Published in final edited form as:

Am J Trop Med Hyg. 2005 December ; 73(6): 995–998.

PERSPECTIVE NATURAL COURSE OF LYMPHATIC FILARIASIS: INSIGHTS FROM EPIDEMIOLOGY, EXPERIMENTAL HUMAN INFECTIONS, AND CLINICAL OBSERVATIONS

T. V. RAJAN*

Boehringer-Ingelheim Professor of Immunology, Department of Pathology, Farmington, Connecticut

Abstract

Lymphatic filariasis has been described as a “spectral disease”. Analysis of the natural course of infection in nonendemic individuals as well as experimental infections of “volunteers” suggests that the filarial parasites are not inherently aggressive infectious agents. Experimental infections of humans with infective larvae result in transient, low-level microfilaremia, if at all. Nonendemic individuals with limited exposure show no evidence of persistent infection or pathology. Nonendemic individuals exposed to repeated infections show accelerated pathology. It is tempting to speculate that normal, immunocompetent residents in an endemic area show either (a) no pathology (endemic normals) because they are subject to the relatively low levels of infection or (b) chronic pathology if they are repeatedly infected. It would appear that only those individuals rendered immunologically tolerant to filarial parasites become productively infected with the filarial parasites. The intensity of transmission may underlie the differences in clinical presentation seen in diverse global pockets of endemicity.

NATURAL HISTORY OF INFECTION IN AN ENDEMIC AREA

Lymphatic filariasis was recognized as a disease by ancient Chinese and Indian physicians. Centuries later, British physician/scientists, working in China, India, and Sri Lanka (then called Ceylon), discovered the causative agent of this disease. The past 100 years of research in filariasis has been particularly robust, with the elucidation of many aspects of the biology, immunology, natural course, and therapy of this disease. Now that we are engaged in a global effort to eradicate this disease, it is perhaps time to attempt a synthesis about the natural progression of filarial infection in the human host.

There are two unusual features of lymphatic filarial infection that one needs to address to understand the natural course. First, it would appear that the organism is not very infectious to normal, immunocompetent individuals. The second is that it is an endemic disease, occurring in certain geographic areas at high rates and skipping other areas.

Most reviews of lymphatic filariasis therefore concentrate on the course of disease and its manifestations among these endemic populations. Within the endemic populations, patients fall into a relatively wide spectrum of manifestations, which have puzzled and intrigued most investigators. Individuals who are presumably of similar genetic constitution and ethnic origin, exposed to the same parasite strain transmitted by the same vector, exhibit very different

* Address correspondence to T. V. Rajan, MD, PhD, *Boehringer-Ingelheim Professor of Immunology, Professor and Interim Chairman, Department of Pathology, 263 Farmington Avenue, Farmington, CT 06032. E-mail: rajan@neuron.uchc.edu*

Author's address: T.V. Rajan, MD, PhD, *Boehringer-Ingelheim Professor of Immunology, Professor and Interim Chairman, Department of Pathology, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06032, E-mail: rajan@neuron.uchc.edu.*

outcomes of infection. Individuals may have no evidence of disease or infection (endemic normals), be asymptomatic, but bear significant parasite burdens (asymptomatic microfilaremic), or be amicrofilaremic with disease. The precise distribution among these subsets varies from one geographic area to the other. A great deal of the immunologic literature over the past decade has focused on the nature of this “spectrum of disease” in lymphatic filariasis. In an influential review in 1992, Ottesen suggested that the two polar groups were individuals with chronic pathology and no microfilariae in circulation versus individuals with abundant microfilariae in circulation, but no symptoms.¹ Attempts have been made to explain the mechanisms underlying the clinical presentations based on the Th1/Th2 dichotomy. Most of these explanations, however, seem unsatisfactory in explaining the difference.

