, daily activities, and productive output. But this should not deflect attention from the finding that infection by *S. mansoni* at recorded egg loads, altered activity patterns in the cotton fields.

### The effects of *S. mansoni* on female activities in the domestic sphere

Twenty-four women (12 pairs) took part in the study of domestic work and nursing behaviour. Every woman was observed for two consecutive days and her pair - where possible - on the following two days. These observations took place between 0700 hours and 1300 hours and they were undertaken on a minute by minute basis. On the premise that the number, type, and overall configuration of activities may generate useful information about the nature and extent of disability, I recorded every single activity that a woman attempted - with or without her newborn infant.

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[7]The results from this study and the following study are not presented in a tabular form. See Parker (1989) for this detailed information.

Paired t-tests were used to analyze these observational data and the most important results may be summarized as follows:

First, women infected by *S. mansoni* had an arithmetic mean egg load of 574 eggs/g and their egg loads ranged from 144 eggs/g to 1584 eggs/g.

Second, infected women did not spend significantly different amounts of time engaged in domestic work (such as food preparation, sweeping, washing-up, etc) than women free from infection ($p = 0.734$).

Third, the type of domestic work undertaken by women did not vary by infective status. Domestic work activities require women to expend different amounts of effort and energy and these activities may be divided into three groups: activities requiring heavy effort, moderate effort, and light effort.[8] Paired t-test analyses showed that infected women did not spend significantly more or less time engaged in these three types of activities than women free from infection.

Fourth, woman infected by *S. mansoni* did not spend significantly less time caring for their infants and/or other children than women free from infection ($p = 0.518$). In fact, women infected by *S. mansoni* spent similar amounts of time in the five main types of infant and childcare activities identified. These were breastfeeding, supplementary feeding, cleaning the infant, holding the infant, and caring for other children within the household. In terms of the effort expended to undertake activities concerned with infant care, paired t-test analyses also showed that infected women did not spend significantly more or less time engaged in very passive, passive, active, or very active ways toward their infants than women free from infection.[9]

Fifth, the time engaged in social activities, such as circumcision ceremonies and social visits to friends and relatives, did not vary by infective status ($p = 0.555$).
Sixth, women infected by *S. mansoni* did not spend significantly more time resting (e.g. sleeping, lying down) than women free from infection ($p = 0.198$). Seventh, the time engaged in non-essential activities such as "platting hair" and "taking a *dukhan* (smoke) bath" did not significantly vary by infective status ($p = 0.177$). In sum, women infected by *S. mansoni* at recorded egg loads, behaved in similar ways to women free from infection.

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[8]These groups are based upon the perceptions of the women with whom I worked as well as my own observations in the field. Inevitably, they are crude and highly subjective.

[9]Categorizing a mother's behaviour toward her infant into four main groups is extremely crude and subjective. Very passive behaviour included the mother and infant sleeping side by side. Passive behaviour included the mother sitting with her legs outstretched and holding her infant in her lap. Active behaviour included the mother holding her crying infant in a standing position and removing loose stool from his/her legs; and very active behaviour included the mother playfully throwing her infant in the air while she made some coffee. See Parker (1989, pp. 390-404) for a list of the different types of behaviour undertaken by mothers toward their infants.

These observational data raise an important question. If women infected by *S. mansoni* behave in similar ways to women free from infection on a daily basis, does it follow that infection by *S. mansoni* is not a cause of weakness and fatigue? This is a difficult question to answer! It is important to identify and understand the impact of infection on daily activities as schistosomes are capable of altering an individual's state of health irrespective of their knowledge about the pathogen and any links they perceive between infection, disability, and well-being. It cannot be assumed, however, that schistosomal infection is not a cause of weakness and disability from these observational data alone. The observations are essentially descriptive. They do not indicate the energy and effort required to perform a certain task, nor do they give any indication of outcome - of whether the food cooked by an infected woman or the quality of her breast milk was better or worse than that supplied by an uninfected woman.

Nonetheless, the analysis of biomedical information supported the findings generated by continuous observational data. That is, anthropometric, parasitological, and haematological data were collected from the 24 women engaged in this piece of observational work and their infants at five weekly intervals over a period of eight months. These data provide a crude measure of the "success" with which infected women were able to care for their infants - compared with women free from infection.

Paired t-tests were used to analyze these data and they showed that maternal infective status did not have any significant impact on the rate of growth and development of their nursing infants. The results thus suggest that the physical health of infants was not impaired; and that infection with *S. mansoni* had no detectable effect on a woman's ability to care for the physical health of her infant.

### The differential impact of *S. mansoni* on female activity patterns

The research described in the previous two sections suggests that *S. mansoni* exerts a differential impact on female activity patterns in the agricultural and domestic sphere. This variability is probably due to the following factors. Women engaged in agricultural activities work for longer and more continuous periods of time than women engaged in domestic work. They are also exposed to direct sunlight whereas women engaged in domestic work undertake their activities in the home and/or enclosed cooking areas. They are protected from intense solar radiation. In other words, variations in work load and heat load, rather than egg load, account for the differential impact of *S. mansoni*.[10]

The implications of these results for public health policy are not straightforward. The reasons are many and include the following: first, the results presented in this section are not applicable to populations outside the Gezira/Managil irrigation scheme. These two studies clearly show that *S. mansoni* only impairs daily activities in combination with certain social, cultural, and ecological factors. Because the social, cultural, and ecological context varies within a village, it is more than likely that *S. mansoni* exerts a differential impact among women engaged in different activities in different regions and/or countries. Second, it would

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[10]See Parker (1989) for a detailed explanation of the differential impact of *S. mansoni* on female activity patterns in Omdurman aj Jadida.

be folly to draw firm conclusions about the impact of *S. mansoni* on daily life in the Gezira/Managil irrigation scheme from a single and exploratory piece of research. It would certainly be interesting and helpful to know if similar results could be generated in this region by employing similar designs but working with two larger groups of women.

The fact that *S. mansoni* exerts a differential impact on female behaviour within a village suggests, however, that it is inappropriate to rely on epidemiological information to gauge whether *S. mansoni* presents a major public health problem. This raises another more general question: how much weight should be given to the clinical, physiological, behavioural, social, and economic aspects of infection? What criteria, if any, can usefully be applied to the evaluation of these different aspects of infection? Future research workers should try and address this question.

**State of the Art**

This paper has focused on one question: does schistosomal infection impair the health of women? The biomedical, economic, and sociological literature have been reviewed and it should now be apparent that we know very little about the effects of schistosomes (whatever the species) on women's health.

There are a number of reasons for this state of affairs and two have been highlighted in this paper: first, research workers in the biological and social sciences have preferred (with varying degrees of consciousness) to work with men and children rather than women. This bias is not, of course, restricted to the study of schistosomiasis. Cotton (1990) has recently shown, for example, that women have been excluded from a wide range of biomedical research. Indeed, he even says that research workers have preferred to work with male rather than female rats!

Second, biomedical research workers have tended to conceptualize women's health in terms of reproductive organs and reproductive performance. Needless to say, this has limited the type of questions that have been raised and the type of women that have participated in the research process. The fact that economists and sociologists have preferred to study men rather than women suggests that they have unthinkingly accepted biomedical approaches to the study of women's health. Basically, they have ignored the issue of gender.

A great deal of the literature reviewed in this paper thus refers to men rather than women. This male-orientated review shows there is considerable disagreement among biomedics, economists, and sociologists about the effects of schistosomes on public health. It has been suggested that future research workers should work in an inter-disciplinary way as this will enable a more holistic picture of the effects of schistosomes on public health to be developed. In this respect, the inter-disciplinary research that I carried out in Omdurman aj Jadida, Sudan is rather promising.

This research did not show how to develop a holistic picture of the effects of *S. mansoni* on health and well-being. It did show that it is possible to blend biomedical, ethnographic, and continuous observational data in a single study and thereby develop a more integrated picture of the effects of *S. mansoni* on one component of health: behaviour. It remains to be seen whether future research workers will investigate the epidemiological, behavioural, social, and economic aspects of infection from a multi-disciplinary or inter-disciplinary way. It is likely that attempts to work in this way will help us to resolve the

question of whether schistosomal infection is a major public health problem in the tropical and subtropical world.

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# A Synoptic Inventory of Needs for Research on Women and Tropical Parasitic Diseases with an Application for Schistosomiasis

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*The world of experience of any people - from biology and ecology over social relations to ideas and culture - is essential, when we try to relieve illness and disease in any context.*

## Summary

The determinants of major parasitic infections in women have never been studied systematically. Much work remains before vital gaps in knowledge have been covered. We have designed a protocol that categorizes the determinants of parasitic diseases and functions as an inventory for research needs and priorities.

The protocol is tested by matching it against scientific knowledge of schistosomiasis at hand. Available data and existing lacunae are discussed briefly. Issues that need to be addressed are proposed by priority. We conclude that environmental, economic, sociocultural, nutritional, genetic, biological, and immunological factors that determine schistosomiasis in women are largely unknown. There is an urgent need for systematic and interdisciplinary investigations before proper and sustainable interventions can be initiated.

## Introduction

The determinants of major parasitic infections in women have not yet been studied systematically. In contrary, the patchy knowledge existing has been accumulated in a rather spurious and erratic way. The environmental, economic, sociocultural, nutritional, genetic, biological, and immunological factors that determine the epidemiology and the natural history of these infections in women are by and large unknown. The spectrum of genuine and associated pathology, the sensitivity and specificity of diagnostic methods, and the efficacy of treatment in women as well as the role women play in the transmission of the infectious agent are also almost unknown. The same holds true for the impact parasitic diseases may exert on the physical and mental well-being of women, their reproduction, their education of children, and their involvement in family and community life.

The state of the art thus leaves much to desire; much work remains before vital gaps in knowledge have been covered. To facilitate the inventory of important research needs for parasites like malaria, trypanosomiasis, leishmaniasis, schistosomiasis, and filariasis, we have designed a protocol that covers the broad categories of determinants that might affect female morbidity in these diseases. We show that these categories are composed of a variety of

variables, which in themselves constitute important subjects for systematic and interdisciplinary investigations. In the second part of the paper we test the protocol by matching it against the available knowledge of schistosomiasis.

The application of this protocol will pay off in several ways. First, investigators may, with the help of it, systematically look for lacunae in knowledge of sex-related determinants of infection in an encompassing sense. Second, it reveals that most issues cannot be explored by a single discipline and thus interdisciplinary studies will be fostered. Third, it lays bare that conventional perspectives and approaches will usually not suffice to study the issues listed. The development of a new methodology should then be the logical consequence, which in itself will pay off for the study of tropical diseases in general. Fourth, funding organizations and national health services may use the protocol to identify and select research topics according to priorities set in a given environment.

## Materials and Methods

A method developed by system analysts was used to design a protocol that allows the assessment of the various aspects of a major parasitic infection in women (Fig. 1). Six interrelated categories (six angular boxes) were defined based on the chronology of parasitic cycles and on the course a parasitic infection may take. The categories were chosen so as to form a structure of an information base for the design and implementation of effective control measures.

Each of the categories in the protocol is determined by the previous one, and, in addition, by a variety of determinants (oval boxes) that in turn must be considered as multi-factorial variables. Seven classes of factors (arrows) are considered: sociocultural, educational, environmental, economic, nutritional, biological/genetic (related to female physiology and/or genetic markers of female) and immunological. These classes are not mutually exclusive; mostly they interact in a very complex and intricate way.

The Medline database was searched using the keywords schistosomiasis and female from 1977 to May 1991. Relevant monographs and literature at the libraries of the scientific institutions of the authors were also consulted.

The existing information for each category is summarized briefly with a short discussion of available data or existing lacunae. This leads to proposed issues to be addressed by priority to understand the complex interactions. Propositions are made regardless of whether or not established methods exist for studying the problem.

## Needs for Research on Women and Schistosomiasis

### Factors that determine the epidemiology of infection in women

#### *Water contact and exposure to infection*

*Current knowledge* Activities ensuing water contact play an eminent role in daily life in tropical environments. Thus, from a teleological point of view, a parasite that relies on

water contact for transmission and propagation increases its chances for survival and spread.

Water contact activities that imply the risk for infection with schistosomes can be schematically divided into domestic, recreational, hygienic, occupational, and religious. For each type of activity the degree of exposure is related to age and sex of the individual, but also to environmental, sociocultural, economic, and religious factors (22, 70). Usually, several factors act in common. Robert et al. (61) showed that differences in prevalence of *S. haematobium* among different ethnic groups in Cameroon living in the same village depended on cultural attitude and occupational water contact obligations. Butterworth et al. showed that family economics, the environment, and behaviour were risk factors for water contact at a very young age (9). It may be assumed that women, who usually care for privacy when bathing, may be forced to use public water bodies rather than to carry water to their homes, if the residence is too far away. Water contact pattern influenced by sex and age are summarized in Table 1.

On the other hand, cercarial density and infectivity depend on physical variables. These are, among others, water temperature and velocity, time of day, and intensity of light. Hence, the selective risk of infection is best regarded as the summing up of multiple interacting parameters such as quality, duration, and daytime of water contact on one side and on cercarial density, infectivity, and host permissiveness on the other side.

Intrinsic characteristics of vector biology also play a role. Whereas the transmission of *S. mansoni* is erratic and unpredictable without a clearcut seasonal transmission pattern, transmission of *S. haematobium* exhibits a marked seasonal pattern. It is most intensive during the hot, dry season and very light during the rainy season (2, 14). Exposure of females to infection may thus coincide with temporal activities of women during different seasons of the year.

The complexity of the determinants explains why women are differently exposed to infection than men and why the risk of infection varies from one geographic area to another.

*Conclusion* Water contact activities are the predominant determinants that govern the epidemiology of schistosome infection. Because women, due to social and hygienic reasons, as a rule have frequent, long, and intense water contacts, female water-contact patterns are the prerequisite to understand the epidemiology of infection in general and in women especially. However, water contact activities of women as well as the underlying variables have never been studied systematically.

*Issues to be addressed*

- Quantitative and qualitative assessment of water contact activities of women and girls in relation to:
  - the nature of the transmission site (type of water body),
  - type of endemic area (rural, urban; irrigation scheme, artificial lake),
  - age,
  - season of the year, weather.
- Analysis of factors that govern water contact activities of women in relation to:
  - education,
  - religion,
  - family/community economics,

- marital status; presence/absence of pregnancy,
- socially controlled behaviour patterns,
- perception of personal hygiene (e.g. during menstruation, after coitus, after defecation),
- place of residence (accessibility of existing water bodies to women.

- Analysis of criteria by which water contact sites are chosen from available water bodies for:
  - drinking water,
  - washing,
  - recreation,
  - defecation/urination.

*Penetration of cercariae*

*Current knowledge* Penetration of cercariae through the skin is a dynamic process involving complex parasite-host interactions. Experimental evidence suggests that essential fatty acids and prostaglandins play a critical role in penetration of the cercariae (63). Eicosanoids released from schistosomulae during transformation are also involved (34).

*Conclusion* Differences in essential fatty acids and/or prostaglandins contents in the female skin could have enhancing or inhibitory effects on the penetration of cercariae and the transformation into schistosomulae. Because female oestrogens and progesterons may interfere with cercarial binding to skin cell receptors, qualitative and quantitative changes of these hormones during puberty or pregnancy may interfere with (or enhance) attachment of cercariae and penetration of schistosomulae through the skin.

*Issues to be addressed*

- Experimental investigation of:
  - parasite-host interactions in the process of cercarial penetration,
  - enhancing of inhibitory capacity of essential fatty acids and prostaglandins found in female skin,
  - enhancing of inhibitory capacity of female hormones.
- Investigations into the permissiveness of female skin in relation to:
  - parasite species,
  - age,
  - oestrogens and progesterons,
  - pregnancy.

*Prevalence and intensity of infection*

*Common knowledge* A considerable number of studies in widely different endemic areas have shown that prevalence and intensity of infection: (1) are age-dependent; (2) may be considerably different between men and women; and (3) may be dispersed within a community, with the majority of individuals harbouring light and a minority very heavy infection (5). The reasons for this are immunological, biological, and genetic parasite-host

interactions. Nevertheless, nutritional, environmental, and sociocultural factors may also play a role.

In the case of *S. haematobium*, prevalence and intensity are usually higher in males than in females (13, 18, 22, 40, 57, 61, 77). In *S. mansoni* a similar pattern was observed in Cameroon (61), but the opposite was found in Brazil (49). Even within the same endemic area in Burundi, completely different patterns were observed (39). No difference in prevalence and intensity of infection was observed in an urban area with intense transmission of *S. intercalatum* (6). In a study on *S. japonicum* in the Philippines (75) prevalence and intensity of infection were higher in men than in women for all age groups but for the 45 to 54 age group.

An analysis of age-dependent prevalence and intensity patterns in *S. haematobium* shows the difference between male and female to be most prominent during years of maximal sexual activity (females between 15 and 30 years of age). This could point to a possible influence of female hormones, but would not exclude other determinants as cofactors. Thus, not surprisingly, whereas Dalton and Pole, Chandiwana and Christenson found differences in prevalence and intensity to be related to differences in exposure patterns, the contrary was observed by Wilkins et al. (22, 13, 78). Yet another studies (49, 70) found prevalence related to the transmission potential of water factors seemed to determine the epidemiology of infection.

*Conclusion* Prevalence, intensity - and possibly dispersion - of schistosome infection seem to be sex-related. However, it is not known to what extent environmental characteristics, economic constraints, inherited or acquired immunity, female biology, diet, and sociocultural background contribute to these indicators of infection and whether there exist similar effects on parasite species. Furthermore, it is not known to what extent female hormones interact.

*Issues to be addressed*

- Prevalence, intensity, and dispersion of schistosome infections in relation to:
    - parasite species (*S. haematobium, S. mansoni, S. japonicum, S. intercalatum* and mixed infections),
    - sex,
    - age,
    - population dynamics; proportion of women of childbearing age and pregnant.
- Analysis of these epidemiological indicators in relation to:
    - water contact patterns and actual exposure,
    - presence/absence of protective immunity; presence/absence of other parasitic diseases,
    - diet; nutritional deficiency,
    - ethnicity,
    - family/community economics,
    - education,
    - sociocultural patterns.
- Assessment of longevity and egg producing capacity of adult schistosomes in females in relation to:

- age at primary infection,
- hormonal status,
- number of pregnancies.

- Development of mathematical models to predict prevalence, intensity, and dispersion of schistosome infection in women in defined endemic areas by using estimates of determinants mentioned above.

**The natural history of infection in women**

The course schistosome infection may take is summarized in Fig. 2. Generally speaking, there is sufficient evidence that frequent re-exposure (usually during the first two decades of life) leads to a high intensity of infection, which in turn ensues in development of severe pathology. However, the outcome of infection may be altered at each of the levels. Factors that are assumed to play a role are: duration of infection (usually reflected by age); duration of time during which a high parasite load develops; age at first infection; differences in host genetics (e.g. in HLA-DR, HLA-DQ); differences in parasite strains; concomitant infections (e.g. malaria, hepatitis); nutritional deficiencies/diet/fatty acid metabolism; hormonal status; maternal infection/maternal immune status; environmental/economic/ behavioural constraints.

Those factors that may specifically influence the natural history of infection in women or contribute to disease manifestations in children born to infected mothers are depicted in Fig. 3.

*Female vasculature and resistance to infection*

With infection, up to 50% of eggs are carried involuntarily along with the portal blood flow. Once sequestered in intrahepatic portal venules, granuloma develop, which by their size can effectively block the portal blood flow to several functional units of liver tissue. As parasite load builds up and more and more granuloma develop, the portal blood flow becomes increasingly blocked, eventually leading to portal hypertension and the appearance of porto-systemic anastomoses that direct the blood flow around the liver. In mice, such collaterals can already be detected 12 weeks after infection and the varices that develop not only permit ova, but also schistosomula and adult worms to escape from the portal system and shift to the lungs (80). In addition to extrahepatic porto-systemic shunting, functional modification of the intrahepatic vasculature, i.e. the development of a leaky liver, also provides routes for schistosomes out of the portal to the systemic system. Recently it has been shown that resistance to infection in 129/3 mice is sufficiently explained by innate peculiarities of the vasculature to allow the shunting of almost all schistosomula to the lungs, where they are sequestered and eventually die (80).

The pace and degree of the development of intra-hepatic and porta-caval collateral circulation in an infected individual may therefore not only explain presence or absence of severe pathology, but also yet unexplainable differences in parasite load in individuals with a similar pattern of exposure. Moreover, anatomic differences in vasculature and the ensuing haemodynamics may account for pharmacologically unexplainable species specificity of schistosome drugs like metrifonate (24) or the immuno-dependent action of praziquantel (47).

Because women differ in pelvic vasculature from men and the vasculature in women shows adaptive changes during puberty and especially during pregnancy, these anatomical differences may significantly influence the natural history of infection in women.

*Conclusion* There is convincing experimental evidence that, at least in schistosomiasis mansoni, shunts between the portal and the systemic circulation confer resistance to reinfection. On the other hand, clinical evidence suggest a close relationship between the integrity of hepatic vasculature and development of severe pathology. As females differ in or undergo adapting changes in pelvic vasculature during their child-bearing years, female anatomy may significantly influence the development of pathology, resistance to reinfection, and efficacy of chemotherapy.

*Issues to be addressed*

- Clarification of the interactions between vasculatory changes inside and outside the liver, sex-related peculiarities of pelvic and abdominal vasculature, adaption of female vasculature during pregnancy, and development of resistance to infection and for pathology.
- Assessment of the presence and degree of intra- and extra-hepatic collaterals in women with schistosomiasis in relation to:
  - parasite species,
  - duration of infection,
  - age at first exposure/infection; age at first pregnancy,
  - presence/absence of acquired immunity/immunomodulation,
  - number of pregnancies.

*Female hormones and lipid metabolism*

*Common knowledge* Parasite as well as host lipids are important in maturation and fecundity of schistosome worms (34). Peculiarities in female fatty acid metabolism may thus influence the biology of schistosomes, which in turn could alter the natural course of infection in women

*Conclusion* The putative relationships between fatty acid metabolism of women, gonad-related hormonal fluctuations and maturation, fecundity, and longevity of schistosome worms have never been examined.

*Issues to be addressed*

- Analysis of putative relationships between female fatty acid metabolism, gonad-related hormone fluctuations and worm maturation, fecundity, and longevity in relation to schistosome species.

*Influence of environment on course of infection*

*Common knowledge* The considerable influence the environment imposes of the course of schistosome infection has recently been stressed by a series of studies on schistosomiasis mansoni in Kenya (9). Whereas in village A - typical of the long-settled rural areas of Kenya - hepatomegaly in school children correlated to intensity of infection, but splenomegaly was virtually absent, in village B - having been more recently settled - both hepatomegaly and splenomegaly were preponderant and correlated to intensity of infection. Because inhabitants of the two villages were from the same tribe, genetic differences between village populations could not explain the different clinical course. However, the two settlements varied according to environmental, economic, and sociocultural factors (Table 2). The complex interactions between socioeconomic and environmental variables have recently been analyzed by Nordbeck et al. (52).

*Conclusion* Environmental, economic, sociocultural factors and nutrition seem to influence the course of schistosome infection. Women may be especially sensitive to such factors.

*Issues to be addressed*

- Identification of environmental, economic, sociocultural, and dietary factors that influence the course of infection in females in relation to:
  - parasite species,
  - ethnicity of women.

*Impact of schistosomiasis of mothers on their offspring*

During gestation, delivery, and breast-feeding, children born to and/or fed by infected mothers are potentially exposed to circulating schistosome antigens (10, 26). In addition, high levels of the mother's antischistosome antibodies have been documented in neonates born to or fed by *S. mansoni* infected mothers (64). Transfusion of sensitized maternal lymphocytes during delivery may equally occur. Theoretically, the idiotypes expressed on transfused maternal antibodies should influence the immune status of the child and may have a profound impact on the immunological repertoire subsequently expressed by the offspring (68). Clinically, prenatal and/or perinatal sensitization with schistosome antigens and transfusion of maternal antibodies is correlated to a high frequency of intradermal immediate-type and delayed-type hypersensitivity reactions to schistosome antigens in children born to or fed by infected mothers in Egypt (28, 67).

The activation of the idiotypic-anti-idiotypic immune network is also predictable on pure epidemiological grounds. First, age-prevalence curves show that schistosomal infections usually have their highest prevalence during early child-bearing years. Thus, in endemic areas, infection must occur in many - if not in most - pregnant women. Second, the longevity of adult schistosomes and the chronicity of the disease lead to long-term, continuous stimulation of anti-schistosomal immune responses. Both factors make the development of idiotypic-anti-idiotypic antibodies very likely. On immunological grounds it has to be

assumed that in a child born to an infected mother and than later infected itself, the altered immune response will be revived and by this the clinical outcome of infection may change.

Recently the existence of such idiotypic-anti-idiotypic interactions has been shown in children born to mothers with schistosomiasis mansoni (20). Even more important, a correlation was observed between failure of down-regulation of granuloma formation in children with hepatosplenic schistosomiasis and the recognition of and responsiveness to certain antibody idiotypes (21, 28). These findings support the hypothesis that some patients previously born to infected mothers may lose their capacity to respond to regulatory stimuli induced by certain idiotypes and/or are prone to develop hepatosplenic complications. Accordingly, severe acute schistosomiasis (Katayama fever) is almost exclusively seen in nonresidents (mostly visitors) of an endemic area (44), thus probably in individuals without activation of the idiotypic-anti-idiotypic network because they were born to mothers without schistosomiasis.

In this context, the recent observation gains importance that infants born to mothers with active *S. mansoni* infection have lower titres of anti-HBs after vaccination than children from noninfected mothers (37). If this finding is consistent, schistosomiasis of the mother may curtail the benefit of any vaccination used for children in the tropics.

*Conclusion* Immunological, epidemiological, and clinical evidence suggest that children born to infected mothers may react in a different way than those born to healthy mothers, when they later become infected with schistosomes themselves. The immunological consequences may range from specific anergy to failure of down-regulation of inadequate, putatively harmful immune responses. Katayama fever and hepatosplenic schistosomiasis may be the clinical expression of such antenatally or perinatally altered immune responses.

*Issues to be addressed*

- Impact schistosomiasis of the mother may have on the clinical outcome (Katayama fever, chronic pathology) of the offspring in relation to:
  - parasite species,
  - intensity/duration of infection of the mother,
  - immune status of the mother,
  - concomitant infections of the mother,
  - genetic traits of mother and child,
  - age of mother at first pregnancy,
  - time and type of exposure of child.
- Efficacy of antibacterial, antiviral vaccines in children born to schistosome-infected mothers.

## Pathology

### *Genuine pathology*

*Schistosomiasis of the genital tract - Current knowledge* Schistosomiasis of the female

genital tract is part of a generalized pelvic disease involving bladder, ureters, and rectum as well as the external and internal reproductive organs (35). Probably due to the close proximity between venous plexus of the urinary bladder and those of the female genital organs, pathology of the female genital tract due to *S. hematobium* seems to be more common than in the case of infections with *S. mansoni* or *S. japonicum* (35, 45).

