STATUS OF BRUGIAN FILARIASIS RESEARCH IN INDONESIA AND FUTURE STUDIES

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ABSTRAK

Penyebab penyakit filariasis di Indonesia adalah *Brugia malayi* dan *B. timori*. Penyebaran kedua jenis parasit tersebut, serta berbagai masalah perbedaan geografis dari B. malayi, baik pengobatannya dengan *chemotherapy* maupun immunodiagnosisnya telah diketahui. *B. pahangi* yang bersumber pada binatang juga telah dilaporkan. Nyamuk-nyamuk sebagai vector untuk B. malayi dan B. timori telah pula disebut. Binatang-binatang liar juga telah dilaporkan sebagai sumber penularan yang sangat potensial melalui subperiodic *B. malayi*.

Brugian filariasis, transmitted by various mosquito species, is endemic in rural areas primarily. Lymphatic filariasis includes urban and rural bancroftian filariasis, affects about 20 million people in Indonesia, and about half or more of these numbers are affected by brugian filariasis (Arbain Joesoef & Cross, 1978). In Indonesia, brugian filariasis consists of several species. Among these, two parasite species are involved as causative agents of human filariasis, i.e. *Brugia malayi* (Lichtenstein) and *Brugia timori* (Partono et al.). *Brugia pahangi*, Buckley & Edeson, closely related to *B. malayi*, is found parasitic in some wild and domestic animals. This latter parasite has been shown to be capable of developing in man (Edeson et al. 1960), but so far it has not been shown for certain to infect man naturally. Unlike malaria, which causes high mortality rate in hyperendemic areas, brugian filariasis causes high morbidity. It is, thus a disease of socio-economic and public health importance.

PARASITES

Brugia malayi is widely endemic in Sumatera, Kalimantan, Sulawesi and adjacent islands, but its distribution is limited by the Weber Line, which separates Irian from the Seram-Ambon islands (Brug, 1928; Lee & Rees, 1958; Lee, 1970). In man it is usually associated with elephantiasis of the lower limbs, recurrent lymphadenitis and lymphangitis. The parasite in man is classified into two physiological forms, the periodic and subperiodic, (Turner & Edeson, 1957). Both these forms are present in Indonesia (Lie, 1970). Microfilariae of periodic *B. malayi* have the tendency to exsheath in thick blood smears under normal drying conditions at room temperature. More than 80 % of the microfilariae shed their sheaths compared to less than 8 % in

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the subperiodic form (Wilson et. al. 1958). Thus, the percentage of exsheathed microfilariae seen in thick blood smears between the periodic and subperiodic *B. malayi* from both Malaysia and Thailand, has been used as important characteristic in the separation of two forms (Sivanandam & Dondero, 1972; Guptavanij et. al. 1971). Morphological studies of microfilariae in periodic *B. malayi* in 13 microfilariae (Mf) carriers from South Sumatera (Mashat, 1960), 12 Mf carriers in Bengkulu, Sumatera (Sudomo et. al. 1982) and 18 Mf carriers in Kendari Regency, Southeast Sulawesi (Arbain Joesoef et. al. 1984) found sheathed microfilariae in each of these studies were 52 — 100 %, 44 — 100 % and 42 — 100 % respectively. These findings revealed that the periodic *B. malayi* in Indonesia behaves differently to that shown either in Malaysia or Thailand.

The character of microfilarial periodicity is useful not only for the epidemiology relation but also for phytogeny of the filariae in their type. Thus, it is essential to define the term "periodicity" which is used in the designation of strains. Different strains show varying tendencies of rhythmic variation in microfilarial density in the peripheral blood during the 24-hour cycle. This characteristic is term "periodicity" which can be summarized in the "periodicity index" and the "peak hour" of the wave of microfilarial density as defined by Sasa & Tanaka (1974). They postulated that the rhythmic variation of microfilarial density corresponded to that of a harmonic wave form described by the formula $y = m + a \cos. 15 (h - k)$ where the microfilarial ratio (y) at a given hour = (microfilarial count = mean count of observations over 24 hours) x 100; m = mean microfilarial ratio of all patients at a given hour; a = periodicity index; h = hour and k = peak hour. Through trigonometric conversion, the formula becomes $y = m + h \cos. 15h^\circ + c \sin 15h^\circ$ and allows for easier calculation ($a^2 = b^2 + c^2$; $b = \frac{2\Sigma y \cos 15^\circ h}{n}$; $c = \frac{2\Sigma y \sin 15^\circ h}{n}$; n = number of observations in 24 hours; $\tan 15^\circ k = \frac{b}{c}$) (Tanaka, 1981).

Kanda et. al. (1979) studied microfilarial periodicity on 15 Mf carriers from Mahang and Lampihong (South Kalimantan), 9 in Bengkulu (Sumatera) and 11 in Palolo (Central Sulawesi). They found 13 Mf carriers in South Kalimantan which belong to aperiodic *B. malayi* (APBm) and two of nocturnally subperiodic (NSPBm), while all the 20 cases in both Bengkulu and Palolo were nocturnally periodic (NPBm). A re-analysis of the periodicity data of three NSPBm from East Kalimantan by Sudomo et. al. (1980) found all the three cases were APBm. Recently one case of diurnally subperiodic form in East Kalimantan was observed (Sujadi, 1982). The results revealed that there are three distinct pattern of periodicities, the NPBm, NSPBm and APBm in Indonesia. The SPBm has two types, the nocturnally and the diurnally subperiodic.

Lim (1985) demonstrated that the distribution of these various *B. malayi* forms in Indonesia is related to the landscape ecology, reservoir hosts and mosquito vectors. He observed there is a gradual change in the microfilarial periodicity from aperiodic to highly periodic corresponding to the change in the ecology of the habitats and its intermediate host and non-human primate reservoir hosts. By implication therefore, it would mean that as ecological changes occur, parasite behaviour as reflected in the periodicity and peak hour will have to evolve and adapt to situations present to ensure its continued transmission. What mechanism operates to achieve this is unknown. The periodic strain is essentially a human parasite and although it can be experimentally

transmitted to laboratory animals like the cat and gerbil, the resultant infection is not as lasting as that of the subperiodic form (Mak et. al. 1980, 1982). In Indonesia adult *B. malayi* were recovered from wild monkeys in periodic endemic areas of south and north Bengkulu (Lim et. al. 1984). In contrast, subperiodic *B. malayi* is considered a zoonotic parasite and it has been observed that in areas of intense endemicity the infection rates in domestic and wild animal hosts (cats and monkeys) are correspondingly high (Palmieri et. al. 1980, Lim et. al. 1984).

