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AGE SPECIFIC PATTERNS OF CHANGE IN THE DYNAMICS OF *WUCHERERIA BANCROFTI* INFECTION IN PAPUA NEW GUINEA

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Abstract. Results of a longitudinal study of the age-specific dynamics of *Wuchereria bancrofti* infection in a community of East Sepik Province, Papua New Guinea (PNG) are described. Microfilarial (mf) density and serum levels of *W. bancrofti* phosphorylcholine-containing antigen (PC-Ag) in individuals were used as indirect measures of adult worm burden. These parasitological data were collected from 126 subjects >4 years of age at two time points, 12 months apart, prior to the administration of the antifilarial drug diethylcambamazine (DEC). No significant changes in levels of mf density were observed for the study population between these two time points. However, significant changes in the levels of circulating PC-Ag were noted in subjects ≤20 years of age, but not in subjects >20 years of age, between these two time points. The apparent shorter half life of circulating PC-Ag compared to that of mf makes antigenemia a more sensitive measure of the dynamics of adult worm populations. These data are discussed in terms of a basic mathematical model describing the dynamics of adult worm populations in relation to their life expectancy and attrition of larvae during establishment. Consideration of these data in the context of this simple immigration/death model suggests that the differences observed in patterns of change in intensity of infection between subjects ≤20 years old and those >20 years old may be consistent with the acquisition of resistance to superinfection with increasing age.

The role of protective immunity in the epidemiology of lymphatic filariasis in humans is unknown.[1] This issue has recently become of interest as the development of vaccines against filarial parasites is being considered.[1] Evidence from trickle infection experiments in *Brugia pahangi*-infected cats, an important animal model for human filariasis, indicates that cats become resistant to challenge infection after many repeat infections with infective larvae (L3).[2] This exposure-dependent acquisition of resistance to reinfection/super infection in cats suggests that humans repeatedly exposed to L3 in an area of stable transmission may also acquire resistance with time. Recent epidemiological studies of reinfection with *Schistosoma mansoni*[3] and *S. haematobium*[4] in humans after treatment with a drug that kills adult worms have examined the role of acquired resistance in schistosomiasis. These longitudinal studies, which controlled for age-specific as well as individual variation in exposure to infection, have provided strong evidence that humans acquire resistance to reinfection with increasing age (i.e., experience of infection) and that this resistance is immune-mediated. In contrast, no evidence for acquired resistance to intestinal nematode infections has been demonstrated by reinfection studies after chemotherapy.[5]

Similar age-structured population studies of reinfection rates after chemotherapy have not been attempted in lymphatic filariasis. This is in part due to the fact that diethylcambamazine (DEC), the drug currently available for treatment of lymphatic filariasis in humans, is only partially macrofilaricidal;[6] this makes reinfection data difficult to interpret. Inability to directly quantitate adult worm burdens, where this life cycle stage resides in the lymphatics, further complicates such studies. The relative inefficiency of transmission after chemotherapeutic intervention with DEC would require that the time scale to evaluate reinfection rates in lymphatic filariasis be considerably longer than that for schistosomiasis and intestinal nematode infections. Field strategies to control for individual variation in exposure to the mosquito vector which transmits the infective stages of lymphatic filariae have not been attempted.

This paper describes a longitudinal study aimed at defining the dynamics of *Wuchereria bancrofti* infection in the absence of drug treatment. This study was designed to address two questions. First, do age-specific changes in intensity of infection occur in a *W. bancrofti* endemic area of Papua New Guinea (PNG) over a 12-month period? Second, if such changes occur, can they be attributed to an age-dependent acquisition of resistance to superinfection?

Two indirect measures of intensity of adult worm burden were used. The first was microfilarial (mf) density, which is an indicator of the reproductive output of adult male and female worms. The relationship of mf density to adult worm burden is unclear and likely to be complicated by anti-mf immunity and the age of the adult worms. Presumably, mf density and adult worm burden are related in some density-dependent manner, as is the case for both schistosomes and intestinal nematodes in which fecundity per female worm declines with increasing worm burden.[5] The second index of *W. bancrofti* adult worm burden was the measurement of levels of circulating phosphorylcholine-containing antigen (PC-Ag). This antigen, M_r 200,000 by Western blotting, is specifically found in the circulation of humans infected with *W. bancrofti*,[7-10] and is thought to be an indicator of adult worm burden[11] for a number of reasons. First, levels of this molecule decline but do not completely clear after treatment of *W. bancrofti*-infected subjects with DEC.[10, 11] This observation is consistent with the view that DEC, when used in conventional doses, does not appear to kill all adult worms in an infected host.[6] Second, levels of PC-Ag correlate with the total worm mass and adult female worm burden in a density-dependent manner in *B. malayi*-infected jirds.[12] The relative merits of mf density and antigenemia as indicators of the dynamics of adult worm burdens are assessed in the context of the longitudinal study described below.