Although longitudinal studies within an endemic area are difficult to carry out, there have been at least two studies of patients who were moved from endemic areas to nonendemic areas and who were therefore subsequently followed without the further complication of an ongoing transmission. Many of these individuals in both studies were microfilaremic at the time of movement from either Surinam² or American Samoa³ to The Netherlands or the United States, respectively. Many of these remained microfilaremic for approximately 8 years after their move, consistent with the generally believed life span of the adult female of 8 years. After this period, microfilaremia gradually disappeared. Very important for our understanding of the course of infection, none of these individuals developed chronic disease. Thus, the idea that filarial infection proceeds from microfilaremia to acute to chronic disease may be incorrect. It would appear that most individuals who are microfilaremic remain microfilaremic without developing chronic disease subsequently. Steele and others have also examined the long-term course of filarial infections in the Cook Islands. Here as well, endemic normals remain disease or infection free over the 17 years of follow-up, despite continued exposure to infection.⁴

Most longitudinal studies seem to suggest that whether one is endemic normal or asymptomatic microfilaremic is fixed relatively early in life and one remains phenotypically consistent over long periods of time. What are the determinants of this difference? In coming to an understanding of its nature, it is probably worth discussing the course of infection not only in individuals in an endemic area, but also in nonendemic individuals and volunteers subjected to experimental infections. I believe that a dispassionate analysis of the literature leads one to a conclusion that is at variance to the prevalent models of infection and disease.

INFECTION IN NONENDEMIC HUMANS

There are at least two large-scale studies of individuals moved from nonendemic areas into areas endemic for filariasis as adults. In one instance, American GIs with a mean age of 26 years were located in Samoa and certain other islands in the South Pacific. While different U.S. armed forces contingents were placed here, the most comprehensive data come from the U.S. Navy, largely through the efforts of Coggeshall, who reported that 38,300 Naval personnel were exposed to filarial infection in the South Pacific Islands.⁵ Of these, a remarkably high number (10,421 individuals) were diagnosed to have contracted acute filarial fever. These young people were studied extensively by a number of investigators including Coggeshall⁵ and Trent⁶ and summarized in a U.S. Army medical bulletin.⁷ Wartman, from the Armed Forces Institute of Pathology, wrote a detailed review of the clinical course of infection in these young men and described the pathologic findings in a magisterial review.⁸ The usual manifestation of acute filariasis was painful swelling of the scrotal contents, the arms or the legs, singly or in combination. The affected part(s) showed evidence of acute inflammation, including redness, swelling, and edema. Often there was itching. Interestingly, constitutional symptoms associated with acute filarial fever, notably fever, chills, and rigor, were unusual.

Many of these individuals have been followed over the past 50 years since the end of the Second World War. Many have been lost to follow-up, but it would appear that only about 20 of these individuals have been documented to have developed microfilariae. To quote Wartman, "Microfilariae were not found in the peripheral blood in a great majority of cases." Behm and Hayman (quoted by Wartman) say, "No microfilariae were found in any of these groups (709 patients) while at the hospital (Moore General Hospital, Swannanoa, NC). Microfilariae had been repeatedly demonstrated, however, in one man in Group A while in Woodlark and in a second before arrival at this hospital. Neither of these men was available for study. In addition to these two, the records of two other men of Group A recorded the finding of a single microfilaria in one examination. These two were examined repeatedly over a period of several months, but no microfilariae could be found."

It appears fair to say that of this cohort of 33,000-odd individuals of whom 10,000 were documented to have developed filarial infection, a very small number, at best 20, ever became microfilaremic.