BRUGIA TIMORI

Brugia timori n.sp. was described by Partono et.al. (1977) after confirmation of adult worms recovered from experimental animals. The parasite is endemic in Flores and Alor islands only (Oemijati & Tjoen, 1966; Kurihara & Oemijati 1975). Periodicities studies of Mf carriers revealed nocturnal periodic (Kanda et.al. 1979). The parasite has so far been found in man only. The parasite causes elephantiasis of the lower limbs below the knee, lymphadenitis and lymphangitis (Dennis et. al. 1976; Partono et.al. 1978; Partono & Purnomo, 1978a).

BRUGIA PAHANGI

Brugia pahangi was described from adult worms recovered from a monkey and a cat in Pahang, Peninsular Malaysia by Buckley & Edeson (1956). In Malaysia, this parasite occurs in a wide range of animals but does not infect man (Wharton, 1962). In Indonesia, the parasite was found from wild monkeys and cats in South Kalimantan (Masbar et.al. 1981), from cats in Jambi, Sumatra (Sudomo et.al. 1984) and from cats and wild civets in Bengkulu, Sumatera (Lim et.al. 1984). Transmission experiments have shown that infective larvae will develop to maturity and will produce microfilariae in man. It has been shown also that infection with this parasite will produce clinical symptoms in man (Edeson et.al. 1960). Thus, *B. pahangi* cannot be ignored and may play some part in the epidemiology of human filariasis.

MUSQUITO VECTORS

In Sumatera, the incriminated vectors of periodic *B. malayi* are *Mansonia* spp. primarily *Ma. bonneae/dives* group and *Ma. uniformis*. Potential anopheline mosquitoes were *An. peditaeniatus* and *An. nigerrimus* (Suzuki et.al. 1981). The *Mansonia* spp. breed in open swamp areas, and the *Anopheles* spp. were found breeding in ricefields. The indoor peak biting cycles of *Ma. bonneae/dives* gp. were between 1800—2000 hour with a lesser peak between 0300—0400 hour. Outdoor biting peaks were between 1800—1900 hour with a lesser one from 0200—0300 hour. *Ma. uniformis* has two indoor biting peaks, one immediately after dusk and one at midnight, and it bites throughout the night and morning hours in outdoors, with peaks at 1800—1900 hr and 0300—0500 hr, and a lesser third peak at midnight (Sudomo et.al. 1984a). Early workers established *Ma. dives* and *Ma. annulata* as vectors (Brug & Rook, 1930).

That of the subperiodic *B. malayi*, the vectors are also *Mansonia* spp. They are *Ma. uniformis, Ma. indiana, Ma. bonneae/dives* which breed in fresh water swamps adjacent to secondary and distrubed primary forests. *An. nigerrimus* which breeds in ricefields, is a potential vector (Sudomo et.al. 1984).

In Java island of West Java, the vector of subperiodic *B. malayi* is *Ma. indiana* which breeds in swampy places around the endemic areas (Oemijati et.al. 1977). Earlier workers incriminated *Ma. uniformis, Ma. indiana* and *An. hyrcanus* gp. (Rodenwaldt, 1934).

In Kalimantan, the vectors of subperiodic *B. malayi* are *Mansonia* spp.

primarily *Ma. uniformis* which breeds in freshwater swamps adjacent to secondary and disturbed primary forests, and in rubber estates (Klokke, 1961; Partono et. al. 1977a; Sudomo et.al. 1980).

In Sulawesi, the vectors of periodic *B. malayi* are *Anopheles* spp. and three *Mansonia* spp. The anophelines are *An. barbirostris* and *An. nigerrimus*, and the mansonoids are *Ma.uniformis*, *Ma. indiana* and *Ma. bonneae/dives* gp. The primary vector is *An. barbirostris*, and the rest are secondary vectors. The *Anopheles* spp. breed in ricefields, ditches, ponds and open swamps (Atmosoedjono et.al. 1976; Bahang et.al. 1984). The *Mansonia* spp. also breed in the same ecological niches as that of *An. barbirostris*, but they are also found in swampy areas adjacent to secondary forest (Kirnowardoyo et.al. 1984). The indoor biting peak cycles for *An. barbirostris* were between 2400—0300 hours, and that of *An. nigerrimus* were from 1900—2200 hours (Bahang et.al. 1984). Earlier workers incriminated *An. barbirostris* and *Ma. uniformis* as vectors (Brug, 1937; Jurgens, 1932).

In Maluku, the vectors of periodic *B. malayi* were supposedly to be *Ma. uniformis* and *An. bancrofti* (Brug & Rook, 1933). These were not confirmed.

The vectors of *B. timori* are three *Anopheles* spp. *An. barbirostris* is the confirmed vector which breeds in ricefields, open swamps, disused ponds and ditches (Atmosoedjono et.al. 1977). *An. vagus* and *An. subpictus* were also incriminated, but have yet to be confirmed.

The vector of *B. pahangi* is still not known.

PAST RESEARCH AKTIVITIES (1925 — 1970)

Brugia malayi was not authentically identified until 1927, then it was known as *Filaria malayi* (Brug, 1927). The microfilariae were found to be morphologically different as well as in the manifestation of the disease from that of *W. bancrofti*, and in the same year, Lichtenstein changed the generic name to *Brugia* but retained the specific name as *Brugia malayi* (Lichtenstein) 1927. Pinhoa (1961) and David and Edeson (1964, 1965) were the ones who detected microfilariae in man which resembled *B. malayi* in Portuguese Timor, and subsequently found from Indonesian Timor, Flores and Alor islands (Oemijati & Tjoen, 1966; Kurihara & Oemijati, 1975). The microfilariae of *B. pahangi* was first detected in dogs of endemic *B. malayi* areas (Lie, 1970). During this period, research activities were concentrated on the distribution and prevalence of infection by both the parasites with special attention to *B. malayi*. Chemotherapy treatments with DEC were carried out in hyperendemic areas of *B. malayi*.

Mosquito vectors were incriminated based on recovery of infective stage larvae in the mosquitoes. In some cases, wild caught mosquitoes were fed to Mf carriers for further confirmation of the vectors.

PRESENT RESEARCH ACTIVITIES (1971 — 1984).

Based on results from past findings, research activities on brugian filariasis gained momentum during the 1970s. With more advanced technology made available such as suitable animal models, immunological techniques and development of alternative methodology of chemotherapy treatment, recent research workers view the disease with new perspective. During this period more intensive systematic surveys are being carried out to further update the mapping distribution of the parasites, more in depth on the epidemiology of the disease was studied and additional mosquito vectors were conclusively incriminated.

SURVEILLANCE OF *BRUGIA MALAYI* AND *B. TIMORI.*

Since 1970, surveillance studies on *B. malayi* were intensified, and the results are presented in Table 1. A total of 189, 184 people from 305 villages of 16 provinces in 5 islands were surveyed. Of these 253 or 83.0% of these villages were shown to be *B. malayi* endemic areas. The prevalence rates in these villages ranged from 0.2 % to 26.5 % with an overall rate of 11.5 %. Among the five islands surveyed, the highest prevalence rate was 23.1 % in Maluku, followed by 15.0 % in Kalimantan and 11.9 % in Sulawesi. Lower rate of 6.7 % was observed in Sumatera. and the lowest was 1.7 % in Java (Table 2.). The high microfilariae rate in Maluku was probably reflected by the small sampling made.