Extensive pathological studies by Smith and Christie (65) have demonstrated four characteristics of genital lesions in schistosomia haematobium: (1) the severity of the disease and the probability of complications seem to be closely related to the intensity and duration of infection; (2) genital disease progresses through an active into an inactive, though still dangerous, stage; and (3) egg disposition is non-uniform and may randomly focus on physiologically vital areas at any time during the course of infection. Whereas ovaries and fallopian tubes have sometimes high egg burdens (mean 2000 eggs/g), uterus and vagina usually have lower ones.

Data on genital involvement in schistosomiasis japonicum are scarce and contradictory (46, 62). Two reports on *S. mansoni* showed no female genital pathology in 3232 autopsies performed in Puerto Rico and 18 pathological findings from 78,238 surgical specimens in Brazil (6, 46).

It has been suggested that in pre-pubertal females the lower genital tract is more commonly afflicted, whereas the upper genital tract is more frequently engaged in adult females (45). This could be explained by adaptive changes in the pelvic vascularization during child-bearing age. Afflicted genital organs, symptoms, and possible sequelae are summarized in Table 3.

Although heavy infestation with *S. haematobium* may predispose to genital schistosomiasis, lesions in reproductive organs have also been observed in lightly infected tourists (38, Feldmeier H, unpublished observation). Thus genital pathology may also be suspected in women of migrating populations who only transiently stay in an endemic area.

*Conclusion* Systematic studies on prevalence and long-term sequelae of female genital schistosomiasis are lacking. There are no data available on genital involvement by *S. intercalatum* although this parasite may produce pathology similar to that of *S. haematobium.* Adequate diagnostic methods for genital schistosomiasis are lacking and diagnosis is generally erratic.

*Issues to be addressed*

- Prevalence of genital schistosomiasis, type, and degree of genital organs involved, symptoms, and sequelae in relation to:
  - parasite species (*S. haematobium, S. mansoni, S. japonicum, S. intercalatum,* mixed infections),
  - intensity and duration of infection,
  - age,
  - sexual activity, number of pregnancies.
- Toxicity of egg substances for specialized genital tissue cells.
- Regression of genital granuloma after elimination of the adult worm by chemotherapy.
- Development/application of non-invasive diagnostic techniques to detect genital

schistosomal lesions (e.g. high-resolution ultra-sonography, immuno-histochemical examinations of vaginal smears and discharge).

*Hepatosplenic and pulmonary schistosomiasis - Current knowledge* Schistosomiasis-induced liver fibrosis is the final outcome of a complex pathophysiological cascade involving interactions between various immune cells, fibroblasts and parasitic products. The frequency of hepatosplenic schistosomiasis varies widely and has been found to range between 0.2 and 33% (9).

Clinically, pulmonary schistosomiasis is an even more rare complication and is caused by sequestration of schistosome ova in the lungs, as a consequence of which pulmonary fibrosis and hypertension develop. None the less, in 14% of asymptomatic patients and in 48% of patients with liver fibrosis, eggs have been found in the lungs at necropsy (16). Prevalence and degree of hepatosplenic and pulmonary schistosomiasis in relation to sex have never been studied.

Even in advanced cases of periportal fibrosis, normalization of liver function, liver haemodynamics, and immune competence is achieved by treatment with praziquantel (82, 83). Thus sclerotherapy and porto-caval shunting, though still frequently performed, seem no longer advisable (32).

In women with mild intestinal schistosomiasis japonica the regular intake of low dose progestin and oestrogen oral contraceptives did not show an adverse effect on liver function tests (66). However, the issue of efficacy and side effects of oral contraception has never been addressed for women with severe complications.

*Conclusion* Hepatosplenic and pulmonary schistosomiasis are relatively rare, but severe, complications of infections with *S. mansoni* and *S. japonicum*. It is conceivable that women may be more prone to suffer from such life-threatening complications, but sex-related risk-factors have never been looked for.

*Issues to be addressed*

- Prevalence and clinical aspects of women with hepatosplenic/pulmonary schistosomiasis in relation to:
  - parasitic species,
  - intensity, duration of infection,
  - age,
  - hormonal status; number of pregnancies,
  - diet/nutritional deficiencies,
  - markers of the major histocompatibility complex,
  - family economics/education.
- Relation between liver haemodynamics, liver function, and immune competence in women with hepatosplenic schistosomiasis.
- Efficacy of chemotherapy in women with hepatosplenic/pulmonary schistosomiasis.
- Efficacy and adverse effect of oral contraceptives in women with hepatosplenic/pulmonary schistosomiasis.

*Schistosomiasis and anaemia - Common knowledge* Haematuria is the most common sign of urinary schistosomiasis. It has been estimated that infected individuals loose between 2-6 and 126 ml of blood per day (31). It is therefore not surprising that anaemia occurs twice as frequent in female as compared to male schistosomiasis patients (39). By constant, blood loss urinary schistosomiasis should exacerbate iron and other mineral deficiencies in women from the menarche to the menopause and thus have a considerable impact on their physical well-being, working capacity, and resistance to infection.

Blood losses in intestinal schistosomiasis have never been studied systematically.

*Conclusion* It is highly conceivable that urinary, and presumably also intestinal schistosomiasis, play a significant role in anaemia in women in the tropics. Dietary habits, nutritional deficiencies, sociocultural factors, and concomitant infections interactively may exacerbate the degree of anaemia.

*Issues to be addressed*

- Quantitative and qualitative (type of anaemia, deficiency of iron, magnesium, folate, vitamin B12, leucocytopenia, and thrombocytopenia) assessment of anaemia in schistosome-infected women in relation to:
  - parasite species,
  - intensity of infection,
  - clinical presentation of disease (e.g. bloody diarrhoea, intestinal polyposis),
  - concomitant parasitic infection (e.g. malaria, hookworm),
  - dietary habits,
  - age,
  - menstrual character,
  - Pregnancy/previous abortions,
  - sociocultural patterns.
- Efficacy of antischistosomal treatment in combination with iron, magnesium, folate, vitamin B12 supplementation to reverse schistosomiasis induced anaemia.
- Assessment of prevention of anaemia through repetitive and targeted mass treatment of women.

*Associated pathology in women*

*Schistosomiasis and cancer of the female genital tract - Common knowledge* Several types of cancer have been found in patients with schistosomiasis: squamous cell carcinoma of the bladder in *S. haematobium*, intestinal polyposis in *S. mansoni*, and colon carcinoma in *S. japonicum* infection (17). Epidemiological, pathological, and experimental data support the notion of a cause-effect relationship between schistosomiasis and these types of cancer (36).

Because cervical schistosomiasis has been found in 14% of women with cervical carcinoma (51), a causative association between adenocarcinoma of the cervix and genital schistosomiasis may exist in which schistosomes act as an carcinogenic cofactor (19, 30, 81) and yet undefined sex-related risk factors play an ancillary role. De Koning et al. (42) pointed out that smoke emissions from biomass fuels used for cooking contain poly-cyclic

organic components like benzopyrenes that are highly carcinogenic. As women are predominantly exposed to this smoke, they might be at a higher risk to develop cancer if other cancer inducing factors are simultaneously present.

*Conclusion* A complex cause-effect relationship between schistosomiasis, other infections, and cofactors and cancer of the female genital tract is considerable, but due to lacking data remains so far just speculative.

*Issues to be addressed*

- Prevalence of female genital cancer in relation to:
  - parasite species,
  - intensity of infection; focalization of infection; duration of infection; previous chemotherapy,
  - age; age at first intercourse; sexual behaviour,
  - marital status; number of pregnancies,
  - genital bacterial and viral infections,
  - dietary habits,
  - exposure to hazardous smoke emission.
- Experimental studies to verify a possible carcinogenic effect of schistosome substances on specific female reproductive tissue.

*Impact of schistosomiasis on reproduction, fitness, behaviour, and economics*

*Schistosomiasis and infertility - Common knowledge* Since Magdi (45) reported asymptomatic pelvic schistosomiasis in 13 infertile women, the relationship between genital schistosomiasis and infertility has been repeatedly stressed (27, 35, 41). Several lines of pathophysiological evidence have been put forward to explain infertility as a consequence of schistosome infection. First, fallopian and ovarian schistosomiasis may lead to infertility only, if, secondary bacterial superinfection causes adhesion of epithelial cells (56). Second, granuloma formation in the pelvic-peritoneal area may cause anatomic obstruction and thus interfere with physiological flexibility of the ovaries and the fallopian tubes (41). Third, a less mechanistic explanation regards genital schistosomiasis as a complex self-perpetuating inflammatory process during which various cytokines and regulatory molecules are produced, which in their turn may effect physiological functions of female genital organs, and which eventually result in fibrosis of the affected tissues. Fourth, rupture of ectopic pregnancy caused by granuloma in the fallopian tubes may result in sterility. Fifth, in 63% of infertile women with cervicovaginal schistosomiasis anti-spermatozoa antibodies have been found (27).

Interestingly, in uninfected mice transfused with anti-schistosome antibodies a lowered reproductive efficiency is observed (4). Finally, growth failure, delayed puberty, and protracted menarche have been associated with the hepatosplenic form of schistosomiasis. In these patients, oestradiol and somatomedin-C levels are abnormally low (12). Ten percent of patients with hepatosplenic schistosomiasis presented with primary infertility lasting longer

than 5 years (1). Hyperprolactinemia was observed in 13% and galactorrhoea in 10% of patients in this group.

A combination of under nutrition and an altered metabolization of sex steroids and growth hormones due to liver fibrosis and altered liver dynamics have been put forward to explain growth failure and delayed puberty in hepatosplenic schistosomiasis. However, hypogonadism leading to delayed puberty may also be related to the fact that schistosomiasis are able to produce propiomelanocortin (POMC) as well as beta-endorphin and ACTH and that POMC and POMC-derived peptides are implicated in gonad endocrine regulation and/or gonadotropin release (11).

Despite antischistosomal treatment and correction of ovulatory defects only 46% of infected infertile women later developed pregnancy (27).

*Conclusion* A causal relationship between schistosomiasis and infertility/sterility is highly likely. The pathophysiological mechanisms involved are not understood, nor is the prevalence of this disease condition known. The endocrinological basis of delayed puberty in hepatosplenic schistosomiasis is also unknown.

*Issues to be addressed*

- Prevalence of primary/secondary infertility in women with schistosomiasis in relation to:
  - parasite species,
  - intensity of infection; duration of infection,
  - clinical presentation of disease,
  - endocrinological aberrations,
  - dietary habits,
  - sexual behaviour.
- Analysis of pathophysiological mechanism eventually leading to infertility.
- Endocrinological/immunological parasitological basis of delayed puberty in hepatosplenic schistosomiasis.

*Schistosomiasis and pregnancy - Common knowledge* Based on existing literature, Moore and Smith (48) concluded that in endemic areas schistosomiasis frequently gives rise to complications of pregnancy and that these complications may affect up to 20% of pregnant women. Schematically three types of complications are known: ectopic pregnancy; complications during normal pregnancy; and placental involvement eventually leading to damage of the foetus or the newborn.

Egg-induced granuloma in the submucosal or intramural parts of the fallopian tube may interfere with the progression of fertilized eggs to the uterus resulting in ectopic pregnancies (54, 55, 59) eventually leading to acute bleeding into the peritoneum.

On the other hand, whereas for the gynaecologist outside the tropics, the finding of blood in the peritoneal cavity is synonymous with ectopic pregnancy, this is not necessarily true in schistosomiasis endemic areas. Picaud et al. (55) in a retrospective study in the Gabon found 17 of 429 cases of haemoperitoneum due to erosion of an ectopic schistosomal granuloma. When examining 257 pregnant women with schistosomiasis japonica McNeeley (46) found 73% of patients to have severe anaemia, 62% to present with jaundice, 10% with

diarrhoea, and 7% with ascites. Forty-one percent of these women had difficult labour. Profuse bleeding due to the thrombocytopenia in hepatosplenic schistosomiasis complicated another pregnancy (43). In addition, there is anecdotal evidence that even women who have been successfully treated may suddenly deteriorate during pregnancy (46). An increased frequency of premature birth and abortion in women with schistosomiasis has also been attributed to parasitic infection (4, 46).

It remains purely speculative whether miscarriage, prematurity, and intra-uterine demise are due to vasoactive or neuroactive peptides produced inside the egg-granuloma (74). A direct involvement of the placenta could also be responsible (46). This notion is supported by a study in which 22% of placentas of women not previously known to have schistosomiasis were found to contain schistosome eggs (60). Schistosome eggs have also been found sporadically in the amniotic fluid, but there is no documented instance of finding schistosome eggs in stillborn infants (44).

*Conclusion* Although there is strong evidence that schistosomiasis may induce ectopic pregnancy, cause bleeding in the peritoneum, and impair the normal course of pregnancy, the frequency and distribution of such complications and its impact on the unborn child have never been studied systematically.

*Issues to be addressed*

- Prevalence of ectopic pregnancy in woman with present or previous schistosomiasis in relation to:
  - parasite species,
  - intensity and duration of infection,
  - age,
  - number of previous pregnancies,
  - hormonal status.
- Differential diagnosis of haemoperitoneum in women in the tropics.
- Monitoring of pregnancy in patients with hepatosplenic disease and schistosome induced uropathy.
- Assessment of foetal stress in mothers with schistosomiasis.
- Prevalence and type of placental involvement in relation to:
  - parasite species,
  - intensity of infection,
  - age,
  - number of previous pregnancies.
- Parasitological and immunological examinations of placentas for presence of adult worms and worm products in villous vessels and placental tissue, respectively.
- Examination of women with spontaneous abortion for presence of genital schistosomiasis.
- Examination of stools and urine of newborn from infected mothers for the presence of eggs.

*Impact of pathology on physical fitness and working capacity*

In an attempt to summarize the existing knowledge of the impact of schistosomiasis on physical fitness, working capacity, and productivity, Tanner (69) found conflicting results. Of 16 studies performed in adult patients with schistosomiasis haematobia, mansoni, and japonica, 11 studies reported significant decrease of physical fitness and/or working capacity in infected persons. None of these studies, however, dealt with women. Moreover, study results were not comparable even within parasite species as incongruent methodologies were used and patients were incompatible for age and intensity of infection. Warren provided the rough estimate that each infected patient looses 600-1000 working days during their life (73).

*Conclusion* It is assumed that female schistosomiasis, at least in heavily infected individuals, significantly influences the physical and mental well-being, working, and educational capacity of girls and women. Only if these disease consequences have been qualitatively and quantitatively assessed will it be possible to estimate the impact on work allocation, education, and economy of schistosomiasis on the household and/or the community.

*Issues to be addressed*

- Impact of schistosomiasis on physical fitness, mental ability, working capacity, and productivity of women in relation to:
  - parasite species,
  - intensity of infection,
  - age,
  - nutritional status,
  - presence or absence of additional stress factors.
- Impact of schistosomiasis of female family leaders on education and welfare of the younger/elder household members.
- Impact of schistosomiasis of female family members on household and community economics.
- Impact of schistosomiasis of female family members on social activities/duties.

*Attitudes of society toward the diseased*

*Common knowledge* Haematuria, the most common symptom of urinary schistosomiasis, is obvious to such a degree that it cannot go unnoticed in the community. As heavy haematuria usually begins at onset of puberty, the temporary association of the pathological and physiological event have in some societies led to a belief in a causal relationship. Among the Song people in Nigeria, haematuria is considered to signify the coming of age (3). It is therefore common to inquire discreetly if a suitor has attained manhood as indicated by the passing of blood in the urine. Similarly, the Margi people consider gross haematuria as a prerequisite for initiation into certain cults (3).

*Conclusion* In the community, symptoms and signs of urinary and intestinal

schistosomiasis are interpreted and explained in a traditional way and by culturally determined concepts. Notions of cause-and-effect may differ from those of the biomedical school and may have consequences for the disease progress. Such interpretations are well known for gross haematuria in young males, but no information on similar attitudes exist for the infected female.

*Issues to be addressed*

- Perception, classification, and social impact of symptoms associated with schistosomiasis in women in relation to:
  - ethnic/cultural background,
  - parasite species.

**Diagnosis**

*Common knowledge*

Diagnosis of schistosomiasis can be established by parasitological and immunological means or by detection of disease-specific pathology. All three approaches may be seriously biased in women.

Urine filtration is the standard method in the diagnosis of urinary schistosomiasis. However, in women of childbearing age, paper, as well as polycarbonate filter membranes, tend to be clogged by epithelial cells, especially when larger volumes of urine have to be filtered to detect low intensity infections (Feldmeier H., unpublished observation). Heavy contamination of urine by menstrual blood is obvious and requires lysis of erythrocytes through addition of hydrochloric acid to disclose schistosome ova in sediments or on filter membranes (33a).

Immunodiagnosis through detection of antibodies may also be influenced by sex. El Rasiky et al. (28) showed that anti-schistosome antibodies - measured by IFAT and COPT - were lower in, and less frequently detectable in, pregnant patients then in non-pregnant ones. The contrary seemed true for the presence of schistosome antigens in circulation.
Detection of haematuria by urine analysis reagent strips has been found a cheap and sensitive tool for mass screenings of urinary schistosomiasis (33b, 50). However, false positive results are to be expected when patients include women of childbearing age.

Ultrasonography is considered to be the most efficient means to diagnose severe pathology. Although these disease patterns may be influenced by female anatomy or may change during pregnancy, this issue has not yet been considered even in a recent meeting of WHO experts (76).

*Conclusion*

Standard methods for diagnosis of and/or detection of pathology may have different sensitivity, specificity, as well as prognostic value in infected females as compared with infected males. Prospective population based studies to clarify this issue have never been performed.

*Issues to be addressed*

- Sensitivity, specificity, and predictive value of urine/stool examination methods in infected women in relation to:
  - parasite species,
  - intensity of infection,
  - age,
  - sexual activity; pregnancy,
  - menstrual cycle.
- Sensitivity, specificity, and predictive value of detection of antibodies, antigen, and delayed type hypersensitivity reaction in women in relation to:
  - parasite species,
  - intensity of infection,
  - age,
  - sexual activity; pregnancy,
  - menstrual cycle.
- Sensitivity, specificity, and predictive value of haematuria as measured by dip-stick for diagnosis of urinary schistosomiasis in women in relation to:
  - age,
  - sexual activity; pregnancy,
  - menstrual cycle.
- Sensitivity and prognostic value of ultrasonography to assess severe pathology in women in relation to:
  - age,
  - presence/absence of pregnancy.

**Treatment**

*Common knowledge*

Drugs previously and actually used for treatment of schistosomiasis are associated with various side-effects. Women in endemic areas may therefore fear hazardous effects of drug treatment for themselves or their unborn child and withdraw them or show a low compliance for drugs that require repetitive administration (e.g. metrifonate).

It is assumed that compliance of women to participate in chemotherapy will depend on social and cultural perceptions of what is considered proper, e.g. whether the drugs are recommended by a male or a female, by a foreigner or a local inhabitant, by a member of the national health service or by somebody highly ranked socially. Finally, classification of illnesses are known to vary widely between cultures and societies and usually only single classes of diseases are believed to become relieved through cosmopolitan, western-style drugs (7).

Since recently it is known that the pharmaceutical action of praziquantel - the drug most widely used - is immunodependent (47). As the hormonal status of women may enhance or depress their immunological competence, a different efficacy of antischistosomal drugs according to the hormonal status of a patient is conceivable and has been confirmed (8).

The possible interaction between oral contraceptives and antischistosome chemotherapy has been studied only once (29). The results of this study simply point out that praziquantel and metrifonate do not alter the pharmacokinetics of oestrogen and progesterone oral contraceptives.

*Conclusion*

There are serious problems in the treatment of schistosomiasis that are related to sex. Drugs in use may have different and unproportional high adverse effects in female as compared with male patients. Feared side-effects may influence women's compliance to chemotherapy and thus the efficacy of control measures. Socially and culturally determined attitudes toward treatment are expected to significantly influence mass chemotherapy programs.

*Issues to be addressed*

- Frequency and pattern of side-effects of metrifonate, praziquantel, and oxamniquine in infected women in relation to:
  - parasite species,
  - intensity of infection,
  - age,
  - sexual activity; pregnancy,
  - menstrual cycle,
  - belief in, or fear of, side effects,
  - sociocultural background.
- Analysis of the immunodependent action of praziquantel in relation to:
  - humeral and cellular immunocompetence,
  - degree of acquired immunity,
  - menstrual/hormonal status,
  - presence or absence of pregnancy.
- Analysis of possible interactions between anti-schistosome drugs and oral contraceptives.
- Studies on perception of the disease and its symptoms in women as a prerequisite for compliance in chemotherapy.
- Impact of mass treatment programs and their organizational structure on the compliance of women in relation to:
  - fear of adverse effects,
  - sociocultural context,
  - existing classification of illnesses,
  - education,
  - family/community economics.

**The role of women in transmission of schistosomiasis**

The role of women in transmission of human schistosomiasis is influenced by many

factors, but our understanding of the way they interact is still very incomplete. The most important factors are listed in Table 4. The complexity of environmental and socioeconomic determinants of these factors has recently been summarized by Nordbeck et al. (52). The role sex-related knowledge about plant molluscicides may play in interruption of transmission has been illustrated by Ndomba et al. (53).

*Dynamics of host-parasite relationship in women*

*Common knowledge* In an attempt to analyze helminth-host dynamics on a population level Anderson and May (5) hypothesized that: (1) differences in life-span between women and men may contribute to prolonged transmission; and (2) that sex may influence parasite population growth in the human host by limiting the density of adult worms, their fecundity, and survival time. However, these questions have never been studied in human schistosomiasis.

*Conclusion* Female biology, differences in life span between women and men, and differences in mortality rates in age-groups with high intensity of infection may considerably influence the transmission of human schistosomiasis.

*Issues to be addressed*

- Establishing of mortality profiles of females in schistosome endemic areas in relation to:
  - parasite species,
  - family/community economics,
  - education,
  - marital status,
  - age at first pregnancy/number of pregnancies,
  - disease manifestation/intensity of infection at necropsy.
- Impact of female biology on worm density, worm survival time, and worm fecundity in relation to:
  - parasite species,
  - sexual activity; number of pregnancies.

*Deposition of excreta by women*

*Common knowledge* Epidemiological studies have persistently shown that only a small portion of an infected population is responsible for the majority of eggs excreted into the environment. In St Lucia, the transmission potential of the 5- to 14-year-old age group was estimated to be 58% of the total potential transmission (71). In contrast, in northern Nigeria, in a population infected with *S. haematobium*, males under 21 years were found to have a relative transmission potential of 77%, whereas for females over 15 years this figure was only 50% (58). It is important to stress, though, that these calculations indicate potential rather than actual environmental contamination.

Only a single study has been performed that addresses the issue of excretion behaviour and its relation to probable contamination of transmission sites. Cheesmond and

Fenwick (15) in a study in the Gesirah province in the Sudan observed that urination did not require privacy and accidentally occurred near possible transmission sites, but that for defecation a site was looked for which offered a maximum of privacy (usual a special type of canal with dense vegetation). However, whereas women took water in a bowl and spilled the dirty water onto dry ground, men tended to perform ablution more strictly by washing the dirty water directly into the canal after defecation. It seems therefore conceivable that transmission of *S. mansoni* in this area probably occurs when remains of faecal matter around the anus are washed into a water body, by men by ablution, and by women when they take a bath.

As egg-excretion in urine shows a clear-cut circadian pattern and may differ by a factor of 10 between the hours of the day (23) circumdian patterns of urination (and defecation in the case of intestinal schistosomiasis) in women may significantly influence transmission. Taboos rigorously restrict the use of water-bodies by women for hygienic activities after urination/defecation in some societies (7). Thus under such diverse circumstances women may contribute significantly less or more to actual transmission than indicated by their potential transmission capacity.

*Conclusion* It must be anticipated that behaviour related to deposition of urine and faeces varies considerably between male and female, may change with age, and differs from one endemic area to another because these habits are socially and culturally inherited (25). Economic constraints (presence or absence of latrines, running water, distance of house to nearest water body) and education are also important determinants to consider.

*Issues to be addressed*

- Analysis of hygienic behaviour from a sociocultural perspective and quantitative assessment of actual transmission potential in relation to:
  - endemic area; parasite species,
  - urine, faeces,
  - sex, age,
  - circumdian patterns (time of the day) of excreta deposition,
  - education,
  - sociocultural context,
  - environment (natural water bodies, artificial irrigation schemes, artificial lakes),
  - location of house/location of water bodies,
  - availability of piped water, presence/absence of pit latrines,
  - type of settlement (permanent, semi-permanent, irrigation).
- Factors that determine preparedness to invest in piped water/pit latrines in relation to:
  - family/community economics,
  - sociocultural context,
  - education,
  - type of household.

*Women and spread of schistosomiasis*

*Common knowledge* Men, as well as being the source of infection, must be considered as a vector, for the movement of infected subjects is responsible for the spread of the infection (79). In arid areas of West Africa, young females are known to migrate to urban areas during the dry season (7). Future spread of transmission must be envisaged with increasing population stresses in densely inhabited areas, increasing mobility due to facilitated transportation, or access to new water resource developments. The part women play in decisions for such movements and in their realization has never been touched upon from an epidemiological perspective.

*Conclusion* Perennial migration by nomads and seminomads, immigration from rural areas, and multi-partner sex along traffic axes or at construction sites may all contain the risk of spread of schistosomiasis.

*Issues to be addressed*

- The role of women in decisions and realization of population movements to and from putatively areas of transmission in relation to:
  - age,
  - sociocultural context,
  - education,
  - economic constraints,
  - type of movement.
- The role of single migrating women, with or without their families, in spread of infection from rural urban areas in relation to:
  - age,
  - sociocultural context,
  - education,
  - economic constraints,
  - type of movement.

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Table 1. Type of water contact activities and risk of infection.

| | Relative risk | |
|---|---|---|
| Activity | Women | Girls |
| Domestic[a] | +++ | + |
| Washing laundry | +++ | +[b] |
| Washing utensils | +++ | +[b] |
| Fetching water | +++ | + |
| Watering animals | ++ | + |
| Personal hygiene | + -- +++[c] | +[d] |
| Recreational | +[c] | +++ |
| Religious, sociocultural[f] | -/+ | - |
| Occupational | + -- +++ | - |

[a] It is anticipated that in schistosome endemic areas a strict division of labour as to sex and age governs most domestic water contact activities and that girls tend to accompany their mothers for domestic water contact activities.
[b] In rural communities prepubertal girls are frequently fetching water, washing utensils and watering animals.
[c] Due to sociocultural factors women may be restricted to single water contact sites indiscriminately.
[d] The need of water for personal hygiene will increase with regular menstruation.
[e] According to distance, limited walking capacity during pregnancy etc.
[f] e.g. ablution in Muslim communities, ritual washing after coitus.

