Infection and disease in lymphatic filariasis: an epidemiological approach

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INTRODUCTION

A major question in the study of any parasitic disease is the relationship between infection and clinical disease. The public health importance of lymphatic filariasis has generated a large body of research in this area, both in laboratory studies (Ottesen, 1984,1989; Maizels & Lawrence, 1991) and in the field (Hayashi, 1962; Hairston & Jachowski, 1968; Denham & McGreevy, 1977; Vanamail *et al.* 1989*b*; Bundy, Grenfell & Rajagopalan, 1991; Srividya *et al.* 1991*b*). Despite this, there is still no conclusive explanation for the apparently complex relationship between infection and clinical disease observed in human communities. At least part of the problem may lie in the current impossibility of measuring adult worm burden *in vivo* (Pichon *et al.* 1980; Denham & Fletcher, 1987; Das *et al.* 1990; Grenfell *et al.* 1990). Although there has recently been significant progress in the development of immunological markers for infection status in humans (Ottesen, 1989; Day *et al.* 1991*a*), microfilaraemia is still the most reliable measure of current infection in the field. Studies in endemic areas indicate that, far from there being any simple direct relationship between microfilaraemia and disease status, it is possible to find some individuals with microfilariae in their blood but no disease, and indeed with all other combinations of infection and disease status (Hairston & de-Meillon, 1968; Hairston & Jachowski, 1968; Beaver, 1970; Bryan & Southgate, 1976; Denham & McGreevy, 1977; Pani *et al.* 1991). Furthermore, the proportions of people in different categories are often observed to vary between endemic areas (Denham & McGreevy, 1977; Day *et al.* 1991*a*).

Immunological explanations of these patterns have tended to concentrate on the possible role of (possibly genetic) differences between groups of individuals in generating various categories of response (Ottesen, 1980, 1984). An alternative approach is to focus on the age-specific *dynamics* of infection and disease using simple mathematical models (Hairston & de-Meillon, 1968; Hairston & Jachowski, 1968; Vanamail *et al.* 1989*b*; Bundy *et al.* 1991; Srividya *et al.* 1991*b*). Recent work along these lines provides evidence for the operation of density-dependent (possibly immunologically related) limitations on infection rates (Vanamail *et al.* 1989*b*; Das *et al.* 1990), as well as a relatively simple relationship between the rate of loss of infection and the onset of chronic disease (Bundy *et al.* 1991; Srividya *et al.* 1991*b*). This parallels much current laboratory-based work, which provides evidence for the dynamic nature of immunity to lymphatic filarial infections in animal models and humans from endemic areas (Denham & Fletcher, 1987; Day, Gregory & Maizels, 1991*b*) and the potentially important role of *immunological tolerance* in modulating the dynamics of infection and disease (Nutman, Kumaraswami & Ottesen, 1987; Lammie *et al.* 1991; Maizels & Lawrence, 1991). The tolerance hypothesis is that appropriate parasite antigens may induce an anergic (tolerant) state in the host, increasing the duration of infection and perhaps reducing subsequent immunopathology (Nutman *et al.* 1987; Maizels & Lawrence, 1991). Tolerance may be acquired either transplacentally (Weil *et al.* 1983) (neonatal tolerance) or from subsequent infection (Maizels & Lawrence, 1991). Recently, Lammie *et al.* (1991) have produced epidemiological evidence for the operation of neonatal tolerance, in terms of a significantly higher prevalence of infection in the children of infected (compared to uninfected) mothers.

This paper discusses the relationship between infection and disease in lymphatic filariasis from a population dynamic viewpoint, based on data from both field and laboratory disciplines. It begins by drawing together the results of recent work in this area, and then refines current models to provide a preliminary analysis of the epidemiological implications of neonatal tolerance.

DYNAMICS OF INFECTION AND DISEASE

The principal dynamic processes underlying the infection/disease relationship in lymphatic filariasis are summarized schematically in Fig. 1. The fol-

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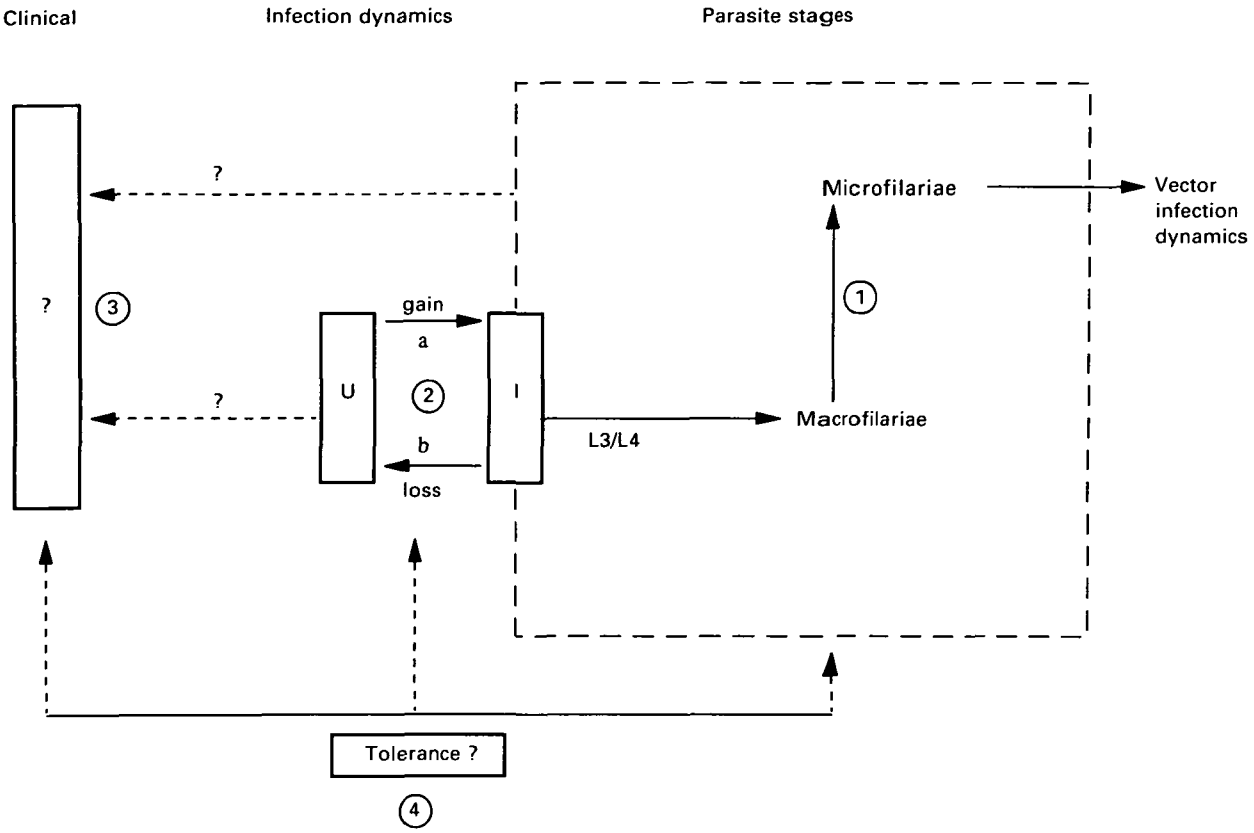