Brugia malayi endemic areas in Java islands is confined to Adipala and Kresek of West Java only, and Bali is found to be free from the disease. The limited focal areas and low prevalence rate of the parasite is probably due to the original habitats of *B. malayi* in Java are being rapidly opened for developments into urbanization. Bali island, on the other hand, still retains some of the habitats and potential mosquito vectors (*Mansonia* spp.) and non-human primate reservoir hosts *(Macaca fasciatus)* are present, thus the absence of this parasite in the island poses some searching questions.

During the period from 1975 to 1980, a total of 15,572 people from 18 villages in Alor and Flores islands were surveyed, and the results are presented in Table 3. All the 18 villages surveyed were endemic with timorian filariasis. The prevalence rate in these villages ranged from 7.9 to 23.8 % with an overall rate of 9.1 %. Alor island had a much higher microfilariae rate than Flores island. Partono et al. (1978) studied the disease in a newly established village, Karakuak, West Flores, revealed that development of elephantiasis in the human population was associated with residence in the new village of Karakuak.

IMMUNOLOGICAL STUDIES

Studies on the immune responses to microfilarial antigens in human was conducted in 1979 in an endemic area of South Kalimantan. This seroepidemiological approach was taken to elucidate the relationship between anti-sheath immunoglobulins, microfilaremia and filarial disease. The results revealed that the prevalence and titer of anti-sheath IgM was found higher than that of IgG and IgA classes using Indirect fluorescent antibody technique. There was an inverse relationship between the presence of microfilaremia and anti-sheath antibody of the IgM class, that was not found in the IgG and IgA classes. Anti-sheath antibodies were not related to filarial disease (Mc Greevy et al, 1980).

Cellular immune competence of 101 *B. malayi* cases were evaluated in South Kalimantan, with lymphocyte transformation assay. Amicrofilaremic and/or asymptomatic individuals reacted to microfilarial antigens, while microfilaremic individuals did not react. Only elephantiasis individuals reacted to adult worm antigens. The results indicated that patent infection was associated with a state of specific cellular immune unresponsiveness. Various clinical manifestations of filariasis were suggested to be the result of different types of immune responses to distinct antigens associated with different development stages of filarial worms (Piessens et al. 1980a). Further studies in this area showed that IgG anti-sheath antibodies were more prevalent in elephantiasis. Antibodies from amicrofilaremic subjects with high IgG antisheath antibody titer promoted the adherence of leucocytes from normal individuals to *B. malayi* microfilariae. Furthermore, amicrofilaremic subjects ex-

Table 1. Summary of microfilaria rate of *Brugia malayi* based on published data from 1972 — 1984.

Area	Reference	No. of villages surveyed	No. of villages positive	No. of persons examined	% with m.f.	Density of mf in whole pop.	Density of mf per positive	% with elephantiasis
West Java	Arbain Joesoef et al 1978	2	1	2,667	0.2	—	—	—
Kresek, West Java	Sri Oemijati et al 1978	6	2	813	6.8	—	—	—
West Kalimantan	Partono et al 1977a	8	4	3,035	11.7	—	—	18.0
Waru village East Kalimantan	Sudomo et al 1980	6	6	562	9.3	4.5	22.7	6.0
Babulu village (Transmigration area) East Kalimantan	— do —	1	1	676	0.4	—	14.1	—
Hulu Sungai Tengah Reg. South Kalimantan	J.H. Cross et al 1975	4	4	12,992	25.0	—	—	—
South Kalimantan	Partono et al 1977c	7	7	2,764	25.0	11.4	—	5.5
South Kalimantan	Arbain Joesoef et al 1978	12	12	22,863	14.4	—	—	—
East Kalimantan	— do —	9	5	7,585	5.2	—	—	—
Central Kalimantan	— do —	21	19	7,699	9.1	—	—	—
Jambi, Sumatera	Sudomo et al 1984	1	1	139	18.7	4.2	25.7	5.0
Riau, Sumatera	Arbain Joesoef et al 1978	5	5	1,690	21.9	—	—	—
Aceh, Sumatera	— do —	10	7	2,354	12.4	—	—	—
Bengkulu, Sumatera	— do —	9	9	15,276	8.4	—	—	—
South Sumatera	— do —	17	13	11,251	3.2	—	—	—
West Sumatera	— do —	5	5	4,754	2.8	—	—	—
North Bengkulu, Sumatera	Sudomo et al 1982	2	2	197	25.9	7.8	38.4	1.5
Harga Air Periukan Bengkulu, Sumatera	Suzuki et al 1981	8	8	781	26.5	9.5	47.5	1.0
Lampung	Arbain Joesoef et al 1978	5	4	4,505	0.8	—	—	—
Margolembo, S. Sulawesi	Partono et al 1972	3	3	635	25.2	12.1	36.6	7.4
Banggai Regency, Central Sulawesi	J. Putrali et al 1977	4	3	336	3.6	—	—	—
Palolo valleys, Central Sulawesi	P.F.D. Van Peenen & Richard See, 1977	?	?	477	17.0	—	—	—

Area	Reference	No. of villages surveyed	No. of villages positive	No. of persons examined	% with m.f.	Density of mf in whole pop.	Density of mf per positive	% with elephantiasis
Palu valley, C. Sulawesi	John H. Cross et al 1977a	4	4	3,651	25.0	—	—	—
Torro valley, C. Sulawesi	E.E. Staffort et al 1980	?	?	392	25.0	—	—	—
Palu valley, C. Sulawesi	Partono et al 1976	7	7	3,658	25.0	5.4	19.4	2.8
Rampi & Seko valleys South Sulawesi	W.P. Carney et al 1977	7	7	734	19.2	4.2	—	—
Kalamanta, C. Sulawesi	— do —	2	2	236	10.6	3.8	—	—
North Lore district Central Sulawesi	W.P. Carney et al 1977a	11	11	972	10.0	—	—	—
Malili, South Sulawesi	S.W. Joseph et al 1978	9	9	985	15.1	8.0	—	—
Kendari, S.E. Sulawesi	Arbain Joesoef et al 1984	4	4	3,497	13.6	6.7	38.6	0.2
Kecamatan Mangkatuna (Transmigration areas) South Sulawesi	Gandahusada et al 1980	24	16	8,488	7.6	—	—	0.9
Kecamatan Mangkutana South Sulawesi	— do —	21	20	5,990	9.7	—	—	1.1
Kecamatan Nuha, South Sulawesi	— do —	20	17	5,420	3.6	—	—	1.0
Kecamatan Wotu , S. Sulawesi	— do —	17	14	11,163	3.5	—	—	0.3
North Sulawesi	Arbain Joesoef et al 1978	7	1	963	1.2	—	—	—
Central Sulawesi	— do —	14	13	27,653	15.1	—	—	—
South Sulawesi	Arbain Joesoef et al 1978	7	6	10,907	11.4	—	—	—
Maluku	— do —	6	1	324	23.1	—	—	—
		305	253	189,184	11.5	—	—	—