MATERIALS AND METHODS

Study design

In June 1984, approximately 560 residents of the Dreikikir area of East Sepik Province, PNG, participated in an epidemiological survey (Survey 1) for bancroftian filariasis. Details of the study area, survey procedure, and vectors of *W. bancrofti* are given elsewhere.[13, 14] Twelve months later, 156 of the same residents were resurveyed to obtain baseline parasitological and clinical data prior to mass administration of the antifilarial drug, DEC (Survey 2). The residents who were surveyed twice are the subject of this longitudinal study, which focuses on parasitological changes in this group over the 12 month period between Surveys 1 and 2. Residents who left the endemic area for a total of >1 month were excluded from the longitudinal analysis. Absence from the endemic area was ascertained by historical interview technique at six and 12 months after the first survey. Using this residential classification, 126 subjects were considered for the longitudinal study. None of these subjects used any form of vector control (e.g., bed-nets).

Ten-milliliter blood samples were collected from individuals in the study population between 10:00PM and 2:00AM during Surveys 1 and 2. Two-milliliter blood volumes were filtered by Nuclepore filtration using 5 μm filters; these were later Giemsa-stained and examined microscopically to determine mf densities. The other 8 ml of blood were used for serum collection and subsequent antigen analysis.

PC-Ag assay

Serum samples of each subject in the study from Surveys 1 and 2 were analyzed by immunoradiometric assay (IRMA) using the PC-specific monoclonal antibody designated Gib13 (as described previously).[7] Due to intra- and inter-assay variation, serum samples from Surveys 1 and 2 from the same individual were assayed in duplicate on the same plate. Results were expressed as an antigen index (AI).

$$\text{AI} = \frac{\text{cpm bound with test serum}}{\text{cpm bound with control serum}}$$

The control serum pool was made up of 10 sera from residents of Melbourne, Australia who had never visited a filariasis-endemic area. The upper limit of normal values was taken as AI = 1.8 ± 0.1.

Sera from all mf-negative subjects at Survey 1 were also screened for M_r 200,000 PC-Ag by immunoadsorption and Western blotting, as described previously.[11] Presence of the M_r 200,000 PC-Ag in the sera of these amicrofilarenic subjects verified the *W. bancrofti* origin of PC-containing material detected by Gib13 IRMA.