Table 2. Clinical course of schistosomiasis in two different villages in Kenya. Village A: presence of hepatomegaly, absence of splenomegaly; hepatomegaly correlates to intensity of infection. Village B: presence of hepatomegaly and splenomegaly; hepatomegaly correlates to intensity of infection (9).

| | Village A | Village B |
|---|---|---|
| Environment | fertile, well-watered | harsh, arid |
| Economics | relatively prosperous | poor |
| Age at first exposure | older child | small child* |
| Concomitant infections | less malaria | malaria prevalent |
| Nutritional status | well nourished | poorly nourished** |
| Duration of infection in mothers | >5 years | <5 years |

* mothers were reluctant to leave young children at home for fear of baboons and therefore carried their small children with them during water contact activities.
** hepatomegaly correlated with skin-fold thickness.

Table 3. Schistosomiasis and the female genital tract (+ = proven, but rare; 0 = not proven, no data; SH = *S. haematobium*; SM = *S. mansoni*; SJ = *S. japonicum*; SI = *S. intercalatum*).

| Organ | Findings | Symptoms, sequelae | SH | SM | SJ | SI |
|---|---|---|---|---|---|---|
| Breast | Granulous mimicking the mammographic pattern of carcinoma (72) | None | + | 0 | + | 0 |
| Vulva (vestibule labia) | Ulceration with carcinomatous appearance; granulous rapidly increasing in size | Irritation/pruritus secondary infection destruction of the external meatus | +++ | + | + | 0 |
| Vagina, vaginal fornices | Polypoidal granulomas, papillomatous growth; vesica-vaginal fistulas | Fibrosis | +++ | + | + | 0 |
| | | Incontinence | + | + | 0 | 0 |
| Cervix | Erosion, ulceration polypoidal granuloma, papillomatus growth | Fibrosis; bloody discharge, dyspareunia, intermenstrual bleeding | +++ | + | + | 0 |
| Uterus | Endometritis | Lower abdominal pain; menstrual irregularities, menorrhagia | +++ | + | + | 0 |
| Falopian tubes | Salpingitis, granulomas | Chronic backache, lower abdominal pain, dsymenorrhea, menstrual irregularities, sterility, ectopic pregnancy | +++ | + | + | 0 |
| Ovaries | Oophoritis[b] | Delayed menarche, primary menorrhea, menstrual irregularity, sterility | +++ | + | + | 0 |

[a] An extremely devastating condition that is difficult to treat even with sophisticated plastic surgery.
[b] 8.2% of all ovarian lesions seen in a 10-year-period in a pathology department in Egypt were due to schistosomiasis.

Table 4. Factors that influence transmission of schistosomiasis.

| |
|---|
| Geographic distribution of parasite species and strains |
| Population dynamics of the intermediate host |
| The pattern of environmental contamination with excreta |
| Water contact pattern |
| Dynamics of host-parasite relationship in man |
| Development of protective immunity |
| Development of severe pathology leading to death |

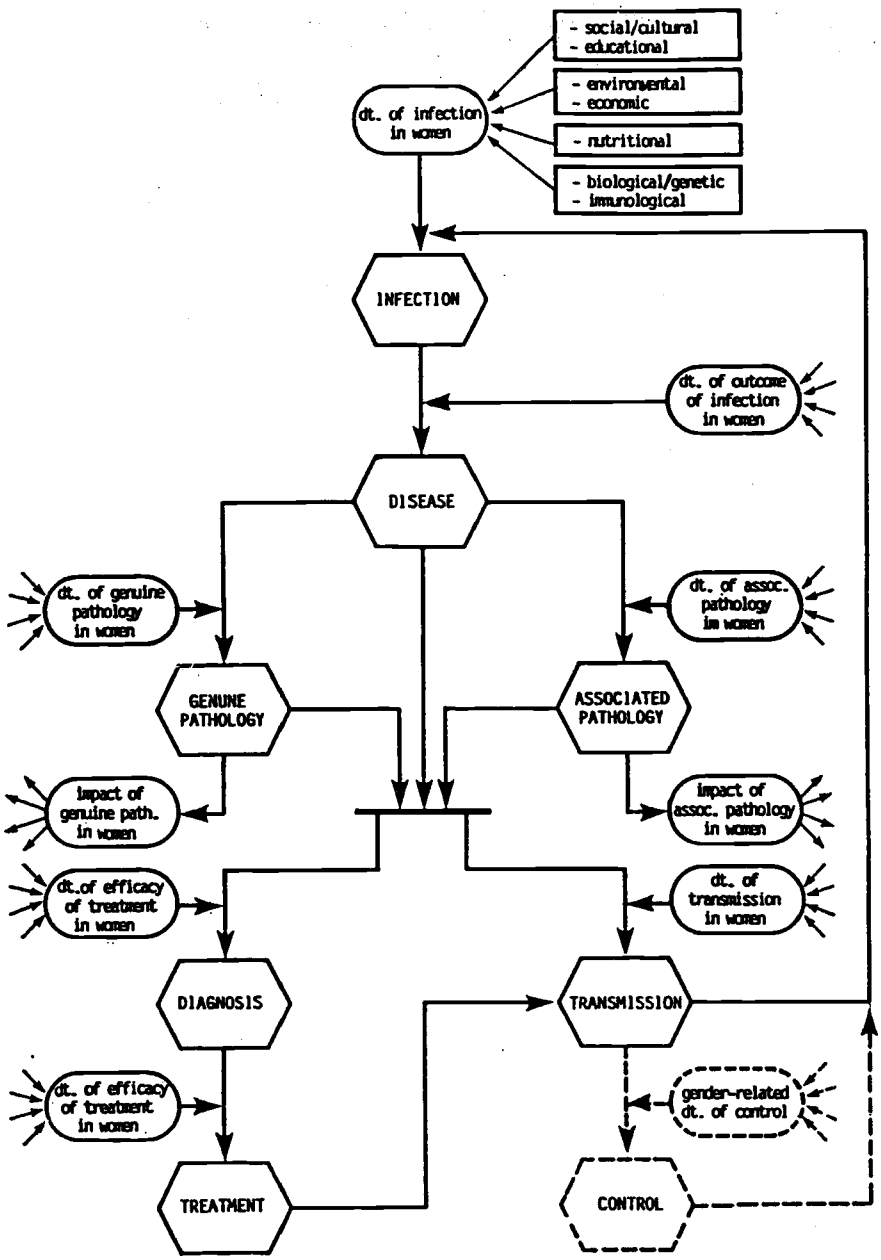


Fig 1. Protocol to allow assessment of the various aspects of a major parasitic infection in women.

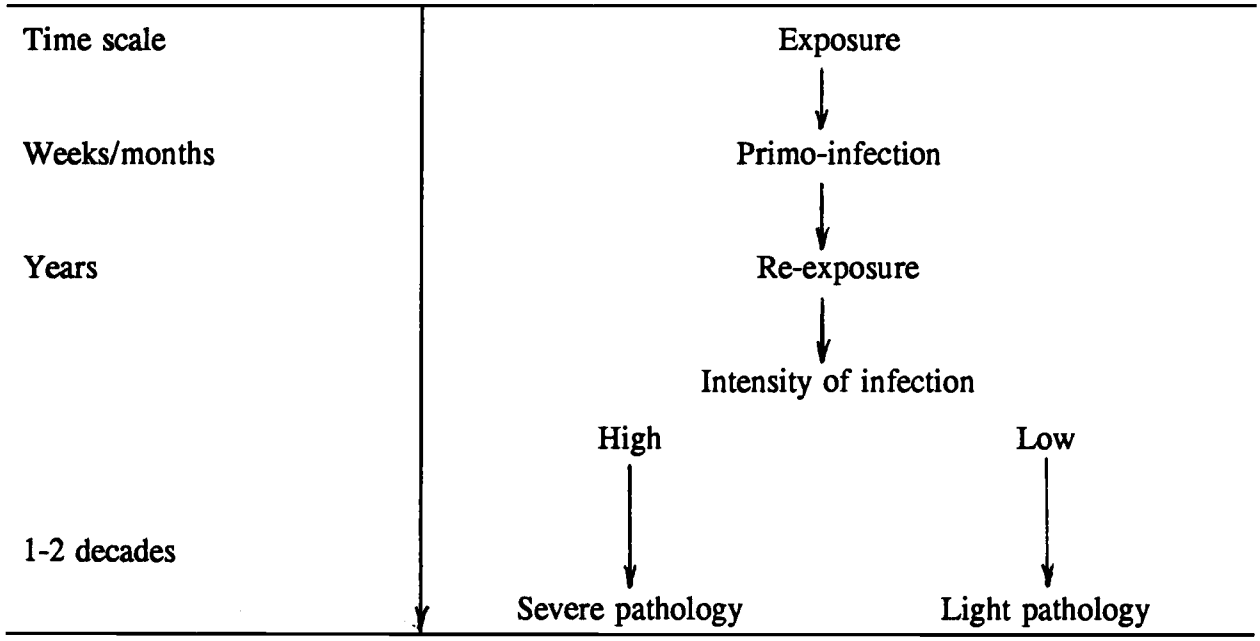


Fig. 2. Natural history of schistosome infection.

| Time scale | Water contact patterns | Exposure |
|---|---|---|
| Weeks/months | Female biology of skin | |
| | Innate resistance (genetics) | |
| | Antenatal/perinatal sensitization of child | Primo-infection |
| | Environment → | |
| | Socio-cultural factors | |
| | Economy | |
| Years | Migration | |
| | Location of settlements → | Re-exposure |
| | Water contact patterns | |
| | Innate resistance (genetics) | |
| | Female biology (vasculature) | |
| | Acquired immunity | |
| | Antenatal/perinatal sensitization of child | Intensity of infection |
| | Concomitant infections* → | |
| | Environment | |
| | Socio-cultural factors | |
| | Economy | ←(−) Chemotherapy |
| 1-2 decades | Innate resistance (genetics) | |
| | Female biology (vasculature) | |
| | Immunomodulation → | |
| | Antenatal/perinatal sensitization of child | ↓ Pathology |
| | Concomitant infections** | |
| | Socio-cultural factors | |
| | Economy | |

Fig. 3. Factors that may modify the natural history of infection in women: * leading to immunosuppression or induction of cross-reactive immunity; ** leading to immunosuppression or immunopathology.

# Clinicopathologic and socioeconomic impact of Chagas disease on women: a review

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## Summary

Chagas' disease or American trypanosomiasis is caused by infection with the protozoan flagellate parasite, *Trypanosoma cruzi*. The most common route of transmission is by the insect intermediate host, a triatomid bug. Other documented routes of transmission include congenital and transmammary infection and transmission by blood transfusion. Chagas' disease is widespread in poor, rural areas in Latin American because of the predilection site of the vector for walls and roofs of houses traditionally constructed of mud and thatch.

Clinically, Chagas' disease is characterized by an acute illness following infection - with the possible development of chronic clinical disease an average of 10-20 years later affecting heart, gastrointestinal tract or the nervous system. The impact of Chagas' disease on health and productivity of women in Latin America has received little attention in the scientific or sociological literature. This paper reviews the pathologic and clinical changes associated with Chagas' disease as well as discussing housing, education, reservoir hosts, vectors, and other factors influencing transmission of the infection. Specific areas for future research are proposed concerning the pathogenesis of disease in women and the role of women in affecting parasite transmission.

## Introduction

American trypanosomiasis or Chagas disease, also called Darwin's illness, is a zoonosis caused by the haemoflagellate protozoan *Trypanosoma cruzi*. First described by Carlos Chagas in 1909, Chagas' disease is a major public health problem, causing significant morbidity and mortality amongst the poor in rural agricultural areas of Central and South America. Although current prevalence rates are sketchy and probably underestimated, recent research estimated that about 20 million people are infected and an additional 90 million people are at risk of becoming infected (1, 2, 3).

The parasite *T. cruzi* is an infectious protozoa that has one of the most complex life cycles of the trypanosomes found in humans (4, 5). The disease is mainly transmitted by the hematophagous reduviid insect vector (subfamily Triatominae), commonly referred to as the kissing or assassin bug. The vector bites preferentially at mucocutaneous junctions, such as the outer canthus of the eye or angle of the lips (thus giving rise to the name "kissing bug"). After biting, the insect deposits faeces containing the trypanosomes on the skin. These are

then rubbed or scratched into the puncture wound by the human host. Other routes of infection that have been described include congenital and transmammary transmission, blood transfusion, kidney transplantation (6, 7, 8, 9) and sexual intercourse (10, 11, 12).

The prevalence of the disease and the severity of infection appear to be confined to the geographical areas of specific strains or zymodemes of the parasite (13, 14). In vitro, colonies developing from the same isolate may exhibit very different pathologic behaviour in experimental hosts (15). Many questions concerning the variability in parasite behaviour and their relevance to the development of symptomatic disease are yet to be answered.
One of the most serious complications of Chagas' disease is cardiac damage that may result in heart failure (16). Once this occurs, little can be done and death is inevitable. Sudden death as a result of ventricular fibrillation in chagasic patients contributes to about 37.5% of the overall mortality of 12.8% of Chagas' diseased individuals (17, 18).

Transmission of American trypanosomiasis is directly related to human behaviour and the socioeconomic conditions under which people live. The major determinants of infection in identified endemic areas involve social, cultural, behavioral, economic, and medical factors (19, 20, 21). This review will summarize current knowledge of the disease and factors influencing transmission of the infection. Attention will also be drawn to the absence of a significant body of research addressing the disease in women or the specific role that women may play in affecting transmission rates. Finally, suggestions will be made for future research to increase our understanding of the impact of this important disease on women.

## Clinical and Pathological Effects

### Clinical features

The manifestations of American trypanosomiasis take a variety of clinical forms. The symptoms that develop are protean and are often misdiagnosed.

The acute phase of the disease often passes unnoticed and is best defined by the ease with which trypanosomes are seen in peripheral blood smears, the appropriate diagnostic test for the acute phase. Following an incubation period of 4-26 days after the introduction of the organism (22, 23, 24), the disease during the acute phase is characterized by general malaise, fever, muscle pain, sweating, and occasional vomiting and diarrhoea. Sometimes a subcutaneous inflammatory or ulcerative nodule, known as the Chagoma, may be present at the site of the bite. It can persist for several weeks and then disappear leaving a depigmented area. Soon after the acute symptoms begin, lymphocytosis, lymphadenopathy, and moderate hepatosplenomegaly may follow.

Neurological signs may also develop. Irritability, headache, and drowsiness are common. *T. cruzi* has been demonstrated in the CSF of patients with acute Chagas' disease (25). Mild to severe myocardial signs can be present, with cardiac failure and electrocardiographic changes (23, 26). Electrocardiographic (ECG) changes during acute disease are variable, and include first and second degree heart block, atrioventricular block, and depressed R-wave amplitude (26, 27). The acute infection can occur at any age, although it is most common in children, where there is a 5-10% fatality rate (28, 29). The acute phase

ends after approximately 2-3 months, rarely lasting up to 4 months (23, 30). After some weeks, the circulating trypanosomes can only be detected by xenodiagnosis. A small number of the parasites continue to circulate indefinitely in most individuals. Regardless of the route of transmission, spontaneous resolution of the acute illness occurs in most patients, who then enter the indeterminate phase of the disease.

The indeterminate phase of the disease has been described as the silent/asymptomatic phase characterized by lifelong, low-grade parasitemia, positive serology, and abnormal ECG following pharmacologic overload (31, 32). It presents a gradual and asymptomatic course, during which the serum test may be negative though alterations of the ECG are present (33). The ECG is more sensitive than any other method in detecting cardiac pathology in Chagas' disease (33, 34). An estimated 10-30% of persons in the indeterminate phase eventually may develop chronic Chagas' years or decades after the acute episode (35) or may be asymptomatically infected for the rest of life (23). The chronic phase of the disease, is characterized by subpatent parasitemia detectable only by xenodiagnosis and the appearance of antibodies to a variety of parasite antigens (36). Cardiomyopathy is a common feature causing disability and mortality in endemic areas (37). Once the symptoms of myocarditis develop, death will follow within 6-12 months (30). Cardiac lesions are mainly observed in the 20- to 40-year-old age group and cause electrocardiographic abnormalities such as complete right bundle branch block, in addition to cardiomegaly, arrhythmias, cardiac failure, and sudden death (27, 38). Unusual clinical manifestations of Chagas disease, such as chest pain unaccompanied by major coronary changes, are attributed to an imbalance in the cardiac autonomic nervous system (39). Neurologic manifestations include pelvic limb ataxia, weakness, and depression. Hyperreflexic spinal reflexes have also been reported (40, 41).

Another complication of chronic infection is dilatation of tubular organs, or the so called "mega" phenomenon, which leads to signs of dysphagia, regurgitation of undigested food, and constipation as a result of megaesophagus, megacolon, or megastomach. This "mega" disease is common in certain endemic areas of South America (42, 43). The infection rarely leads to megaureters, megabladder, megagalbladder, or bronchiectasis (23, 12). Thyroiditis and hypothyroidism have also been associated with chronic Chagas' disease in endemic areas (12). It is important to note, however, that the literature is lacking studies of the effect of the mega phenomena and thyroid disorders on women's health, and reproduction.

Congenital disease is caused by transplacental transmission. Congenital infection may occur even during the asymptomatic phase of the disease and its mechanisms have yet to be identified. In endemic areas it is responsible for 10% of all abortions (30). If the fetus survives, it is born prematurely with hepatosplenomegaly, cardiomegaly, and megaesophagus, and usually dies within a few weeks as a result of encephalitis, myocarditis, or secondary infection (44, 45). Very few may survive after treatment but most do not respond (46). Birth weight has been observed associated with congenital transmission of Chagas' (46, 47). In cases of congenital infection, the placental villi are bulky and ischemic. Microscopically, the chorionic villi may show focal necrosis and edema as well as histiocytic and occasional giant cell infiltration. The intracellular parasite can variably be demonstrated in histiocytes (30, 48). The parasite has also been found in the amniotic fluid (45), which could present a hazard not only to the foetus but also to obstetricians and gynaecologists.

**Pathological features, pathogenesis, and treatment**

In the acute stage the haematogenous spread of the parasite leads to invasion of various tissues and organ systems. The invasion is accompanied by an intense inflammatory reaction (23), manifested as lymphocytosis, lymphadenopathy, and hepatosplenomegaly (22, 23, 30). The cardiac lesions are characterized by the presence of the parasite within the myocytes without cyst walls (pseudocyst) and an inflammatory process. Ventricular aneurysm, pericarditis, and acute cardiomyopathy are possible sequelae (49). The meningoencephalitis may be multifocal or diffuse, sometimes adopting a necrotizing character. Parasites are seen mainly in macrophages and glial cells and occasionally in neurons (40, 50). Rupture of the parasitized cells will lead to death, especially when they rupture in the cerebellum and the basal ganglia (40, 51).

In the chronic stage there is a gradual destruction mainly of the heart and nervous tissue (22, 23). However, the demonstration of the parasite in blood and tissues is difficult. The pseudocyst in the myofibril can be demonstrated only in 30% of cases (52). Chagas' cardiomyopathy is the leading cause of sudden death in Latin America. These cases are frequently associated with complications of arterial embolism (emboliogenic cardiomyopathy) that may lead to myocardial infarction in young patients.

Thromboembolism is also suggested as a possible cause of regional myocardial infarction in chronic Chagas' disease. Cardiac and pulmonary thrombosis and embolism have been reported in chronic cases (53). The myocardial pathologic changes are comprised of focal myocytosis, contraction band necrosis, and fibrosis, which resemble the pathology of other congestive cardiomyopathies (50).

"Mega" disease in the form of megaesophagus or megacolon may be observed in the gastrointestinal tract in chronic cases due to fibrosis and sclerosis of the parasympathetic plexuses (24, 42). Peripheral nerve fibre damage is also described in human and experimental animals (54, 55).

Immunosuppression may occur during the acute phase and continue into the postacute stage of the disease. The mechanism that mediates this suppression is poorly understood. This nonspecific suppression of immune responses occurs in experimentally infected animals and human infections (56). It contributes to the inability of experimental hosts to mount an effective anti-parasite immune response (57, 58) and increased susceptibility to secondary infections or neoplasia.

The mechanism(s) involved in the pathogenesis of the clinical manifestations and pathology of Chagas' disease is poorly understood (22, 24, 59, 60). In chagasic myocarditis the relationship between tissue inflammation, tissue parasitism, and parasitemia, especially in the chronic stage of the disease, is unknown (61, 62). The areas of most marked inflammation were not necessarily the most heavily parasitized.

The lesions during acute infection are primarily attributed to destruction of cells of various organs and blockage of the reticuloendothelial system by *T. cruzi*, leading to functional disability and possibly death (22, 37). However, undetermined mechanism(s) are also postulated.

Most workers suggest immune-mediated or autoimmune reactions, increased endothelial injury and platelet reactivity, toxic effects, immunosuppression, or increased catecholamine and calcium flux as the major mechanisms responsible for the development of

clinical and pathological manifestations associated with *T. cruzi* infection. These mechanisms may act singly or in concert. However, most of these suggested mechanisms are still to be investigated.

*Treatment*

Active drugs for mass treatment of the disease are not available. The most effective chemotherapeutic agents are benznidazole, and nifurtimox. They are effective only in the acute phase, causing suppression of parasitemia and tissue parasitism. However, they do not alter the progression of the late phase myocarditis (63). Treated individuals still show ECG disturbances as frequently as do infected non-treated patients (63). Undesirable effects of these drugs such as weight loss, nausea, vomiting, nervous excitation, insomnia, depression, convulsions, headache, drowsiness, myalgia, hepatic intolerance, and signs of ovarian and testicular injury were also reported (64, 65, 66).

These drugs can cross the placental barrier and bind covalently to maternal and fetal proteins of experimental animals. However, their effects on pregnant women are unknown (67). The nitroarene compounds have been found to increase the prevalence of lymphoma in experimental animals (68, 69), but whether they have a similar effect in humans in unknown.

In the long-standing chronic disease, symptomatic treatment is all that can be offered. Surgical intervention is suggested in the "mega" disease. In the absence of adequate, effective chemotherapy and chemoprophylaxis a vaccine would be a major advance in dealing with the infection. However, all attempts to vaccinate animals with various *T. cruzi* antigens (live attenuated or nonproliferative organisms, killed intact parasites, cell homogenates, or subcellular fractions) resulted in lack of protection to challenge infection (70) or production of pathologic side effects resembling those of the chronic form of the disease.

## Epidemiology and Ecology of the Disease

The infection rate of Chagas' disease is age dependent. The infection is most commonly acquired in childhood between the ages of a few months and 2 years and persists through life (22). A high rate of infection has been detected in people less than 20 years of age (71) and in some localities of Brazil, 13% of all deaths between the ages of 15 and 74 are attributed to Chagas' disease (72).

Transmission of the parasite by the insect vector is the most common route of infection. Successful transmission depends upon the appropriate vector, virulence of the parasite, confluence of reservoirs, and susceptible host in a suitable habitat. Infection of the mammalian host occurs when the metacyclic trypomastigotes in the faeces of the vector are deposited at the bite wound, or on abraded skin or mucous membrane (23, 36).

### Vector

*Triatoma infestans, Triatoma dimidata, Panstrongylus megistus*, and *Rhodnius prolixus* are the most efficient vectors of Chagas' disease because they feed on both humans and reservoir mammals(dogs, cats, pigs, guinea pigs, monkeys) (73) and cohabit

prolifically near humans. These vectors were found to have infection rates ranging from 50% to 100%. Vectors emerge to feed primarily at night. They live in cracks, holes, and grass, and are also commonly found in beds, clothes, furniture, and the lower 2 metres of house walls. Others are found at higher levels on walls and in roofs, from where they drop onto sleeping people or onto food. Both the adult insect and its juvenile stages can be infected with *T. cruzi* (74, 75).

All stages require a blood meal for moulting and the adults feed several times during their relatively long life. They become infected following ingestion of a blood meal from an infected host or can be infected directly by cannibalism or coprophagy (76). Kissing bugs are capillary feeders and their bites cause little pain. Abdominal distension from the ingested blood often causes the insect to defecate while biting. Some species defecate later, usually after leaving the skin. If blood meal sources are insufficient, adults fly to new sites whereas immature bugs die.

Following ingestion by the insect, the trypomastigote form of the parasite from the mammalian blood meal is transformed to the epimastigote form and multiplies in the vector. Transformation of the epimastigote back into metacyclic trypomastigotes subsequently occurs in the hindgut of the vector (in about 1-2 weeks) (22, 77, 78) before passage in the faeces. Once the insect vector is infected, the parasites can remain for life (1-2 years).

**Vegetation**

Palm trees located in rural areas of Latin America are known breeding grounds for triatomines and increased rates of human infection are evident in areas of dense palm stands (20). Often after a forest is cleared for agricultural purposes, the inhabitants build near remaining standing palms and use them as building material. The connection therefore can be made between palm trees and Chagas', possibly providing an explanation for the initial introduction of *T. cruzi* into the human population (20, 79).

**Reservoirs**

The role of reservoir animals in maintaining domestic cycles of trypanosome infection needs more investigation. Domestic and wild animals act both as reservoirs of the parasite and sources of bloodmeals for the vector. Domesticated animals facilitate the transmission of the disease to the humans with whom they coexist. Infected dogs and cats are frequently found in endemic areas. Feline infections can be traced to ingestion of infected rodents. The role played by dogs is considered to be more important, however, since they remain in the house at night, when the bugs are active. Further, seropositive dogs have been shown to have an even greater capacity to infect triatomine bugs than do humans (80, 81). Elimination of dogs to reduce risk of human transmission is unlikely because of both their economic and social value to owners. In a study conducted in Argentina, dogs were used for hunting fur or leather animals (60%), as guard-dogs for houses or goats (21%), as labour-dogs (10%), and only 5% were considered as pets (82).

The guinea pig may also contribute to the transmission of Chagas' disease. These animals are used both as a source of food and as a household pet. Guinea pigs are known to be one of the natural reservoirs of *T. cruzi*. Their domestic breeding for food and local trade

are common practices among Andean communities in South America. Natural *T. cruzi* infections in large animals are rare and these species are unlikely to be important reservoirs for human infection. However, 100 naturally infected wild animals have been shown to harbour the parasite and may act as reservoir hosts (83). Both wild and common house rats have been found to be infected with the same zymodeme that causes acute Chagas' disease in humans (84). These rats are dominant creatures in rural houses. Although they are not domesticated pets, they interact within reach of humans and are a source of parasites and blood meals for the vector.

**Other routes of transmission**

Transplacental or congenital infection constitutes a real hazard in areas with a high prevalence of trypanosomiasis (47, 85, 86). Although the true rate of congenital transmission is unknown, it is speculated that it may be as high as 5% in areas of high endemicity (47). Despite the fact that a large population of women of reproductive age is infected in Latin America there has been no serious study of the epidemiology of congenital infection or the mechanism of this mode of transmission.

Transmission by maternal milk has been described (87). The presence of the parasite in the milk has been reported in guinea pigs, mice, and humans (10, 88). Mice became infected with *T. cruzi* following injection with colostrum from infected women (89). Intracellular amastigotes were found in the mouse mammary glands (88). However, some studies suggest that breast feeding may not successfully transmit infection during the latent stage of infection unless there is intermittent parasitemia or nipple bleeding (90). At this time no studies have been undertaken to establish the importance of lactational transmission in infections of children with *T. cruzi*. Despite the importance of breast feeding in developing countries, there have also been no efforts to examine the effect of the parasite on the quality or quantity of milk produced, although the parasite has been shown to establish in the mammary glands of mice.