Fig. 1. Schematic outline of processes involved in the dynamics of infection and clinical disease in lymphatic filariasis. Circled numbers refer to sections in the text. U, proportion mf negative; I, proportion mf positive; ? current areas of uncertainty.

lowing sections discuss how theoretical models, along with the analysis of field and laboratory data, can be used to shed light on these relationships.

Macro- and microfilarial dynamics

The relationship between macro- and microfilarial intensity. The only current way to shed light on this relationship is by the experimental infection of animal models (Wong, 1963; Denham & McGreevy, 1977; Denham & Fletcher, 1987; Wenk, 1991), and subsequent (ideally serial) sacrifice of groups of individuals to obtain parallel estimates of worm burden and microfilarial density in the blood. Overall, the best model for human filariasis (in terms of both infection dynamics and pathology) is the cat/*Brugia pahangi* model (Denham *et al.* 1972*b*, 1983; Denham & Fletcher, 1987). Fig 2A summarizes the observed relationship between macro- and microfilarial counts from an extensive series of primary infection experiments with the cat model, carried out by D. J. Denham and his co-workers (Denham *et al.* 1972*a*; Denham & McGreevy, 1977). The simplest hypothesis here would be a linear proportional relationship between adult burden and the blood density of microfilariae. Although the two sets of counts are significantly positively related (Fig. 2A), there is clearly much variability. In a more extensive analysis, Grenfell *et al.* (1991) show that this relationship varies in a complicated way with the infection regime, although the overall pattern, of a positive but variable relationship, remains. An important point to note is that there is no evidence of saturation of microfilarial output at high microfilarial density–such a pattern would indicate the operation of a density-dependent constraint on *per capita* fecundity.

The cat model results are more variable than is observed in some other model systems (Wenk, 1991). Explaining these sources of variation in terms of the complex relationship between macrofilarial burden and microfilarial blood density is clearly a major priority for future experimental work.

Microfilarial dynamics in the field. Estimates of microfilarial intensity using night blood samples from human populations in endemic areas are even more variable, largely because a proportion of (as yet uninfected or formerly infected) individuals are mf-negative (Sasa, 1974; Das *et al.* 1990; Grenfell *et al.* 1990). The best empirical statistical description of mf frequency distributions in the field is a zero-truncated negative binomial distribution (Pichon *et al.* 1980; Grenfell *et al.* 1990), which reflects a random (Poisson) blood sampling process of a skewed mf density distribution in the blood. Recently, Das *et al.* (1990) have used a detailed age-stratified microfilarial data set for bancroftian