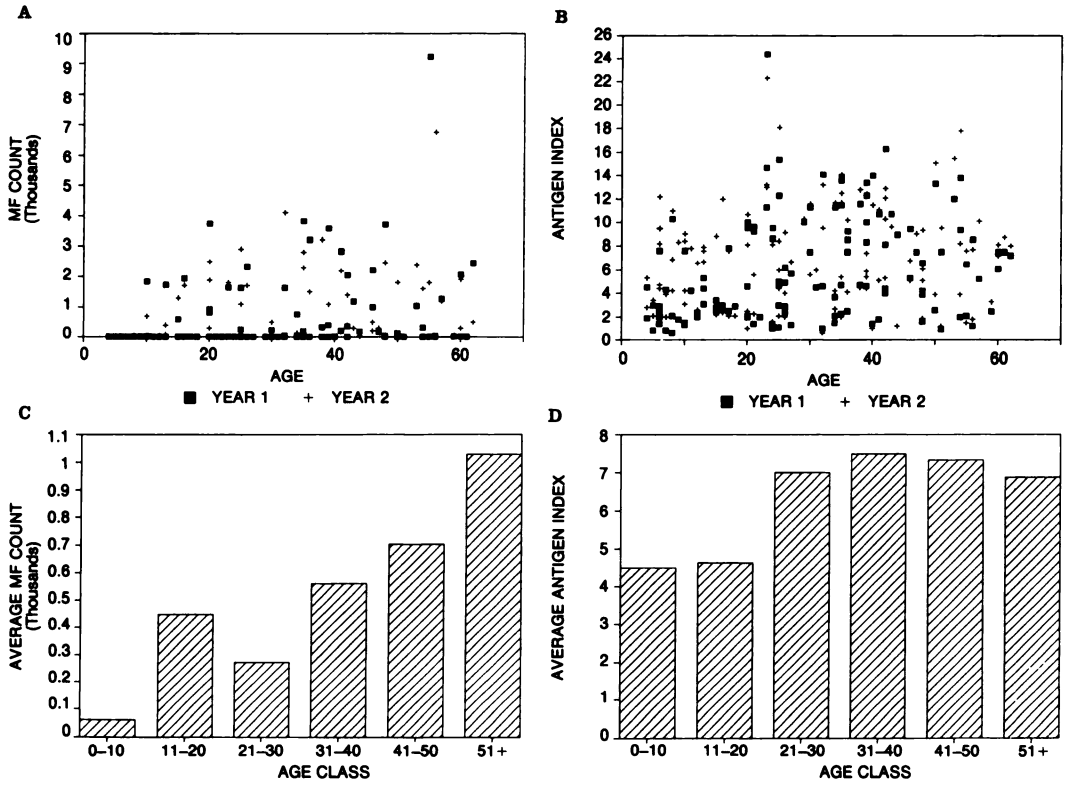

FIGURE 1. Age-specific intensity of infection in the study population. **A.** Individual variation in mf density. **B.** Individual variation in AI values. **C.** Mean mf density. **D.** Mean AI.

RESULTS

Horizontal analysis of age-specific intensity of infection

Considerable individual variation in both mf density (Figure 1A) and AI values (Figure 1B) was observed for the 126 subjects in the study population. This variation was noted within all age classes. However, both mean mf density and mean AI increased with age (Figures 1C and D), the latter to a plateau at ~20 years of age. Unlike intestinal nematode infections,[5] no convexity in the age intensity curves was noted, either for mf density or mean AI.

Change in infection intensity with time

Microfilareae density and AI values were compared at the start of the longitudinal study (mf 1, AI 1) and 12 months later (mf 2, AI 2) for 126 subjects. For these comparisons, the study population was divided into two age classes: those ≤ 20 years of age (41 subjects) and those > 20 years of age (85 subjects). Twenty years was chosen as the age to subdivide the population because mean AI values appeared to plateau at this age (Figure 1D).

Figures 2A and 2B show age-specific graphs of log (mf 1 + 1) versus log (mf 2 + 1). No significant differences in age-specific patterns of change of mf density were noted between the two age classes. In contrast, plotting AI 1 versus AI 2 for subjects ≤20 years of age and for subjects >20 years of age showed a clear age-dependent pattern of change (Figures 3A and B). For the 85 subjects >20 years of age, AI 1 and AI 2 were not significantly different (paired t-test; $t = 0.77$, df = 84, $P = 0.45$), leading to a linear relationship between the two sets of counts (Figure 3B; r = 0.867, $P < 0.0001$). By contrast, the relationship between AI 1 and AI 2 for the 41 subjects aged ≤20 years is less well-defined (Figure 3A), although the counts are still significantly correlated (r = 0.498; $P < 0.01$). The AI 2 values in this group were generally greater than AI 1 ($t = 4.67$; df = 40; $P < 0.0001$), suggesting that worm bur-

dens were increasing in this age group. This age-dependent pattern of change is seen most clearly when the ratio of AI 2/AI 1 against age is plotted (Figure 4). This ratio decreased with increasing age. Adults >20 years of age generally had a ratio of 1, whereas the ratio was >1 in subjects ≤20 years of age.

The observed decrease in AI ratio with age could be explained by proposing that there is an age-specific increase in rate of clearance of circulating PC-Ag with increasing experience of infection, i.e., with age. To examine whether differential rates of clearance of circulating PC-Ag occurred in children compared to older subjects, the mean age-specific half-lives of this antigen (after DEC treatment of the study population) were calculated as described previously,[11] assuming a first order decay process; i.e.,

$$P(t) = e^{-at}$$

where P is the proportion of antigen remaining at t (time) and a is a rate constant. Results are summarized in Table 1. No significant difference in mean half lives for PC-Ag antigens was observed for subjects in the four age groups examined.