Table 2. Distribution of microfilariae rates of *Brugia malayi* by provinces in Indonesia

Provinces	No. of villages surveyed	No. of villages positive	No. of persons examined	No. of persons with mf	% positive
JAVA					
West Java	8	3	3,480	60	1.7
KALIMANTAN					
West Kalimantan	8	4	3,035	355	11.7
East Kalimantan	16	12	8,823	449	5.1
South Kalimantan	23	23	38,7,9	7,231	18.7
Central Kalimantan	21	19	7,699	701	7.2
	68	58	58,276	8,736	15.0
SUMATERA					
Jambi	1	1	139	26	18.7
Riau	5	5	1,690	370	21.9
Aceh	10	7	2,354	292	12.4
Bengkulu	19	19	16,254	1,541	9.5
South Sumatera	17	13	11,251	360	3.2
West Sumatera	5	5	4,754	133	2.8
Lampung	5	4	4,505	37	0.8
	62	54	40,947	2,759	6.7
SULAWESI					
South Sulawesi	108	92	44,322	3,505	7.9
Central Sulawesi	42	40	37,375	6,220	16.6
North Sulawesi	7	1	963	12	1.2
Southeast Sulawesi	4	4	3,497	476	13.6
	161	137	86,157	10,213	11.9
MALUKU	6	1	324	75	23.1
TOTAL	305	253	189,184	21,843	11.5

hibited either evidence of cellular response to microfilarial antigen or antifilarial antibodies, but not to both (Piessens et al. 1980b).

Adherent cell type was found to be specifically suppressing the reaction to microfilarial antigens. It was also shown that serum factors suppressed the specific reaction. These results suggested that the unresponsiveness was due to active suppression of immune response directed against the parasite and not to an intrinsic inability of infected individuals (Piessens et al, 1980c). Helper and suppressor T cells in infected individuals were enumerated to determine the association of

specific hyporeactivity with the changes of lymphocyte subpopulation. Suppressor T cells were found increased in microfilaremics and elephantiasis individuals. The increase correlated with the hyporeactivity of filarial antigen, but not to non-parasite antigens. The immune response was activated after removal of suppressor T cells, which suggested that the immune suppression was a possible mechanism of survival in immune competent host (Piessens et al, 1982).

Study on the effect of treatment with DEC to the specific immune responses were performed. In vitro lymphocyte proliferative responses to microfilarial antigen were increased in patients who became amicrofilaremic after treatment, while no changes were observed in patients who remained microfilaremic after treatment. It was indicated that DEC partially reversed the stage of cellular unresponsiveness while serum titer to microfilarial sheath did not change (Piessens et al., 1981).

Twenty individuals settling from non endemic area to a malayan filariasis endemic area in Southeast Sulawesi had been evaluated for 26 months, for their specific humoral and cellular responses. Despite that, they remained parasitologically negative throughout the study period, their antibody responses to *B. malayi* microfilaria extract in the ELISA were significantly higher if compared to the non-endemic controls. These antibody responses were encountered as early as 8 months of exposure. Specific cellular responses to *W. bancrofti* microfilaria were seen in one year exposure (Kurniawan, 1986a).

Comparison of immune responses between natives and newly exposed individuals in malayan filariasis endemic area was performed in Central Sumatra and Southeast Sulawesi. Natives of three villages with different microfilarial rates were compared with the settlers who had settled for 6, 9 and 36 months. Antibody responses were measured with ELISA using crude extract of *B. malayi* microfilaria. The findings suggested that when people settled in an endemic area from a non endemic area, initially the immune response increased, but after a certain period the response decreased until a certain level that were similar to the natives. (Kurniawan, 1986b).

Furher studies on the immunopathogenesis of malayan filariasis is now going on in Jambi and Buton island, Southeast Sulawesi. It is expected that in these studies differences in the immune response of people having microfilaremia and filarial disease compared to the amicrofilaremic and asymptomatic individuals could be seen.

Studies on the immune profile in villagers, where timorian filariasis as well as malaria were endemic, had been conducted in Flores. *B. timori* microfilaremia was associated with reduced levels of total IgE, while acute filariasis showed increased total IgG levels (Higgens et al 1985).

Antigens analysis of *B. timori* were performed with surface labelling technique. Iodinated preparation from infective larva, adult worm and microfilaria were used to test timorian filariasis individuals. It was shown that levels of antiparasite antibody appeared to increase as filarial disease became more severe. Antibody to microfilarial surface antigens were present in microfilaremic as well as amicrofilaremic individuals. It was concluded that reaction to infective larval antigen was the clearest indicator in infection (Maizels et al, 1983).

Antibody responses of the IgG class in Timorian filariasis are being evaluated using crude extract of infective larva of *B. timori* with the enzyme linked immunosorbent assay (Sutanto — per.-comm.). Detection of circulating antigen using monoclonal antibody in Immunoradiometric assay in the serum and urine

is being performed.

CHEMOTHERAPY

Mass treatment with DEC (diethyl carbamazine citrate) was carried out in Sidondo and in six villages of the Gumbasa irrigation area in Central Sulawesi (Putrali & Kaleb, 1974; Putrali et al. 1975). The regimen was 5 mg per kg body weight of DEC given for 6 consecutive days with a total dosage of 30 mg/kg/BW. In Sidondo the prevalence rate was reduced from 28.5 % to 4.3 % and from 24 % to 5 % in the Gumbasa area after 3 months of treatment. The results revealed that mass treatment and the daily dosage scheme were practical for public health teams, side effects were not severe, and the public acceptance was good. In contrast mass treatment conducted in a village on a rubber plantation at Banjar district of South Kalimantan in 1974 by Ibrahim et al, (1977) was a failure. In 1973 the prevalence rate was 15 % which was increased to 18 % after treatment in 1974. The authors opined that the failure of DEC mass treatment was due to the immigration of potent carriers to the treated area and also continued transmission. They found that the migration rate of people in villages on rubber plantation was higher than that in traditional villages.

