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Trip Report

**Thailand: Evaluation of the Potential
for Conducting Ivermectin Trials
in the Control of Filariasis**

by

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CE-035-4

Author

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Background

Lymphatic filariasis caused by two different parasites, Brugia malayi (in the southern provinces) and Wuchereria bancrofti (primarily in the northwest), has been recognized in Thailand since the 1950s and 1960s. Since the 1970s, control measures have been undertaken by the government, currently by the Filariasis Division of the Department of Communicable Disease Control in the Ministry of Public Health. U.S. Peace Corps volunteers have been assigned to the Filariasis Division for the past two years (two volunteers per year, each staying for two years, so that there are four volunteers in the Division at any one time).

VBC vector biologist Lawrence Lacey, Ph.D., made an assessment of "The role of Peace Corps in the Filariasis Division in Thailand: Assessment of potential for collaboration with PCVs" in 1988. He suggested that certain areas of Thailand might be good study sites for Phase III (village-based) trials of the antifilarial drug ivermectin and that such trials might usefully involve the Peace Corps volunteers. The purpose of this visit, therefore, was to follow up on this suggestion and to look in detail at the feasibility of conducting ivermectin studies in Thailand.

Briefing at Filariasis Division, CDC, Ministry of Public Health

Participants:

Dr. Bundit Chanhaswadikul, Director, Filariasis Division
Ms. Kopkan Kanjanopas, Entomology Subdivision
Ms. Salinee Sensathein, Epidemiology Subdivision
Mr. Sirichai Phantana, Parasitology Subdivision
Dr. Suwit Dhamapalo, Epidemiology Subdivision
Ms. Karen Lanham, Peace Corps Volunteer
Mr. Narintr Tima, Program Specialist (Health), USAID

The Filariasis Division employs approximately 100 persons distributed among the central office in Bangkok and six field sites in endemic areas throughout the country. The field station groups carry out surveys to determine prevalence of filariasis by finger-prick blood sampling and microscopy. They spend approximately 10 days of each month in the field and the remainder examining the blood films and handling data. Each field station can survey 20-30,000 individuals per year. The areas chosen for study are those that meet three of the following criteria: being a previously recognized endemic area, having an environment conducive to transmission of filariasis, having an entomology survey be positive for mosquito-borne infective larvae, or having patients with elephantiasis.

After the blood survey is complete (with meticulous records of each individual being kept), those villages with a microfilaremia rate of greater than one percent are given "mass drug administration." This involves distribution of full courses of DEC (6 mg per kg per day for 6 days for Brugia malayi infections and 6 mg per kg per day for 12 days in W. bancrofti cases) to all villagers who are then instructed to take the medication on their own. "Coverage," as defined by this distribution, is usually 80 to 90 percent of the population.

Several changes in the existing routine are envisaged by the new division director, Dr. Bundit, who has held his post for only three months. Some of these changes are described in more detail below. Their primary objectives are obtaining broader prevalence data, developing better strategies for treating individuals with lymphatic obstruction or microfilaremia, and making the collected data more accessible through computerization.

Visits to Endemic Areas

A. Naratiawat

This province of half a million people in 459 villages covers 4,400 square kilometers and, as the southernmost state, borders Malaysia. The population is predominately Muslim.

The province has been surveyed for filariasis since 1974. In the past three years since the new center was built in Naratiawat, approximately 70 villages per year (30,000 people per year) have been surveyed. The overall prevalence of microfilaremia (all caused by Brugia malayi) is 0.62 percent, and an additional 0.1 percent have elephantiasis.

The province's villages are generally loose aggregates of houses often spread out at considerable distances from each other. The major occupations are farming, tapping rubber trees or traveling across to Malaysia to find work. The area is largely swampland. Efforts at drainage and planting are underway, but the abundant swampy areas provide ample opportunity for pistia and similar plants to thrive and serve as breeding sites for the Mansonia mosquitoes that are the vector of subperiodic B. malayi found here. Fourteen staff members and one Peace Corps volunteer are assigned to the center to carry out human and entomological surveys and drug administration.

B. Kanchanaburi

This center is in the northwestern part of the country and is responsible for a large region extending to approximately 350 kilometers north of Bangkok along the Thai-Burmese border. In this region, the country is mountainous. The lowlands are planted in sugar cane and bamboo and the

mountain areas are heavily forested. The villages are discrete collections of closely adjoining homes often made of bamboo and supported on stilts.