DISCUSSION

A field study to examine the age-specific dynamics of *W. bancrofti* infection has been described in this paper. Two assumptions were made in the study design. The first concerns age-specific exposure to infection. Exposure to *Anopheles punctulatus,* the vector of *W. bancrofti* in the study area, is not occupation-related; rather, exposure occurs during sleeping hours, as this is a night-biting vector.[13] Village residents generally sleep in houses in family groups, and no interventions against mosquitoes (e.g., bed-nets) were in use in the study population. Given the night-biting habit of the vector and the sleeping arrangements of the study population, it would be reasonable to assume that exposure to infection is no greater in children than in adults. In fact, the converse may be true, as adults present a greater surface area to female mosquitoes. Clearly, individual variation in host/mosquito interactions will occur due to behavioral and genetic factors, but there is no evidence that this is age-specific in this endemic area.

The second assumption made in the study was that both AI and mf density are indirect measures of adult worm burden. Reasons justifying this assumption come mainly from animal model experiments.[12] Phosphorylcholine-containing antigens have been used to detect immature worms (L4) in the late stages of development in experimental animals.[12] Thus, it is possible that we are considering the dynamics of this life cycle stage as well as adult worms in the longitudinal study. In the time frame of this study, measurement of AI rather than mf density appeared to be a more sensitive indicator of the apparent dynamics of adult worm populations. Presumably, this is due to the significantly shorter maximum half-life of the PC-Ag (50 days)[11] compared to that for mf (6 months)[6] and the variance known to occur in consecutive measurements of mf density in an individual.

During the longitudinal study, AI was observed to increase in subjects ≤20 years of age but not in subjects >20 years of age. This age-specific increase cannot be readily explained by age-related exposure to L3. Measurement of levels of circulating PC-Ag in primary infections of *W. bancrofti* in *Presbytis cristatus* monkeys[15] and of *Onchocerca volvulus* infected chimpanzees[16] indicate that a masking or more rapid clearance of this antigen may occur as levels of anti-PC antibody increase. However, significantly different rates of clearance of PC-Ag were not observed between subjects ≤20 years of age and those >20 years of age as judged by mean age-specific half-lives of this antigen.

The antigen detection assay used to measure changes in levels of PC-Ag employed an anti-PC monoclonal antibody designated Gib 13.[7] It was thus possible that the increased AI ratios observed in subjects ≤20 years of age could have been due to increased prevalence of infection with non-filarial pathogens, which release circulating antigens containing PC(e.g., *Streptococcus pneumoniae*), in this age group compared to subjects >20 years. This possibility was excluded on the basis of the following control data: sera were collected at the two time points of the longitudinal study from subjects of both age groups (10/group) resident in another village, Bonahoi, where transmission of *W. bancrofti* infection had been interrupted by a 20-year insecticide spraying program for malaria control from 1961 to 1981 (K. P. Day, unpublished data). This village was only 26 km by road from the endemic area. There were no marriage, agricultural, or linguistic ties to the *W. bancrofti*-endemic village in the