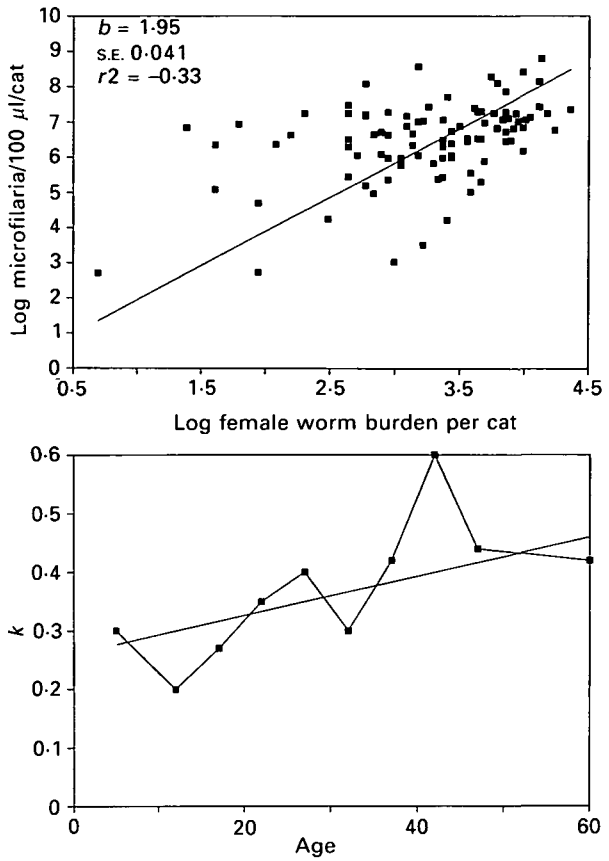

Fig. 2. (A) The relationship between microfilarial blood counts and adult female worm burdens in cats infected with *Brugia pahangi* (based on Denham *et al.* 1972*a*) plus unpublished data from D. A. Denham (Michael *et al.*, manuscript in preparation). Results were taken from cats given a primary infection of either 100 or 200 L3. (■) Natural logarithms of the mf counts measured in 100 μl of blood samples of each cat (averaged over 3–5 sample counts over 21 days prior to host sacrifice and post-mortem). (—) Slope of a simple linear regression through the origin ($t = 46{\cdot}813$, $P > 0{\cdot}001$). (B) Age-specific variation in the degree of aggregation (measured by the negative binomial parameter (k) of 20 μl of microfilarial blood counts from Pondicherry, South India (Rajagopalan *et al.* 1989). Estimates are from a joint maximum likelihood fit to a total sample of 24946 individuals (Das *et al.* 1990).

filariasis (from Pondicherry, South India) to demonstrate a significant decrease with host age in the degree of aggregation of the mf distribution (indicated by an increase in the negative binomial parameter, k – Fig. 2B). This effective shortening of the tail of the mf distribution with age provides indirect evidence for the operation of a density-dependent constraint on infection – interestingly, a similar analysis for brugian filariasis in Kerala (where transmission rates are much lower) does not indicate this pattern (Srividya *et al.* 1991*a*). Obviously, the bancroftian filariasis result must be treated with caution, given the observed variability of mf counts (Fig. 2A); however, it does corroborate recent evidence of immunological constraints on parasite

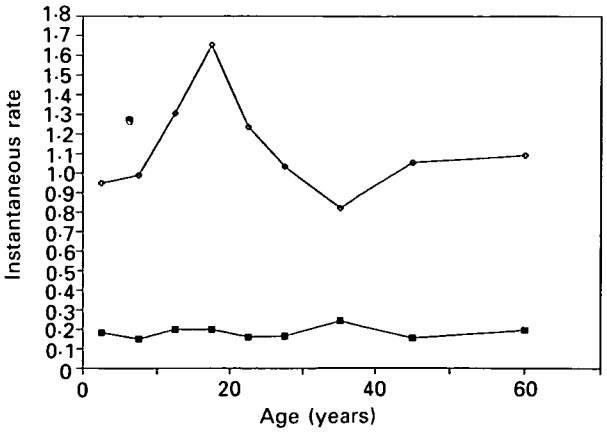

Fig. 3. Age-specific *per capita* instantaneous gain (◇) and loss (■) rates of infection (measured by mf prevalence) with *Wuchereria bancrofti* in Pondicherry, South India. Parameters were estimated from a detailed longitudinal microfilarial data set (Vanamail *et al.* 1989*b*).

establishment, both in the cat model (Denham *et al.* 1972*b*, 1983) and from field data (Day *et al.* 1991*a*).

Transmission dynamics

Prevalence or intensity? The ideal mathematical model for filariasis dynamics would use the intensity of the various parasite stages (L3), (mf), (adults etc.) as its basic coinage. This is particularly important in terms of modelling vector infection dynamics, and a number of studies have addressed this problem (Hairston & Jachowski, 1968; Pichon, 1974; Pichon *et al.* 1980; Wada, Tsuda & Suenaga, 1989; Rochet, 1990). Quantifying the vector transmission process is a vital step in assessing the performance of control interventions, for example along the lines of recent successful models for onchocerciasis (Remme *et al.* 1986). However, the difficulty of assessing the relationship between infection and disease in lymphatic filariasis (and the associated problem of quantifying adult burdens) would seem to make this a more difficult task. Fortunately, as a first step in solving this problem, we can use models based on parasite *prevalence*.

Catalytic infection models. A number of workers (and in particular the seminal study of Hairston & Jachowski, 1968) have used catalytic infection models to represent the age distribution of microfilarial prevalence in the human population (Hayashi, 1962; Hairston & Jachowski, 1968; Hairston & de-Meillon, 1968; Webber, 1975; Remme *et al.* 1986; Wada *et al.* 1989; Vanamail *et al.* 1989*b*; Srividya *et al.* 1991*b*). Catalytic models (Muench, 1959) assume that the host–parasite system is at equilibrium, and measure the acquisition and loss of infection prevalence (measured here by mf positivity) with host age. Recently, Vanamail *et al.* (1989*b*) and Srividya *et al.* (1989*b*) have adopted a reversible catalytic model

(proposed for filariasis by Hairston & Jachowski, 1968) to analyse detailed age-prevalence data for bancroftian filariasis from Pondicherry, South India. Their model can be expressed in the following rate equations

$$\frac{dI(t)}{dt} = aU - bI$$

$$\frac{dU(t)}{dt} = -aU + bI. \quad (1)$$

Here, $U(t)$ and $I(t)$ are respectively the proportions mf negative and positive at age t ($U(O) = 1$, $I(O) = O$), and the rates of transition between them are controlled by the *per capita* gain and loss rates of infection, denoted by a and b respectively. Equations (1) lead to the standard solution (for a and b independent of age)

$$I(t) = \frac{a}{a+b}[1 - \exp(-(a+b)t)], \quad (2)$$

which gives the prevalence of infection at age t. Equation (2) indicates a relatively rapid rise in prevalence in younger individuals, followed by an asymptotic approach with age to a plateau at $a/(a+b)$ (Hairston & Jachowski, 1968).