Subsequently in 1978—1979 experimental chemotherapy with DEC of different dosages as a short-term and long-term mass treatment were conducted in Sungai Baru and Pengiuran villages of Banjar district in South Kalimantan by Jan Rush et al., (1980). The regimen for long-term mass treatment was 2 mg/kg/BW given daily for 25 consecutive days, and that of the short-term was 5 mg/kg/Bw given 2 times a day for 5 consecutive days with a total dosage of 50 mg/kg/BW for each method. The results showed that the reduction on the prevalence of microfilaremia for both methods was not significant at 12 months post treatment. The MFD_{50} was not significant either at 6 and 12 months post treatment. The general reaction was less prevalent in the long term than in the short-term mass treatment. The results show that the long-term mass treatment was as effective as that of the short-term mass treatment. A study on the adverse reactions occurring after treating microfilaremic patients infected with *B. malayi*, revealed that all reacted to a single oral dose of DEC (5 mg/kg). There seem to be no association between the time of fever onset and microfilarial density, but there was a tendency for more severe reactions to occur in patients with higher microfilaria counts (Inge Sutanto et al. 1985). Medicated salted DEC treatment to microfilariae carriers was carried out in Takuti and Pasiraman villages of South Kalimantan. The treatment was found to be successful and no side-effect of the patients was observed. Twelve months after treatment the microfilariae rates were reduced by 76% and 78% in both the treated villages (Harijani et al. 1983).

The control of *B. timori* by mass treatment using 50 mg DEC per kg/BW followed one year later by short-term selective re-treatment in highly endemic area, reduced the Mf rate by finger stick from 24 % to 0 and by Nuclepore *membrane* Filtration from 30 % to 2.5 %. The disease rates wre also affected favourably (Partomo et al. 1979). The demonstrated low dose of DEC treatment supplemented by selective re-treatment through community participation was found to be successful for *B. timori*. Mass treatment using low dosage DEC on a weekly basis for 18 month period through community participation and supported by health education was carried out in 3 endemic villages in West Flores. Mild side effects were encountered during the first few weeks of treatment. One year after treatment, the microfilaria rates decreased

dramatically to very low levels, even by Nuclepore membrane filtration. The adenolymphangitis rates also decreased and several persons with lymphoedema or elephantiasis realised that their limb sizes were also decreasing (Partono et al. 1984). Follow-up studies showed that all cases with lymphoedema could be treated with DEC irrespective of the size of the swelling, and in most cases the swelling disappeared within one year. For people with elephantiasis it took two to four years for most of the swelling to disappear. Elephantiasis of the arms was easier to treat than of the legs, and bilateral elephantiasis. Elephantiasis of less than three to five years' duration were easier to treat than of longer duration, and individuals with a higher grade of elephantiasis were more difficult to treat than those with a lower grade of elephantiasis. The age and sex of patients did not influence the outcome of the treatment. (Partono, 1985).

SURVEILLANCE OF MOSQUITO VECTORS.

Since 1972 nine mosquito vectors (6 *Mansonia* and 3 *Anopheles*) of *B. malayi* were incriminated, and the results are presented in Table 4. The natural infection rates for the six *Mansonia* spp. ranged from 0.04 — 1.4 % and 0.1 — 4.3 % for the three *Anopheles* spp. The natural infections of these vectors were based on the recovery of filaria larvae in them. Experimental infections in 7 of the 9 mosquito spp. to human Mf carriers showed that these mosquitoes were highly susceptible with infectivity rates ranging from 20 — 81.7 %. However, infective larvae from *An. barbirostris*, *An. nigerrimus*, *Ma. indiana* and *Ma. bonneae/dives* gp. developed to adult worms through laboratory animals were obtained (Bahang et.al.1984; Kirnowardojo et.al. 1984). The experiments further confirmed that these mosquitoes were natural vectors of *B. malayi*. For *B. timori*, among the three mosquito spp. incriminated, *An. barbirostris* is the only one, so far, being confirmed as a vector, either naturally or experimentally. The mosquito vector for *B. pahangi* in nature is still not known, but newly emerged *Ma. uniformis*, *Ma. dives* and *Ma. bonneae* fed to infected field cats *(Felix cattus)*, and infective larvae recovered from these mosquitoes developed to adult *B. pahangi* worms through laboratory animals experimentally (Lim et.al. 1984). This indicates that these mosquito spp. were highly susceptible to the *B. pahangi* parasite.

CONCLUSION

The distribution of the *B. malayi* and *B. timori* and mosquito vectors is presented in Fig. 1. Data on the map have been conducted in the more accessible places, along the coast and inland on major rivers and roads in the five islands. There are still many smaller islands in the eastern parts of Indonesia which have yet to be surveyed. Based on the results of resent published data, it was apparent that *B. malayi* is widely distributed throughout the country. The prevalence rates were shown to be higher in those islands that are less developed than those which are better developed. It also revealed that *B. malayi* strains are shown to be more complex in Indonesia than that found in its neighbouring countries. The data also indicate that *B. malayi* in highly developed areas, is beginning to disappear. *B. timori*, on the other hand, has so far been found in islands of Nusa Tenggara Timur only. It is interesting to note that the parasite has not been found in its adjacent islands of West Nusa Tenggara where only *Wuchereria bancrofti* is reported, although mixed infections of both these parasites were detected in inhabitants in endemic areas of *B. timori* (Arbain Joesoef and Cross, 1978).

Table 3. Summary of microfilariae rate of *Brugia timori* based on published data from 1975 – 1980.

Area	Reference	No. of villages surveyed	No. of villages positive	No. of persons examined	% with Mf	Density of Mf in whole pop.	Density of Mf per positive	% with elephantiasis
Alor Island Nusa Tenggara Timur	Arbain Joesoef & David T. Dennis, 1980	2	2	1418	7.9	—	—	—
Karakuak West Flores	Felix Partono et al 1978a	1	1	202	23.8	16.2	38.4	11.0
Wae Manis West Flores	Felix Partono & Purnomo, 1978.	1	1	59	10.2	—	20	18.6
Nusa Tenggara Timur	Arbain Joesoef & Cross (1978)	13	13	13,788	8.8	—	—	—
Lekebei area Flores	Takeshi Kurihara & Sri Oemijati, 1975	1	1	105	11.4	—	—	—
		18	18	15,572	9.1	—	—	—

Table 4. Reported vectors of *Brugia malayi* in Indonesia.