The filarial parasite in this region is entirely W. bancrofti transmitted by Aedes. Two features of this infection are particularly interesting: first, the W. bancrofti is apparently subperiodic, with peak microfilaremia levels occurring in the early evening; and second, the transmission is seasonal, because the cooler, dryer climate prevailing between November and April keeps the mosquitoes from breeding during this time. Transmission occurs only between May and October during the rainy season. Microfilaremia rates vary widely in this area, with some villages having rates of up to 15 percent.

The center is staffed by about 15 individuals who are able to survey approximately 30,000 people per year.

Assessment

A. Potential for Conducting Chemotherapy Studies with Ivermectin

As the Division is currently organized, in-hospital (Phase II) trials are not really feasible and, indeed, are probably unnecessary because other such trials are being conducted elsewhere in the world.

Phase III (village-based) trials could be conducted either in one of the Brugia malayi endemic areas of the south or in the W. bancrofti regions of the north, at least in terms of the Division's manpower and organizational framework. The biggest potential impediment to carrying out such trials is the lack of relatively concentrated numbers of microfilaremic patients. (Currently, "generic" Phase III trial protocols are being devised by WHO and Merck Sharp and Dohme, in conjunction with epidemiologists and clinicians, who will determine what types of populations would be best for such trials.) If the microfilaremia rates in these communities are too low, Phase III trials of ivermectin would be difficult to carry out in Thailand.

There is, moreover, still uncertainty about the true prevalence in many areas. The reasons for this uncertainty center around the sampling techniques being used. First, studies of the parasites' periodicity (whether diurnally subperiodic, nocturnally subperiodic or nocturnally periodic) have not been carried out in all of the endemic areas, and it is possible that the sampling time (6 pm to 10 pm in all areas) may not be the best for detecting microfilaremia in all areas. Second, the 60 cubic millimeter blood sampling technique used now probably underestimates the prevalence of positive cases compared to what would be found by using a 1 cc concentration technique (either Nuclepore filters or Knott's technique).

Pilot studies to determine the underestimation of "true prevalence" will probably be conducted at selected sites in order to obtain better estimates of prevalence. This new information could be important in deciding whether or not these areas are appropriate for the Phase III trials. A decision can be made only after the requirements for such study areas are defined by WHO and after the local epidemiology of the infection is determined.

However, even if the endemic regions of Thailand prove unsuitable for Phase III trial sites, there are other important ways ivermectin could be employed to study the effectiveness of control strategies (see below).

B. Other Research Projects Particularly Appropriate for Study in Thailand

1. Treatment and Control Strategies

There are two distinct needs for chemotherapy in lymphatic filariasis. One deals with treatment of the disease (i.e. lymphangitis and lymphatic obstruction) and the other with the abolition of microfilaremia in order to reduce transmission by the mosquito.

One would predict that ivermectin would be extremely effective for reducing microfilaremia. Therefore, in developing a control strategy, it would be particularly interesting to use ivermectin as a tool for eradicating filariasis from Thailand. Ivermectin should be especially valuable in treating bancroftian filariasis in Thailand because its effectiveness in decreasing microfilaremia is maximal during the first six months after treatment and the period of transmission (because of the dry, cool season) is also only about six months. Therefore, single-oral-dose treatment of the relatively accessible villages in the northern focus at the beginning of the transmission season should abolish microfilariae from the blood when mosquitoes are present. If the microfilariae return to the blood during the second six months following treatment, it will be of little consequence because there will be no vectors to transmit the infection. Therefore, yearly treatment of these areas (or twice during the rainy season) should stop transmission of the infection and be an extremely effective practical control measure.

The fact that the single-oral-dose mode of administration does not require the same degree of compliance on the part of patients (who may develop side reactions) as is required for the 12 days of DEC chemotherapy overcomes one of the major obstacles to the success of control programs based on DEC. The reason, of course, is that the side reactions develop precisely in those who have no clinical manifestations of the disease (and therefore think themselves normal), so that their motivation to continue the 12-day course of DEC is minimal.

On the other hand, the individuals who are not motivated to take DEC are those who have clinical manifestations of the disease (either recurrent lymphangitis or frank elephantiasis). Since there is evidence that taking DEC over a prolonged period of time helps to resolve even the pathology induced by long-standing filarial infection (probably through killing the adult stage of the parasite and preventing the development of new infections), it makes sense that these patients who are already self-motivated to take medicine that helps them should be provided ready access to DEC. Such access could be via the volunteer health workers in each village, who could be issued a large supply of DEC to dispense to affected patients when they developed acute manifestations of infection (e.g., lymphangitis) or regularly according to some other selected regimen. Such treatment programs would get away from the traditional vertical management of this disease by health ministries and would embrace a concept already proven valid in Indonesia and India.