Vanamail *et al.* (1989) fitted a refinement of this model to allow for variations in a and b with age to detailed longitudinal mf data for Pondicherry. The resulting parameter estimates (Fig. 3) suggest that b is relatively independent of age, and indicates a mean duration of infection, $1/b = 5$ years, within the range of previous estimates (Bundy *et al.* 1991). By contrast, the rate of gain of infection (a) peaks relatively sharply in the young adult age classes. This effect is responsible for a slight but significant convexity in the observed mf age–prevalence profile for Pondicherry (Fig. 4A).

In terms of our comparison of the results of field and laboratory approaches, this peak and subsequent decline in infection rate with age is again consistent with immunological evidence of the operation of immunity to parasite establishment (Denham & Fletcher, 1987; Vanamail *et al.* 1989*b*; Day *et al.* 1991*b*). Other possible explanations for this pattern will be discussed below.

Dynamics of chronic disease

Fig. 4 shows the age–prevalence of microfilaraemia and chronic obstructive lymphatic disease in Pondicherry (Bundy *et al.* 1991; Srividya *et al.* 1991*b*) and coastal Tanzania (McMahon *et al.* 1981), which are respectively low and high prevalence areas for bancroftian filariasis. Because diagnosis of chronic obstructive bancroftian filariasis is much more unequivocal in males (Vanamail *et al.* 1989*a*), Fig. 4 is based on male data (similar arguments to those that follow can also be applied to the female data sets; Srividya *et al.* (1991*b*)). By contrast with the

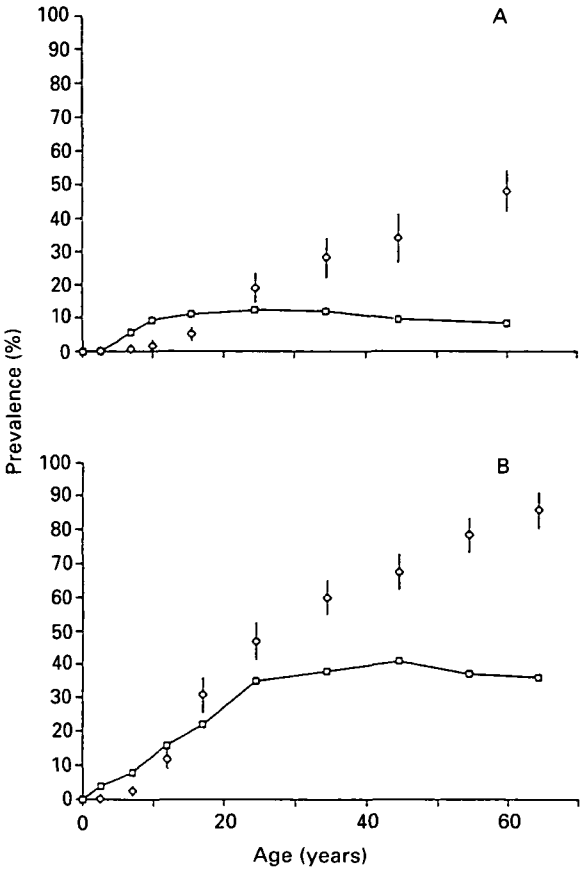

Fig. 4. The lack of a direct relationship between the age–prevalences of microfilaraemia (□) and obstructive lymphatic disease (◇) in the male populations from (A) Pondicherry, South India and (B) Tanzania (McMahon *et al.* 1981; Srividya *et al.* 1991*b*).

peak and slight decrease in microfilarial prevalence, disease prevalence in these (and other) data sets increases more or less linearly to significantly higher levels than the peak mf prevalence (Hairston & Jachowski, 1968; Bundy *et al.* 1991; Srividya *et al.* 1991*b*). Since the majority of chronically infected individuals tend to be mf-negative (Vanamail *et al.* 1989*b*), this pattern suggests that individuals may lose infection and then proceed to chronic disease.

In terms of the basic infection model (equations (1)), the prevalence of previously (but not currently) infected individuals is given simply by

$$R(t) = 1 - \exp(-at) - I(t), \quad (3)$$

where $I(t)$ (equation (2)) is the current prevalence. Fig. 5 shows a plot of R in males as a function of age for Pondicherry and Tanzania, superimposed on the equivalent age–prevalence curves of chronic disease. For Pondicherry, the proportion who have previously been infected matches the prevalence of chronic obstructive disease very closely, and this correspondence is also apparent in an analysis of the equivalent female data (Bundy *et al.* 1991; Srividya *et al.* 1991*b*). The fit for the Tanzanian data is also good in younger individuals; however, R progressively under-estimates the prevalence of clinical disease

