



EXPERT COMMITTEE ON LYMPHATIC FILARIASIS

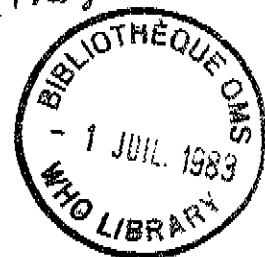
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*Lymphoedema - transmission/parasitology  
Microfilaria - parasitology*

INTENSITY OF TRANSMISSION AND DEVELOPMENT OF DISEASE:  
THEIR RELATIONSHIP IN LYMPHATIC FILARIASIS

by

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The concept of intensity of transmission in dioecious helminthic infections of man is inherently difficult, and none of the methods which have been used to measure it is ideal. In the case of the lymphatic filariases, the most useful measure would be the rate of acquisition by man of sexually mature adult worms, regardless of whether such worms were mated and fecund, or not. However, it is not feasible with any available technique to measure this factor, nor are such techniques likely to become available in the foreseeable future. Intensity of transmission can thus only be measured by methods which are to a greater or lesser extent unsatisfactory. The third report of the WHO Expert Committee on Filariasis (WHO 1974, pp. 24-27) discussed some of these methods, and in its Annex 3 (pp. 50-54) considered techniques for the diagnosis of the crucial factor of microfilaraemia. Nevertheless, some important factors in the intensity of transmission were not dealt with, and these will be included in the present paper.

Similarly, there are difficulties in defining the presence of filarial disease. Most of the symptoms and signs usually associated with filarial infections have alternative non-parasitic causes, and even when they are detected in endemic areas and in persons known to be infected or to have been infected with a filarial parasite, it may be impossible to assign them with absolute confidence to a filarial aetiology. The determination of filarial disease is inevitably to some extent subjective, and opinion and observer variation can affect the results of surveys, even when a carefully prepared, simple, unambiguous and uncontroversial clinical protocol is used (WHO 1974, pp. 48-50). Furthermore carelessness and lack of clinical skills can give bias to survey results (e.g. minor degrees of leg, arm and breast enlargement can easily be missed unless meticulous measuring is carried out), and in some areas of the world certain types of clinical examination (e.g. inspection of male and female genitalia) may prove unacceptable to people in the circumstances of population surveys.

In spite of these numerous problems, measurements of intensity of transmission and of amount of disease have been made, and related one to the other. Not unexpectedly, high transmission is generally found to be associated with a high prevalence and severity of disease. This paper will examine the relationship, will explore additional factors which could improve measurements of transmission intensity.

Intensity of transmission - measurements in the human host

Given the impossibility of measuring the rate of acquisition of new adult filarial worms by man, the best indicator of intensity of transmission that relates to the human population is the incidence-rate of new cases of microfilaraemia, either in the whole population, or in certain appropriate or easily accessible sub-sections of it, such as children in carefully defined age-groups. It must be clearly recognized that the detection of microfilaraemia means the detection of one or more mated, fecund female worms, and in diseases such as the lymphatic filariases where unpaired adult worms, and even unisexual infections can be responsible for pathology (Hairston and Jachowski, 1968), incidence-rates of microfilaraemia can be expected to show less close relations to disease than the analogous incidence-rates of

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new cases of egg output in schistosomiasis or new cases of skin microfilarial infection in onchocerciasis, since in these infections pathology is determined largely by the production within the human body of eggs or microfilariae respectively. At present, the only direct method of measuring the incidence-rate of microfilaraemia is by one of the parasitological techniques described in WHO (1974). None of these methods is completely sensitive, and this together with the long pre-patent period in lymphatic filariases (especially *Wuchereria bancrofti* infections), the impeded access of microfilariae to the blood in cases of lymphatic damage, and the possible suppression of microfilaraemia or microfilarial production by immune mechanisms led McMahon et al (1979) to conclude that measures of incidence were ineffective in the evaluation of control programmes and hence by implication in the estimation of intensity of transmission.