Thus, one could devise and evaluate a comprehensive filariasis treatment strategy in Thailand that uses different drugs and different management approaches to the two distinct expressions of the infection, asymptomatic microfilaremia and symptomatic lymphatic pathology. If such a management approach were successful and its effects carefully documented, this strategy could be relevant to many other areas of the world where devising a filariasis control program is of major practical importance.

2. Epidemiological Studies

Two studies would be valuable here. The first would be more descriptive, with the goal of defining the "true prevalence" of the filarial infection and disease in Thailand. This true prevalence survey would have to involve validation of the techniques used (including sampling time in relation to parasite periodicity [as described above] and error estimates resulting from finger-prick rather than venipuncture methods of blood sampling), as well as selection and randomization of "representative" groups of about 20,000 people in each of the six survey districts.

The second epidemiologic study could focus on trying to define the causes underlying the observations that the infection caused by Brugia malayi manifests itself in markedly different ways in two adjacent provinces whose similarities are great. In Surat Thani, the infection is almost exclusively found as asymptomatic microfilaremia, whereas in Pat Nakhong Si Thammret, microfilaremia is uncommon but elephantiasis is quite common. Such a situation is ideal for analysis by a case-control epidemiologic study that would, of course, involve both the human population and the mosquito vectors.

3. Clinical Studies

Though the data are not extensive, scattered reports (as well as more detailed documentation by members of the Filariasis Division) have indicated that two types of periodicity (nocturnal and subperiodic) are seen of the microfilaremia W. bancrofti infection and also of Brugian filariasis in Thailand. Given the rich diversity of these periodicity findings, Thailand presents itself as an ideal site for research on periodicity, a subject that has received very little attention in the past. Exactly what research questions ought to be asked is not certain, but clearly this is a fertile area for much-needed further study.

Another clinical problem that could be investigated effectively in Thailand and that is of extreme interest and importance to the discipline worldwide, is the definition of lymphatic pathology in both symptomatic and asymptomatic patients, as defined by lymphoscintigraphy. Pioneering studies in Brazil have defined the types of abnormalities seen (even in asymptomatic microfilaremic individuals) in bancroftian filariasis. It would be fascinating to compare the differences in the lymphatic changes between Wuchereria and Brugia infections. Since Thailand has both lymphatic filarial infections, it should be quite straightforward to make valid comparisons, especially because it is clear that there are different clinical manifestations resulting from the lymphatic changes in these two infections. Several modern hospitals within and outside of Bangkok are able to carry out nuclear medicine studies, so that the feasibility of such an investigation is great.

4. Immunologic Studies

Determination of the presence of active infection with a living parasite is still an extremely important but unrealized goal in lymphatic filariasis. If one could determine when parasites were alive or dead, evaluation of the effects of chemotherapy would be much simpler and more accurate. Similarly, if one knew whether a patient with obstructive pathology still had living parasites, it would be easier to make a decision about how much chemotherapy was appropriate. Several potential antigen-detection assays have been created in the laboratory, but have not been well-studied in the field to determine their practical value.

Since the Filariasis Division needs to know how to detect active infection and has the patient material and opportunity to collect the appropriate specimens, its staff would be particularly well-placed to ask such important research questions. The feasibility of such studies is all the greater since one of the Division staff members (Mr. Sirichai) is also doing master's thesis work with the one experimental filariologist in Thailand (Dr. Wanlop Chusattayanon). Dr. Wanlop and his immunology-

trained wife have laboratory facilities at Mahidol University that could easily support such a research project. Indeed, Dr. Wanlop already has a grant from USAID to do a similar type of immunologic study.

A second project that could be considered for collaboration between the Division and Dr. Wanlop's laboratory would involve collection of different parasite materials from around the country (since there is such a diversity of parasites in Thailand) and using this collected material to look for strain variations among the different Brugian or Bancroftian parasites. The techniques could include monoclonal antibody detection of unique epitopes (something with which Dr. Wanlop already has facility), but would more likely rely on molecular biology tools as these become available. In any case, the collection of parasite material is a first (and absolutely critical) step in this direction and one that would be of value to many people around the world who study filarial infections.