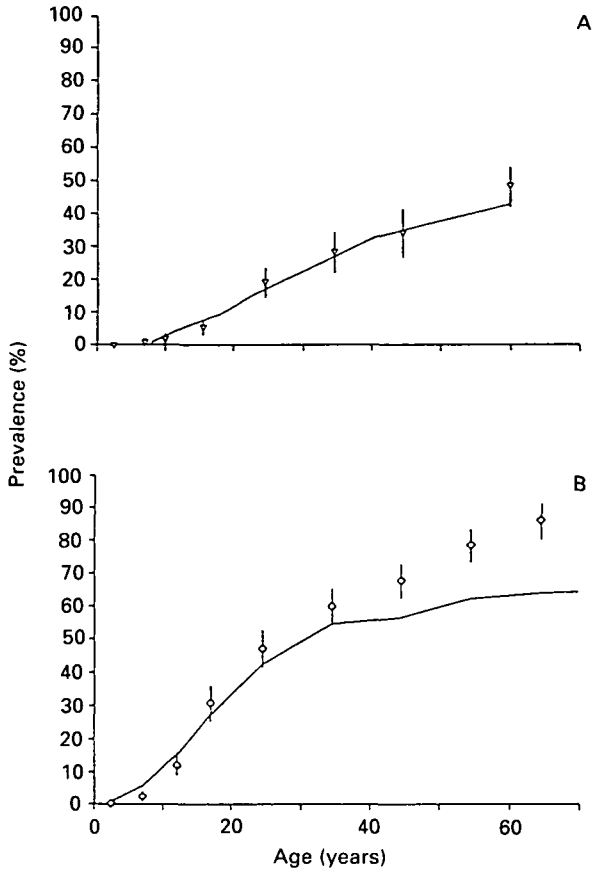

Fig. 5. The relationship between the estimated age-specific proportion of the population who have been infected but have subsequently become amicrofilaraemic (—) and the observed point prevalence of obstructive lymphatic disease (▽, ◇). Based on data from (A) Pondicherry (Vanamail *et al.* 1989*b*; Srividya *et al.* 1991*b*) and (B) Tanzania (McMahon *et al.* 1981). The estimated proportion with a history of microfilaraemia corresponds closely to the observed prevalence of disease. Note that the prediction and observation are derived from entirely different and independent data sets (see Bundy *et al.* 1991).

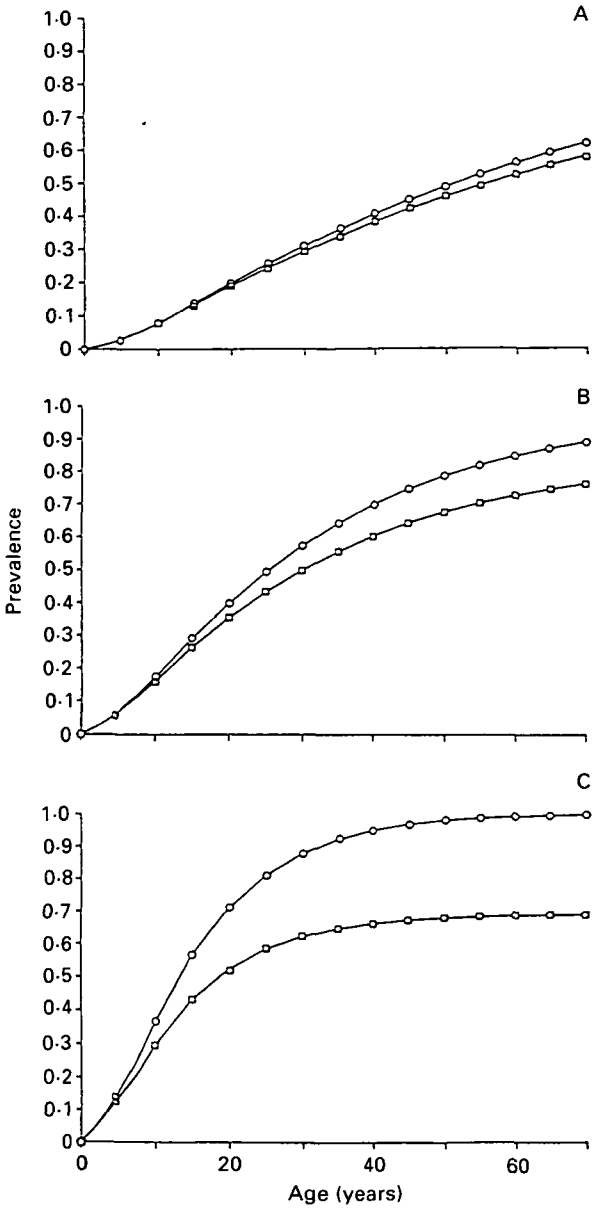

Fig. 6. The estimated proportion of the population who have at any time been microfilaraemic (□) and the cumulative proportion who have become amicrofilaraemic (○) in areas of (A) low (Pondicherry), (B) medium (Calcutta) and (C) high (Tanzania) incidence. The difference between the lines represents the population who have secondarily become microfilaraemic. (Data from Gubler & Bhattacharya, 1974, McMahon *et al.* 1981; Vanamail *et al.* 1989*b*). Note that the number with secondary microfilaraemia is related to the incidence of infection.

above around age 30. Since Tanzania has a much higher infection prevalence than Pondicherry, this discrepancy could be due to the omission of the proportion of individuals who have lost infection in the past and are currently reinfected. Fig. 5 explores how this addition affects the estimation of those susceptible to chronic disease in regions of different endemicity for lymphatic filariasis. The inclusion of previous infections is likely to be insignificant in low prevalence regions such as Pondicherry, but is more important and may account for the discrepancy between disease prevalence and R in highly endemic regions such as Tanzania (Fig. 6: Bundy *et al.* 1991; Srividya *et al.* 1991*b*).

These results concur with current immunological ideas, that individuals lose infection and then experience immunopathological reactions which lead to chronic disease (Ottesen, 1980, 1984, 1989; Bundy *et al.* 1991; Srividya *et al.* 1991*b*). An important point to note is that equation (4) successfully represents the observed disease prevalence without requiring a class of 'endemic normal' individuals, who are immune from infection and do not acquire disease (Ottesen, 1984, 1989). Future models in this area need to be refined to allow for additional immunological classes (and the spectrum of acute clinical manifestations), and the data analysis extended to consider data sets from a range of

epidemiologically distinct areas. However, the major priority here is to bring together detailed and extensive epidemiological data sets, such as that for Pondicherry, and laboratory-based immunological techniques for identifying the infection and disease status of individuals.