Wartman performed careful pathologic examination of biopsy material from 57 of these GIs at the Armed Forces Institute of Pathology.⁸ Eight contained adult worms. In all instances, the worms were surrounded by granulomatous inflammation. In his description, Wartman writes, "Typical changes in nodes which were infected with adult worms consisted of marked hyperplasia of cells of the reticuloendothelial system, tissue eosinophilia, and nodule formation. Macrophages are numerous and moderate numbers of foreign body type giant cell were present. Nodules were found chiefly around adult parasites, but occasionally around microfilariae or even in the absence of parasites. Eosinophils, plasma cells, lymphocytes and neutrophils were present through the granulomas, but were especially numerous at the edges. In older lesions where the worms were dead, or had been present for a long time, macrophages and exudative cells were less conspicuous and they were concentrically arranged layers of bands of acellular collagen." While Wartman refers to the structures around the worms as "nodules," it is important to emphasize that this is not a precise pathologic term. A nodule may be cellular or acellular, neoplastic or inflammatory. It is, however, clear from the histopathology illustrations in his review that his "nodules" are granulomas, composed primarily of macrophages with the formation of some foreign body giant cells. Further, Dr. Wartman clearly concludes that his data prove that the granulomatous inflammation takes place around living, rather than dead, worms.

The other group of nonendemic individuals exposed to filariasis as adults were Indonesians from Irian Jaya who were relocated to Flores. In a review in the CIBA Symposium on Filariasis, Partono describes the clinical course of filariasis in previously unexposed migrants. Within 2 years of migration, a great number of these individuals (43%) had evidence of acute filarial infection as manifested by adenolymphangitis. A substantial percentage of them developed lymphodema or elephantiasis within this period of time (21%). However, only a small percentage (2 individuals or 5%) developed microfilaremia. No detailed pathologic evaluation, similar to that conducted by Wartman, is available for these individuals. However, it appears that this group of nonendemic individuals exposed to the filarial parasites as adults eliminate them, without developing patent infection. There is, however, a major difference between the American GIs who were exposed to parasites for a limited duration and the Indonesian transmigrants who were exposed for the rest of their lives. The former cleared infection without any pathology; the latter developed pathology at high rates.

Thus, it appears that the course of filarial infection in individuals who have not been previously exposed to filariasis is that of quantitative clearance without the development of patent infection. In those instances where the infection is of a limited intensity and duration, as in the case of American GIs, it appears that the disease does not develop and these individuals remain

clinically normal for the rest of their lives. On the other hand, if infection is persistent and repeated and takes place over a long period of time, individuals develop chronic pathology rapidly, without necessarily becoming patently infected. Further, it would appear that the mechanism by which the parasites are eliminated ultimately is by surrounding them with “nodules” or, more appropriately, granulomas.

EXPERIMENTAL INFECTIONS OF HUMANS

There have been five studies in which L3 larvae were injected experimentally into volunteers (reviewed by Nutman⁹). The data from these studies must be interpreted with caution, because most were conducted in endemic areas, presumably using individuals who may have had prior exposure. Thus, authors of one of the papers¹⁰ point out that “this is not to say that prior exposure to infection played no part in the experiment; it may well have modified the individual reaction to inoculation and we should like to see the experiment repeated, using volunteers with no previous exposure to infection.” Despite this complication, a majority of individuals in these studies did not become microfilaremic. In the four experiments for which we have documented data, a total of 12 individuals appear to have been injected with substantial numbers of infective larvae. Of these, only 5 became micro-filaremic, all of them transiently. Buckley attempted to transmit *Brugia malayi* to a human being. The volunteer remained persistently negative for microfilariae. The title of the communication is revealing: “Anomalous results from an experimental infection of man with *Brugia malayi* (Brug, 1927).” The “anomaly” being that Buckley fully expected that the infection would proceed to patency.

In another study using a total of four volunteers, Edeson and others¹⁰ found microfilariae (mf) in only one. Even in this individual, mf were present transiently in circulation (from Days 84 to 140) and in small numbers. Even more surprisingly, patency developed in one of the two individuals given *B. pahangi* larvae and not in either volunteer receiving *B. malayi*. In discussing this issue, Edeson and others write, “The broad similarity of the events in all four volunteers and the appearance of *B. pahangi* infection in one of them makes the failure to establish a *B. malayi* infection all the more puzzling. The clinical reaction suggests that the infective larvae had survived and were developing; yet although this particular strain of *B. malayi* had come from man, it was apparently unable to establish themselves in these two volunteers of the result of a single inoculation.”