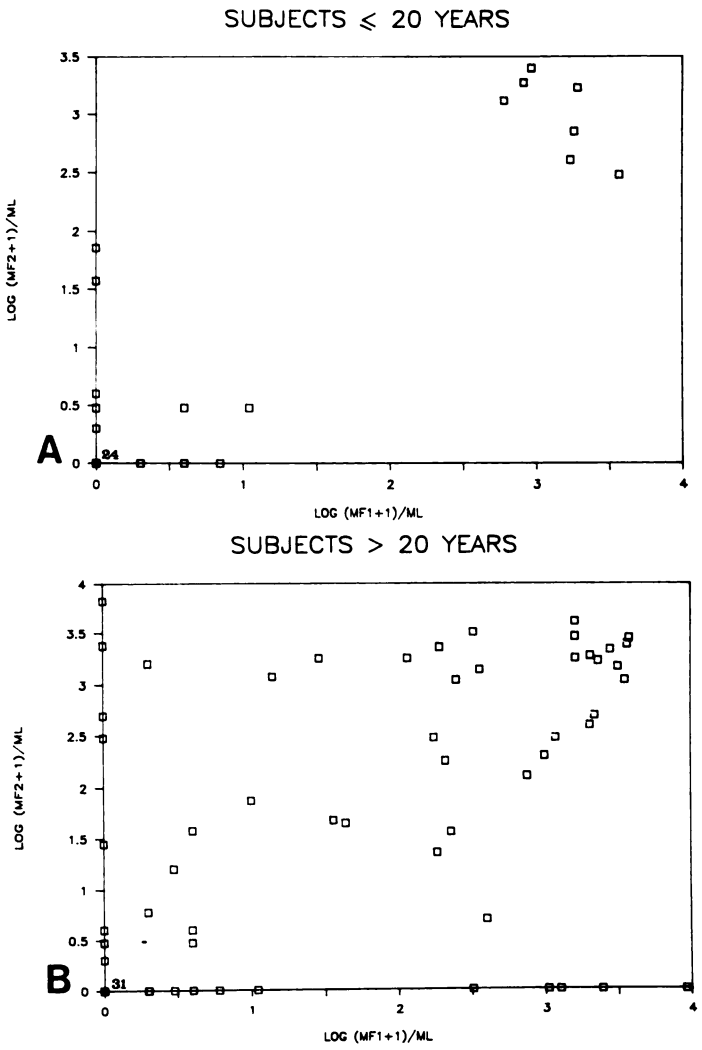

FIGURE 2. Age-specific dynamics of microfilaremia in the study population. **A.** Log_{10} (mf 1 + 1) vs. log_{10} (mf 2 + 1) for subjects ≤20 years of age. Twenty-four subjects did not have detectable microfilaremia in either survey. **B.** Log_{10} (mf 1 + 1) vs. log_{10} (mf 2 + 1) for subjects >20 years. Thirty-one subjects did not have detectable microfilaremia in either survey.

longitudinal study. Thus, there was no migration of *W. bancrofti*-infected individuals into this area. No significant increase in AI 2 versus AI 1 was observed in children or adults from the control village, indicating that there were no non-filarial pathogens that resulted in increased circulating prevalence of PC-Ag in the area at the time of collection of the first and second blood samples. Indeed, AI values were negative at both time points for children and adults from Bonahoi.

Given acceptance of the above assumptions, cross-sectional data from population studies (age vs. intensity of infection: Figures 1C and D) and data from the longitudinal study of the dynamics of infection (Figure 4) show that the worm burden in individuals increased rapidly during childhood and reached a plateau at ~20 years of age. This observed age distribution of intensity of *W. bancrofti* infection must arise as a result of a balance between the infection rate of hosts with L3, some of which survive to become adult worms, and the mortality pattern of these adult