Epidemiological consequences of immunological tolerance

The infection model. One area where laboratory and field studies of lymphatic filariasis are currently being brought together is in investigating the role of immunological tolerance (Weil *et al.* 1983; Hitch, Lammie & Eberhard, 1989; Maizels & Lawrence, 1991; Lammie *et al.* 1991). Of particular note here is a study, by Lammie *et al.* (1991), of the mf prevalence and immunological status of children in Leogane, Haiti, which is a region of high prevalence for bancroftian filariasis. These authors found that the prevalence of microfilaraemia in children up to age 10 was significantly higher in the offspring of infected mothers, compared to those of uninfected mothers (28·4% for children in the former group versus 9·7% for children in the latter). Since there was no such association with the father's infection status, and uninfected children were less immunologically responsive to filarial antigens if their mothers were infected, this picture is consistent with the operation of neonatal tolerance (Lammie *et al.* 1991; Maizels & Lawrence, 1991).

We can explore the epidemiological implications of neonatal tolerance using a simple extension of the reversible catalytic model (equations (1)). Since the mf age–prevalence curve reaches an approximate plateau in adults (Fig. 4), and is fairly similar in males and females (Rajagopalan *et al.* 1989), we can assume that this average adult prevalence, P^*, determines the proportion of individuals born to infected mothers. Dividing the population into maternally-tolerized individuals (Group 1) and untolerized individuals (Group 2) then leads to the following expression for P^* at equilibrium

$$P^* = P^* I_1^* + (1 - P^*) I_2^*. \tag{4}$$

Here, I_1^* and I_2^* are the adult infection prevalences within Groups 1 (neonatally tolerized individuals) and 2 respectively and, for example, $P^* I_1^*$ is the contribution of Group 1 to the total adult prevalence. Rearranging equation (4):

$$P^* = \frac{I_2^*}{1 - I_1^* + I_2^*} \tag{5}$$

allows us to calculate how total adult infection prevalence is influenced by the proportion of tolerized individuals infected. Finally, we can move from prevalence to infection dynamics by noting that the within-group adult prevalences correspond approximately to the maximum (asymptotic) infection rate of the reversible catalytic model, i.e. from equation (2)

$$I_j(t) = \frac{a_j}{a_j + b_j} \quad (j = 1,2). \tag{6}$$

Predicted patterns of infection. Equations (5) and (6) express the adult prevalence in terms of the gain ($a1$ and $a2$) and loss rates ($b1$ and $b2$) of infection in Groups 1 and 2. The simplest epidemiological model for the higher infection rate observed in children of infected mothers (Lammie *et al.* 1991) is that the infection rate of the neonatally tolerized group is relatively large (i.e. $a_1 > a_2$), whereas the corresponding loss rates are the same ($b_1 = b_2$). Assuming from above that $b_1 = b_2 = 0{\cdot}2$ per year, a_1 and a_2 can be calculated from the average infection prevalence up to age 10 ($I_1(10) = 0{\cdot}284$, $I_2(10) = 0{\cdot}097$; Lammie *et al.* (1991)) from an iterative solution of

$$I_j(t) = \int_0^t I_j(s)\, ds \quad (j = 1,2;\ t = 10), \tag{7}$$

using equation (2). This procedure yields the estimates $a_1 = 0{\cdot}133$, $a_2 = 0{\cdot}0372$, i.e. on the basis of this simple model, Group 1 (the tolerized individuals) have an infection rate 3·57 times higher than Group 2.

The implications of this relatively large difference in infection rates between the two groups are explored in Fig. 7. Fig. 7A shows the expected age–prevalence of infection (Groups 1, 2 and the total) in a high prevalence area. It illustrates the basic result that, when adult prevalence is high, a substantial proportion of individuals will have been born to infected mothers (and will therefore potentially be tolerized). This relationship is explored more systematically in Fig. 7B, which compares the average adult prevalence of Group 1 and Group 2 infections predicted at a range of transmission rates (corresponding to areas with different overall infection prevalences). The effect of infection intensity is dramatic. In low prevalence areas (such as Pondicherry), relatively few females will give birth whilst infected, so that the overall prevalence is dominated by group 2 individuals. As infection increases, however, neonatal tolerance becomes potentially more important, and would dominate the adult prevalence in regions of high infection.

It is important to assess how these results depend on the model's assumptions. Firstly, although the patterns shown in Fig. 7 are sensitive to the difference in infection rate between the two groups, the same qualitative patterns apply as long as $a_1 > a_2$. Other important assumptions concern the relative loss rate of infection in the two groups and their basic infection dynamics. In terms of the infection loss rates, tolerance is, if anything, likely to prolong infection (Maizels & Lawrence, 1991) (i.e. $b_1 < b_2$) – in the model the result of this is to increase the