Equally noteworthy is the communication by Yokogawa,¹¹ which appears to be one of the few instances in which *Wuchereria bancrofti* was used as the infective agent. The author was one of the five volunteers used in the study. Most did not become microfilaremic at all. In two instances, two microfilariae were recovered from 2 mL of blood examined at night. This is hardly a high level of a microfilaremia. The author further writes, “Since then, several weeks have elapsed, without any microfilariae being discovered in the peripheral blood by continual nightly examination.” Thus, in the one well documented experiment with *W. bancrofti*, patent infection was uncommon and transient.

Finally, in the report by Liu and others, a single volunteer was exposed to infected mosquitoes and subjected to an estimated 200 infective larvae.¹² On Day 142, he had 9 mf/μL of blood. Seven days later, this number decreased to 3/μL. It is tempting to speculate that he would have spontaneously cured himself of the infection. But the subject was treated with DEC over the next 16 days. He remained free of mf for all subsequent examinations.

WHY ARE THERE INFECTED HUMANS?

In the case of humans, the real question in filarial infections of man is not why endemic normals are “resistant to infection,” but why asymptomatic microfilareemics harbor worms, whereas most normal, immunocompetent humans possess the immunologic machinery to eliminate the

infection. The possibility of a fundamental immunologic difference between the endemic “natives” and whites was suggested in the early literature. Wartman writes, “There is little doubt that our armed forces had ‘mumu.’”⁸ *Mumu* is a Samoan word and describes a rapidly developing clinical course with acute symptoms. Wartman further adds, “This form of disease is apparently different from filariasis as it is seen in natives in India, where mumu is supposed to be unusual.” Southgate, speculating on the differences in manifestation of filarial infection in endemic versus nonendemic individuals, raised the possibility that the endemic individuals may be tolerant to the filarial parasite or its antigens. In the CIBA symposium on Filariasis, Southgate writes, “It is conceivable that this observation links up with other factors, such as being born to a mother who is antigenaemic (sic) or microfilaremic, to account for the immune responses in the disease states you have seen.”

This idea that microfilaremia may occur in very special individuals has been further highlighted by the work of Lammie and others from Haiti¹³ and Steel and co-workers from the Cook Islands.¹⁴ In both instances, there is a substantial increase in the microfilaremia levels in individuals born to mothers who are microfilaremic. This correlation is not perfect. It is clear that there are microfilaremic individuals in these patients in whom maternal microfilaremia cannot be documented and, in converse, not all individuals who had microfilaremic mothers become microfilaremic themselves. Thus, while it appears that having a microfilaremic mother predisposes one to microfilaremia, the correlation is not absolute. It is, however, likely that microfilaremia or a specific antigenemia at a particularly sensitive stage in the development of the fetus may be the relevant fact, and we may still not have a measure of this particular relationship.

CONCLUSION

In conclusion, it appears that contrary to widely held belief, the filarial parasites are not particularly aggressive. Hyma and others¹⁵ have calculated that it takes approximately 15,500 L3s to be transmitted to an endemic population to develop a single microfilaremic patient. This is, of course, in contrast to the situation in malaria where a single sporozoite is enough to establish infection, or giardiasis, where it has been estimated that 10 spores are sufficient to give rise to a clinical case. From the exhaustive studies by Wartman, it is clear that in individuals who have been previously unexposed to filariasis, the mechanism of host protection is the formation of granulomas that encase the parasites at various stages of development and prevent them from reaching maturity.

It appears likely that when exposed to filarial infection, humans either mount an immune response and eliminate the parasite or are unable to mount adequate immune response due to neonatal tolerance and permit it to survive. In the case of those individuals who do kill the parasites effectively, it would appear that there are two classes. One class shows no evidence of infection subsequently and resembles the American GIs. The second class resembles the Indonesian transmi-grants with the development of chronic disease. It is tempting to suggest that the endemic normals are individuals who are exposed to relatively low levels of infection, either because of their own resistance to mosquito biting or because of socioeconomic status that makes them less exposed to mosquitoes. On the other hand, those who develop chronic disease may, for unknown reasons, be exposed to substantially larger burdens of the infective parasite, resulting in sequentially increasing amounts of granuloma formation resulting in sclerosis of the lymphatics.