Islands/ Provinces	Mosquito species	Experimental infection (in percent)		Natural infection (in percent)	Forms of *Brugia* Strains	References	Areas examined
		Mosq. fed to human carriers	Infected larvae from mosq. innoculated to jerds				
SUMATRA							
Bengkulu	*Ma. bonneae*	41.4 (347)	—	1.4 (8,883)	NPBM	Suzuki et.	Marga
	Ma. dives	42.9 (177)	—	1.3 (4,447)		al. 1981	Andalas,
	Ma. annulata	22.3 (197)	—	0.6 (7,132)		& Sudomo	Marga Air

	Ma. uniformis	57.3 (260)	—	0.6 (4,881)		et al 1982,	Periukan,
	An. peditaeniatus	38.0 (239)	—	0.1 (4,089)		1984a & b	and Lais.
	An. nigerrimus	30.0 (60)		0.6 (1,990)			
JAMBI	*Ma. dives*	—	—	0.3 (293)	NSPBM	Sudomo et.	Puding
	Ma. uniformis			2.3 (210)		al. 1984	
	Ma. indiana			1.7 (180)			
	An. nigerrimus			3.2 (61)			
NORTH SUMATRA	*Ma. uniformis*			20.0 (35)	NPBM	Lien et al 1975	Medan
KALIMANTAN							
East Kalimantan	*Ma. uniformis*			0.2 (862)	APBM	Sudomo et. al. 1980	Balikpapan
South Kalimantan	*Ma. bonneae/dives*			0.45(27,342)	NSPBM	Lee et al 1981	Martapura
	Ma. uniformis			0.04(16,388)			
	Cog. crassipes			0.05(8559)			
SULAWESI							
Southeast Sulawesi	*An. barbirostris*	81.7 (60)	6adults *B. malayi*	0.6 (20,520)	NSPBM	Bahang et al 1984	Kendari
	An. nigerrimus	20.0 (30)	—	05. (615)			
	Ma. indiana	76.7 (73)	5 ,,	0.5 (4426)			
	Ma. uniformis	63.3 (30)	4 ,,	0.4 (6895)			
	Ma. bonneae/dives	—	—	1.5 (390)			
South Sulawesi	*An. barbirostris*	—	—	4.3 (145)	NPBM	Partono et al 1972	Margolembo
Central Sulawesi	*An. barbirostris*			10.4(115)	NPBM	Atmoseodjo-no & Van Peenen, 1976	Bobo & Kalawara

NPBM = Nocturnally periodic *B. malayi*
NSPBM = Nocturnally sub-periodic *B. malayi*
APBM = A-periodic *B. malayi*

Figures in parentheses denote actual number of mosquito examined.

The only antihelminthic which has been used to treat brugian filariasis in man is DEC (diethyl carbamazine citrate). DEC is a difficult drug to administer and in mass chemotherapy programmes the proportion of the population who default on their dosage can be high as a result of side-reactions. Even with minimal default rates, transmission may continue from carriers harbouring ultra low densities of persistent microfilariae. Until transmission ceases, control will rely on continual surveillance and individual treatment. Experimental chemotherapy with DEC of different dosages as a short-term and long-term treatment for *B. malayi* showed that both these methods were equally as effective; there was not much side-effects among recipients in long-term mass treatment than that experienced by the short-term one (Jan Rush et.al. 1980). For *B. timori* low dose of DEC treatment followed one year later by short-term selective re-treatment through community participation and was found to be successful in the control of the disease in endemic areas (Partono et.al. 1979). It was apparent from both these treatment results that the modified methodology can serve as an alternative chemotherapy treatment than the conventional method of treatment.

Environmental development appears to have a great impact on the reduction of *B. malayi*. Java, being the most highly developed island, the prevalence of *B. malayi* is lowest, and is now restricted to two isolated endemic areas only if compared to other islands that are not as rapidly developed.

The existence of innate immunity to *Brugia* in man is not clear. In clinical-epidemiological surveys non-patent individuals are always found. However, immune status of these people is not known because their parasitological histories are lacking. It is also known how frequently they are bitten by infective mosquitoes or if their resistence is acquired or innate. In view of recent advances in the understanding of the genetic basis for susceptibility of vertebrates to parasitic infection (Bradley, 1974; Wasson et.al. 1974; Allison 1975; Wakelin 1975), a careful analysis of resistence to filarial infection may be fruitful.

The natural vectors of the two forms of *B. malayi* are generally different species which have allopatric distributions. Based on the reported mosquito vectors (Table 4), these two forms of *B. malayi* have similar vector hosts, and the distribution of these vector host is related to the landscape ecology in accordance to the focal areas of these two forms of parasite (Lim, 1985). The periodic form of *B. malayi* is found in the agricultural areas with its predominant anopheline and secondary mansonoid vectors, while the subperiodic form is found in the forest with its predominant mansonoid and secondary anopheline vectors. Generally the anopheline vectors of periodic *B. malayi* do not invade nearby forest nor do the vectors of the subperiodic form leave for agricultural areas. The exceptions to this rule are some of the mansonoid spp., which transmit both forms of *B. malayi* and are found in both areas.

The larval stages of *Mansonia* are unique among the culicidae because they attach to water plants by their siphon to obtain oxygen. Each *Mansonia* sp. has a preference for a variety of plants, particularly water lettuce, *Pistiastratiotes*. These plants are widely distributed in open swamps, ditches and ponds nearby human habitation and in forest areas. These plant-covered ponds are found in profusion where they support the development of large populations of *Mansonia* which transmit both periodic and subperiodic *B. malayi*.

The anopheline vectors are associated

with clean sources of water. Although anopheline larvae are found in ditches, ponds and wells, they prefer the ricefields around villages where they breed in large numbers. *An. barbirostris*, a predominant vector of both periodic *B. malayi* and *B. timori* is a good example.

The wide range of mosquito vectors incriminated for *B. malayi*, suggests that this parasite is not as host specific as that shown for *B. timori*. In the latter parasite, the comfirmed vector to date is *An. barbirostris* only, although two other species are known to be potential vectors, but unconfirmed.

Animal filariasis (Table 5) shows that the subperiodic *B. malayi* is commonly found in domestic cats and monkey spp., while *B. pahangi* also is found in domestic cats and other forest carnivores. Microfilariae and adult worms of *B. malayi* were obtained in monkey spp *(Presbytis cristatus* and *Macaca fascicularis)* in Sumatera and South Kalimantan (Lim et.al. 1984; Palmieri et.al. 1980). In Malaysia, Mak et.al. (1980) found in high microfilariae rate of 23.8% in endemic area of subperiodic *B. malayi*, 60 % (5) of the cats examined were also infected with the parasite. By contrast, in endemic periodic *B. malayi* area, none of the cats examined was infected. Similarly, none of the 66 cats in a newly-opened settlement scheme was infected though an infection rate of 0.7 % was detected among the settlers. The result of their findings show an increase in the microfilarial rate in man and was accompanied by a corresponding increase in that of cats. Thus, they postulated that cats are probably infected with subperiodic *B. malayi* from humans and their infection rate is a reflection of the endemicity of the area. The transmission route of zoonotic filariasis due to subperiodic *B. malayi* between non-human primate and human hosts has yet to be established. As *B. pahangi* could experimentally infect man, its common infection in cats, dogs and wild carnivores again focuses attention to its potential zoonotic transmission to man from these animals (Fig. 2).

FUTURE RESEARCH ACTIVITIES.

Based on the reported results of the current research activities, there are still some basic informations on the ecology of the disease need to be elucidated. Methodology on parasite surveys also required standardization so that results obtained from different endemic areas are comparable. The suggested activities are as follows :

1. *Standardization of methodology*

a. Parasitological.