Incidence rates of microfilaraemia can be calculated rather than measured using a reversible catalytic model (Muench, 1959) and a number of such studies have been published, notably by Hairston and Jachowski (1968) and Hairston and de Meillon (1968); alternatively two-stage catalytic models can be used (Hayashi, 1962) if it is assumed that positive persons who become negative never become positive again. The work of Hairston and Jachowski (1968) is especially interesting as it permits calculation of the rate of acquiring unmated worms as well as microfilaraemia, and demonstrates a remarkably close relationship between the acquisition of paired or unpaired worms and the development of filarial disease. However, there are a number of drawbacks to the use of catalytic models for the calculation of intensity of transmission, most importantly that they depend on the assumption that the age and sex specific microfilaraemia prevalence data on which they are based have remained constant for very long periods of time, and in many situations where estimates of intensity of transmission are required, the epidemiological picture is dynamic, and such assumptions are invalid. Nevertheless, this work has shown convincingly that intensity of transmission in at least one geographic area determines the development of disease.

Microfilaria prevalence and intensity data, preferably expressed in age and sex specific form, provide the most easily obtained retrospective estimates of intensity of transmission from examination of human populations. The collection of such data must be rigorously standardized in terms of technique and time of blood collection, volume of blood examined, technique of examination used, and at least in some areas where seasonal fluctuations in microfilaraemia occur (Southgate, 1979), month of the year. The quality of the data is subject to the same limitations discussed under incidence above, but imperfections of techniques and other sources of error are much less important in prevalence-rate studies. For comparative analytic studies, data may be expressed in summary form using five parameters (Sasa, 1967; Southgate, 1974): percentage of population positive;  $MfD_{50}$ ;  $a$  and  $b$  the regression coefficients of the cumulative percentage of microfilaria-positive cases against the microfilaria density in the log-probit scale; and  $r$  the correlation coefficient of these two variables. In general, high intensities of transmission will give rise to high percentages positive, high  $MfD_{50}$  values and low values for  $a$  and  $b$ ;  $r$  is of use as a check on the linearity of the relationship between cumulative percentage and microfilaria density since this method of analysis assumes that the distribution of microfilaria densities in a population approximates to the log-normal distribution, whereas often a closer fit to observed data is given by a truncated negative binomial distribution (Pichon et al, 1976a). Numerous studies in the past have shown that high microfilaria prevalence-rates and  $MfD_{50}$  values in a community are associated with high frequencies of disease. Many examples are given country by country in the section on geographic medicine of filariasis in Sasa (1976), although a large number of these studies can be criticized on the grounds that only prevalence-rates were quoted, the selection of persons for blood examination was non-random, unspecific or even unmeasured blood volumes were used and the times of blood sampling were often far from ideal. Nevertheless, a clear general picture emerges that the amount of filarial disease in a community increases with microfilaria prevalence-rates, and even more strikingly, where results are quoted, with intensity of microfilaria infection. Marked variations are seen in geographic regions, and the South Pacific islands for example, tend to have more disease at a given microfilaria prevalence-rate than urban areas of Asia. It must always be remembered that transmission, appearance of microfilaraemia and development of disease are occurring on different time-scales; Lagrault et al (1973) provided an ingenious classification of Bancroftian filariasis into four clinico-epidemiological types as follows:

Clinico-epidemiological type	Microfilaria prevalence	Microfilaria density	Clinical signs
1	++++	++++	++++
2	++++	++++	+
3	+	+	++++
4	+	+	+

Their explanation for the occurrence of these four types allowed for the vital factors of delay in development of microfilaraemia and clinical signs after infection, population movements, and invasion by filariasis of hitherto unaffected areas. They believed that Type 1 was a normal situation of stable intense transmission; Type 2 represented the relatively recent importation of filariasis; Type 3 occurred when young undiseased people, many of them microfilaraemic emigrated from an area, leaving behind the old, severely diseased and often amicrofilaraemic population groups; Type 4 was a normal situation of stable low-level transmission. However, Brunhes (1975) explained the Type 2 situation as due to a recent increase in intensity of transmission, and Type 3 as due to a recent decrease in intensity of transmission.