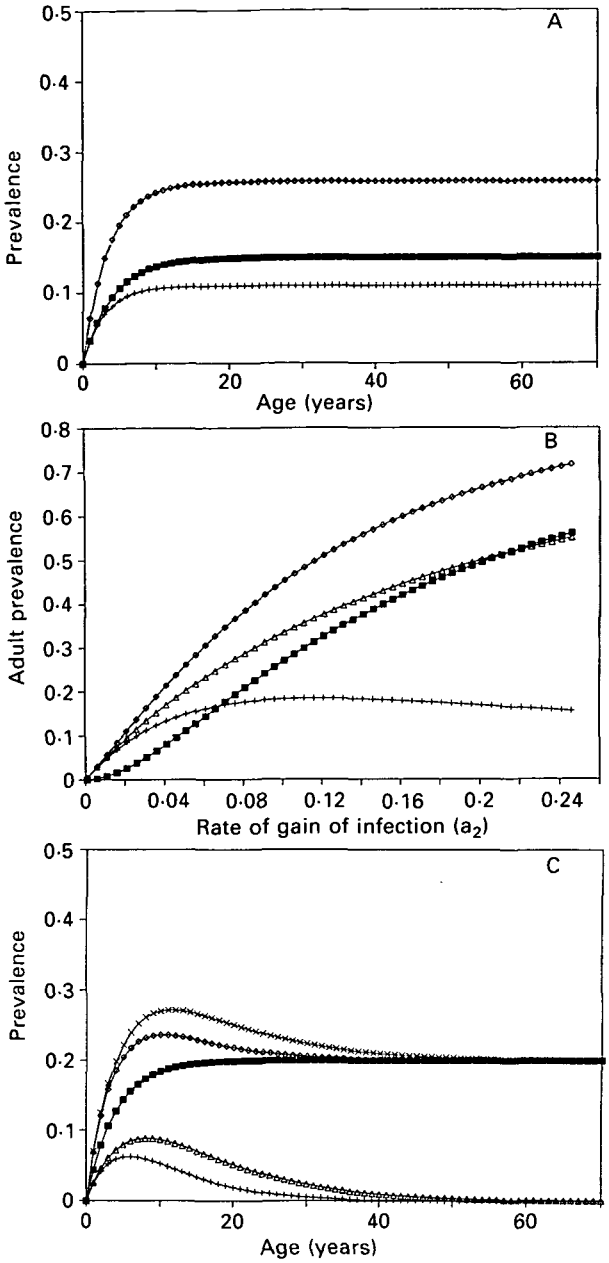

Fig. 7. Results of a simple model for the effects of maternal tolerance on the infection-disease relationship in lymphatic filariasis. All the infection dynamics results assume that the infection rates of tolerant (1) and non-tolerant (2) individuals obey $a_1/a_2 = 3{\cdot}57$, and vary a_2 to simulate different regions. (A) Age–prevalence of infection curves for neonatally-tolerant (+), and untolerized individuals (■) and the total population (◇); based on equation (4) with $b_1 = b_2 = 0{\cdot}2$ per year and $a_2 = 0{\cdot}05$. (B) Adult prevalences (tolerized, not tolerized and total, based on equation (7)), with symbols as in (A) at a range of basic infection rates (a_2); the adult prevalence of the equivalent populations without tolerance (◇) is also shown. (C) Age–prevalence curves as in (A) but using equation (8) for the prevalence of tolerized individuals; (i) non-tolerized individuals (■), (ii) tolerized individuals and total population assuming $b_1 = 0{\cdot}2$ (× and ◇, respectively), (iii) tolerized individuals and total population assuming $b_1 = 0{\cdot}1$ (△ and +, respectively). Because non-tolerant individuals make up a higher proportion of the population here, their infection prevalence is higher than in (A).

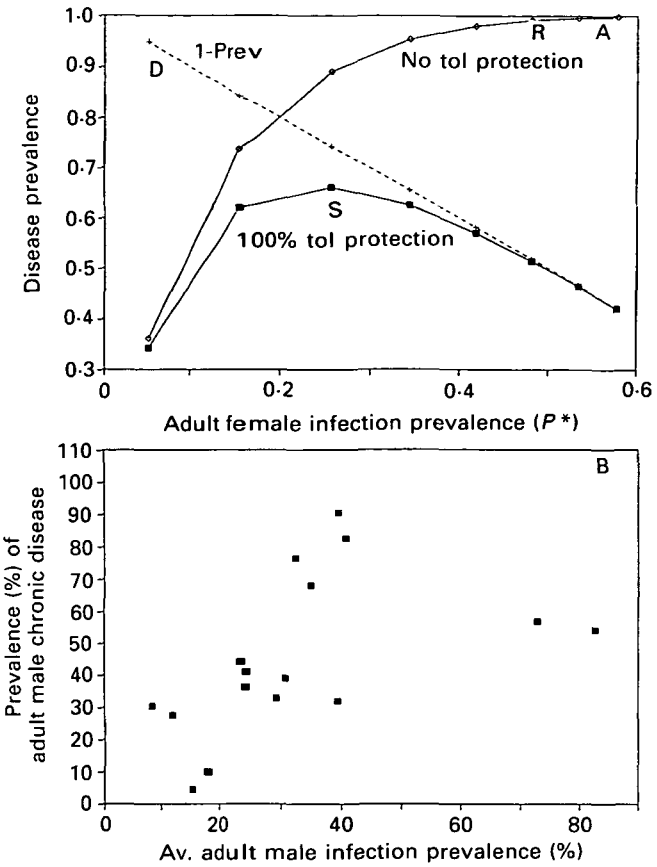

Fig. 8. (A) A simple model for the effects of maternal tolerance on the potential for chronic disease. The predicted relationship between adult mf-prevalence (P^*) and the maximum (D, equation (9)) and adult (S, equation (10)) proportions of chronic cases assuming 100% protection of neonatally-tolerized individuals against chronic disease. The estimated chronic disease prevalence without tolerance protection (R, equation (3)) is also shown for comparison. (B) Equivalent field data from published studies in a range of endemic areas. The data used were as follows: India (Nair, 1961; Dondero *et al.* 1976; Pani *et al.* 1991), Bangladesh (Barry, Ahmed & Khan, 1971; Wolfe & Aslamkhan, 1972), Philippines (Grove, Valeza & Cabrera, 1978), Papua New Guinea (Knight *et al.* 1979; Kazura *et al.* 1984), Tanzania (McMahon *et al.* 1981), Kenya (Wijers, 1977) and Nigeria (Udonsi, 1988). Further details will be given in a subsequent paper.

relative prevalence of tolerant individuals (since they lose infection more slowly).