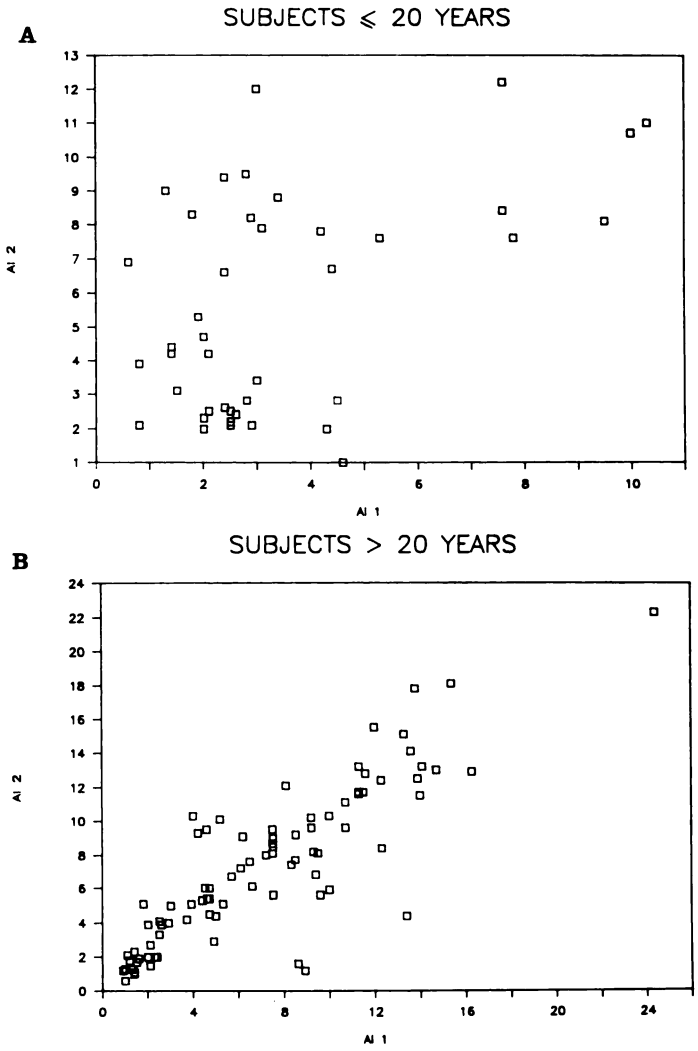

FIGURE 3. Age-specific dynamics of antigenemia in the study population. **A.** AI 1 vs. AI 2 for subjects ≤20 years. **B.** AI 1 vs. AI 2 for subjects >20 years.

worms. In order to further explore the above results, we shall review a standard mathematical model[17] which describes this immigration/death process for helminth parasites.

The simplest quantitative expression of this balance between immigration and death can be described by the following differential equation:

$$\frac{dM}{dt} = \lambda - \mu M$$

Here the rate of change of the adult worm burden per host (M) with time (t) depends on the difference between the net infection rate λ (new infections per unit of time) and the net death rate of adult parasites (μM). In the simplest realization of the model, λ and μ are constants and are unaffected by factors such as host age or parasite density. This allows the solution of Equation 1 as follows:

$$M(a) = \frac{\lambda}{\mu}(1 - e^{-\mu a})$$

where, for endemic infections at a steady state in a community, time (t) can be described by age

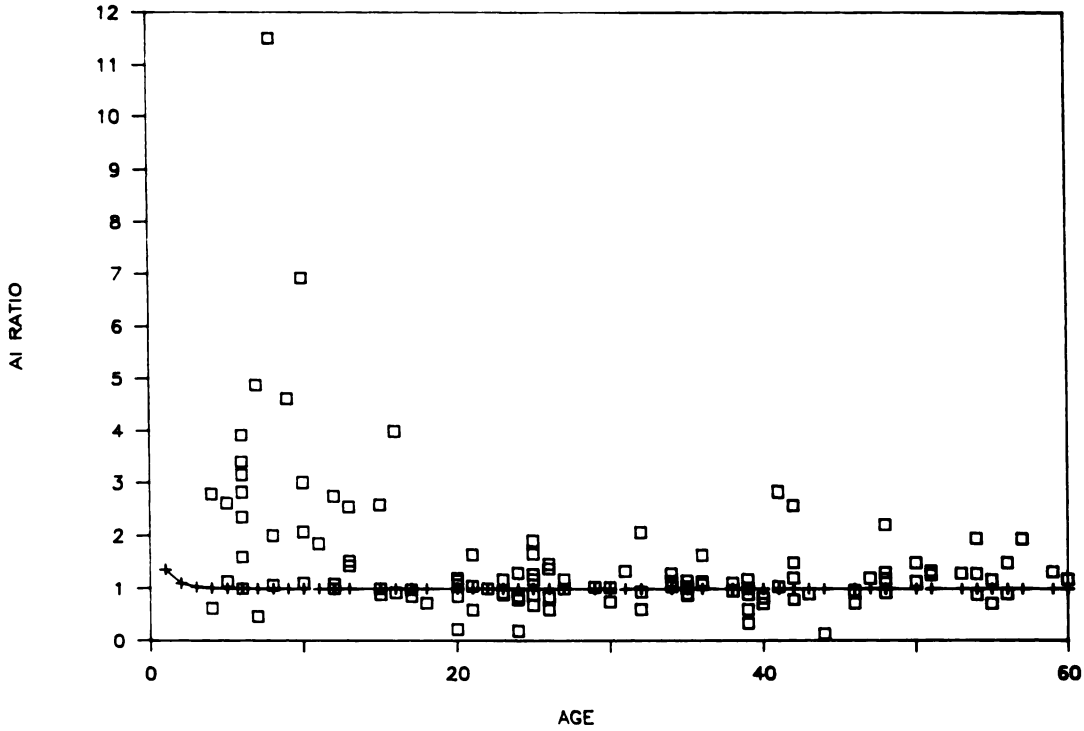

FIGURE 4. Age-specific ratio of AI 2/AI 1. Solid line represents solution to Equation 3.