Blood transfusion with infected blood is another important route of transmission (32). Tens of thousands of people become infected every year in Latin America by this mechanism. It has been reported that repeated blood transfusions cause a significant risk for *T. cruzi* infection in Central America (91) and the risk of transmission from infected blood has been suggested to be as high as 50% (22, 92). Cases of Chagas' disease have also been reported in USA and Canada as a result of blood transfusions from chronically infected asymptomatic Latin American immigrants (32). Most cases of illness associated with blood transfusion are mild, possibly because they occur in adults. In immunocompromised patients, however, the illness may take a fulminant course (91, 93, 94). Although serological tests could be used to eliminate positive blood, false positive results occur due to cross reactions with other protozoan infections (95). Trypanosomes in blood supplies can be successfully eliminated by treatment of blood with gentian violet (96) or phenolic compounds (97). However, the efficacy of these compounds is not limited to the parasite; they are also toxic to host cells (98).

*T. cruzi* may also be successfully transmitted by food contaminated with the infected bug or its faeces (24, 99) and by ingestion of infected meat.

## Social, Cultural, and Economic Factors

Chagas' disease is a problem of poor, rural agricultural areas. The social, cultural, behavioral, and economic conditions under which people live are directly proportional to the rate of infection (19, 21) and several specific factors can be described that influence transmission.

### Housing

Houses in Central and South America are usually built of local materials. Typically, walls are made of mud slapped onto a wooden lath frame, whereas the roof is made of wood, turf, palm thatch, and tile. Such construction provides an ideal habitat for the vectors of *T. cruzi* and consequently housing becomes the major component in the transmission of Chagas' (19). In addition to the house, triatomids also can reside in wooden floors, mattresses, and furniture (20). Although replastering the walls can reduce contact with humans, the insects may move under beds where possessions are kept and hence create another focus of infection. The custom of replenishing the roof of the house with fresh-cut palm fronds introduces a new population of the vectors (100). Replacement of wood and palm thatch roofing with corrugated iron was found to improve the houses and reduce the population of the bugs (101). Control of vectors by housing improvement or repeated insecticide use are long-term, costly enterprises that depend more on political than technical decisions. To improve houses in rural areas the income level must be improved as well.

### Firewood and dirt floors

Stacked near the cooking or kitchen area of houses, firewood provides a breeding ground for triatomines in rural endemic areas of Costa Rica (20, 102). Between 1980 and 1981, Zeledon and Vargas (103) focused on the passive transmission of *T. cruzi* via infested firewood stacks and dirt floors. These two factors along with the use of infested palm thatch for roofs and mud-stick housing, increased the likelihood of infection. Replacement of dirt floors with cement and the use of electricity instead of wood for fuel are suggested control methods. However, economic conditions under which most rural Latin America people live limit their ability to utilize such methods, despite their efficacy in controlling transmission. Family Size: The number of individuals living in the house is a factor related to the presence of bugs in that house. Large families or families that receive frequent visitors were found to have higher numbers of resident infected insects (104, 105).

### Education

Factors like poor standards of hygiene and inadequate household and health education also play a role in transmission of Chagas' disease. In some localities where no health eduction is available, the triatomid bug is often regarded as simply another nuisance like bed bugs, cockroaches, and difficulty finding water, food, and firewood (106). Very limited understanding of Chagas' disease and its transmission in affected communities has been described (101). In some areas the bugs are regarded as potentially therapeutic in reducing

blood pressure, while in Nayarit, Mexico, triatomids are considered to have aphrodisiac powers if eaten, and to be useful against warts if rubbed on the skin (101, 107).
In some agricultural areas the farmers prefer to use available insecticides on their crops (101), unaware of the toxic effects of insecticide residues. It is evident that health education could play an important role in increasing public awareness of the problem and in establishing safe and hygienic practices that would result in control of the kissing bugs and hence the disease.

### Immigration

The immigrants to the rapidly developing urban slums of Latin American cities may bring triatomid bugs in their clothes, furniture, and other belongings. Additionally, *T. cruzi* is carried to cities in the circulation of infected people. The recent shift of populations to urban areas has led to the increased importance of direct routes of infection such as congenital and lactational transmission and infection by blood transfusion (108).

### Direct economic effects of infection

The most significant economic factor that facilitates Chagas' prevalence is poverty. The disease itself causes disability and the disabled family member becomes a financial burden to the family and aggravates its poverty. In Brazil it has been estimated that 1363 working years per 100,000 women are lost due to Chagas' disease (101). Since most people acquire the infection during their childhood, a period of 10-20 years elapses before cardiac lesions occur. Consequently, the effects of disease often develop during the period when high economic productivity is expected.

The use of residual insecticides for the control of the disease is costly and toxic and their use requires an expensive infrastructure. The estimated cost for spraying one house in 1979 was 5 USD (101). Today that figure has absolutely increased at least 100%. Benzene hexachloride (BHC, Gammexane) is considered the insecticide of choice although it does not kill the triatomid eggs. The first spray usually reduces the population of bugs but continuation of spraying accompanied by house improvement is important. BCH is relatively inexpensive and less toxic than other insecticides. However, organochlorine chemicals have become increasingly difficult to obtain as concern over their long-term environmental effects has mounted (101). Other insecticides such as dieldrin, DDT, carbamates, and pyrethrins are either more toxic or more expensive. In the case of dieldrin, populations of the vector have developed resistance to the chemical (101).

Negative ecological effects of insecticide use have not been determined. The chemicals used also kill the natural enemies of the bug such as ants, spiders, lizards and mice (109). Cases of domestic animal intoxication after spraying are not uncommon (101). Although insecticide application causes impressive initial mortality of the bugs, reinfestation of treated houses is common. This may be due to the disruption of respraying schedules, immigration of bugs from neighbouring untreated areas, or introduction of infected bugs via human population movement from infested to noninfested areas (101).

The presence of palm trees and the traditional use of the parts of these trees in house construction and roofing are a primary source of infestation and reinfestation.

## Women and Chagas' Disease

Chagas' disease in women in Latin America is clearly important because of its impact on the health and productivity of individual women. Additionally, women are important in the ecology of the infection because their activities and position in society give them the potential to significantly alter prevalence and patterns of infection with *T. cruzi*.

### Impact of Chagas' disease on women

As we have previously described, research on the effects of American trypanosomiasis in women is largely absent from the literature. In endemic areas it can be anticipated that a large proportion of rural, poor women will be infected. The limited number of studies available do show a clear effect of disease on women's lives. In Brazil, it was found that 14% of infected women lost their jobs because of trypanosome related illness (101). In many Latin American cities, employment is not offered to rural immigrants if they are positive for infection (101). Increased cardiac disease morbidity due to Chagas' disease in women was found between 15 and 53 years of age with average of 27.3 years (34). Therefore, infection will reduce women's abilities not only to care effectively for their families, but also to contribute economically to the household. Because it has been estimated that women and their children in developing countries account for at least 50% of food production (110), losses due to Chagas' related disease in women alone in endemic areas may substantially alter the economic status of entire communities.

The potential pathogenic effects of American trypanosomiasis on the female reproductive system have also been neglected. The recognized ability of the parasite to alter the function of tubular organs ("mega syndrome") may have some important implications for the ability of women to conceive and bear children. Because infection occurs most often in children, the entire reproductive life of women may be affected by the trypanosome. Furthermore, the immunosuppressive effects of trypanosome infection may make women more susceptible to other diseases, including those of the reproductive system.

### Impact of women on Chagas' disease

Women are at the enter of both biological and social cycles of *T. cruzi* infection. Their ability to transmit the parasite congenitally and through milk potentially results in thousands of new cases annually in infants, although data establishing true rates of infection by these routes is lacking. The risk factors for infection by these routes have also not been identified, i.e. stages during infection when congenital transmission may occur, etc. Knowledge of these factors may lead to specific recommendations to minimize transmission by these routes.

The social role of women as primary care givers in the family provides them with opportunities to interfere with transmission of the parasite at several levels. First, they can

directly impact transmission to family members by taking measures to limit contact with the vectors. Unfortunately, many of these measures (use of insect repellents or mosquito netting on beds) would be prohibitively expensive in many endemic areas. Second, women could educate children about the parasite, routes of infection, and development of disease. Mata (111) found in work with a Mayan Indian village that maternal attitudes and practices had greater impact on disease transmission in the family than socioeconomic class or level of education. However, the success of educational efforts by women depends in turn upon their accurate understanding of Chagas' disease. In a study conducted in a rural community in Bolivia, 59% of women did not realize that triatomine bugs transmit disease, although they knew the bugs and had seen them in their houses (34). Improved education for women should also limit transmission of other important infectious diseases.

## Future Research

Throughout this review we have emphasized that research on Chagas' disease in women is absent from the literature and we propose in this section the following specific projects that will increase understanding of the parasite in women and also potentially lead to improved control of *T. cruzi*.

(1) Epidemiologic studies in endemic areas to better determine infection rates in women and additional specific risk factors for infection. Concentrating research efforts in limited areas in Latin America may be more productive than attempting more superficial studies on a wider basis.

(2) Accurately determine morbidity and mortality rates for Chagas' infected women in selected endemic areas. Determine effects of disease on economic status of infected women.

(3) Conduct studies to identify factors that may predispose women to the development of chronic Chagas' disease (malnutrition, hormonal changes, concurrent infections, etc.)

(4) Using experimental animal models, determine whether infection with trypanosomes has specific pathologic effects on the female reproductive tract and their possible effects on conception, fetal viability and growth, birth, and milk production.

(5) Undertake toxicologic studies to evaluate the effects of antitrypanosomal drugs on pregnancy and fetal development.

(6) Laboratory and field studies should be undertaken to determine the mechanisms and epidemiologic characteristics of transmammary and congenital infection with *T. cruzi*.

(7) Evaluate communication strategies for educating women about Chagas' disease, basing programs on existing women's groups within the community.

(8) Assess the ability of women's education programs to alter behaviours influencing the transmission of *T. cruzi*.

(9) Initiate cost-benefit analysis of present and possible future programs based on women's education or treatment programs.

## Conclusion

American trypanosomiasis is primarily a disease of the rural poor with little social or

economic status (PAHO 1970) and available data on women in Latin America show that most live in poverty (110). At this time, the knowledge and technology exist to dramatically lower rates of infection with *T. cruzi* by improving housing conditions. However, proposals for improvement in women's health by preventing Chagas' disease cannot be divorced from the economic conditions in Latin America as a whole. As SWC 1989 concludes: "almost every economic signal points to the fact that development has been derailed" in Latin America. Given the limited resources available, it is increasingly necessary to give equal consideration to costs of control measures for infectious diseases when evaluating their benefits. As a result, more limited initiatives to educate women to protect and similarly educate their families may be of greater value than large scale, expensive efforts directed at vector control or alterations in housing.

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# Materno-Fetal Malaria: Multiple Dyadic Dilemmas

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## Summary

The unappreciated severe impact of malaria on gravid women, fetuses, and neonates are reviewed, with special relation to newer knowledge of alterations in immunity, to the definitions of dyadic hazards, and to pharmacological and harmful effects of available drugs. Suggestions are made concerning possible priorities for fundamental and practical research into the pathophysiology and realistic management in this specific vulnerable period.

## Introduction

Malaria in the 1990s remains an unconquered indeed a resurgent disease, whose existence as a cause of morbidity and death among individuals of all ages especially, children and non-immune foreigners has been recognized for centuries. Recent assessment suggests that more than 1 million deaths occur annually and, importantly, a significant impact on pregnant women, involving mother, fetus, and newborn. The euphoria in the 1960s, following the success of residual insecticides and of new synthetic antimalarials, was relatively short-lived owing to a increasing resistance of both mosquitoes and plasmodia, and operational difficulties. This has lead to the urgent need for further research and applied knowledge in many fields. Progress has indeed been made as the necessity for efficacious drugs to combat the most malignant and common form of malaria *Plasmodium falciparum*, as well as *P. vivax, P. malariae*, and *P. ovale*, are urgently required. But with each step reached, vital pieces of information are lacking as, for example, in the areas of mosquito vectors and their resistance to the majority of insecticides commonly used, the resistance of plasmodia to drugs or a combination of these, and the complex problem of immune responses as revealed, both by in vivo and in vitro studies in experimental animals, as well as in parasites, and in individuals of different ages, sex, and ethnicity. Newer laboratory techniques used in basic and applied research are helping to redefine the multiple gaps in knowledge at the global level.

The fresh impetus in the field of training malariologists, and the need for educating communities in participatory techniques to protect themselves are encouraging. A sense of disillusionment in achieving rapid breakthroughs in the vast field of malaria is pervasive in many publications; the situation has been described as "grim" (1) in terms of forms of effective treatment and many subjunctives (2) are used to describe progress in the cultivation of malarial parasites. The interaction of malaria and red cells and the prevailing difficulties in the basic pathophysiological mechanisms in the anaemia of *P. falciparum* are among the

many avenues of research in progress. However, reliance must be placed, even in these recessionary times, on the innate resilience of the human race, the dedication of scientists whose collaboration has become by design and necessity multidisciplinary in focus, transcending the boundaries of political ideologies in the face of combating a formidable mutual enemy. This global disaster, unlike the rapid spread of HIV infection which rightly has been much in the limelight and has tended to overshadow the equally tragic spreading plague of malaria. The latter is a less media-opportunistic disease, which unlike the former, deals with two vectors, four species of plasmodia, and involves many environmental and health issues as well. For its possible eradication, which has failed over the years, it does not rely on sexual abstinence, the use of condoms, and face-to-face education and media assistance, but on many broader issues that include as well the search for effective drugs. The following few are mentioned, the many species of mosquitoes involved, the synecological systems in which they persist, their behaviour, vigour, and vectorial capacity, the morphology of parasites, the effectiveness of larvicides (including hydrophytes, metabolites of microorganisms as well as the use of larvicidal-eating fish, genetic manipulation of insects by a number of methods, among other issues to be addressed.

The acceptance and compliance of populations to effective appropriate treatment, if such exists, has been mitigated by a decreasing sensitivity to drugs (1, 2, 3, 4), their side effects, lack of stability of drugs in the tropics affecting potency in treatment (3), self-medication and non-health seeking behaviour, and the cost of treatment among many factors (6). Other difficulties encountered include the large-scale and continuing movement of populations, such as air travellers on many missions, tourists, the two-way flow of expatriate workers returning to their homelands for visits. These individuals are capable of acquiring malaria in mild or severe forms, and becoming carriers of the disease and thus innocent "vectors," if treatment received has been only partially effective (7, 8). Other groups include "refugees" using the original definition (e.g. fleeing political or religious persecution), as well as ecologic or economic migrants moving from non-malarious to malarious zones, and/or to adjacent countries, to, clandestinely or legally entering new countries (19). In the many wars that have been ongoing or are still in progress, malaria as well as other diseases have shown a rapid spread.

Transmission of the disease in malarious and non-malarious areas has been reviewed and includes: (1) nosocomial infections, acquired more commonly now in hospital facilities via blood transfusions, where no routine testing of blood is undertaken and/or the non-use of homologous antigens that are species-specific; (2) improper sterilization of syringes (disposable or non-disposable) by health professionals (10) and/or drug addicts and unexpected opportunistic infections such as the proximity of an infected patient in a nearby hospital ward in a non-malarious area of a country, but in which the appropriate mosquito vector is present (11); and (3) the release by baggage handlers of infected live mosquitoes, hiding in holds of planes, landing in temperate zones, and infecting non-immune residents living in the proximity of the airport (12). These examples of transmission of malaria species worldwide are just a few illustrations of the dilemmas facing health organizations, scientists, health professionals, and the populations they serve and how in turn, pregnant women, and their fetuses and their newborn children will be even more affected by events in the near future that can lead to illness or untimely dead.

As correctly stated in 1982 (13), over the years the concept of eradication has

gradually dwindled due to a number of interrelated factors. These include, among others, the decline of the use and effectiveness of residual insecticides to control mosquitoes and their changing feeding and resting habits. Also (13), importantly the increasing opposition by householders and more recently environmentalists to the use of insecticides, lack of staff at different levels, and the cost of new repellents, etc, must be considered. A combination of methods, which includes chemical control, is obviously still required. The dilemma remains unsolved. Will any magic bullets, long anticipated and long overdue, become a reality? What choices exist and what priority rating does this disease acquire in a world beset by a multitude of problems also requiring instant solutions?

## Immunity in malarial disease with special reference to gravid women

The issues of materno-fetal malaria can only be put in context in relation to the complexity of immune responses during this hazardous period of life. The subject of immunity to malaria has been studied for over eight decades and still remains fraught with complexities because results from numerous in vitro and fewer in vivo studies are often contradictory, and the components of numerous factors among individuals and populations within regions of a country or of the world at large vary considerably (14). For the purpose of simplicity, the immune mechanism can essentially be divided in natural resistance (15) of immunity, which is dependent on host species, although this may only be relative. Influences, among others, include a mix of events such as age, physiological status and genetics of the host, nutritional status, the interaction of blood cells and plasmodia, the role of the spleen, and ecological factors among other considerations. Acquired adaptive (immune response) will arise when the first and subsequent encounters with the malarial parasite provoke a response and possibly resistance to the infection. Natural (innate) resistance, which includes the presence of certain glycoproteins, known as surface receptors, that permit invasion of red blood cells by merozoites but which only pertain to species-specific parasites and the blood groups of the host.

### *Abnormal haemoglobins*

Other factors have been studied to elucidate the molecular structure of some abnormal haemoglobins that may have a protective factor against malaria. These have included, for example in Africa, heterozygous children with the sickle cell traits (AS) stated to have lower parasite densities and a lesser frequency of malarial episodes, than children with normal haemoglobin (AA) (16, 17); but such a protection does not extend to children with sickle cell disease, haemoglobin (SS), among whom fatalities can occur. Some scientists endorse these findings, but many unproven theories have been put forward to substantiate these claims. However, a widespread belief exists that genetic influence will favour persistence of a harmful mutant by selective pressure in parts of the world such as in Africa (15). In glucose-6-phosphate dehydrogenase (G6PD) deficiency (beta-thalassaemia), the effect of malaria on individuals in whom this genetic enzyme deficiency is found, has been investigated and protection has been stated to be afforded to female heterozygotes (18). This red cell disorder is common in parts of the Mediterranean region, India, S.W. Asia, and tropical Africa. Opinions regarding its protective effect against malaria differ by countries and by workers. In

Africa, Gillies et al. (16) reported lower parasite levels among young African children whereas Martin and his colleagues (19) stated such a response did not occur in their study. In Thailand, in two investigations, parasite rates were similar in G6PD affected children as in children without the defect. Also, some normal children had higher parasite densities, but the mortality rate was similar in both groups (20). Other workers have shown that resistance to malaria may ensue with the effect of oxidants, e.g. if fava beans are ingested, parasitized cells will be damaged more readily in G6PD infections, than invaded normal cells (31). Haemolytic anaemia appears to occur in some cases when antimalarials such as primaquine and sulphonamides are given to patients with this genetic disorder (15). In immunity to malaria, both humeral and cellular responses are involved. The role of the former in protecting against malaria necessitates further research, both at the laboratory and clinical levels. For example, the phenomenon of repeated regions within proteins in this disease, their cellular organizations, divergent roles, and the amino acids involved (22), also in vivo studies on human leucocyte antigens (HLA) merit further investigations.

The specific effect of malarial antibody using modern up-to-date techniques has identified, in the sera of infected patients, increases in immunoglobulins especially IgG. The latter is of great importance as it can be transferred via the placenta to the fetus, whereas other immunoglobulins, e.g. IgM, IgA, and IgE will be produced in older infants and growing children up to 12 years of age sequentially at a later stage. In the complex realm of cellular responses, many studies undertaken have focused on the immune response to malarial infections at the asexual erythrocytic state, and antibodies produced are mainly found in the IgG fraction of the serum. More recent investigation in *P. falciparum* disease has shown the presence of a specific circumsporozoite antibody in the blood of West Africans being surveyed (15). Some new on-going research has been concerned with the possible impairment of macrophage function in malarial infections as in vitro studies have indicated these cells may be damaged when ingestion of malarial pigment may interfere with immune response and the role of IgG needs to be further elucidated (23).

### *The spleen in malaria*

The role of the spleen in the immune response process still remains more fully to be explored. It has been generally recognized that splenectomy increases the danger of relapses in latent infections, and can precipitate death in non-lethal infections both in mice and in humans (14, 15). A physical role has been attributed to this organ, which traps abnormally shaped parasitized erythrocytes. However after ingesting parasitic debris, macrophages may produce soluble substances, which in turn have themselves a cytotoxic effect on parasitized red cells. Both T and B cells are found in this organ. The sequence of blood circulation to tissues returning to the lymphoid system permits lymphocytes to mix, allows for contact with other cells, and has been described by Bruce-Chwatt as the foundation of "immunological memory of the body's immune system" (15). Research on the tropical "splenomegaly syndrome" (14) and the nephrotic syndrome (14) has also been a subject of interest to many workers. Malaria immunity was defined by Bruce-Chwatt as: "A state of resistance to the infection brought about by all these processes which are involved in destroying the plasmodia or in limiting their multiplication. It also comprises the factors which modify the effects of

the invasion of the organism by malaria parasites and aid in the repair of damaged tissues" (15).

*Development of immunity*

It is rare for complete immunity to malaria to occur, most commonly a partial species and strain-specific immunity will ensue, following repeated infections (24). In endemic areas, in which transmission exists almost year-round, a high level of immunity can be reached by the indigenous population, especially adults, who may be asymptomatic, despite a low level of circulating parasites, thus achieving premunition. The process of acquiring a semi-immune status for adults residing in endemic areas remains complex (15). However, a number of antibodies dominate the immunity scene and more research is needed on their specific functions and action, e.g. the immunoglobulins and their response to infection brought about by some common antigens shared by the four species of plasmodia. Each species in turn possesses antigenic differences when the life cycle of these parasites is considered, but more information is available on *P. falciparum*, on which research has been focused. More needs to be learned, for example, about specific function of T cells and lymphokines, of antibody mediated phagocytosis, the possible action of oxygen derived radicals (25), the function of B cells, killer cells, or K cells and complement and their roles, as well as non-malarial specific antibodies, as controversy remains in many areas. Recent developments in monoclonal antibody research to assist in the serological diagnosis of plasmodia at different levels of development may help clarify some aspects of this maze of conflicting opinions before the parasite-species themselves are able to evade most of the immune response in humans.

*Immunity in children*

In young children the transient passive placental immunity and levels of antibodies and titre diminish. After this stage, unprotected infants and young children from 2 or 3 months to 3 years may acquire frequent bouts of malaria, which vary in severity, and are often fatal. Survivors will gradually acquire in response to these malarial episodes, a slow rise in antibody titres, which eventually will reach the levels found in adults (15). However, in later childhood, clinical disease will become less manifest, but lower parasitemia and splenic enlargement will be present.

*Immunity in pregnant women*

The frequency of malaria in pregnant women, especially in tropical regions, will vary according to the level of malarial endemicity in the area in which they are living. The frequency of infection and the impact will be higher in regions of low or unstable endemicity, but lower if they have been exposed to frequent attacks of this disease in a holoendemic area (26). Commonly, clinical malaria becomes exacerbated in terms of prevalence and higher rates of parasitemia will exist. The women most at risk have been shown to be in the majority of studies primipara, and who commonly have been stated to have a low immunity almost "child-like" reaction to infection (22). Multiparous women on the whole appear to be less seriously affected themselves, and fetal growth is usually less

impaired, although this does not always apply in the higher birth ranks. Brabin (27), in a holoendemic area of West Kenya, found a peak prevalence of malaria of 85.7% in women having their first child, compared with 51.7% in multipara. The disease was noted at 13-16 weeks of gestation, but prevalence and density of parasitemia decreased in the second or third trimester.

Many theories have been suggested to explain the breakdown in immunity in pregnancy that has been reported in most publications. Studies on the serum immunoglobulins levels in an area of stable malaria among adult Gambian women (26) were depressed in pregnancy especially IgG and IgA, the lowest mean level of IgG was reached in the last 10-week period of pregnancy possibly due to haemodilution and the transfer from the mother's to the fetal circulation. Over the first 30 weeks, mean levels of IgA fell but rose in the last 10 weeks, mean levels of IgM appeared to change little during the pregnancy (26). However, in placental malaria, other workers in the Gambia found that the mean IgG concentration in the plasma was significantly increased.

Controversy has arisen when studies undertaken to assay specific antibody levels in pregnancy both in the Gambia (26) and in El Salvador (28) were undertaken among non-pregnant and pregnant women with or without parasitaemia and at different stages of gestation, as results varied. In a rural area of Gambia, in which *P. falciparum* was holoendemic, other workers investigated the suppression of cell-mediated immune response to malarial antigens in pregnancy (29). Lymphoproliferative responses to this strain of malaria were found to be depressed in pregnant women especially primigravida, compared to parity-matched non-gravid women. It was also noted that immunosuppression in pregnancy could persist for some weeks or months after delivery and post-parturition malaria can occur (44). Malaria antigen induced gamma interferon (Gamma- IFN) production was also depressed in pregnancy, but less so than the suppression of lymphoproliferation, which might indicate that some subsets of T cells could be affected in different ways during parturition. It has also been stressed that parturient women are more prone to be at risk of acquiring other infectious diseases such as tuberculosis, cytomegalovirus, and toxoplasmosis. Non-gravid women are more likely, when other factors are considered, such as nutritional status among others, to be protected against infections by cell-mediated immune system. And as the latter mechanism has been stated to be an important factor in the context of immunity to malaria, this could explain in part the propensity of pregnant women to acquire this disease.

Some workers have also stated that non-specific immunosuppression could be due to the production of hormones such as alpha-2-glycoprotein (29,30) as well as oestrogen, progesterone, and cortisone, the effect of the latter has been noted under specific experimental conditions (26).

*Placental malaria*

This has been the subject of research since the beginning of the 20th century, such as early studies undertaken in Eastern Europe and Panama, but emphasis has importantly been focused in tropical areas mainly in Africa (26, 30) and in a number of Asian countries. Nowadays with the overwhelming prevalence of resistance to most drugs used both in prophylaxis and treatment, this condition is more likely to become exacerbated. Despite its importance, insufficient attention on the whole has been drawn to this problem and many

public health workers are unaware of the status of the placenta as a "privileged site" for the sequestration of malarial parasites such as *P. falciparum, P. malariae* and *P. vivax* (31), though earlier workers have drawn attention to "havens of safety" and local and organ specific malarial immunity (26). In more recent years, the knowledge that phagocytic activity occurs in the bone marrow, the liver, and the spleen is more widespread and with both in vitro and in vivo studies the concept of capillaries of the brain, the retina, and testes shelters for *P. falciparum* are receiving more attention (33, 34).