This formulation of the nature of filarial infections in humans has important implications for the global effort to eradicate the disease. A vaccine may not be necessary, possible, or perhaps even desirable. If asymptomatic microfilareemics are tolerant, it might be impossible to break this tolerance postnatally. On the other hand, endemic normals are probably exposed to

relatively limited infectious burdens and appear to deal with it quite adequately, and do not require vaccinations. If individuals with chronic symptoms become so because of repeated infections, vaccination may only hasten the development of disease, as happens in the Indonesian transmigrants. Thus, despite the enormous effort that has been placed on vaccine development over the past two decades, it may be well that such efforts have not borne fruit.

On the other hand, the very fact that humans may be more or less resistant to filarial infection implies that once transmission has been lowered to the point that there are not many women in their reproductive phase who are currently infected, filarial infection may not return after one generation. This is an optimistic and encouraging possibility.

REFERENCES

1. Ottesen EA. The Wellcome Trust Lecture. Infection and disease in lymphatic filariasis: an immunological perspective. *Parasitology* 1992;104(Suppl):S71–S79. [PubMed: 1589302]
2. Leeuwin RS. Microfilaria in Surinamese living in Amsterdam. *Trop Geogr Med* 1962;14:355–360. [PubMed: 13929220]
3. Jachowski LA, Otto GF, Wharton JD. Filariasis in American Samoa. I. Loss of microfilaria in the absence of reinfection. *Proc Helminth Soc Washington* 1951;18:25–28.
4. Steel C, Guinea A, Ottesen EA. Evidence for protective immunity to bancroftian filariasis in the Cook Islands. *J Infect Dis* 1996;174:598–605. [PubMed: 8769619]
5. Coggeshall LT. Malaria and filariasis in the returning servicemen. *Am J Trop Med Hyg* 1945;25:177–196.
6. Trent S. Reevaluation of World War II veterans with filariasis acquired in the South Pacific. *Am J Trop Med Hyg* 1963;12:877–887. [PubMed: 14072443]
7. Anonymous. U.S. Army Medical Department; Washington, DC: 1945. Bulletin U.S. Army Medical Department.
8. Wartman WB. Filariasis in American Armed Forces in World War II. *Medicine* 1947;26:333–394.
9. Nutman TB. Experimental infection of humans with filariae. *Rev Infect Dis* 1991;13:1018–1022. [PubMed: 1962076]
10. Edeson JF, Wilson T, Wharton RH, Laing AB. Experimental transmission of *Brugia malayi* and *B. pahangi* to man. *Trans R Soc Trop Med Hyg* 1960;54:229–234. [PubMed: 13819290]
11. Yokogawa S. Transmission of *W. bancrofti*. *Trans R Soc Trop Med Hyg* 1939;33:363–364.
12. Liu JY, Wang GQ, Chen YN, Tu ZP, Fang Z. Observations on the clinical manifestations and treatment of an experimental infection with *Brugia malayi* in man. *J Trop Med Hyg* 1989;92:93–96. [PubMed: 2565406]
13. Lammie PJ, Hitch WL, Walker AE, Hightower W, Eberhard ML. Maternal filarial infection as risk factor for infection in children. *Lancet* 1991;337:1005–1006. [PubMed: 1673168]
14. Steel C, Guinea A, McCarthy J, Ottesen E. Long-term effect of prenatal exposure to maternal microfilariemia on immune responsiveness to filarial parasite antigens. *Lancet* 1994;343:890–893. [PubMed: 7908359]
15. Hyma B, Ramesh A, Gunasekaran K. Lymphatic filariasis in Madras, India. *Soc Sci Med* 1989;29:983–990. [PubMed: 2814584]