(a). In other words, the adult parasite burden (M) increases rapidly in the young age classes, but then reaches a plateau set by the ratio of λ/μ in older hosts (Figure 5). In summary, λ represents the net establishment of new parasites and μ their per capita death ($1/\mu$ is the average life expectancy of the parasite).

Clearly this model is a considerable oversimplification. In particular, it does not account for the possibility of acquired resistance or other density-dependent phenomena.[17, 18] However, it does provide a simple framework for discussing conditions under which acquired resistance might manifest itself. In terms of Equation 1, acquired resistance could, broadly speaking, act by decreasing establishment (λ) and/or by increasing the adult worm death rate (μM) as a function of experience of infection, which obviously increases with age and may be described by immunological memory.[18] In epidemiological terms, acquired resistance is observed most clearly as a convexity in the age vs. intensity of infection profile where exposure to infection does not decrease with age. In lymphatic filariasis, the balance of evidence indicates that there is generally little or no convexity in the age vs. density curve (Figures 1C and D, and K. P. Day, unpublished data). Lack of convexity in such curves leads us to examine the data presented in Figure 4 in the context of the immigration/death model defined by Equations 1 and 2.

TABLE 1

Mean age-specific half-lives of PC-containing antigen in circulation after 72 mg/kg DEC treatment

Age group (years)	No. subjects	Mean half life ± SEM (days)
5–10	10	53.5 ± 9.3
11–20	19	46.8 ± 7.0
21–40	12	34.5 ± 5.2
41–60	18	42 ± 6.0

Although considerable variation in the pattern of AI with age was observed (Figure 1), more consistent patterns emerged when the ratios of successive antigen measurements for individuals were determined (Figure 4). Large increases in AI were observed in subjects $\leq$20 years old, but the majority of subjects >20 years old showed no increases; that is, AI 2/AI 1 was approximately unity in this age group. It is possible to

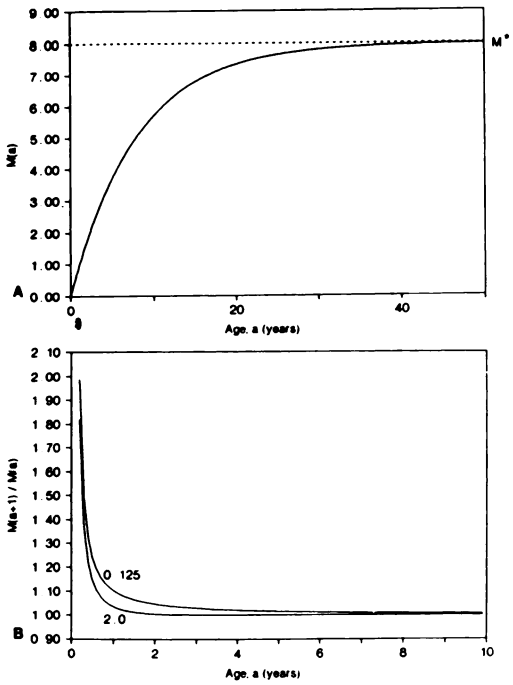

FIGURE 5. **A.** Typical profile of infection intensity with age arising from a simple immigration-death model (Equation 2) with infection rate λ (=1) and adult parasite death rate μ (=0.125, corresponding to a mean adult parasite life span of 8 years).[6] Infection intensity rises with age towards an asymptote, $M^* = \lambda/\mu$. **B.** The intensity ratio M(a + 1)/M(a), calculated from Equation 3, as a function of age. Two cases representing a high parasite death rate (μ = 2 years^{-1}, average life span = 0.5 years) and the level of mortality typically estimated (μ = 0.125 year^{-1}, average life span = 8 years[18]) are shown to indicate the ratio's relative insensitivity to this parameter. The expected ratio at very low parasite death rates ($\mu \to 0$, M(a + 1)/M(a)$\to$(a + 1)/a) is graphically indistinguishable from μ = 0.125.

explore the implications of this result further in the context of the immigration/death model described above using Equation 2.