*Variations in prevalence*

Many differences were found in studies undertaken especially during the mid-1950s and the late 1960s when resistance to malaria was not so acute. A prevalence of 4-7% was found in the Panama Canal zone, and a range between 20 and 34% in Africa (many studies were undertaken in West Africa) (26); in East Africa, which was considered an area of lower endemicity, prevalence was 16.1-21.5% (31).

*The mothers*

Commonly, a heavy parasitaemia of the placenta with an absence of fever and a negative peripheral blood in mothers was noted. Also, if dual parasitaemia existed, these were usually heavier in nulliparous women, who were often younger and possibly could not have acquired as much immunity as their older counterparts. In some studies, rates of parasitemia generally have been found lower in urban residents, in which areas malaria transmission may be less common, and access to hospital care may be utilized (26). The season of the year for malaria transmission has been investigated, some authors often found the wet season to be the danger period, others have found no difference in transmission between the dry or wet season. Other studies included mainly haematological investigations (26) or only examination of placental sections in women farmers (35a). Some included data on morbidity and mortality rates in mothers, fetuses, or neonates. The main area of agreement in all these studies was that infants born to mothers with infected placentas, especially in the first parity, gave birth to smaller babies, but little data on the whole was given to the nutritional status of mothers or further anthropometric measurements of the dyad.

To this end, the present author undertook a study at Makerere University, Kampala, Uganda to investigate the differences between prematurity versus the "small size for gestational age" of infants born of mothers with a placenta positive for malarial strains. As with many studies undertaken in overcrowded maternity wards, lacking staff and many facilities, such as a minimally well-equipped laboratory, lacunae existed in the project undertaken over a year, including both the wet and dry seasons (31). All examinations of mothers for clinical signs of nutritional status, anthropometry of mothers, neonates and placentas, haematology, for malaria identification in mothers, infants, and placentas, and questioning of mothers regarding medications taken, diet, etc, were undertaken by the author. Data regarding gestational status were obtained by reviewing the obstetrical case sheets filled in by the medical officer in charge of the patient.

*The sample*

This was a convenience sample as homogeneous as possible. Women in the project were all wives of small farmers or slum-dwelling labourers, 64% of the women were Baganda, the remainder represented 12 different East African tribes who had been resident in Uganda for several years. By WHO criteria, Kampala at that time was considered to be an area of low endemicity and resistance to antimalarials as yet had not been noted.

*Exclusion of factors stated to have an impact on birth weight*

As many as possible of these were investigated. For example, all mothers below the height of 150 cm were excluded, as were women with sickle cell anaemia or other known genetic variations, toxaemia, hydramnios, and also rest taken in pregnancy because of specific health reasons. Many of the more difficult conditions to ascertain, such as occasional viral or bacterial infections, or esoteric ones such as uterine deformities or heart size were not known. However, the 630 women in the initial sample who were in their third trimester of pregnancy, stated they would work until term if possible. Smoking and drinking were stated to be uncommon; each woman was also questioned on the subject of recent febrile episodes and if malarial prophylaxis or treatment had been taken. Although the answers were not always convincing, as the women were unaware of the names or nature of drugs they may have received early in pregnancy, only those who had been afebrile and whose case history showed no prescription for antimalarials were included in the sample. The altitude in Kampala was not conducive to lowering the birth weight (1300 m) as in more mountainous regions.

*Nutritional information*

Mothers did not state if they restricted their diet intentionally, in order to have an easier delivery. The usual meals consisted mainly of *matoke* (steamed green plantain), beans, and various relishes, with at times, animal products, such as meats, if they were affordable although some food proscriptions were known to exist, such as eggs and chicken and possibly other foods were not eaten. On examination, none of the women appeared clinically malnourished. The mean weight and height level for both Baganda and non-Baganda women fell within the WHO desirable range (35b) as judged clinically, 4.0% of them had a poor musculature but 1.2% could be considered obese, 15 women had a mild follicular keratosis, one had evidence of glossitis, and two enlarged parotid glands. No gross oedema of the extremities was noted, nor other possible nutritional stigmata were seen. There were no significant differences in maternal weights, heights, or incidence of minor nutritional deficiencies among the two tribal groups. Studies among women in the homes of a similar socio-economic group, using a 24-hour questionnaire and food consumption study (personal communication, Rutishauser 1965) had shown that the daily protein intake varied from 34 to 75 g of protein, obtained mainly from plant sources, and dietary energy varied from a low 1704 to 2590 kilocalories. The weight gain of the women in pregnancy was not known, but in many Third World countries weight gains are often of the order of 5-7 kg for the whole period of gestation. Some women even gain no weight, or may lose weight (35b).

*Blood examination*

Neonates and mothers. A thick blood film was taken from the peripheral circulation of both mother and child between the first and 22 hours after delivery. Placentas. Two thick films were taken from the placenta as follows: (1) a superficial incision was made and a smear taken from the maternal surface; and (2) a deep incision was also made between the maternal and fetal surfaces centrally and the blood was removed by pipette for the preparation of thick films. The umbilical cords. Each cord was incised at 6 in (15 cm) from its place of attachment and another thick film was made. All blood films were stained with Giemsa. Anthropometric measurements in infants were analyzed by sex and birth rank and included weight, birth length (crown heel), head, chest, and mid-arm circumferences, subcutaneous triceps skinfold, and mean arm muscle circumference, and mean fat weight/ratio.

*Results*

Of the 630 women initially in the study, 60 of them were not included in the final analysis: 15 women delivered stillbirths; 38 women aborted; and 7 women delivered of twins. The pathological causes of the stillbirths and abortions were not known. The remaining 570 women were delivered at term of singleton babies, but 29 required a caesarian section. The gestational age was presumed to be approximately correct to according to fundal height measurements and obstetrical observations. However, mothers were not always sure of the exact date of the cessation of their menses. The analysis was undertaken for all 570 women, neonates, and placentas, but also the sample was desegregated into Baganda and non-Bagan.

Results are summarized in the tables. In Tables 1 and 2 the prevalence of malarial infections are recorded as well as the comparative weights of babies with infected and non-infected placentas. In Tables 3, 4, and 5 the prevalence of low birth weight among full-term babies is shown as well as the weight of babies by sex and birth rank. Table 6 illustrates the lighter birth weights in neonates born with placentas infected with a heavier density of *P. falciparum* which showed on microscopy a culture-like appearance seen in cerebral malaria, heavier birth weights are noted in mixed infections of *P. falciparum* and *P. malariae* which was relatively common in Uganda (37), and also with *P. malariae* alone which contained fewer parasites, but a considerable amount of very dark pigment. All the placentas with pigment alone indicated evidence of a massive recent infection.

*Small for dates infants*. In recent paediatric practice certain reference data are used to assess whether an infant can be termed undersized and not premature. The only measurement that was unaffected in these series of babies was the subcutaneous fat fold, no satisfactory explanation can be given for this finding.

In Table 7 selected standards anthropometric criteria were used to assess the percentage of undersized babies with infected and non-infected placentas. Babies in the infected category demonstrate diminished anthropometric measurements. Various ratios of weight for height have been suggested as more correctly reflecting the body proportions of young babies. For the newborn the Rohrer's Index (RI) or Ponderal Index (38, 39) is still

commonly used. In this the formula, Weight (g)/Length (cm)3 X 100, is employed to categorize neonates who are who are under or overweight for length. Babies in the study were categorized as such between 1 to 22 hours after delivery (mean time, 5 hours). Suggested levels for the following categories are obese >2.93, moderately obese >2.85-2.93, malnourished (moderately malnourished) 2.32-2.26, and severe malnutrition <2.26. In Table 8, results demonstrate that these babies are or have a low birth weight for gestational age.

*Possible reasons for low birth weight in placental malaria.* Many factors may be involved in the lowering of birth weight including specifically factors that may interfere with the nutrition of the fetus. Garnham, in his detailed work on placental malaria stated in 1938-39 that "in certain stages of malaria the intervillous spaces, which should contain nothing but blood, are almost a solid mass of reticuloendothelial cells, and it is difficult to understand how the fetus is nourished" (36). The mystery is still unsolved. However, when the metabolic needs of the parasites are considered, glucose, levulose, maltose, and glycerol are oxidized by the parasites, and riboflavin, calcium pantothenate, biotin, folic acid, as well as oxygen are among the substances required for their growth and survival. The fetus is also competing for supplies of all these nutrients, e.g. glucose, as a source of calories, as well as oxygen. Studies on oxygen requirements of the fetus and placenta have been estimated by Hytten and Leitch (36) to be at term 12.5 ml per minute for the fetus and 3.7 ml for the placenta.

The carrying capacity of oxygen in the non-anaemic mothers has been calculated. However, the severity of anaemia, which will also depend on parasite density, makes one wonder to what degree of anoxia some fetuses may be generally exposed to in an anaemic mother, with heavy placental parasitization. Because of practical difficulties in this study, anaemia could only be detected by clinical signs, especially the conjunctival pallor which when observed did not indicate severe anaemia. Such moderate pallor was noted in 58% of women among 62.2% of whom had infected placentas. Also the nutrient needs in this study of microfilariae (*W. bancrofti*) found in 4% of the placentas would also have to be considered (37).

*Placental weights.* One hundred unselected placentas were weighed, of these 13 were found to be parasitized, although no significant macroscopical differences were observed, between infected and non-infected. The mean weight of the former was 45.3 g less. Uncertainty exists regarding the hypothesis that birth size generally may be limited by placental size, but probably the major changes occurring in parasitized placenta could be an exception to the rule (36).

*Milk and malaria.* Controversy has existed for several years regarding the role of the amino acid, para-amino benzoic acid (PABA) and the decrease in the multiplication and growth of malaria parasites. This has been shown in experimental animals in which malaria immune bodies can be transferred to the offsprings via breast milk. The situation is not clear as yet for human infants. PABA in breast milk is low, usually sufficient folic acid exists for the infant to utilize, but the malarial parasite must synthesize folic acid for its own needs from available PABA, when fed dried milk or breast milk. The need to observe densities of

parasites in very young infants suffering from malaria is important, as to date only suppression of infection, not prevention is believed to occur (40).

**Specific hazards of malaria in pregnancy**

*Fetus and newborn*

*Fetal mortality.* Precise data, regarding "reproductive wastage" is generally unknown, it has been found to be common in epidemics of malaria. It appears to vary inversely with the level of tolerance to the disease at the community level (15, 41). Some workers consider the subject to be anecdotal; others, because of the difficulty of assessing gestational age, include abortions and stillbirths together and report no association can be made with fatalities such as stillbirth rates and malaria (42). With a low community tolerance, a high fetal mortality, has been stated to occur with a concomitant elevated total and free serum concentrations of cortisone in pregnancy, also in acute episodes of malaria, placental insufficiency may occur, but signs of fetal distress may not always be sought for. A relationship between pyrexia and abortion in malaria has been debated, some workers have attributed stimulation of the metabolism of prostaglandins could promote abortions (43).

However, very commonly case histories do not always reflect an accurate health profile of mothers attending clinics late in pregnancy with fever or with some distant memory of untreated febrile episodes, which could be associated with many other types of infections, including malaria. In the present study a rate of 6.0% of abortions prior to the 7th month of gestation was found in the total sample of 630 women. The subsequent examination of 119 aborted placentas (ages 6-7 months) revealed parasitaemia in 15% of them, one of which was heavily infected with microfilariae. Garnham (1938), stated that prior to the 4th month of gestation despite heavy infections with *P. falciparum* in the peripheral blood, post ring forms could not be detected (44). The debate concerning the role malaria plays in stillbirth rates on-going for at least seven decades continues. The rate has been found to be higher in babies with malarial placentas. In the Ugandan study (31), the rate was 2.4% among the infected group, and another infant died within 1 hour of birth. Personal review of records of autopsies undertaken at Mulago Hospital (1953-1964) showed malarial pigment in the liver and spleen in only 1 out of 99 babies dying immediately after birth. In Zimbabwe (1981) of 61 gravid women admitted, presenting with over a period of 2 years, 39% aborted, 3.3% delivered stillborn babies (45). It can be argued that stillbirths and deaths within 1 hour or the first week of life, are also seen in babies with parasite-free placentas, and the causes of death are often unknown. Under the frequent unsatisfactory conditions existing in overcrowded clinics and maternity wards, a realistic conclusion to the extent of fetal damage cannot be reached. It is possible that the rise in "birthing huts" and "waiting homes" for "at risk" mothers in the third trimester which are close to better-staffed hospitals may decrease the mortality of mothers and their fetuses.

*Congenital malaria.* This condition has been reported to be rare, but a clear definition must be given in the presence of parasites in fetal or neonatal circulating blood. It may be increasingly possibly in areas of unstable malaria or due to the ineffectiveness of malarial drugs given to infected mothers, but it is necessary to examine both the cord and neonatal

bloods. Emphasis has been centred in the past mainly on case reports from Africa, in recent years data from parts of Asia, South and North America, the Pacific Rim countries, and recently from Europe, have been available. The mechanism of transfer across the placenta still remains obscure. In a review of this condition in 16 African countries between the years 1915 and 1972 in a sample of over 50 women, 22% of whom had infected placentas, only 16% of cords were positive (45). In Tanzania, a low density cord blood infection was found in 3.5% of newborn, in contrast to the Ivory Coast in which an incidence of 21% was recorded (43). In the Ugandan study (36), two cord bloods were infected with *P. falciparum* resulting in one baby whose placenta was small, dark in colour and ragged, and had a positive parasitaemia 2 hours after birth. Despite examination of 500 fields, the other baby at 20 hours after birth had a negative blood film. In a further two cords infected with microfilariae, the neonatal bloods proved negative (36). In Mexico, infection was found in only one twin who was successfully treated with chloroquine, the mechanism of protection of the second twin has been debated (48).

*Possible method of transmission to the fetus or neonate.* Parasites in the cord may not be demonstrated in the infants blood, likewise, neonates may be asymptomatic, even if the mother's placenta and blood are positive. Mothers can transfer malaria to the fetus prior to the onset of labour, transfer of some maternal erythrocytes across the placenta can happen in normal pregnancies, and in malaria the same process occurs but with infected red cells crossing into the fetal circulation (co-natal infection). In non-immunes, there may be a breakdown of the placental barrier. Infections in the fetus may be transmitted during delivery if the placenta is damaged or the skin of the newborn has been scratched or wounded permitting transmission. All species of parasites can cause disease in neonates, but congenital malaria has been noted with no evidence of placental damage or of clinical malaria in pregnancy (43, 46).

Many hypotheses have been raised, whether parasites in the cord are neutralized, remain at a low level until birth, when the baby is exposed to biological and environmental changes which permit proliferation or parasites, simulating possibly, at a later date, what may be thought to be a post-natally acquired infection due to mosquito exposure (43). Infants with both cord and peripheral blood infections with *P. falciparum* have been shown to clear their infection within 48 hours post-partum (Steketee RV, personal communication 1991). Protection afforded the fetus and new born baby is mediated by a number of factors such as: (1) importantly, the maternal passive transfer of antibodies; and (2) the role of three haemoglobins - (a) fetal haemoglobin (HbF) retards the growth of parasites and its presence in red blood cells seems to inhibit invasion by *P. falciparum*, (b) abnormal haemoglobin in the sickle cell trait and G6PD deficiency, (c) in *P. ovale* infections, higher rates of ovalocytosis protect in part, against *P. vivax* and *P. falciparum*, (d) the role of the placenta, which when uninfected can be an important site of local antibody formation, because of heavy infiltration with lymphocytes as it forms part of the reticuloendothelial system. Parasites in infected placentas may assist in lowering cord blood levels, due to absorption in sufficient amounts of enough antibody (14), (e) PABA in breast milk may assist in decreasing multiplication and growth of parasites (40), and (f) the role of the spleen (15).

Despite the commonness of low birth-weight babies in placental malaria, many of whom are below 2500 g, in many countries the criterion for survival has changed as babies

above a 2000 g weight with a good sucking reflex are deemed sufficiently mature to be discharged from the hospital, the cost of nursing less fragile babies, and release of cot space are important advantages, as well as not separating the dyad.

*Clinical diagnosis of congenital malaria (24)*

In view of the rapid spread of the disease at the global level, health professionals should be knowledgeable in this area. The classical signs include an incubation period of 9 to 30 days which is consistent with an infection occurring after delivery. The signs and symptoms vary from those seen in older children and adults; fever is usually present. The infant is restless, drowsy, and does not feed normally. Bouts of vomiting, diarrhoea are frequent, and the baby may be pale and cyanosed. Hepatosplenomegaly and jaundice will be present, and careful history of the mother should be taken regarding her possible recent exposure to malaria. As *P. vivax* and *P. malariae* can be the cause of the disease, it must be borne in mind that no exoerythrocytic stages exist in congenital malaria caused by these agents. Thus treatment must be carefully reviewed.

*Other hazards in malaria in pregnancy*

*Maternal health.* In *P. falciparum* malaria, reference is commonly made to severe and complicated malaria. The virulence of this type is well known with the highest mortality occurring in children between 1 and 3 years. The loss of immunity in pregnant women has been shown to vary because of a number of factors already described. All pregnant women are an at risk group prone to certain complications, which may present with some different features.

Criteria of severe disease in falciparum malaria have been defined by WHO as follows: (1) cerebral malaria (unrousable coma); (2) severe normocytic anaemia; (3) renal failure; (4) pulmonary oedema; (5) hypoglycaemia; (6) circulatory collapse, shock; (7) spontaneous bleeding/disseminated intravascular coagulation; (8) repeated generalized convulsions; (9) ascidaemia/acidosis; and (10) malarial haemoglobinuria. Other manifestations include: (1) impaired consciousness but rousable; (2) prostration, extreme weakness; (3) hyperparasitaemia; (4) jaundice; and (5) hyperpyrexia. Because of the complex features which arise in severe *P. falciparum* malaria in practical work, the list of manifestations needs to be considered in a sequence symptoms, signs, laboratory tests. A brief description follows of some manifestation which may be encountered in pregnant women.

*Cerebral malaria.* This condition is associated with *P. falciparum* and is a frequent cause of mortality in pregnant women. It may develop early or over a few days (43). Manifold symptoms have been noted, with high pyrexia, headaches, drowsiness and convulsions, hallucinations, delirium and coma, which has been defined as rousable or unrousable. Much controversy has arisen over these definitions and the interpretation of the results of a number of tests (43).

In recent years attention has focused on the role of the cytokine tumour necrosis factor (TNF) which appears to be produced by T cell lymphocytes and activated

macrophages. Both in vitro and in vivo studies have been undertaken. The level of TNF has been found to be increased in patients with hypoglycaemia and in those with cerebral malaria. It is possible that this cytokine may have beneficial effects in enhancing immune response and may provide some defense against infection, but in falciparum malaria it may have equally deleterious effects, because TNF concentrations have been significantly associated with more severe disease and deaths (24, 43, 53).

*Anaemia in pregnancy*

*General considerations.* The commonness of anaemia in pregnant and lactating women is well known as it is derived from a number of interacting factors, diet, absorption of nutrients, food taboos in the active child-bearing period, poverty and lack of practical health and nutrition education etc, but the importance of malaria is not stressed sufficiently. Routine supplements of iron and vitamins offered to them have provoked many controversies including the possibility that iron and vitamins may increase parasitaemia (4, 51). The highest mortality is attributed to malaria as it invades both young and old red blood cells, as well as causing dyserythropoetic changes in the bone marrow and the severity of infections with this parasite must be given stronger emphasis.

*Definition of severe anaemia.* A normocytic anaemia with a haematocrit of $< 15\%$ or haemoglobin $< 5$g/dL associated with a parasitaemia of more than 10,000/ul (iron deficiency and thalassaemia/haemoglobinopathy must be excluded in the presence of hypochromic or microcytic anaemia (43). Severe manifestations and complications of *P. falciparum* malaria are well described in several texts (43, 50). The degree of anaemia is often linked with the degree of parasitaemia including, schizontemia, and both creatinine concentrations and total serum bilirubin (24). In pregnant women, retinal haemorrhages (34), which are now thought to be a prognostic sign of cerebral malaria, are seen in anaemia, as in jaundice, and sudden and severe drops in haemoglobin levels. The woman is also at risk of many opportunistic infections, e.g. meningitis, pneumonia, and urinary tract infections (43).

Acute renal insufficiency may also occur in pregnant women with heavy parasitaemia, this condition may lead to anuria, which will require some form of dialysis and the prognosis is usually poor (24).

*Acute pulmonary oedema.* This condition may present in pregnant women on admission, or after some days of treatment, or commonly post-delivery in women with a positive fluid balance. The earliest clinical sign is an increase in respiratory rate prior to other chest signs. If no radiological services are available, a mistaken diagnosis can be made. Hypoxic patients may die very rapidly from convulsions and loss of consciousness.

*Hypoglycaemia.* Often common and has been associated with the use of quinine which causes hyperinsulaemia. Nowadays the drug is used frequently, as available alternatives have become parasite-ineffective or dangerous for mother and fetus, or are under trial. Despite its reputation as a possible abortifacient, the balance of risks is in favour of preventing death in the pregnant woman. Hypoglycaemia has been shown to develop in some studies in 50% of women with cerebral malaria, and high rates were also found in other pregnant women with

severe malaria. However the condition has also developed in women to whom quinine was not given (43). In pregnant women, the condition may be asymptomatic, but it can be associated with fetal disorders, bradycardia, and fetal distress. In the severely ill patients, lactic acidosis may be present often with a fatal outcome. Physicians must be aware that gravid women, commonly asymptomatic, may display certain features which mimic manifestations seen in cases of cerebral malaria, e.g. erratic behaviour, sweating, sudden loss of consciousness. In hypoglycaemia, the blood concentration is defined as less than 40 mg/dL. In order to exclude a wrong diagnosis, blood sugar evaluation must be undertaken such as blood dip stick methods, or therapeutic tests giving an intravenous infusion of 25-50 $cm^3$ of 50% dextrose, and good results have been noted in patients with cerebral malaria. Unfortunately severe relapses are problematic as intravenous infusions cannot be repeated as these could result in circulatory overload and hypokalanaemia. Unconscious patients may be fed glucose solution via a nasogastric tube (49).

*Malarial haemoglobinuria (Blackwater fever).* This condition has not been reported as frequently as in past years, when typical cases of the syndrome were found among expatriates who took irregular doses of quinine for bouts of fever. The pathology was unknown, but it was also noted occasionally among indigenous children and pregnant women, whose immunity to *P. falciparum* was probably low. The sudden onset of the disease is accompanied by an acute extravascular haemolysis and by haemoglobinuria and haemoglobinaemia, with a scanty parasitaemia. Among many signs which are present, the cardinal one is the colour of urine which is almost black. In recent years, if haemoglobinuria is observed it is usually attributed to G6PD or other enzymatic disorders, or particularly to the oxidant effects of some antimalarial drugs (15, 43). But with the advent of the renewed use of quinine as an antimalarial, pregnant primiparous women may take irregular doses of quinine and a resurgence of the disease may be seen.

*Prophylaxis and drug treatment for malaria in non-pregnant women*

The status of prevention of malaria and treatment of the disease is in a state of crisis. For many years, resistance to a number of drugs has been recorded. In the past decade, resistance is becoming practically worldwide to well established drugs as well as new ones and combinations of drugs. Some countries have established guidelines for travel to different regions of the world. The knowledge of pharmokinetics, especially safety and possible side-effects is vital, as is the compliance of each individual traveller (8). In 1989, some data were available regarding chloroquine resistance and multiresistance in four world regions by country - the Americas (10), Asia (15), Africa (31), Oceania (3). Resistance to the drugs was moderate or high, and varied in countries and regions of countries and island nations (55). The following categories of drugs are in use or undergoing trial, but the main emphasis is placed on effectiveness of drugs in *P. falciparum* infections: (1) cinchona alkaloids - quinine, quinidine; (2) 4-aminoquinolines - chloroquine, amodiaquine; (3) 4-quinoline methanols - mefloquine; (4) 9-phenanthre-methanols - holofaritrine; (5) acridine derivatives - quinacrine, pyronaridine (under evaluation); (6) ouinghaosu and derivatives - artemisinin, artemether, arteether, artesunate; (7) DHFR inhibitors - pyrimethamine, proguanil and analogues, cycloguanil, trimethoprim; (8) other antibacterial drugs - tetracycline, sulpha drugs, clindamycin (54).

Each group of drugs must also be considered for their functions as blood or tissue schizonticidal activity, either suppressing the disease by destroying asexual blood forms or preerythrocytic intrahepatic forms. In vivo resistance to normal doses of chloroquine has been graded by WHO as: RI parasitaemia - reappears 1 to 3 weeks after termination of treatment; RII - decreases with treatment, but does not disappear during the first week of treatment; RIII - no decrease or increase in parasitaemia during the first week of treatment. The probable reasons for this resistance have been attributed to: (1) drug pressure selecting pre-existing mutant strains; (2) the intensity of transmission perpetuates the problem; and (3) resistance is maintained as non-immune individuals become infected and continue the disease cycle.

Resistance to other drugs such as sulphadoxine-pyrimethamine has spread into areas of chloroquine insensitivity, e.g. South America and Eastern Asia and some East African countries, resistance to mefloquine is increasing, e.g. Burma, Thailand (1), and some African countries "without pressure." Isolated cases of quinine and amodiaquine resistance have been reported (4).

*Prophylactic and therapeutic drugs in pregnancy.* For many years, an information gap has existed regarding the suitability of drugs for this special group including effectiveness, side-effects in the mother, and teratogenicity in the fetus. Because of increasing insensitivity of *P. falciparum* to a number of drugs, new compounds have been under trial for a number of years, and conflicting reports from animal studies regarding safety, have promoted necessary caution in the needed release of positive information. A recent review by WHO, which has taken into consideration many cultural socio-economic problems and the settings in which information and drug distribution are given, has revealed the suitability of only two drugs, chloroquine (which does not cause hypoglycaemia) and quinine (50). In situations in which low birth weight, and severe parasitemia and fatal complications are known to occur in *P. falciparum* infections, specific recommendations have been made that weekly prophylaxis with chloroquine, given in a safe suppressive dosage should be instituted in areas in which it remains effective. This poses a conundrum. In some discrete studies, reported improvement in haemoglobin levels and decreased parasitaemia were noted, even in the presence of chloroquine resistance. Other workers remain sceptical about the dosage recommended and compliance of African women, as the bitter taste of the pills, the intense pruritus, unrelieved by antihistaminics, may make prophylaxis unacceptable, especially if the benefits are slight because of high drug insensitivity (56). Quinine has been used mainly as a therapeutic drug. Other compounds have a well-proven record of toxic side-effects and are no longer used in pregnancy (50). In view of the precarious reliance on only two drugs, on-going clinical trials using mefloquine have been instituted, despite resistance and side-effects. In one study, with a small sample size undertaken in Thailand, it appeared to be a safe therapeutic drug, to be used if no alternative was available, in the first 12-14 weeks of pregnancy because of danger of teratogenicity in the fetus (50).