The parasitological results in this report were based on different volume of peripheral blood smears, such as 20 mm^3, 40 mm^3 and 60 mm^3 examined. In some studies Nuclepore Membrane Technique (Dennis and Kean, 1971) was also used. A standardized technique is needed for comparison of related results obtained by different people from different areas. Generally, 60 mm^3 peripheral blood smears for detection of microfilaremia is more preferable. In low density microfilaraemia this may not detect the parasite and the Nuclepore Membrane technique which screens 1 ml of peripheral blood very rapidly and efficiently would be an advantage. The procedures of this technique are described by Mak (1981).

b. Immunodiagnosis.

In recent years various serological tests like the indirect fluorescent antibody (IFA), enzyme-linked immunosorbent assay (ELISA), counter-immuno-electrophoresis (CIE) and indirect haemagglutination (IHA) tests have been introduced and used. Groves & Davis (1978) showed that the IFA test using frozen sections of adult *B. malayi* worms to be a useful indicator of infection while that using

Table 5. Summary of reported animal filariasis in Indonesia

Locality	Vertebrate hosts	Number examined	Positive with Mf of Filaria parasites	References
SUMATERA	PRIMATE			
South Bengkulu	*Presbytis cristata*	23	8.6% *B. malayi* (3); 34.7% *D. magnilarvatum* (7)	Lim et al., 1984
	Macaca fascicularis	35	2.8% *B. malayi*; 42.8% *D. magnilarvatum* (2) 8.6% *E. malaysiensis* (2)	
	WILD CIVET			
	Paguma larvata	1	100% *B. pahangi*	
	DOMESTIC CAT			
	Felis cattus	58	39.7% *B. pahangi* (2)	
South Bengkulu	*Felis cattus*	56	23.2% *B. pahangi*	Suzuki et al., 1981.
North Bengkulu	*Felis cattus*	28	7.1% *B. malayi*	
	Macaca fascicularis	5	20.0% *B. malayi*; 60% *E. malaysiensis* (2)	Sudomo et al., 1982.
Jambi	*Felis cattus*	15	33.3% *Brugia* sp.	Sudomo et al., 1984.
SOUTH KALIMANTAN				
Martapura	*Presbytis cristata*	106	25% *B. malayi*; 8.5% *B. pahangi*; 35% *W. kalimantani* 1% *Cardiofilaria* sp. 1% *Dirofilaria* sp.	Masbar et al., 1981. & Palmieri et al. 1980.
	Paradoxurus hermaphroditus	2	50% *Dirofilaria* sp.	
	Felis cattus	7	2.5% *B. malayi*.	
	Felis cattus	51	25.5% *B. malayi*; 5.9% *D. repens*.	Partono et al., 1977c
South Kalimantan	*Felis cattus*	56	10.7% *B. malayi*.	Cross et al., 1975.
Banjarmasin	*Felis cattus*	51	25.0% *B. malayi*) Confirmed by laboratory 5.9% *D. repens*) experiments in jirds.	Partono et al., 1977c
CENTRAL SULAWESI				
Margolembo	*Felis cattus*	7	0	Partono et al., 1972.
SOUTHEAST SULAWESI				
Kendari Regency	*Felis cattus*	163	11.% *Brugia* sp: 2.4% *D. repens*.	Arbain Joesoef, et al., 1984
	Macaca maura	4	0	,,

Figure in parenthesis denote number of adult worms recovered.

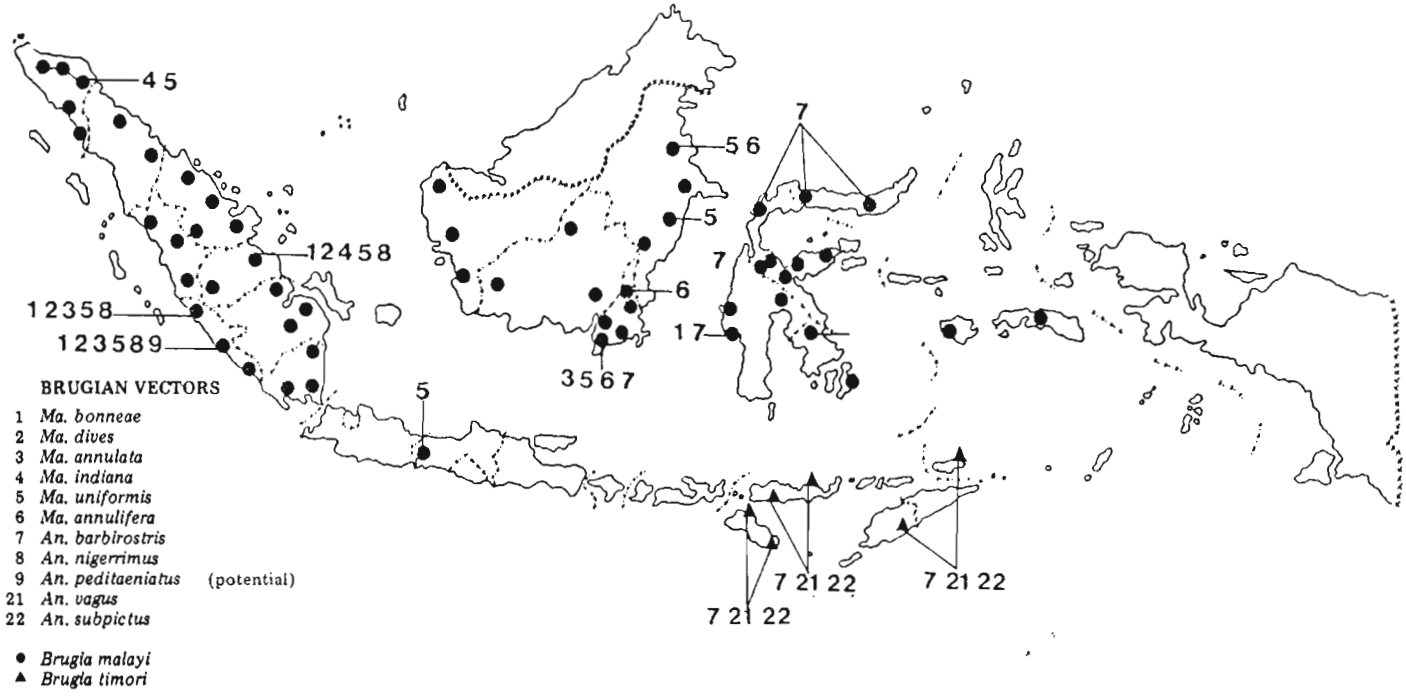

Fig. 1 Map showing distribution of *Brugia malayi* and *B. timori* and its mosquito vector spp. in Indonesia.