#### Intensity of transmission-measurements in the insect host

An alternative measurement of intensity of transmission is provided by the rate of effective contacts between infective larvae and man, estimated directly by observations of the man-biting rate of the local vector and of the proportion of vectors coming to bite man which have infective larvae in their head and mouthparts. The use of such an "entomological inoculation rate" is most developed in studies of the epidemiology of malaria, recently reviewed by Bailey (1982). In malaria, intensity of transmission is directly proportional to the entomological inoculation rate, the factor of proportionality being defined as the proportion of anopheline vectors having sporozoites in their salivary glands which are actually infective to man and expressed by the symbol  $\underline{b}$  by Macdonald (1952;1957). Use of these parameters is complicated in filarial infections by the fact that infective larvae are sexual and have to mature, meet and mate to produce microfilaraemia, whereas sporozoites only have to establish themselves in a hepatocyte and reproduce asexually to produce parasitaemia. Estimates of the numerical value of  $\underline{b}$  have been made in malaria by comparing the entomological inoculation rate in an endemic area with observed age-specific incidence-rates of parasitaemia in infants in the same area by Pull and Grab (1974);  $\underline{b}$  was estimated to lie between 0.015 and 0.026, and this estimation was subsequently refined to 0.054 - 0.093 by Port et al (1980), allowing for differential feeding by mosquitoes on adults and infants. At least one estimation of  $\underline{b}$  has been made for Bancroftian filariasis in Rangoon by Hairston and de Meillon (1968), comparing observed entomological inoculation rates with incidence-rates of microfilaraemia calculated from age-specific prevalence-rates using a reversible catalytic model. The astonishingly low value of  $6.45 \times 10^{-5}$  was obtained, but it has since been shown in the Solomon Islands by Webber (1975; 1977; 1979) and Webber and Southgate (1981) that use of this value of  $\underline{b}$  allowed predictions to be made about the decline of microfilaraemia in areas subjected to vector control that accorded closely with actual observations. The factors determining  $\underline{b}$  in sexually dioecious filarial infections are more numerous and more difficult to evaluate than in malaria, and in particular density, distribution, identification and sex-ratio of larvae in infective mosquitoes must be considered. These factors in their turn depend upon the parameters 2 (a) - (f), 3(a) - (e), 4 (a) and (b) and 5 (a) and (c) listed by WHO (1974,p27) together with the presence of facilitation, limitation or exponential proportionality in the mosquito-filaria host-parasite relationship (Pichon, 1974; Pichon et al, 1974; Pichon et al 1976b). It must also be remembered that ultra low level microfilaraemia, below the threshold of detectability using field techniques, may be capable of producing infections in a significant proportion of mosquitoes feeding on carriers, at least in the case of *W. bancrofti* transmitted by *Aedes* (Bryan and Southgate, 1976; Carme and Laigret, 1979) and probably in the case of *W. bancrofti* transmitted by *Culex* (Jordan, 1959) and *Brugia malayi* transmitted by *Mansonia* (Wharton, 1957 a and b). Preliminary observations (Bryan and Southgate, 1983) suggest that this phenomenon is not important in *W. bancrofti* transmitted by *Anopheles* probably due to the well-developed cibario-pharyngeal armature in this genus.

The greater complexity of  $\underline{b}$  in filariasis compared with malaria, and especially the effects of temperature and humidity in determining the rate of transfer of infective

larvae during a blood-meal, means that estimates of  $b$  are likely to show much greater geographic variability than in malaria. The impossibility of making theoretical predictions of all the variables determining  $b$  means that great efforts should be made to compare the observed entomological inoculation rate with calculated incidence-rates in a number of representative epidemiological situations in various parts of the world. Using the methods of Hairston and de Meillon (1968) with a reversible catalytic model, the efficiencies of transmission ( $b$ ) and their reciprocals (i.e. the numbers of infective bites required to produce a case of microfilaraemia), can be calculated from data published by a number of authors from various parts of the world as follows:

Location	Vector Species	Mean number of infective larvae per infective vector	Efficiencies of transmission ( $b$ )	Number of infective bites to produce microfilaraemia	Authors
Koro Island, Fiji	<u>Aedes polynesiensis</u>	2.3	$1.48_{-5} \times 10^{-5}$	67,764	Mataika <i>et al.</i> , 1970, 1971; Morgan, 1972
Marshall Territory, Liberia	<u>Anopheles gambiae</u>	2.5	$4.74_{-5} \times 10^{-5}$	21,111	Brinkmann, 1977; Maasch, 1973
Jaribuni, Kenya	<u>An. gambiae</u> <u>An. funestus</u>	1.5	$1.16_{-4} \times 10^{-4}$	8,611	Wijers, 1977
Mambrui, Kenya	<u>Culex pipiens fatigans</u>	3.4	$3.69_{-4} \times 10^{-4}$	2,706	Wijers, 1977
Calcutta, India	<u>C.p. fatigans</u>	3.6	$2.60_{-5} \times 10^{-5}$	38,406	Rozeboom <i>et al.</i> , 1968
Calcutta, India	<u>C.p. fatigans</u>	3.2	$7.03_{-7} \times 10^{-7}$	$1.42 \times 10^6$	Cubler <i>et al.</i> , 1974
Rangoon, Burma	<u>C.p. fatigans</u>	4.5	$3.15_{-5} \times 10^{-5}$	31,702	Hairston & de Meillon, 1968

All of these values are calculated from blood-survey data which to varying degrees underestimate the true prevalence rates of microfilaraemia; the Fiji data are based on 60 mm<sup>3</sup> blood-films, the Kenya data on 100 mm<sup>3</sup> blood samples obtained after daytime DEC provocation and counted in a counting-chamber, and the rest on 20 mm<sup>3</sup> blood-films. Nevertheless all show very low values for  $b$ ; the enormous discrepancy between the two values for Calcutta probably illustrates the problems, involved in estimating the entomological parameters in filariasis transmission.

The expressions used for the key entomological parameters involved in measuring intensity of transmission in the lymphatic filariases are probably best summarized in the terms Annual Biting Rate (ABR), Annual Infective Biting Rate (AIBR) and Annual Transmission Potential (ATP); the first and third of these have been used successfully in onchocerciasis (WHO, 1976). Recently Krishna Rao *et al* (1981) have suggested a single parameter, the Transmission Intensity Index, to express intensity of transmission. The segregation of most lymphatic filarial larvae which gain entry to the human body in a single lymphatic compartment, and the production of pathology by adult worms rather than by microfilariae, will mean that the relationship of the ATP to the development of microfilariae and disease will be very different in onchocerciasis and the lymphatic filariases.

### Transmission and disease

The comparatively small number of studies relating entomological transmission to development of microfilaraemia and development of disease have shown enormous variations in infective bites per person per year, microfilaria rates and densities and clinical sign rates in different parts of the world. In particular the efficiency of transmission and of disease production seems to be much higher in sub-Saharan Africa (Maasch, 1973; Brengues, 1975; Brunhes, 1975; Wijers and Kiilu, 1977) than in urban Asia (Hairston and de Meillon, 1968; Rozeboom *et al.*, 1968; Gubler and Bhattacharya, 1974). Wijers (1977) has suggested that strain differences in W. bancrofti may be responsible for these variations. What is certain is that reduction in transmission, whether occurring naturally as in Egypt from 1910 - 1965 (Southgate, 1979), resulting from vector control as in the Solomon Islands (Webber, 1979), or as a result of drug administration in Tahiti (March *et al.*, 1960), leads to a decline or disappearance of microfilaraemia incidence and disease incidence in W. bancrofti endemic areas; the same is true of both W. bancrofti and B. malayi areas in Sri Lanka where combined parasite and vector control have been carried out (Sasa, 1976). The effects of seasonality of transmission on the development of microfilaraemia and disease should be explored further.

At the present time, it is impossible to define a tolerable level of transmission in either Bancroftian or Malayan filariasis, as has been done for onchocerciasis in the Volta river basin (OCP) area of West Africa (WHO, 1976), such that a stated level of parasite transmission produces no disease or disease rates and severities that are of no public health significance to a community. However, the well-documented occurrence of large numbers of cases of clinical filariasis in American servicemen in the Pacific area in World War II in the absence of detectable microfilaraemia (Beaver, 1970) makes it seem highly probable that tolerable levels of transmission, at least for W. bancrofti will probably be below the level necessary to produce an incidence-rate of microfilaraemia i.e. zero, or very close to it.

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