Equation 3, which states

$$\frac{AI2}{AI1} = \frac{M(a+1)}{M(a)} = \frac{[1 - e^{-\mu(a+1)}]}{(1 - e^{-\mu a})}$$

assumes that AI is proportional to worm burden (M[a]) and, in this simple model, which ignores acquired immunity,[17, 18] factors out the effects of the infection rate (λ). It expresses AI 2/AI 1 as a function of the age-specific pattern of adult parasite mortality. The general form of this expected ratio is illustrated in Figure 5; it shows a sharp decline with age over the first two years of infection to an asymptote at unity. Figure 5 also illustrates that this pattern is essentially independent of the level of the rate of adult mortality (μ). Both observed and expected AI ratios were near unity for adult individuals, reflecting the consistency of adult AI over the period of the survey. However, the observed AI ratio for subjects $\leq$20 years was much larger than the expected curve generated from Equation 3 (see Figure 4 for comparison of observed and expected results). This discrepancy indicates that the simple immigration-death model (Equation 2) does not fully explain observed changes in AI among juvenile hosts. It can also be shown that the observed results could not be generated by simple refinements of the model which allowed for the effects of acquired resistance to infection.[17, 18]

The model does, however, provide a framework for discussing these observations. The simplest interpretation of the observed pattern is that children acquire infection, which leads to a surge in PC-Ag production. After this, establishment declines and antigen levels stabilize, reflecting a relatively constant adult worm burden. This interpretation of the data fits well with observations in the *B. malayi* cat model, in which hosts are trickle-infected with L3.[2] These experiments indicate that adult worms in persistent infections are relatively long-lived (life expectancy ~2 years) and arise mainly from early infections, when the hosts are essentially naive. Resistance in these persistent infections seems therefore to be directed mainly at incoming larvae, with the majority being destroyed within 24 hr of injection,[2] and seems to increase with experience of infection. Although the results presented here are consistent with the picture from experimental infections, direct evidence for acquired resistance can only be obtained from more detailed immunological studies, or comparative epidemiological studies of areas with different endemic infection levels. Clearly, *B. pahangi* trickle infections in the cat will play a crucial role in evaluating epidemiological observations made in the human population, since both this cat model and epidemiological data presented in this paper indicate that the target of acquired resistance to filarial infection is early larval stages rather than adult worms. The cat model will be important in identifying immune mechanisms affecting the viability of L3 and the survival of adult worms.

The target epitopes of the monoclonal antibodies AD12.1 and DH6.5, which bind to the

W. bancrofti M_r 200,000 PC-Ag, have been localized to the reproductive organs of male and female adult worms by immunofluorescence.[9] Part of the very sharp increase in AI observed in subjects ≤20 years could, therefore, be due to a switching-on of reproduction. Thus, Figure 4 indicates sharp increases in parasite load and/or reproduction in juveniles, which occurs predominantly in the first 15 years of life. If these large jumps in the AI ratio correspond to onset of infection in individuals (Figure 5B), there is clearly considerable individual variation in age of aquisition of infection.

The significant variation in individual AI values of subjects >20 years of age (Figure 1B) contrasts strikingly with the lack of variability of individual AI ratios for this age group (Figure 4). This result strongly suggests that all individuals reach a plateau of worm burden as a result of both parasite mortality and acquired resistance, but that the height of the plateau is subject to individual variation, which may reflect differing rates of acquisition of resistance or simply innate resistance to infection.

If this interpretation of the longitudinal data is correct, a number of important conclusions can be drawn. Firstly, the mechanism of resistance causing attrition of larvae in subjects >20 years of age has been acquired with increasing experience of infection and is parasite-worm burden independent and could be described as concomitant immunity. Consistent with this mechanism we have described age-specific acquisition of humoral immunity to mosquito-derived L3 in the same study population[19]. The existence of the mechanism in all adults indicates that the mechanisms per se cannot lead to the pathology associated with *W. bancrofti* infection in a proportion of residents of endemic areas. Parasite load and/or host genotype may be important predisposing factors to the development of obstructive disease rather than mechanisms resulting in attrition of larvae. Thus, identification of this mechanism, which is presumably immune-mediated, has important implications for vaccine development.

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