*Continuing research for safe effective compounds.* The mechanism of chloroquine resistance has recently been shown to result from efflux of the drug from parasitized cells preventing toxic build-up in the cytoplasm of parasites and substances have now been

identified which in combination with chloroquine could reverse resistance: (1) calcium channel-blockers, such as veramapil, an achlorpromazil analogue, and a tricyclic antidepressant drug, desipramine, have all been used in animal studies. Careful studies of the toxicity of these compounds used alone or in combination with chloroquine are continuing prior to trials with human subjects (50); (2) use of artemisin and its derivative. Quinghaosu, which is a phytodrug derived from the antimalarial principle obtained from *Artemisia annua* (a fern known as sweet wormwood, etc) has been used successfully as an antimalarial in China for 2000 years successfully and derivatives of the drugs have been developed artemisinin suppositories, artemether for intramuscular injections, artesunate which can be used intravenously, and in the form of tablets. Toxicity assessment has not been adequate for these drugs to be acceptable outside of China. But these compounds have been shown to be fast-acting, effective in the treatment to resistant strains of *P. falciparum* and well tolerated. A carefully conducted study in China in six malarious pregnant women treated with artemether, showed only one relapse in one woman with *P. vivax* malaria, but none in two patients with *P. falciparum*. A follow-up 5 years later, of the children, showed no signs of congenital deformities (57). Other compounds continue to be investigated and research on a suitable malaria vaccine is still under development.

*Comprehensive preventive programmes.* Other malarial control measures. No single approach will protect the over 2.1 billion people at risk of malaria in the 1990s, 2/3 of whom will be mothers and their young children. Although through the health services patients may be correctly diagnosed, advised on the use of prophylactic drugs or receive treatment, little will be achieved if other complementary measures both at the household and community levels are not integrated through the following means: (1) home and environmental management and destruction of adult vectors such (a) use of mosquito repellents in the home, especially of pyrethroid impregnated bed nets (58), which appear in Papua New Guinea to have reduced malarial mortality in children 1-4 years by 63%, other researchers have claimed equally high benefits. Impregnated curtains are also useful, as are topical applications with repellent insecticidal bars, or DEET, and use of soaps containing permethrin, or sprays, and the use of window and door screens is valuable; (2) Reduction of breeding sites, destruction of larvae: (a) prevention of water collecting sites, e.g. water drums, pots, ditches, careful planning of urban or rural development projects, and environmental management. A need for linkages between all actors is vital; (b) use of biological control. Larvicidal fish, such as *Gambusia affinis* and other species have been used and spore-forming bacteria such as *Bacillus thuringiensis israelensis* (Bti) are also important in destroying a number of mosquito species. The product Bti has been used for large scale control in some countries e.g. the USA, in which crops, such as rice are grown, but its cost may be too prohibitive for many less affluent countries. If possible the use of integrated control measures are preferable, to be successful, epidemiological data on the prevalence of malaria, species of vectors, and ecological factors in areas in which such a program would be undertaken must be known.

The successful global malaria eradication plan by the World Health Organization launched in 1957, which was based on vector control with indoor spraying with DDT, and the use of chloroquine to protect and prevent malaria has gradually fallen on hard times. Such calamities as the energy crisis in the 1970s, the increasing resistance by plasmodia to a

number of drugs and vectors to insecticides used mainly by the agricultural sector, seeking to feed increasing populations precipitated its near demise. Many of the excellent vertical malaria programs well-staffed with trained multidisciplinary workers have often fallen into desuetude, replaced by malaria control programs no longer-time limited requiring, even more funding in the 1990s, but competing demands from other sectors worsens the situation. Two pandemics exist, one threatens all age groups, both in the North and the South, the more insidious and equally deadly one malaria has been forgotten by many, but may be remembered by more in the future unless effective treatment and management are available. Funding for AIDS is more likely to be more plentiful. Probably 800 million malaria infections occur each year and more than a million deaths world-wide. The cost-effectiveness of present malaria prevention intervention programs for pregnant women in these transitional times are difficult to calculate as the usual factors, which are many, must be considered, e.g. compliance of mother, if prophylaxis exists, attendance at clinic, transport, fee for medicines, possibly ineffective, use of bed nets, cost of vector control, hospitalization for severe malaria in childbirth or from cerebral malaria, others, such as seasonal transmission, endemicity of region, etc. In simpler times, the estimated cost of malarial control in an endemic area, inhabited by a population of 1 million people, based on one round of spraying or a single treatment using chloroquine was estimated to be per capita in 1975, USD 0.05, by 1982 USD 0.068 (transport, storage of drugs, cost of salaries, or transport of personnel, not included) (15). In 1990, the cost of one treatment for a 60 kg adult using 150 mg tablets of chloroquine needing 10 units per episode, cost was USD 0.08. If quinine was required, 200 mg tablets, 63 units per episode, cost was USD 1.51. If 300 mg tablets were used instead, and 42 units, cost was USD 1.47 (current international prices) (50).

**Suggested research activities in the prevention of malaria**

In view of the worsening health status in many countries, the continued use of basic and applied research compatible with the more limited funding available is required. The following are tentatively suggested:

*General*

The need exists for a multidisciplinary task force or subcommittee on the "Prevention of malaria in pregnancy and materno-fetal hazards." Members would include, professionals from the field of health, nutrition, pharmacology, molecular biology, genetics, social sciences, agriculture, representatives of drug companies among others.

*Specific*

Definitions to be included in the international nomenclature of diseases (WHO): placental malaria and congenital malaria. The use of essential drugs (WHO 1985): "Model list of drugs for primary health care," should include as well as chloroquine, possibly quinine depending on the method of distribution, with the added notation (safe for pregnant women if used in the recommended dosage).

*Immunological studies*

Continued research on: (1) new strategies for vaccine design, in view of the unexpected potential for antigen polymorphism in malaria; (2) molecular genetics of drug resistance, to improve the use of existing drugs and new genetic mapping; (3) the role of free oxygen radicals in malaria, it is believed they may play a part in the rapid antimalarial activity in quinghaosu; (4) the role of cytokines, as well as TNF in severe malaria; (5) the mechanism involved in uncomplicated and cerebral malaria which is reported to produce high levels of serum ferritin; (6) excretion of quinine and chloroquine in breast milk in relation to dose/related intake of the drugs in neonates and older infants.

*Appropriate technology*

(1) Evaluation of the efficacy of the saliva test as a non-invasive procedure to detect compliance by mothers of the use of chloroquine, if culturally acceptable in pregnant women (59); (2) Development of new field assays in malaria, reliable, cheaper and with a longer shelf-life.

*Training*

Suitable modules on malaria with reference to the dangers posed in this disease to the dyad should be prepared to suit the level of sophistication of different categories of health personnel. These should be included in the curriculum of medical students, nurses, agriculturalists, teachers, and community health workers. For illiterate traditional birth attendants, the use of illustrations in booklets or pictograms could be devised, but their pictorial illiteracy must be assessed.

Guidelines must include information in a practical sequence: suggestive symptoms - signs - laboratory tests (if available) - use of appropriate antimalarials according to regulations existing for each cadre of health worker (60).

*Information dissemination*

Use of existing widely distributed newsletters already published, willing to accept including a column labelled "Mothers and Malaria" with the permission from WHO/TDR. This should be written in simple understandable language(s) distributed free to a wide reading audience in developing countries, such as the popular "Mothers and Children" Newsletter (USAID), etc.

*Social marketing*

Development of suitable radio, television spots, videos, dealing with the importance of the attendance of pregnant women at clinics, to receive information, preventive and curative assistance, and be aware of the dangers of this disease in pregnancy (possibly collaboration on these projects between WHO/UNICEF/UNESCO, FAO).

*Determine quality control of laboratories*

At the regional level within the framework of reduced funds.

*Appropriate technology*

(1) prepackaging of clean slides in units of 12 with accompanying disposable lancets could be undertaken centrally for distribution. If careful aseptic techniques are used in operating rooms to prevent sepsis or death equally scrupulously clean slides are essential in identification microscopically of species of parasites and pigment often hidden after staining under layers of dirt, and misleading diagnoses can ensue; (2) information must be given to laboratory technicians for the real need to dispose of "disposable" lancets, and the link which exists with possible transmission of HIV infection; (c) the storage of chloroquine in glass containers needs to be reviewed, because of the reported decrease in the concentration of the drug due to its affinity to bind with glass (61).

*Field studies*

(1) nutrition and malaria. Further double-blind studies need to be undertaken on the relationship between iron supplementation of pregnant women and children with malaria and the possible increase in parasitemia; (2) anthropological studies among pregnant women regarding their knowledge of the causation of malaria, its effect on their health status, on the fetus and neonate, and their attitude toward compliance and use of drugs, the effect on user fees on their behaviour, and the sources from which they may purchase cheaper drugs. Further studies. (1) cost effectiveness studies using statically valid samples among primipara women in 4 WHO regions in areas of stable and unstable malaria, in both urban and rural areas; (2) study regarding the use of indigenous plants stated to be used specifically as a cure for malaria, undertaken together by plant biologist, anthropologist, and indigenous healers, with the possibility in the future to develop phyto-drugs.

*Appropriate technology at community level and income generation*

Use of bed nets. (1) bed frames - local construction of frames made from bamboo or tree poles; (2) develop technology for users of floor mats, instead of beds, to enable them to shelter under a well-secured and safe net; (3) develop a small locally-made net industry with subsidized netting which would provide both employment and income generation.

The implications of low birth weight world-wide are well known, and it has been used for many years as an indicator of social development. All our resources and available information must be used to promote safe motherhood. The present shortage of midwives is much to be deplored (62). If one known cause of low birth weight can hopefully be reduced, emphasis on malaria as a major factor must be widely disseminated to promote improved materno-fetal health and mortality.

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Table 1. Incidence of malarial infection among 570 African women.

| Group | Number | Positive | Percentage |
|---|---|---|---|
| Mothers | 579 | 32 | 5.6 |
| Placentae | 570 | 92 | 16.1 |
| Neonates | 569 (1 died 1 hour after birth | 1 | 0.2 |

Table 2. Comparative weights of 570 neonates in relation to placental malaria.

| Placentae | Number | Percentage | Mean birth weight (g) |
|---|---|---|---|
| Infected | 92 | 16.1 | 2.805 |
| Noninfected | 478 | 83.9 | 3.068 |
| Total | 570 | 100 | 3.025 |
| Difference | | | 0.263 ($p < 0.001$) |

Table 3. Incidence of neonates of low birth weight in infected and noninfected groups.

| Neonates of 2500 g in weight or less | Infected placentae (92) | | Noninfected placentae (478) | |
|---|---|---|---|---|
| | No | % | No | % |
| Total neonates: 66 | 18 | 19.6 | 48 | 10.0 |

Table 4. Weights of males neonates with infected and noninfected placentae by birth weight.

| Birth rank | Infected (g) | Noninfected (g) | Difference (g) |
|---|---|---|---|
| 1 | 2616 (15)[a] | 2929 (52) | + 313 |
| 2 | 2789 (6) | 3040 (43) | + 251 |
| 3 | 2868 (3) | 3083 (56) | + 217 |
| 4 | 2815 (4) | 3173 (46) | + 358 |
| 5 | 3190 (5) | 3145 (24) | - 45* |
| 6 | 2849 (8) | 3268 (42) | + 437 |

[a]Denotes the number of subjects in group.

Table 5. Weights of female neonates with infected and noninfected placentae by birth weight.

| Birth rank | Infected (g) | Noninfected (g) | Difference (g) |
|---|---|---|---|
| 1 | 2497 (10)[a] | 2843 (39) | + 345 |
| 2 | 2869 (12) | 2933 (33) | + 64 |
| 3 | 3074 (11) | 3039 (52) | - 35* |
| 4 | 2790 (8) | 3142 (42) | + 352 |
| 5 | 2978 (3) | 3061 (31) | + 83 |
| 6 | 2721 (7) | 3210 (36) | + 489 |

[a]Denotes the number of subjects in each group.

Table 6. Weight of neonates born from infected placentae with reference to species of malaria infection.

| Infection | Total cases | | Mean birth weight | | |
|---|---|---|---|---|---|
| | No | % | Male (g) | Female (g) | Both sexes (g) |
| P. falciparum | 80 | 54.4 | 2769 (25) | 2720 (25) | 2745 |
| P. malariae | 19 | 20.7 | 2841 (9) | 3100 (10) | 2977 |
| P. malariae + P. falciparum | 4 | 4.3 | 3100 (1) | 2946 (3) | 2985 |
| Residual pigment from recent infection | 19 | 20.7 | 2776 (6) | 2739 (13) | 2750 |

Table 7. Percentage of undersized neonates as judged by accepted anthropometric standards.

| Anthropometric measurements (total no of neonates) | Infected placentae | | Noninfected placentae | | Difference (%) |
|---|---|---|---|---|---|
| | No of neonates | % | No of neonates | % | |
| Birth weight 2500 g or less (66) | 18 | 19.6 | 48 | 10.0 | 9.6 |
| Birth length 47 cm or less (118) | 28 | 33.7 | 90 | 20.1 | 13.6 |
| Head circumference 33 cm or less (199) | 57 | 74.0 | 142 | 43.7 | 30.3 |
| Chest circumference 33 cm or less (37) | 14 | 18.4 | 23 | 7.4 | 11.0 |
| Weight/length ratio 53.2 or less (51) | 12 | 14.5 | 39 | 8.5 | 6.0 |

Table 8. Rohrer' index for undersized infants.

| | Placentas | | |
|---|---|---|---|
| | Noninfected | | Infected |
| Mean weight | 3.068 kg | | 2.805 kg |
| Mean length | 48.8 cm | | 47.5 cm |
| | 2.64 | RI (2.6) | 2.62 |

# Women and Malaria: Social, Economic, Cultural, and Behavioural Determinants of Malaria

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## Summary

This review examines some aspects of the current knowledge on social, economic, cultural, and behavioral factors that are determinants of malaria infection among women in endemic areas. Relevant aspects of the current knowledge on medical factors that are determinants of infection are also examined although the main focus of the review is the social, economic, cultural, and behavioral determinants of infection. Medical determinants are examined since a holistic approach to the problem is desired, and generally social, economic, cultural, and behavioral factors ultimately exert their effect by influencing one or more of the medical host factors or the factors related to the vector, the environment, and the parasite.

Social, economic, cultural, and behavioral factors are examined in their role as determinants of the frequency, severity, and outcome of infection. Not only are various medical, social, economic, cultural, and behavioural factors examined, some of the interrelationships between them are explored. The review also attempts to identify important research gaps and priority issues to be considered in looking at these determinants of malaria infection and its consequences among women in endemic areas.

Though the focus of this review is women, an attempt is made to look at women in the context of their lives as a whole. As such men are not entirely left out since to do so will be to create a biased rather than an objective review. The lives of both sexes are closely interwoven and dependent on each other. Moreover, comparisons between men and women within the same region, country, or community yields information that cannot be obtained from looking at either group entirely separately. Women for the purposes of this review include adolescent girls (defined as age 10-14) and adult women (defined as age 20+).

## Introduction

### Malaria as a public health problem

In terms of world wide distribution (1), as well as numbers of people affected, malaria is a public health problem of immense proportions. According to 1988 estimates, there are about 100 million malaria cases in the world each year (2). Of a total world population of 4818 million, some 2316 million (48%) live in areas where antimalarial measures are carried out. Another 405 million (8%) live in areas where no specific measures are undertaken to control malaria transmission, and where the prevalence of malaria remains virtually unchanged (3).

Apart from the immense morbidity caused by malaria, and the chronic drain on the health of people living in endemic areas, there is also a high mortality. In areas of unstable malaria, mortality is high among all sectors of the population during epidemics. In areas of high endemicity on the other hand, it is the non-immune such as children, or those with diminished immunity complicated by other factors such as anaemia, e.g. pregnant women, who hear the burden of mortality.

The situation is complicated further by the continuing difficulties of malaria control. These difficulties exist in spite of the fact that the technical know-how for control has been available for over 50 years now. In the 1950s and 1960s, there was a worldwide move toward eradication. Some countries were successful. However, in many parts of the world such as sub- saharan Africa where the problems of malaria are greatest, eradication was just not feasible in spite of the technical know-how being available. Among the problems identified, poorly developed basic health services were and continue to be a problem in these areas. Another major problem was and still is, increasing resistance both of the plasmodium and the mosquito to the drugs and chemicals arrayed against them (4, 5). Reported plasmodium resistance to chloroquine is now quite extensive (6).

## The need for research

Worldwide the current approach to the malaria problem is one of malaria control as part of primary health care. Such control must of necessity be envisaged as indefinite in time given our current state of knowledge and the problems already discussed. As such, there is increased recognition of the need for more research into various aspects of malaria as a part of the search for effective and sustainable ways of dealing with the problem.

Control methods need to be selected giving consideration to what has been termed as "the epidemiological approach in its broadest sense" (4). There is a need for research into what has been until recently a fairly neglected area: the sociocultural and behavioural determinants of malaria infection, and combined biomedical and sociological approaches to control (7). The purely technical and biomedical view of health used in looking at parasitic diseases such as malaria is being dropped with the realization that "the prevalence of infection or disease in a community is the outcome not only of exposure and host susceptibility but of social vulnerability" (8) and that "if we search for those things which affect health, we soon find a number of factors which are not commonly thought of as contributing to health or illness. Increasingly it is recognized that our health is affected by the circumstances of our lives: environmental and living conditions, resources and life styles, as well as the political and economic realities" (4).

All possible determinants of the malaria situation need to be considered. The social, economic, and cultural context in which infection occurs plays just as vital a role in transmission as the biological and medical factors.

## Women and malaria

There are sex differences in the epidemiology of many diseases. Quite apart from inherent genetic differences in the response to the infection, which may or may not exist,

there are the external environmental, social, economic, cultural, and behavioural factor which can affect disease transmission, severity, and effect. It is especially important to look at the sexes together as well as separately when we start to take a closer look at the influence of the social, economic, and cultural environment in which disease transmission occurs. Social, economic, cultural, and behavioural influences often differ between men and women. An accurate knowledge of these differences and the reasons for them is important in selecting appropriate interventions. Not much investigation has been done to date on the differences if any in malaria transmission between men and women. The exception to this is studies into malaria infection in pregnancy. Even this is perhaps so because men do not get pregnant rather than because women were being looked at as a special group. There is currently no reason to suppose that there are no other sex differences as well as special risk factors for women worth investigating in looking at determinants of malaria infection.

**Summary of this review**

This review will highlight some aspects of the current knowledge regarding social, economic, cultural, and behavioural factors which are determinants of malaria infection among women in endemic areas. A summary which will not be exhaustive, of relevant aspects of the current knowledge on medical factors which are determinants of infection will be done initially since generally, social, economic, cultural, and behavioural factors ultimately exert their effect by influencing one or more of the medical host factors; or the factors relating to the vector, the environment, and the parasite.

Social, economic, cultural, and behavioural factors will be looked at not just from the point of view of determinants of infection transmission, but also as determinants of the frequency, severity, and outcome of infection. Not only will various medical, social, economic, cultural and behavioural factors be examined, some of the interrelationships between them will be explored.

Though the focus of this review will be women, an attempt will be made to look at women in the context of their lives as a whole. As such, men will not be entirely left out. To do so would be to create a biased rather than an objective review because the lives of both sexes are closely interwoven and dependent on each other. Moreover, comparisons between men and women within the same region, country, or community yields information that cannot be obtained from looking at either group entirely separately. Women for the purposes of this review will include, adolescent girls (defined as age 10-19) and adult women (defined as age 20+).

In the process, this review will attempt to identify important research gaps and priority issues to be considered in looking at major determinants of malaria infection and its consequences among women in endemic areas.

**Determinants of malaria infection**

Malaria infection whether in men or women, is determined by a complex interplay of factors. At the centre is the basic medical and biological tread of man the host, the mosquito the vector, and the plasmodium the parasite. A transmission cycle of "parasite in man" to "parasite in the mosquito" keeps the disease going. These three central biological and

medical determinants: man; the mosquito; and the plasmodium are interrelated within the context of the environment. The environment plays a vital link in ensuring the continuity of the disease cycle; and includes the social, economic, and cultural as well as the physical environment.

The physical, cultural, social and economic environments can be looked at as a second level of determinants of malaria transmission. These are described as a second level of factors, not in the sense of being of secondary importance as determinants of the malaria problem. They are a second level in that they ultimately exert their effects through their influence on the biological and medical factors. In actual fact, all these determinants of the problem are of equal importance in their different ways. The biological and medical determinants of infection do not exist in a vacuum. They are inextricably linked with the environmental factors. Ultimately no factor whether classified as direct or indirect is really independent of the other. They all interact and influence each other to produce the final effect in men or women - the disease and its consequences. These interrelationships are summarized in Fig. 1.

## Medical Determinants of Infection

Host medical factors which act as determinants of infection frequency, severity, and outcome include: sex; age; immunity; polyparasitism; pregnancy; genetic factors; nutrition; and anaemia.

### Sex

A study on the epidemiology and control of malaria carried out in Garki in Northern Nigeria from 1969 to 1976 looked at differences in malaria epidemiology between males and females at all ages. It was found that after 5 years of age, males had rather consistently higher average parasite rates and densities than females. Several of the differences were statistically significant, e.g. the difference in crude *Plasmodium falciparum* prevalence in the age groups 9-18 and 19-28 years. Furthermore, not only did females have somewhat lower parasite rates than males, but they also had higher levels of immunoglobulin M (IgM) and indirect haemaglutination antibodies (IHA) against *Plasmodium falciparum*. Moreover during the resurgence of *P. falciparum* infection after its near removal for 1.5 years by residual spraying and mass drug administration, the parasitological advantage of females was enhanced without a corresponding change in the serological difference. These findings would seem to suggest, though more studies are needed to confirm this, that perhaps barring during pregnancy, females mount a better immune response. They moreover, also either have a stronger natural immunity or a stronger and more rapid cellular response (10).

### Age

Age as a determinant of susceptibility to infection, and severity and outcome of infection is a significant factor in endemic areas. Its effect is related to the fact that immunity in malaria slowly builds up over time with continuing exposure. Younger

adolescents often still have not attained adult immunity. In those endemic areas where early marriage and young adolescent pregnancy is common, these adolescent girls are potentially at significantly higher risk from malaria than the older adolescents, adult women, or their adolescent male counterparts. This so because immunity to malaria is impaired in pregnancy, especially during the first pregnancy (11, 12, 13).

**Immunity**

Immunity to malaria is complicated. It is an area in which in spite of the varied research which has been done, much still remains uncertain. Immunity increases with increasing exposure to the disease. Moreover the immunity is not long lasting or total and even the immune can still get malaria, albeit a milder form than the non-immune. If exposure to malaria ceases, immunity gradually wanes (14). To complicate the issue further, malaria itself is immunosuppressive (15, 16). How important this fact is epidemiologically is not certain. Furthermore, as already mentioned, immunity to malaria declines during pregnancy especially in primigravida in the first and second trimester (11, 12, 13). This decline in immunity makes pregnancy a high risk for increased frequency of episodes of malaria and also increased severity and complications.

**Polyparasitism/multiple infections**

In almost all areas of the world where malaria is endemic, polyparasitism is potentially the rule rather than the exception. The actual extent is unknown. Hookworm infection, ascariasis, schistosomiasis, trypanosomiasis, leishmaniasis, onchocerciasis, and other tropical and subtropical parasitic infection are often present in variable distribution, combination, and severity in these areas. The extent and consequences of this is an area which still needs research. Interactions between these different infections may be synergistic or antagonistic (17). Moreover, unlike for malaria, little study has been done into these diseases whether individually or in combination in pregnancy.

**Pregnancy**

Pregnancy is the one determinant of the frequency, severity, and outcome of malaria infection in women which has been extensively studied (13). Numerous studies have shown that malaria is more frequent and severe in pregnancy, especially in primigravida, though multigravida are also affected (11, 12, 13). The decline of malaria immunity associated with pregnancy has already been mentioned.

**Genetic factors**

The best known genetic factors that influence malaria infection are the sickle cell haemoglobin S gene and the glucose-6-phosphate dehydrogenase (G6PD) gene. Carriers of sickle cell haemoglobin S, as well as those with G6PD deficiency have an increased resistance to *Plasmodium falciparum* malaria and its lethal effects (8). The sickle cell haemoglobin S gene is autosomal. The G6PD gene on the other hand is sex linked, and the full blown defect is seen much more often in males than in females.

### Nutrition

Adult nutrition especially adult malnutrition, and its effects on transmission of a parasitic disease such as malaria is an area where little or no work has been done.

Theoretically, malaria may affect the nutritional status of the host, and on the other hand, the nutritional status of the host may affect malaria. Moreover, host nutritional status can affect immunity, which in its turn can be a determinant of malaria infection. Current evidence of these effects and their importance is on the whole equivocal. Most information available on nutritional studies, like many other studies on malaria, relates to children. The evidence would seem to suggest that well nourished children are more likely to develop severe disease than malnourished ones. However, for the same level of severity, the malnourished child may be at a disadvantage (19). Episodes of malaria often precede growth faltering in children (20, 21, 22).

A study among infants in Papua New Guinea suggests that exacerbation of malaria infections may occur following parenteral administration of iron in infants (23). However, administration of oral iron to patients with iron deficiency anaemia and symptomatic parasitemia did not exacerbate malaria.

Infections with *Plasmodium malariae* may on occasion induce a highly lethal nephrosis often characterized by massive protienuria (24). In its febrile phase malaria induces a negative nitrogen balance (25). Whether this can lead to significant malnutrition is debatable. With the possible exception of improvement in haematological indices, relatively little nutritional benefit to human populations has been observed after successful control of malaria in hyperendemic areas (10, 26).

### Anaemia

Where *Plasmodium falciparum* is highly endemic, malaria associated anaemia is frequent in pregnant women especially those pregnant for the first time. The pathogenesis is still obscure (11). This anaemia often compounds, and is in its turn compounded by nutritional anaemia. Anaemia due to nutritional deficiency occurs most frequently in women of child bearing age. It is estimated that half the non-pregnant women, and two-thirds of the pregnant women in low income countries have anaemia at rates up to 20 times higher than those among men. Anaemia results in lowered resistance to infections, and increased complications during pregnancy and childbirth (27). Dietary deficiency of iron or B vitamins, increased iron losses due to bleeding (including menstruation), or other parasitic diseases such as hookworm and schistosomiasis all contribute to anaemia. Last but not least, low food intake and unbalanced diets can also enhance the problem. Interrelationships between the host medical factors are summarized in Fig. 2.

## Social, Economic, Cultural, and Behavioural Factors

Research on the parasitic diseases today as in the past, is predominantly a biological and biomedical endeavour. As such, there is very little published research on the influence of

social, economic, cultural, and behavioural factors on the frequency, severity, and outcome of malaria infection whether in men, women, or children. However, there is increasing interest in research into socioeconomic, sociocultural, and behavioural aspects of parasitic diseases as part of control efforts (7, 8, 28, 29).

A great part of the following sections of this review will attempt to identify important research areas needed to fill in the gaps in the available information, or to support existing information. Social, economic, cultural, and behavioural factors affecting malaria transmission will be looked at as much as possible individually for the sake of simplicity. However, they are all complexly interrelated and it will not be possible to separate them completely. For example, an economic factor such as the income available for purchasing health care can interact with cultural factors such as knowledge of the appropriate drugs for treating malaria and the type of health care perceived as appropriate for treating malaria in determining what is done during a particular disease episode. This choice of treatment will affect disease severity and outcome. In a similar manner, economic, cultural, and social principles will interact in determining whether pregnant women in endemic areas take chloroquine prophylaxis.