Since tolerance of L5 and adult parasite antigens is likely to be stage specific (Ottesen, 1989; Maizels & Lawrence, 1991) this implies that the infection dynamics of tolerant and non-tolerant individuals may be qualitatively different – for example, tolerant individuals may harbour their first patent infection for a relatively long period, during which time they build up a strong immunity to infective larvae which inhibits further infections. In terms of the basic model, a single period of infection for neonatally-

tolerant individuals modifies their infection prevalence to

$$I_1(t) = P^* \frac{a_1}{b_1 - a_1}[\exp(-a_1 t) - \exp(-b_1 t)], \quad (8)$$

which is a convex curve, peaking and then subsequently declining with age. The resulting model age-prevalence curves (Fig. 7C) are far less dominated by the proportion of neonatally-tolerant individuals (and this is not strongly affected by increasing their duration of infection, $1/b_1$). Interestingly, equation (8) generates a peaked age–prevalence curve for the total population (recall that observed mf age–prevalence curves also tend to be slightly peaked; Fig. 4), even though the model does not make any direct allowance for acquired immunity (although immunity does play an indirect role in protecting tolerized individuals from further infection). Qualitatively similar patterns to these results are generated if (instead of modulating the loss rate of infection) the gain rate (a_1) of neonatally-tolerized individuals declines with age.

Clinical perspective. Whatever the assumption about the infection dynamics of neonatally-tolerized individuals, the above results indicate that they may make up a significant proportion of the total population in regions of moderate to high transmission intensity (Lammie *et al.* 1991). As yet, there is no direct empirical measure of the clinical consequences of neonatal tolerance, although the available immunological evidence indicates that tolerant individuals may be protected from immunopathology and subsequent disease (Ottesen, 1989; Lammie *et al.* 1991; Maizels & Lawrence, 1991). Here we explore the epidemiological implications of the most extreme version of this hypothesis – that neonatally-tolerized individuals are completely protected from subsequent clinical disease. In other words, if P^* is the average infection prevalence of adult females in a given region, then the proportion born to mothers who are not infected:

$$D = 1 - P^* \quad (9)$$

is the *maximum* proportion of the population who can proceed to clinical disease. The corresponding proportion of non-tolerized individuals who have experienced and lost infection (i.e. our simple index of potential risk of disease; cf. equation (3)) can then be calculated from

$$S(t') = [1 - P^*][1 - \exp(-a_2 t') - I_{n2}(t')], \quad (10)$$

here, $S(t')$ is the potential disease prevalence in adults (with mean age t'), and $I_{n2}(t')$ is the associated prevalence of newly infected non-tolerized individuals. Fig. 8A shows the resulting relationships between D, S and P^*, over a range of prevalences reflecting regions with different transmission rates. This very simple model suggests that adult disease prevalence should rise to a *peak* with increasing infection incidence, and then decline at high levels of transmission as the proportion of neonatally-tolerized individuals increases. Fig. 8A also shows the estimated prevalence of chronic disease in the absence of any tolerance effect (i.e. R in equation (3)). This disease pattern is significantly different from S, increasing monotonically with infection prevalence to an asymptote of 100% disease prevalence.

Although a preliminary comparison with equivalent field data from a number of endemic regions (Fig. 8B) does indicate a peak in disease prevalence as a function of infection prevalence, these results are preliminary and, in particular, do not take account of the calibration between blood mf sampling volumes in different studies (Grenfell *et al.* 1990). Clearly, both the model, the analysis of comparative epidemiological data and, in particular, the collection of more immuno-epidemiological information on the relationship between tolerance and immunopathology are necessary to clarify this issue. It is particularly important to establish the precise relationship between infection and disease prevalence. For instance, even if (as seems likely from Fig. 8) neonatal tolerance does not provide 100% protection against disease, a negative relationship at high transmission intensities could have important long-term implications for control programmes. The implication of the extreme case shown in Fig. 8A is that control programmes which only partly reduce infection prevalence in hyperendemic areas could cause the proportion of protected tolerant individuals to decrease in the long term.

CONCLUSIONS

In addition to its public health importance, lymphatic filariasis presents a considerable opportunity to bring together field and laboratory work in elucidating the epidemiological implications of host immunity and immunopathology. The important step here is to consider the relationship between infection and disease as a *dynamic* process.

As discussed above, recent epidemiological studies have approached this problem by analysing large detailed data sets, with simple mathematical models which emphasize the dynamics of transition from infection to disease. By contrast, immunological studies on human subjects in endemic areas have concentrated on obtaining detailed evidence for immunological mechanisms, based on relatively smaller samples (Day *et al.* 1991*b*). The future priority is to combine these approaches, in immunological studies based on large, well-structured epidemiological data sets. The emphasis on such large quantities of data is necessary because of the considerable variability of parasitological surveys based on microfilarial counts. This distributional issue arises partly from the central problem of assessing macrofilarial burdens in the field–animal

models, and in particular the cat–*Brugia pahangi* model, provide the way forward here in terms of calibrating immunological indices of infection for use in the field. The ability to assess the immunological and parasitological status of individuals in the field generates the prospect of elucidating the epidemiological significance of proposed epidemiological categories such as 'endemic normals'. The epidemiological evidence reviewed above suggests that eventual chronic disease in males may be an inevitable consequence of infection in most individuals – however, only direct immuno-epidemiological measurements in the field can be used to confirm this.

Such studies are also the best means to clarify the impact of neonatal and peripheral tolerance on the epidemiology of lymphatic filariasis. The potential importance of neonatal tolerance indicated by the simple model described above emphasizes the need for longitudinal studies of the impact of maternal infection and early experience on subsequent clinical status. The impact of tolerance and other population heterogeneities can only be effectively assessed by collaborations between laboratory and field.

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