C. Involvement of Peace Corps Volunteers and/or NIH in the program of the Division of Filariasis, Ministry of Public Health

The current role of the Peace Corps Volunteers in the Filariasis Division is not completely clear to me, partly because I could spend only about four hours with one volunteer (Karen Lanham), and that on my first day in Bangkok. It appears that the PCVs are incorporated into the survey teams at the four different stations where they are assigned and generally provide additional hands for the very large amount of work that has to be done. They appear to play an active role in the work of the Division and their help is appreciated.

The following are suggestions concerning the role of PCVs in the Filariasis Division:

1. Since one of the concerns of the PCVs was to understand better how they were to fit into the Division and what their role was to be, it would seem appropriate that a "job description" be drawn up in detail by the Filariasis Division staff. The exercise would probably give the Filariasis Division the opportunity to think through the issue and the Peace Corps volunteer would then have some yardstick against which to judge his or her success.
2. Have the local Peace Corps office and the director of the Filariasis Division work together to identify what useful services a PCV could provide to the Division. For example, one of the most useful things that the PCV provides is an opportunity for the Thai staff to speak and practice English. Learning English is extremely important for long-term success in Bangkok and elsewhere, and a PCV should work actively to teach English to fellow staff members in a formal or informal way, as appropriate. Although such teaching may not seem

glamorous to a PCV, it would be extremely important to the Thai staff members and, after all, the primary goal of the Peace Corps is to help as needed. A second need that the Peace Corps could help with is computerization of data for the Division. Certainly some of the volunteers must be facile with computers, and assistance in this sphere would be extremely valuable.

3. PCVs could certainly be of help with any of the study projects (involving ivermectin or otherwise) that are undertaken by the Division. Unfortunately, many of them will have had no research experience, so that they certainly could not serve as consultants. They could, however, be of assistance in carrying out research projects.

The overall conclusion here is that the Peace Corps office should talk to the new director to see how PCVs can be useful to his program and then match the specific needs of the Division with the specific talents of volunteers. Also, definition of specific duties for the volunteers should be formulated and codified.

With respect to the possible linkages between NIH and the Division of Filariasis, there is no question but that there are many areas of overlapping interest and complementary expertise. Should it become advantageous for the Division of Filariasis to have NIH as a collaborator (or vice versa), there is no reason that more formal linkages could not be established.

D. Potential Sources of Funding

Clearly, the Division of Filariasis is in a position to reorganize and expand its program to serve the practical public health needs of the Thai people, as well as to carry out research programs that would contribute significantly to our overall understanding of filariasis and its control. The Division, however, could not undertake such research programs unless special funds designated for this additional work were available. In addition, the Division particularly needs funds for advanced training of its staff members, most of whom are educated through the master's level. Because of these two needs, it may be most efficient for the Division to serve as a focal point for an Institute-Strengthening Grant from the TDR/WHO program in Geneva. A successful application to that agency would provide funds for both training and individual research projects.

Alternatively, proposals for these latter projects, whether they involved ivermectin or not, could be submitted either together or separately for consideration for funding by USAID or the WHO/TDR program. It would be advantageous for the Division to be linked collaboratively with a similarly interested group in the United States. This group might be either the NIH or interested workers elsewhere.

Technical Assistance for Operational Improvements

It was perhaps a particularly opportune time to visit the Filariasis Division as a consultant because a new director had just been appointed. He is enthusiastic about changing the operations and strategy underlying Thailand's approach to filariasis and about studying all aspects of the disease and infection. Indeed, during our two-day site trip to Naratiawat, we spent much time discussing individual patients seen in their homes, both from the point of view of the pathogenesis of the disease and the clinical management of individual cases.

It is clear that the director first wants to improve the prevalence data available for the entire country and that he would like to change the approach to filariasis from an entirely vertical one to something more horizontal and village-based. He is optimistic that a strategy where the two distinct problems of filariasis (i.e., lymphatic disease and microfilaria carriage) are separated in terms of approaches to management and control will lead to greater overall effectiveness. This result would be especially likely if a simple-to-use drug like ivermectin were to become available for control of the microfilaria carriers. With such an approach to the problem (as described above), the director felt that eradication of filariasis in Thailand, given its relatively low prevalence and focal distribution, was an appropriate and feasible goal. Because the manpower is available, I believe that he is correct in setting eradication as the goal of the Filariasis Division. If his creative new program can be effectively and methodically carried out, the result should be a model for filariasis-control programs in all other affected countries.