A study carried out in Guinea illustrates this interaction of various economic, social, and cultural factors to determine major determinants of malaria infection. The study investigated among other things factors which influence the use of malaria chemoprophylaxis in pregnancy by local women in selected urban and rural areas. Access to medical care is difficult in many rural areas of this country. For rural, but not for urban mothers, those women who perceived chloroquine as more affordable, and those who lived nearer to health centres were significantly more likely to take chloroquine during pregnancy. On the other hand for urban mothers, but not for rural mothers, the belief that chloroquine could cause abortion in pregnancy was significantly associated with decreased chemoprophylactic use in pregnancy (30). Different perceptions of chloroquine as a drug, as well as availability and affordability, all influenced whether pregnant women took chloroquine chemoprophylaxis or not in this example.

## Socioeconomic factors

A few studies have looked at socioeconomic determinants of malaria infection in endemic areas. None of these studies looked at men and women separately and compared and contrasted the two with regard to the socioeconomic issues under study.

### *Studies of socioeconomic factors in malaria transmission*

A study in Colombia where after years of decline in the incidence of malaria as a result of the malaria eradication program, a resurgence of malaria had been occurring since 1971, looked at socioeconomic factors associated with malaria infection using a mathematical model. Households (217) experiencing at least one case of malaria and a similar number of non-affected households in the Cunday-Villarica area were interviewed. Malaria status was measured in terms of its prevalence in the past (lifetime malaria), incidence in the last 2 years, as well as present malaria situation of all members of the household.

Using wage income received as measure of economic status, it was found that low income was significantly associated with increased malaria incidence. Separate analyses of income as a risk factor associated with malaria infection were not done for men and women, and it can only be assumed that the effect is the same in both sexes. The study also found that overall lifetime malaria (prevalence in the past) was significantly higher among adult males. Significant differences were not found for incidence in the last 2 years or the present though malaria incidence was more frequent in large households, adults, and males (31). The relationships between these observations and other variables such as income and occupation were not explored. As has already been discussed, there are many potential complex interactions between social, economic, and cultural risk factors for malaria infection. It would also have been interesting to look at sex differences in relation to various income levels and in different age groups, rather than grouped together as a whole.

A study in Papua New Guinea noted a relationship between socioeconomic status and malaria parasitemia. Lower socioeconomic groups were likely to have more parasitemia (32). Again the possible causes and interactions behind this observation were not explored, neither were separate analyses carried out for men and women in different age groups.

Economic development can be a potential risk factor for malaria infection, depending on the kind of projects and how they are planned and executed. Man-made malaria related to economic development is a reality. Development projects may increase vector density, bring non-immune populations to areas of malaria transmission, introduce new strains of malaria parasites, or increase migration to malarious areas inaccessible to the health services (18).

A report from Swaziland (33), describes a resurgence of malaria in sugar estates there related to agricultural development and the use of migrant labour. It was not related, as is often the case, to pesticide resistant strains of Anopheles mosquito. In the case described, ineffective control of malaria within the sugar estates where the irrigation projects create ideal breeding sites for the mosquito vectors, migrant labourers from a malaria endemic area in which there are no real efforts at control, combined with migration of non-immune Swazis into the sugar estate and surrounding areas have all contributed to the resurgence of malaria in an area in which it had previously been brought under control. Though the article does not look at possible differences in these effects between men and women, it mentions the fact that due to difficulties in attracting Swazi labour in the late 1950s and early 1960s, large numbers of women and children were employed to perform the lighter tasks such as weeding, whereas the migrant labourers were recruited for the heavier tasks. Peasant women are often involved in subsistence agriculture in malaria endemic areas, and very vulnerable to the effects of some of these "development" projects.

*Research issues*. There is a need to investigate the income available to women in endemic areas as a possible determinant of malaria related morbidity and mortality. Among other things, the income available to women living in endemic areas determines how much they are willing and able spend on the treatment of an episode of malaria. The severity and outcome of an episode of malaria is related to how it is managed. Income also influences the amount and quality of food eaten. This in turn influences the general health of women and their ability to withstand infection. It is even more critical when there is the added burden of pregnancy with the increased nutritional requirements; the diminished ability to withstand malaria infection in the first and second trimester; and the diminished ability to work and thus produce as much income as formerly.

Low income apart from influencing medical care and nutrition may also influence housing. Poor housing which has no mosquito protection such as mosquito nets over the windows increases the risks of contacting malaria.

It is unknown or unclear in most parts of the world where malaria is endemic, what women's earnings are and how they compare with men's earnings (34). Dwyer and Bruce (35) quote results of a survey of nine developing countries which showed that women earned between 50% (South Korea) and 80% (Burma) of the wages of men who were comparably employed (36). They also quote a review of rural women's income conducted by the International Labour Organization which revealed that women sometimes earn as little as one-third to one-fifth of the wages earned by men for work of greater or equal difficulty (37).

Occupation, time availability and use, and their influence on income need also to be considered. Moreover, time availability and use on its own can act as a risk factor. The less time a woman has to spare, the more she may postpone paying attention to her own health in her efforts to "balance everything all round." To go to a health facility means money as well as time costs. For women living at subsistence level, even a day lost from work and household management is vital. It means loss of income as well as disarray in the household. If there are babies and infants to cope with, it becomes even more difficult to take time off. In many malaria endemic areas with poorly developed basic infrastructures such as roads and public transport, even a "short journey" can become a "long journey."

Another important issue is the demands on such income as women do get. This influences what is available for health and health related issues. Published and unpublished work from Jamaica, St Lucia, Ghana, Kenya, Botswana, Sri Lanka, and Guatemala all suggest that women tend to spend more of their income on everyday subsistence and nutrition for the family as a whole (38).

Finally, the fact that most women are members of households implies that coping with disease will be a joint undertaking of the household with possible redistribution of responsibilities. (39). This must be kept in mind in studying economic risk factors among women in endemic areas. It is necessary to study women within the context of the household. Parallel studies will have to be done of men within the household and the role they play. The possible interactions between women's economic status and the critical individual and household decisions which can influence the frequency, severity, and outcome of malaria infection is summarized in Fig. 3, which has been adapted from Mueller (40).

In Fig. 3, employment refers to work paid either in cash or kind. Support systems represents income outside employment. This can be private such as economic assistance from kinship groups, friends, or other mutual help networks. It can also be public such as free medical care. Support systems may take the form of transfers of money, goods, labour, or other services. Women's social attitudes refers to women's perceptions of themselves, their position, and potentials. Uncertainty regarding access to the necessities of life is likely to affect women's social attitudes. Insecurity may lead to fear of deprivation, inability to take risks, willingness to subordinate oneself to others, and a desire to strengthen family ties and to have large families. Such attitudes can result in part from poverty, and can also contribute to poverty by preventing women from taking action to strengthen their economic position (40).

## Sociocultural and behavioural factors

Sociocultural and behavioural factors that can influence the frequency, severity, and outcome of malaria infection among women in endemic areas include: attitudes to disease and medical services; level of literacy and general education; types of materials and mode of house construction; sleeping habits, i.e. whether indoors or outdoors, with or without mosquito nets; dispersal or agglomeration of homes; traditional economic activities in agriculture or husbandry, and the role of women in these activities.

### *Attitudes to disease and medical services*

Communities and individuals all over the world have their own perceptions and theories about the causation of the diseases that afflict them, the appropriate therapy, and the needed preventive measures. It must not be assumed that what is logical and right from the biomedical viewpoint, is of necessity logical and right to communities living in endemic area. Communities have their own, equally rational and logical, reasoning on which they base their ideas, which moreover, they are not simply going to drop because we say or believe something to the contrary. As Buckley points out in his book on Yoruba medicine, "European scepticism of African ideas is mirrored by African scepticism of European thought. When I suggested to Adebawo (a Yoruba herbalist) that malaria (iba) was caused by mosquito bites, he chuckled gently and replied: Adebawo: Iba is caused by standing in the hot sun. I get bitten by mosquitoes many times each day (he shows me the bites) but I only get iba twice a year. If you don't believe that the sun causes iba, try standing in the sun for an afternoon and see what happens" (41).

Among the many reasons, all related to social and cultural issues, why some remote rural communities in Surinam were resisting the malaria eradication program in the sixties was a disbelief in the mosquito theory of malaria causation. They resisted the spraying of their homes with insecticide and were reluctant to give blood samples (42). Not surprisingly the eradication program was not making headway in these areas.

In a study in rural Ghana, into clinical and sociocultural factors affecting the transmission of malaria among adolescent girls, it was found among other things, that perceptions of malaria causation and treatment are different from conventional biomedical perceptions. Malaria is perceived by the community as an environmentally related disease caused mainly by excessive contact with external heat. Most community members do not connect it with the mosquito in theory or practice. Not surprisingly hardly anyone thinks of trying to control malaria by protecting themselves against the mosquito or attacking the mosquito (43).

A survey carried out by a group of health educators in a semi-urban town in Western Nigeria also showed a difference in biomedical perceptions of malaria, and community perceptions. A malaria drug trial had been going on in this town for the 5 years prior to this, whose aim was to study the immediate and long-term effects of sustained malaria prophylaxis on young children aged 6 weeks to 5 years. The health educators found that despite nearly 5 years of operation of this malaria drug trial, which included regular home visits by field staff, most community members believed that malaria was caused by heat, dust or palm oil;

herbal brews were the best traditional prophylaxis and treatment; and analgesics alone were the correct modern drug for malaria (44).

The way malaria is treated influences its outcome. The question is "what decides how a person will treat a disease episode?" Not only do may people have their own perceptions about disease causation, they often have what to them is an appropriate remedy, often related to the perceived causation. A study in rural Ghana showed that the way people defined a disease and its causation affected what kind of treatment was acceptable for that particular disease (45).

In a study in a rural farming and a rural fishing community in Ghana previously referred to (43), over 90% of uncomplicated episodes of malaria in adolescent girls had or were being treated at home using modern biomedical drugs as well as herbal drugs, according to traditional perceptions of drug use. The result in the cases where biomedicine was used, was highly inappropriate therapy. Chloroquine was hardly used. Very few people perceived it as the appropriate therapy. Analgesics were perceived as the appropriate therapy. Money was wasted on expensive mixtures of brand name analgesics.

A study of self treatment practices in urban Nigeria showed that 77% of respondents preferred self treatment for malaria (46). There is a need to look at treatment choice for malaria in endemic areas, the reasons behind it, and the effect of this choice on malaria infection.

Studies in the literature have looked at medical choice in general. In a comprehensive review of the literature, Kasl and Cobb suggest that the decision to take a particular course of action when a person decides he/she is unwell, is influenced by the perceived value of the action when weighed considering the cost of the action, the past utilization of services, the perceived probability that the action will produce results, as well as personal factors such as age, race, and marital status. Also directly influencing illness behaviour is the perceived value of the action taken, the perceived threat of the disease, as well as the psychological distress brought on by the disease (47).

In a review of the predominantly anthropological literature, Kroeger (48) comes up with a simple somewhat similar integrated -framework for the factors associated with the use and non-use of health services in developing countries. Perceived morbidity interacts with characteristics of the subject such as age and sex, characteristics of the disorder, and perceptions such as etiological model, severe or trivial disease, expected benefits of a particular course of treatment, and finally characteristics of the service options such as accessibility, appeal, costs, acceptability, quality, and communication. The result of this interaction determines the choice of health care resource. Health care resource here includes self treatment, no treatment, drug seller, and modern or traditional healer.

An anthropological study of a rural Mexican community system of medical beliefs, and of how these beliefs relate to the way people deal with illness showed that there were multiple options of both modern and traditional medical care available. These options included self care. In choosing the option for any given disease episode; four major criteria were applied. These were, the gravity/seriousness of the particular illness, whether or not an appropriate home remedy was know for the illness, the faith one has in the effectiveness of folk treatment as opposed to medical treatment in alleviating the illness, and the expense associated with some alternatives and the availability of the resources to meet them (49).

It is worthwhile to look at malaria among women in endemic areas along these lines,

to see which of these factors act as determinants of medical choice and consequently as determinants of infection frequency, severity, and outcome. The reasons behind, and effect of treatment choice, including self-treatment, for malaria in endemic areas needs more attention.

*Level of literacy and general education.* Level of literacy and general education could act as major determinant of malaria infection among women in endemic areas. They can influence knowledge and attitudes to disease prevention and treatment and thus the frequency, severity, and outcome of infection. They can also influence occupation and income. In most malaria endemic areas, women's literacy level is generally lower than that of men (80).

*Other sociocultural and behavioural factors.* Types of materials and mode of house construction, sleeping habits, i.e. whether indoors or outdoors, with or without mosquito nets, dispersal or agglomeration of homes, and traditional economic activities in agriculture or husbandry can all act as determinants of malaria infection through their effects on man-vector contact, and/or on mosquito breeding.

Migration and nomadism can move non-immune persons to malaria endemic areas, or introduce malaria into new areas. Migratory habits may differ between men and women.

*Other social factors*

*Adolescent pregnancy.* Apart from being a medical determinant of malaria infection, adolescent pregnancy can also be a social determinant of infection. General studies looking at the social aspects of adolescent pregnancy in Africa would seem to support increased obstetrical risk related to social factors (51, 52). The social consequences of adolescent pregnancy may not only differ from culture to culture, but can also differ within the same culture depending on the circumstances. Within a given culture, attitudes to married adolescent may be different from attitudes to unmarried adolescents (43). Economic constraints, especially for unmarried adolescents without income generating skills or family support, may make pregnancy a major catastrophe.

*Status of women.* It is difficult to define exactly what constitutes a woman's status. How can it be measured and assessed as a risk factor for malaria infection? It is a complex of economic, social, and cultural factors and is often described in terms of level of income, employment, education, health, and fertility as well as the role she plays within the family, the community, and the society (53). Distribution of ownership of land affects women's income and may also reflects their status and freedom within a given society. Land ownership is variable from culture to culture, and it is worth exploring its influence on malaria infection through its effects on economics and social status. It is easy to get different views of the position of women depending on the angle from which it is looked at. Great care must be taken in maintaining objectivity (54). There is also a danger of observer bias if a superficial assessment of the status of women within a particular culture is done by an observer from another culture. What is "high status" in one culture can conceivably be "low status" in another culture. A way to maintain objectivity in this regard is to look at the experience of women in relation to the experience of men within the same country or region

in assessing social status as a risk factor for malaria infection. Moreover it may help to look at the various components of women's status in a given situation, such as literacy and education, separately before attempting to combine them and draw overall inferences.

*Other issues*

The availability and accessibility of appropriate antimalarials and health services as well as their cost can act as a major determinant of infection in endemic areas. The economic and political situation in any country as well as some sociocultural factors will influence how readily available and accessible appropriate antimalarials are to the average person. Politics influences policy decisions concerning drug importation, licensing of drug sellers and the kind of market system which operates in a given country.

Availability and accessibility includes factors like the cost of the drugs, and the cost involved in getting to where they can be obtained, as well as the expertise to advise on the appropriate use of such drugs as there are. For example is chloroquine available in even the most remote settlements, or do people have to travel long distances to get to a pharmacy which stocks it. Moreover, if it is available, what is the quality of drug? For example, are expired drugs being sold? The fact that chloroquine is available does not guarantee its use. What it does mean is that if people are aware of the fact that malaria is treated with chloroquine, and accept and want to use it, its availability or non-availability can become a limiting or enhancing factor to its use. Research from Cameroon (55, 56, 57), Ghana (43, 58, 59), Philippines (60), Nigeria (61), Mexico (62) would suggest that drugs are available through various outlets, legal and otherwise, sometimes in even the most remote areas of many of the parts of the world where malaria is a problem. However, there is a lack of awareness regarding the appropriate use of these drugs. Moreover, the cost of a full course of therapy may sometimes be prohibitive and people may buy incomplete courses. Moreover, quality is not assured. Health services are often far away or inaccessible because of poor roads and lack of transport.

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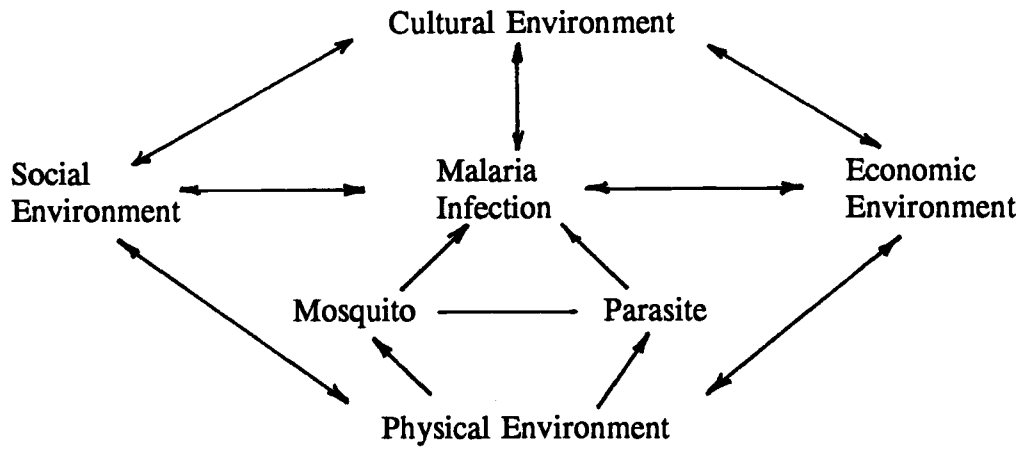
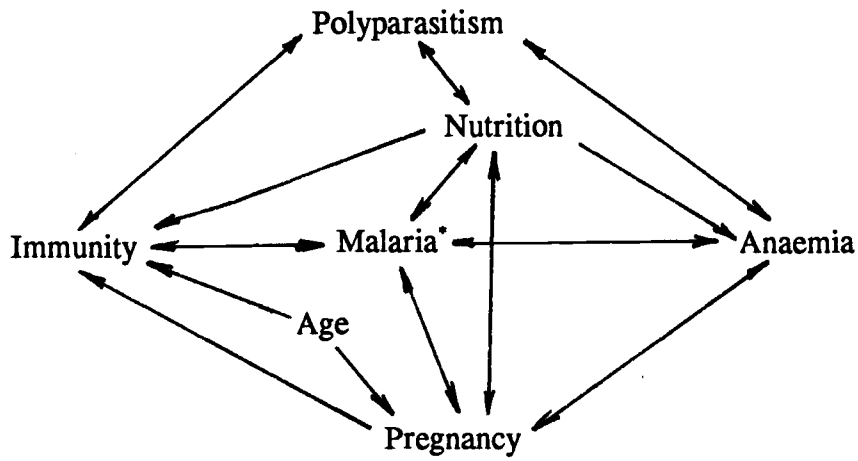



Fig. 1. Interrelationships/determinants of malaria. Arrows show the direction of influence, e.g. physical environment influences mosquitoes.




*Frequency, severity, and outcome of infection

Fig. 2. Medical risk factors of malaria infection in women.

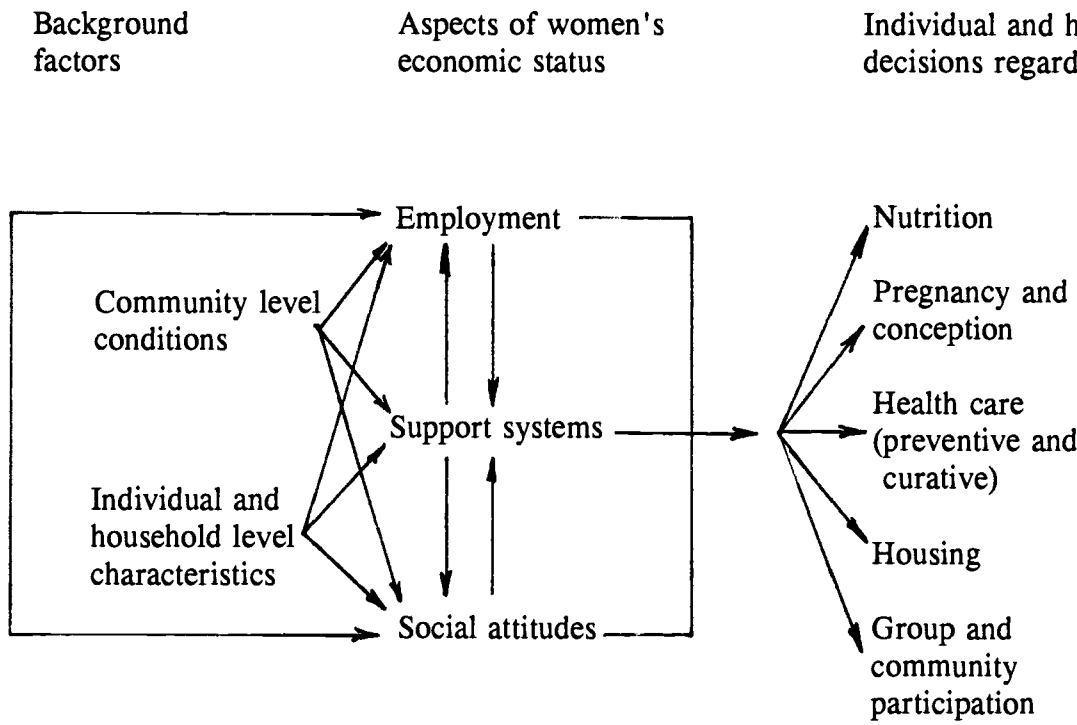



Fig. 3. Economic risk factors of malaria infection in women.

# La Mujer y la Enfermedad de Chagas Congenito en Santa Cruz, Bolivia: Aspectos Epidemiologicos y Socio Culturales

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## Summary

Mothers (910) who attended the Percy Boland Maternity Institute were surveyed: 9.5% of these mothers transmitted Chagas' disease to their children. In the present study, it has been observed that certain sociocultural factors related to the mother, such as increased fertility, early age for motherhood, blood transfusion, as well as migratory flow from other endemic regions of Bolivia and from rural areas from the same department, have led to an increase in the frequency of congenital transmission in Santa Cruz. It is postulated that the maintained urbanization of Chagas' disease may be due to a second generation transmission cycle.

Discussion follows on how endemic regions for congenital Chagas' disease are transformed into risk areas for migrating women from non-endemic regions, as well as on the need for developing an adequate control strategy for this non-vector form of transmission of Chagas' disease.

## Resumen

Madres (910) que concurrieron al Instituto de Maternidad "Percy Boland" de la ciudad de Santa Cruz-Bolivia fueron encuestadas parcialmente. El 9,5% de estas madres transmitieron la enfermedad de Chagas a sus niños. Por este estudio se ha observado que ciertos factores socio culturales de la mujer, como la fecundidad aumentada, la edad demasiado temprana para ser madre; las transfusiones de sangre así como los flujos migratorios de otras regiones endémicas del territorio boliviano y de las áreas rurales del mismo departemento hhan influenciado para un aumento de la frecuencia de la transmisión congénito de la enfermedad de Chagas en esta ciudad. Se plantea que su urbanización mantenida, se deba a un ciclo de transmisión congénita de 2$^{do}$ generación.

Se hace comentarios, como regiones endémicas para la enfermedad de Chagas, se transforman en regiones de riesgo para mujeres migrantes de áreas no endémicas, así como la necesidad de elaborar una adecuada estrategia de control sobre esta forma de transmisión no vectorial de la enfermedad de Chagas.

Bolivia país meditarráneo, se encuentra situado en el corazón de Sud América, tiene como vecinos los paises del Brasil, Perú, Chile, Argentina y el Paraguay. El territorio se divide políticamente en departamentos, provincias y cantones; tiene ena estensión de más de un millón de kilómetros cuadrados. En Bolivia se distinguen tres zonas ecológicas: El altiplano del clima frio y seco, que cubre 16% del territorio y estan los departamentos de La Paz, Oruro y Potosí. Tiene una altura promedio de 3800 metros sobre el nivel del mar y acogen al 38% de la población total. Los valles que participan con el 19% e integran los departamentos de Cochabamba, Chuquisaca y Tarija; de clima templado y sub tropical. La altura varia de 1000 a 2700 metros sobre el nivel del mar y en ellos residen el 42% de la población. Los llanos son las zona más extensas y menos pobladas, cubriendo el 65% del territorio, que acoge al 20% de la población y comprenden los departamentos de Santa Cruz, Beni, Pando del clima tropical y húmedo.

La situación de la mujer en Bolivia desde una perspectiva sociológica, conforman agrupamientos identificables con las condiciones sociales donde se desenvuelven, vinculada indiscutiblemente con la maternidad, de ahí, que en el país se observa una tasa elevada de nacimientos. Su participación en otras actividades (domésticas, económicas y políticas), muestra como dirige sus esfuerzos a la consecusión de mejores condiciones de vida; Asi en las zonas rurales de los valles y del altiplano, especialmente donde se concentran mayores volúmenes de pobreza, la producción destinada a la subsistencia familiar se apoya en gran parte en el trabajo de la mujer.[6]

En Bolivia la enfermedad de chagas fué detectada a través de diversos estudios sero epidemiológicos y se halla distribuida en las regiones tropicales, sub tropicales y los valles de nuestro territorio. Es una enfermedad parasitaria causada por *T. cruzi*, siendo el triatoma infestans ("vinchuca"), la especie vectora la más difundida y epidemiológicamente la más importante en 6 de los 9 departamentos que conforman la república de Bolivia.[7]

Tienen su origen en una zoonosis silvestre que se transformó en problema de patologia humana, gracias a la adaptación de los insectos trasmisores de la enfermedad al habitad de los pobladores, donde predomina viviendas mal construidas, con paredes no rebocadas de baharague simple, motacú, adobe, techos de caña hueca, de paja, que constituyen ecótopos que favorecen la colonización de vectores posibilitando en consecuencia el ciclo domiciliar de la enfermedad, afectando al hombre y animales domésticos.

La prevalencia sero epidemiológica de la enfermedad de chagas fue medida en el Dpto. de Santa Cruz, lugar donde se han realizado muestras observaciones. Existen regiones rurales del departamento que representan una prevalencia serológica superior al 50%[8] La ciudad de Santa Cruz tiene una prevalencia del 39%[9].

La transmisión de la enfermedad se efectúa a través del vector, sin embargo la transmisión por via transplacentaria es igualmente importante al haberse observado que el 5% de los recien nacidos presentaron ena infección congénita por *T. cruzi* y en mayor proporción en los recien nacidos con peso o menor igual a 2500 grs.[1]

El Dpto. de Santa Cruz, se extiende sobre una superficie de 370.621 km$^2$ entre los paralelos de latitud Sud 13° a 21° y meridianos de longitud de 59° a 55°, ocupando la parte oriental o de los llanos de país.

La población departamental es de 1.110.100 habitantes de los cuáles el 40% vive en la capital, el resto de la población vive en pequeños y mediaqnos pueblos (18%) o de manera dispersa en el área rural (42%).[5]

La ciudad de Santa Cruz ha experimentado en los últimos años un crecimiento rápido, debido al auge económico de la agro industria (azúcar, arroz) de los años 60 y la obtención del 11% de las regalías petroleras y gasíferas. La construcción de carreteras y ferrovías de comunicación interprovincial, inter departamental y con paises del exterior, ha ocasionado afluencia migratoria, que se manifesta principalmente en el crecimiento urbano; de donde que al lado de barrios bien urbanizados, existen otros, donde todovía hay deficiencias de servicios públicos (luz, agua, alcantarillado, basura, etc.), que generalmente vive gente humilde, migrante del área rural del dpto.

La planificación urbana de la ciudad, está estructurada en base a anillos radio concéntricos que se prolongan con sus vías principales, al norte con las provincias de Warnes, Montero (llanos), al sudoeste con los valles cruceños, al este con la provincia de Cotoca y al sud con el ferrocarril y la zona industrial. Está zoonificada en la actualidad en 5 anillos:

a) Area central (caso viejo), destinada a usos administrativos e institucionales, para usos mixtos comercio y vivienda.

b) Un primer anillo de circunvalación que rodea el área central.

c) Unidad vecinal con su equipamiento comunitario rodeado de viviendas unifamiliares y multifamiliares con el mismo detalle de anillos 2do. y hasta 5to. anillo.

d) Areas verdes para parques y campos deportivos con el mismo detalle.[4] Dato importante, es que, en todas estas áreas se ubican viviendas de nivel económico alto, medio y bajo.

En el Dpto. de Santa Cruz, la población femenina es del 51%, mayor que la masculina,[4] es joven y está vinculada al igual que el resto de país con la maternidad. Existen una diversidad de factores económicos, sociales y culturales que describen el comportamiento reproductivo de la mujer, con una tasa global de fecundidad de 7,2 hijos por mujer en esta región de los llanos orientales[6].

El la ciudad de Santa Cruz, para la población femenina no asegurada, existe una maternidad, en la cual se atiende un promedio de 9000 a 10.000 partos por año; esto hace suponer que da una cobertura de más o menos el 50% de la población.

En una encuesta sero epidemiología reciente en 6 Dptos. del Bolivia (La Paz, Potosi, Chuquisaca, Cochabamba, Santa Cruz y Tarija), se ha observado una mayor frecuencia de seropositividad en el sexo femenino (56,2%), que el masculino (43,8%).[7] Esta observación tiene alguna relación con lo observado por Azogue y cols. 1985,[1] que muestra una prevalencia serológica en la embarazada del 51%, con una frecuencia de transmisión congéntia de la enfermedad de Chagas del 5%. Esta cifra se ha mantenido y elevado en un reciente estudio al 54% de prevalencia serológica para las madres y 9,5% la frecuencia de la transmisión congénita.[3] A partir del año 1978 en la cuidad de Santa Cruz se detectan los casos de Chagas congénitos a través de un estudio dirigido en el Instituto de Maternidad por Azogue y cols 1981,[2] lo que nos hace pensar, que la transmisión congéntia continúa siendo un problema que preocupa por el número de mujeres infectadas y en edad fértil, constituyendose en la actualidad en un reservorio importante.

El objetivo del presente trabajo, es el de analizar los diferentes factores epidemiológicos, socio culturales que intervienen en la mujer como factores de riesgo en la transmisión congénita de la enfermedad de Chagas en Santa Cruz Bolivia.

## Poblacion y Metodos

Se realiza una encuesta parcial epidemiológica y socio cultural a 910 madres que concurrieron al Instituto de maternidad "Percy Boland" de la cuidad de Santa Cruz, en el período de 1988-1989.

Se llena una ficha donde se consignan datos de procedencia, residencia, conocimiento del vector, aspectos educativos (grado de instrucción), fecundidad. A todas las madres se tomaron muestras de sangre, para realizar la hemaglutinación para Chagas (HAI), considerada esta reacción positiva a una dilución 1/30.

Se definieron los indicadores utilizados en este estudio:

La procedencia se definió al lugar de nacimiento de las madres; luego se dividió en regiones ecológicas. Residencia anterior, lugar de permanencia por años y la actual. En la ciudad de Santa Cruz, se ha buscado la ubicación domiciliaria de la madres y se ha hecho la distribución de acuerdo a lo consignado en el plan regulador.[4]

Fecundidad: al número de gestaciones y se ha relacionado de acuerdo al marco social, cultural y educativo.

Migración de mujeres: externa relacionada a otros departamentos e interna del área rural.

Grado de instrucción: considerando la educación formal en eseñanza básica (primaria), medio (secundaria) superior (universidad) y sin instrucción.

Transfusiones de sangre: que la mujer haya recibido antes o durante el parto.

Conocimiento del vector, si la madre conocía o no la "vinchuca."

Se definió madre con *T. cruzi* cuando el recien nacido haya sido positivo a las pruebas parasitológicas del Strout.

## Resultados

### Estudio de procedencia de las madres

Se ha observado que el 67% de las madres proceden del Dpto. de Santa Cruz y el 33% de otros departamentos del país. En cuanto a la transmisión congénito de la enfermedad de Chagas las madres con mayor riesgo fueron las que proceden de los Dptos. de Chuquisaca y Santa Cruz.

Un dato importante que se debe resaltar es, que, el Dpto. de Oruro que se encuentra a 4500 mts. sobre el nivel del mar, no es una región endémica para la enfermedad de Chagas, no se ha encontrado el vector en la encuesta entomológica; sin embargo muestra un factor de riesgo de 5,3% (ver Tabla 1).

Si agrupamos por regiones ecológicas de acuerdo con la serología (HAI) para Chagas, observamos que el mayor porcentaje proceden de los valles (63%) (ver Tabla 2).

Al analizar el dato de procedencia en el mismo departamento de Santa Cruz, se puede apreciar que el 60% de las madres son oriundas de la ciudad de Santa Cruz (urbana) y el 40% proceden del área rural y como consecuencia con el mayor porcentaje de riesgo para la trasmisión congénita de la enfermedad de Chagas 13,8% (ver Tabla 3).

**Estudio de residencia de las madres en la ciudad de Santa Cruz**

Bor el seguimiento realizado al madres después de la atención del parto en el Instituto de Maternidad, hemos observado que las oriunados de la ciudad, tenían sus viviendas en el área central (casco viejo) y 4$^{to}$ anillo; entre tanto, las que procedían del área rural del Dpto., sus viviendas estaban ubicadas en el 4$^{to}$ anillo y las que procedían de otros Dptos. en el 2$^{do}$ y 3$^{ra}$ anillo. En esta ubicación se encontró en mayor porcentaje a las madres que transmitieron la enfermedad de Chagas a sus niños.

Las viviendas de estas madres en un gran porcentaje no estaban adecuadamente construidas; algunas er an de ladrillo, otras de motacú o de madera, otras ocupaban viviendas familiares; pocas tenían vivienda propia. En cuanto a servicios públicos; en todas lasviviendas había luz, agua potable, pero nolos otros servicios como: alcanterillado, basura.

Estos servicios se encuentran hasta el 2$^{do}$ anillo y en barrios residenciales que tienen la misma ubicación por anillos.

**Estudio de la fecundidad de las madres y sus características contextuales**

Los resultados obtenidos de la observación de este factor, nos indica, que el 37% de las madres que asistieron al Instituto de Maternidad fueron primíparas; 36% estaban en el grupo de 2 y 3 hijos; 16% eran maltíparas con 4, 5, y 6 hijos y el 8% grandes multíparas con más de 6 hijos; habiéndose encontrado un mayor riesgo de transmisión congénita de la enfermedad de Chagas, en aquellas madres multíparas (11%) y grandes multíparas (14%). Las primíparas ocupan también en esta observación, el 2$^{do}$ lugar con el 11%.

Relacionando este factor con los niveles educativos, notamos que cuando la madre tienen un nivel educativo básico, las primíparas, multíparas y gran multíparas tienen igual riesgo de transmitir la enfermedad de Chagas. En cambio en las madres con nivel educativo medio, el riesgo se mantienen en las primíparas, disminuye en las multíparas y desaparece en las grandes multíparas (ver Tablas 4 y 5).

**Estudio de los niveles educativos de las madres**

Se ha encontrado que las madres con nivel educativo básico y sin instrucción tienen un porcentaje de mayor riesgo para la transmisión congéntia, que las que se encuentran en un nivel medio y superior.

**Estudio sobre el conocimiento del vector por las madres**

Se ha encontrado en este estudio, que el 80,2% de las madres conocían al vector (la "vinchuca"), el 19,8% no lo concocía. De las madres que conocían al vector el 10,5% transmitieron la enfermedad de Chagas a sus niños y el 9% las madres que no conocían (ver Tablas 6 y 7).

**Estudio de los antecedentes de transfusión de sangre de las madres**

Se ha encontrado en el análisis que un 8% de las madres había recibido transfusiones antes del embarazo, habiéndose encontrado un riesgo de transmisión congénita de la enfermedad de Chagas de un 11% (ver Tabla 8).

## Discusion

Los datos expuestos en el presente trabajo colocan a la mujer dentro de todo lo que significa, el contexto social y cultural en Bolivia, como representante principal de uno de los grandes problemas epidemiológicos que afectan a la población boliviana en un 45 a 65%, como es la enfermedad de Chagas. Esta enfermedad afecta sobre todo a poblaciones más pobres, generalmente comunidades rurales y marginales que se constituyen en los grupos de mayor riesgo.

Los problemas sociales en Bolivia se han ido ahondando y el desempleo llegó a sobrepasar el 20% de la población económicamente activa, lo que ha ocasionado un aumento importante en el flujo migratorio, que ha dado lugar a un fuerte proceso de urbanización concentrado en las capitales de Dpto. La ciudad de Santa Cruz presenta elevadas tasas de crecimiento como consecuencia de este factor, siendo la tasa promedio anual entre 1976 a 1988 de 6,95%[4].

La importancia del componente migratorio es relativamente reciente en Santa Cruz y está relacionado con el proceso de desarrollo regional basado en la expansión agropecuaria, la producción de hidrocarburos, la explotación maderera y el crecimiento del sector industrial asociado principalmente al procesamiento de la materia prima agropecuaria y forestal. La mujer en este componente de migración tiene activa participación con el mayor porcentaje (51%) de inmigración femenina a la ciudad de Santa Cruz. Los Dptos. de Bolivia que más inmigrantes aportan a la ciudad de Santa Cruz son: Cochabamba, Chuquisaca, y La Paz con 10 años o más de radicatoria. Este dato es importante por el hecho, que estos Dptos. a excepción de La Paz, son endémicos para la enfermedad de Chagas; 63% de prevalencia en las madres procedentes de los valles (Chuquisaca, Cochabamba, y Tarija), con un riesgo de transmisión congénita de estas madres del 8%.

Se ha observado también en este estudio que las madres procedentes de Dptos no endémicos como Oruro han transmitido la enfermedad de Chagas a sus niños. Esto se debe a la infestación de las mujeres que migran de áreas no endémicas, viven en regiones endémicas tomando su ubicación en zonas marginales de la ciudad o áreas rurales donde todavia existen ecótopos que favorecen la colonización de vectores.

Este aspectos migratorio hacia la ciudad de Santa Cruz es ocasionado también por población migrante del área rural (provincias) constituyéndose en otro factor que potencializa la transmisión congénita de la enfermedad de Chagas; 13,8% encontradas en las madres que proceden de estas áreas. Estos datos lógicamente aumentan, si tomamos en cuenta solo a las madres serológicamente positivas.

Un aspecto importante que es necesario destacar, es que en la ciudad de Santa Cruz, las madres oriundas de esta zona urbana, han presentado un riesgo de transmisión congénita del 8%; este dato, más la ausencia de triatominos en sus viviendas, en el seguimiento

efectuado a estas madres, nos hace pensar que ya existiría una transmisión congénita de 2$^{do}$ generación. Esta observación es corroborada por los recientes datos de Azogue y cols 1991,[3] de haber encontrado un mayor porcentaje de recien nacidos positivos a *T. cruzi* del sexo femenino, que se presentaría, si no se hace el diagnóstico precoz y el tratamiento oportuno, manteniéndose el ciclo de transmisión, al convertirse la mujer en un reservorio importante para la enfermedad de Chagas.

Los flujos migratorios de los Dptos. vienen de las zonas rurales y urbanas a la ciudad de Santa Cruz. Los grupos culturales son diferentes de acuerdo con las regiones ecológicas del idioma y el clima. La población boliviana predominantemente es aborigen y mestiza. La población blanca, es la menos numerosa. Los idiomas que se hablan son el español, quechua, aymara idiomas estos últimos que pertenecen al grupo andino que ocupan al Altiplano, las montañas, cordilleras y valles. En la región de los llanos existen otros grupos culturales representados por familias chiriguanas, chiquitanos y guarayos que tiene sus propios dialectos. Estos diferentes aspectos socio culturales limitan a la mujer al libre acceso de la educación. La familia como la sociedad condicionan a ser responsable de la toma del hogar, del cuidado de los hijos y del marido y si son hijas de familia no se libera de esta responsabilidad y es la madre misma que le impide capacitarse, ya que no puede salirse de los cánones tradicionales, que la ha impuesto la sociedad desde su hogar.[5] Es así como de algun manera se explicaría, el porqué la mujer boliviana y en especial la de los llanos orientales tiende a tener mayor número de hijos 7,2% en las áreas rurales y 4,6% hijos en mujeres de las ciudades.[6]

Considerando este aspecto con la enfermedad de Chagas, hemos observado que las madres con mayor riesgo en transmitir la enfermedad son las multíparas, riesgo este, que disminuye o desaparece, cuando los niveles educativos de la mujer mejoran. El grado de instrucción es una variable representativa de las condiciones socio económicas de gran importancia, porque al prepararse la mujer, puede recurrir a una mejor orientación en la planificación familiar. A este respecto a través de algunos estudios en la ciudad de Santa Cruz, se ha demostrado que la mujer que alcanza mejor nivel de instrucción o cuando ingresa a participar del trabajo, para mejorar los niveles económicos de la familia, se reduce la fecundidad.[4]

Tomando en cuenta el aspecto educativo de las madres del estudio, se ha observado que las madres del nivel educativo básico y sin instrucción, son las que tienen el mayor porcentaje de riesgo en transmitir la enfermedad de Chagas, que las que se encuentran en nivel medio y superior; lo que quiere decir que el riesgo existe aún en estos últimos grupos.

En cuanto al conocimiento del vector a un 80% no les fué desconocido el agente transmisor, pero ellas no le han dado la debida importancia para combatirlas, así como no sabían que transmitían una enfermedad.

Existe un dato relevante y es el hecho de haber encontrado madres de un nivel educativo medio y básico que no conocían al vector y habían transmitido la enfermedad de Chagas. Esta observación más la anteriormente comentada nos inquieta más a pensar que nos encontramos frente a una transmisión congénita de 2$^{do}$ generación o hasta una 3$^{ra}$.[3]

Nuestras observaciones a través de este estudio nos indican que la mujer en cierto porcentaje he tenido mayor receptivdad en encarar el problema de la enfermedad de Chagas, cuando se le expuso que ella puede transmitir esta enfermedad a su niño. Hemos tenido concurrencia expontánea de las madres con sus niños a las citas de control. En las visitas

domiciliarias nos encontrábamos con situaciones en la cuales, la mujer que dependía económicamente del esposo, éste no le proporcionaba los recursos económicos necesarios para su traslado a los sitios asignados para sus controles. A su vez las madres que sabían que habían transmitido la enfermedad; pero que ellas, en realidad no presentaban ningún síntome, no aceptaban recibir ayuda terapéutica o a someterse a un mejor examen clínico. En cambio otras madres sintieron motivación, en especial las que contaban con la comprensión y ayuda del esposo o las madres solteras. En otros casos el esposo consideraba que el conocimiento de esta situación agudizaba más sus problemas, prefiriendo en consecuencia obviar, inculcándola a no participar y no concurrir a los servicios de salud.

En conclusión la enfermedad de Chagas congénito en nuestra país Bolivia y en especial en la ciudad de Santa Cruz, es un problema de salud pública que nos preocupa al observar:

1) Que la mujer es un reservorio importante de la enfermedad de Chagas con una prevalencia en el país del 59%[7] y prevalencia serológica en la embarazada del 54% a nivel de Santa Cruz de la Sierra;[3] por consiguiente presente en 6 Dptos. que son endémicos para la enfermedad.

2) Existe en la actualidad un gran número de mujeres en edad fertil serológicamente positivas, que pueden transmitir la enfermedad y mantenerla activamente si no se hace un diagnóstico precoz en el recien nacido o en la mujer antes del matrimonio, aunque existan campañas de erradicación del vector.

3) Que existen factores socio culturales que intervienen en la mujer potencializando la transmisión congénita de la enfermedad de Chagas. Estos factores son los migratorios, la fecundidad aumentada, las transfusiones de sangre que merece un comentario aparte; han urbanizado esta forma de transmisión de la enfermedad.

4) Que ya existe el riesgo de transformación de las regiones no endémicas en endémicas para la enfermedad de Chagas a través del retorno de madres infectadas a sus lugares de origen.

5) Que las madres que hoy estamos observando, sobre todo las oriundas de Santa Curz, correpondan a casos de transmisión congénita de 2$^{da}$ generación o 3$^{ra}$.

Por lo tanto se hace necesario realizar una encuesta social y cultural, así como económica y entológica más completa, que permita elaborar posteriormente un programa de control a través de la participación comunitaria, liderizada por la mujer en los barrios marginales con un adecuado apoyo de las autoridades competentes e infraestructura sanitaria.

La mujer de nuestra región todavía discriminada socialmente, sin protección legal y social de la maternidad en lo cotidiano,[5] puede llegar a cumplir sus anhelos a tener una mayor participación en la toma de decisiones en los diferentes aspectos de la vida.

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Tabla 1. Madres por departamento de procedencia segun transmision congenita.

| | Totales | | *T. cruzi* | | | |
|---|---|---|---|---|---|---|
| | | | Positivo | | Negativo | |
| | Numero | % | Numero | % | Numero | % |
| Totales | 910 | 100 | 85 | 9.3 | 825 | 90.7 |
| Departamento de procedencia | | | | | | |
| Chuquisaca | 57 | 100 | 7 | 12.3 | 50 | 87.7 |
| La Paz | 28 | 100 | 0 | 0 | 28 | 100.0 |
| Cochabamba | 67 | 100 | 6 | 9.0 | 61 | 91.0 |
| Oruro | 19 | 100 | 1 | 5.3 | 18 | 94.7 |
| Potosi | 34 | 100 | 3 | 8.8 | 31 | 91.2 |
| Tarija | 23 | 100 | 2 | 8.7 | 21 | 91.3 |
| Santa Cruz | 609 | 100 | 64 | 10.5 | 545 | 89.5 |
| Beni | 59 | 100 | 1 | 1.7 | 58 | 98.3 |
| Pando | 1 | 100 | 0 | 0 | 1 | 100.0 |
| Exterior | 4 | 100 | 0 | 0 | 4 | 100.0 |
| Desconocido | 9 | 100 | 1 | 11.1 | 8 | 88.9 |

Tabla 2. Madres por departamento de procedencia segun hai.

| | Totales | | HAI | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Positivo | | Negativo | | Sin dato | |
| | Numero | % | Numero | % | Numero | % | Numero | % |
| Totales | 910 | 100 | 481 | 52.9 | 411 | 45.2 | 18 | 2.0 |
| Depatamento de procedencia | | | | | | | | |
| Chuquisaca | 57 | 100 | 46 | 80.7 | 10 | 17.5 | 1 | 1.8 |
| La Paz | 28 | 100 | 10 | 35.7 | 17 | 60.7 | 1 | 3.67 |
| Cochabamba | 667 | 100 | 38 | 56.7 | 28 | 41.8 | 1 | 1.52 |
| Ororo | 19 | 100 | 4 | 21.1 | 15 | 78.9 | 0 | 0 |
| Potosi | 34 | 100 | 13 | 38.2 | 21 | 61.8 | 0 | 0 |
| Tarija | 623 | 100 | 11 | 47.8 | 11 | 47.8 | 1 | 1.3 |
| Santa Cruz | 609 | 100 | 346 | 56.8 | 251 | 41.2 | 12 | 2.01 |
| Beni | 59 | 100 | 5 | 8.5 | 53 | 89.8 | 1 | 1.7 |
| Pando | 1 | 100 | 0 | 0 | 0 | 0 | 1 | 100 |
| Exterior | 4 | 100 | 0 | 0 | 4 | 100 | 0 | 0 |
| Desconocido | 9 | 100 | 8 | 88.9 | 1 | 11.1 | 0 | 0 |

Tabla 3. Departamento de Santa Cruz - madres por area de procedencia segun transmision congenita.

| | | | *T. cruzi* | | | |
|---|---|---|---|---|---|---|
| | Totales | | Positivo | | Negativo | |
| | Numero | % | Numero | % | Numero | % |
| Totales | 609 | 100 | 64 | 10.5 | 545 | 89.5 |
| Departamento de Santa Cruz | | | | | | |
| Urbano | 363 | 100 | 30 | 8.3 | 333 | 91.7 |
| Rural | 246 | 100 | 34 | 13.8 | 212 | 86.2 |

Tabla 4. Madres sin *T. cruzi* segun numero de gestaciones por grado de educacion.

| | | Educacion de la madre | | | | |
|---|---|---|---|---|---|---|
| | Totales | Sin instruccion | Primaria | Secundaria | Universidad | Sin dato |
| Totales | 825 | 37 | 360 | 364 | 24 | 39 |
| Numero gestaciones | | | | | | |
| 1 | 301 | 10 | 121 | 144 | 14 | |
| 2 | 203 | 3 | 72 | 112 | 5 | 12 |
| 3 | 101 | 9 | 36 | 47 | 2 | 11 |
| 4 | 69 | 1 | 42 | 23 | 1 | 7 |
| 5 | 49 | 3 | 28 | 13 | 1 | 2 |
| 6 | 29 | 5 | 13 | 9 | 1 | 4 |
| 7 | 28 | 2 | 18 | 6 | 0 | 1 |
| 8 | 16 | 2 | 10 | 4 | 0 | 2 |
| 9 | 12 | 1 | 9 | 2 | 0 | 0 |
| 10 | 8 | 0 | 5 | 3 | 0 | 0 |
| 11 | 5 | 0 | 5 | 0 | 0 | 0 |
| 12 | 2 | 1 | 0 | 1 | 0 | 0 |
| 14 | 1 | 0 | 1 | 0 | 0 | 0 |

Tabla 5. Madres con *T. cruzi* segun numero de gestaciones por grado de educacion.

| | | Educacion de la madre | | | | |
|---|---|---|---|---|---|---|
| | Totales | Sin instruccion | Primaria | Secundaria | Universidad | Sin dato |
| Totales | 85 | 13 | 36 | 31 | 1 | 4 |
| Numero gestaciones | | | | | | |
| 1 | 33 | 5 | 12 | 11 | 1 | 4 |
| 2 | 11 | 1 | 7 | 3 | 0 | 0 |
| 3 | 15 | 1 | 5 | 9 | 0 | 0 |
| 4 | 8 | 1 | 4 | 3 | 0 | 0 |
| 5 | 7 | 2 | 3 | 2 | 0 | 0 |
| 6 | 1 | 0 | 0 | 1 | 0 | 0 |
| 7 | 3 | 0 | 3 | 0 | 0 | 0 |
| 8 | 3 | 0 | 1 | 2 | 0 | 0 |
| 9 | 2 | 1 | 1 | 0 | 0 | 0 |
| 10 | 1 | 1 | 0 | 0 | 0 | 0 |
| 14 | 1 | 1 | 0 | 0 | 0 | 0 |

Tabla 6. Madres sin *T. cruzi* por grado de educacion segun conoce o no la vinchuca.

| | Totales | | Conoce la vinchuca | | | |
|---|---|---|---|---|---|---|
| | | | Si | | No | |
| | Numero | % | Numero | % | Numero | % |
| Totales | 825 | 100 | 662 | 80.2 | 163 | 19.8 |
| Educacion de la madre | | | | | | |
| Sin instruccion | 37 | 100 | 33 | 89.2 | 4 | 10.8 |
| Primaria | 360 | 100 | 287 | 79.7 | 73 | 20.3 |
| Secondaria | 364 | 100 | 293 | 80.5 | 71 | 19.5 |
| Universidad | 24 | 100 | 21 | 87.5 | 3 | 12.5 |
| Sin dato | 40 | 100 | 28 | 70.0 | 12 | 30.0 |

Tabla 7. Madres con *T. cruzi* por grado de educacion segun conoce o no la vinchuca.

| | Totales | | Conoce la vinchuca | | | |
|---|---|---|---|---|---|---|
| | | | Si | | No | |
| | Numero | % | Numero | % | Numero | % |
| Totales | 85 | 100 | 70 | 82.4 | 15 | 17.6 |
| Educacion de la madre | | | | | | |
| Sin instruccion | 13 | 100 | 10 | 76.9 | 3 | 23.1 |
| Primaria | 16 | 100 | 31 | 86.1 | 5 | 13.9 |
| Secondaria | 31 | 100 | 26 | 83.9 | 5 | 16.1 |
| Universidad | 1 | 100 | 1 | 100.0 | 0 | 0 |
| Sin dato | 4 | 100 | 2 | 50.0 | 2 | 50.0 |

Tabla 8. Madres con *T. cruzi* por grado de educacion segun si recibio o no transfusion de sangre.

| | | | Conoce la vinchuca | | | |
|---|---|---|---|---|---|---|
| | Totales | | Si | | No | |
| | Numero | % | Numero | % | Numero | % |
| Totales | 85 | 100 | 10 | 11.8 | 75 | 88.25 |
| Educacion de la madre | | | | | | |
| Sin instruccion | 13 | 100 | 1 | 7.7 | 12 | 92.3 |
| Primaria | 16 | 100 | 6 | 16.7 | 30 | 83.3 |
| Secondaria | 31 | 100 | 3 | 9.7 | 28 | 90.3 |
| Universidad | 1 | 100 | 0 | 0 | 1 | 100.0 |
| Sin dato | 4 | 100 | 0 | 0 | 4 | 100.0 |

Tabla 9. Madres sin *T. cruzi* por grado de educacion segun si recibio o no transfusion de sangre.

| | | | Conoce la vinchuca | | | |
|---|---|---|---|---|---|---|
| | Totales | | Si | | No | |
| | Numero | % | Numero | % | Numero | % |
| Totales | 825 | 100 | 76 | 9.2 | 749 | 90.8 |
| Educacion de la madre | | | | | | |
| Sin instruccion | 37 | 100 | 2 | 5.4 | 35 | 94.6 |
| Primaria | 360 | 100 | 34 | 9.4 | 326 | 90.6 |
| Secondaria | 364 | 100 | 33 | 9.1 | 31 | 90.9 |
| Universidad | 24 | 100 | 2 | 8.3 | 22 | 91.7 |
| Sin dato | 40 | 100 | 5 | 12.5 | 35 | 87.5 |