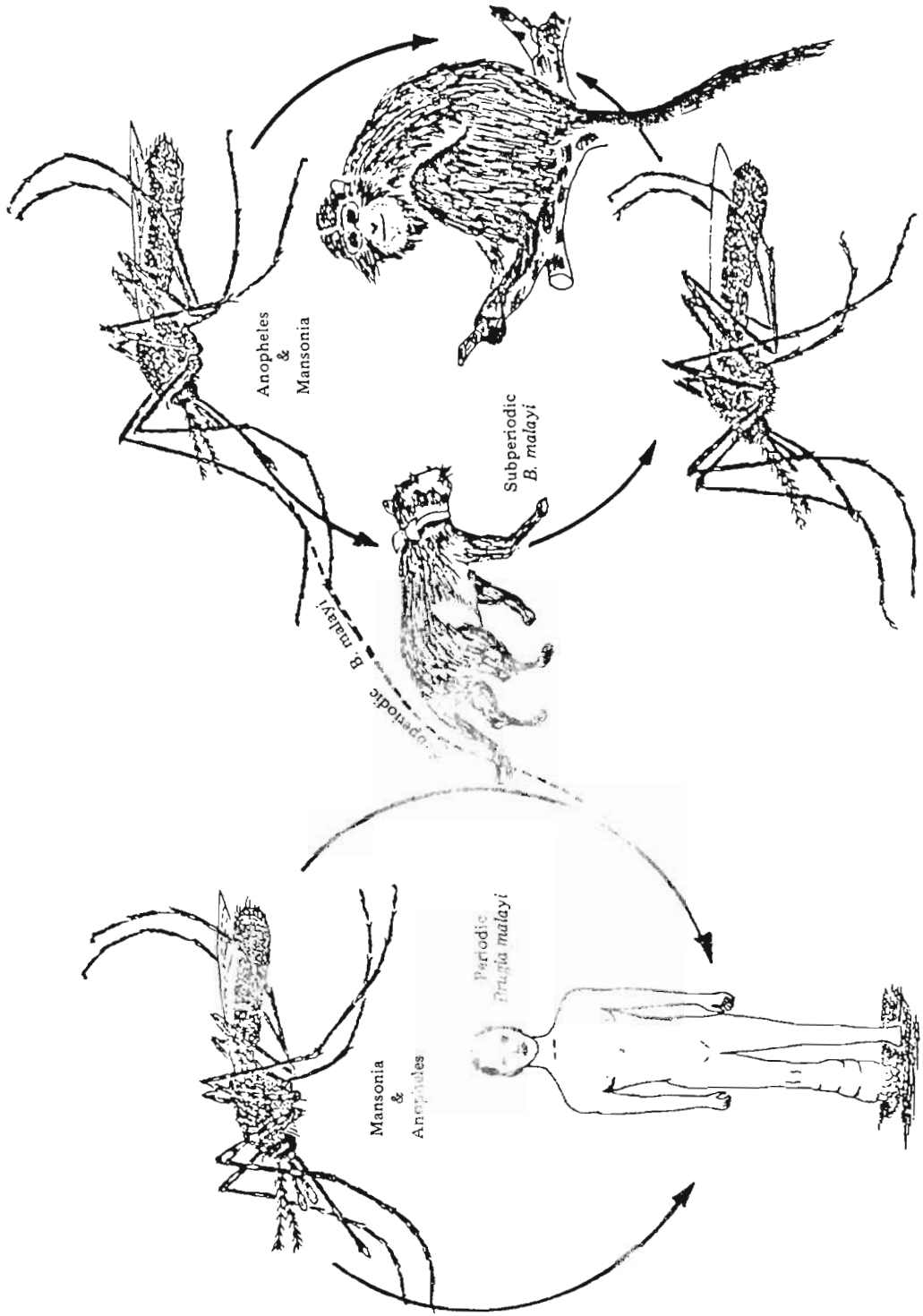

Fig. 2 Route of *Brugia malayi* transmission in nature

microfilaria antigens correlated with disease. Mak (1981) recommended that serological tests used in the diagnosis of filariasis should be a combination of the IFA test using either sonicated or papainised *B. malayi* microfilariae and frozen sections of adult *B. malayi* worms.

Studies on the reactivity of filariasis individuals to different stages of *B. timori* had shown that reaction with infective larva was the clearest indication of infection (Maizels et al, 1983). Antibody assay using purified antigen with test of high sensitivity should be encouraged. Development of assays for filed use in imperative. Circulating parasite antigen would be more promising as the indicator of the disease since antibody detection is unable to distinguish past exposure and current infection.

2. *Research Studies*

c. Control measures.

Control measures can be directed towards three main areas; these being reduction of the reservoir of infection, vector control and finally reduction of human-vector contact.

Mass chemotherapy with diethylcarbamazine citrate (DEC) remains the most effective method for the control of lymphatic filariasis. Low dosage DEC given by the people for the people has been tried in villages infected with *B. timori*, *W. bancrofti* and *B. malayi*, and these developed methodology of treatments have shown to be effective in the control of the disease in endemic areas (Partono et.al. 1984). The advantages with these developed methodologies are (1) side effects are less likely to occur than the standard application, (2) encourage the affected community to participate in health care through informal health education, well in accord with the concept of Primary Health Care, and (3) success offers the affected community greater satisfaction and boosts their confidence for self-reliance More pilot studies on these type of treatments may be needed to further confirm the effectiveness in the control of the disease and when proved successful, it should be included as part of the National Filariasis Control Programme.

Wild animal reservoirs, primarily monkey spp. *(Presbytis cristata* and *Macaca fascicularis)* and domestic cats of subperiodic *B. malayi* contribute to a large proportion of the infective pool and as chemotherapy of these animals is not practical, effective reduction of the reservoir is not achieved. Mak et.al. (1982) found the effect of mass chemotherapy, even after repeated cycles, was disappointing in subperiodic *B. malayi* endemic areas in Malaysia. Further studies need to be conducted to assess how serious wild reservoir hosts, particularly the monkey spp. are involved in their role of zoonotic transmission in Indonesia.

Vector control, particularly *Anopheles* mosquito vectors for *B. malayi* and *B. timori* is, perhaps effective as a spin-off benefit of the Malaria Control Programme's six monthly cycles of spraying in houses with residual insectcides. *Mansonia* spp. vectors, which are exophagic and exophilic in their feeding habits may not be affected by the Malaria Control Programme, and no practical means have so far been developed for destruction of their larvae. Thus vector population reduction is impracticable in subperiodic *B. malayi* endemic areas. Further research studies are needed (1) to assess on the effect of insecticide residual spraying of Malaria Control Programme to find out whether it also affect the filaria vectors *(Anopheles* and *Mansonia* spp.) especially in endemic areas where both malaria and filariasis are found, and in some areas where both these diseases share the same mosquito vector, e.g. *An. barbirostris* in Sulawesi,

and (2) to find alternative control measures, such as environmental manipulation and developed biological means in the control of *Mansonia* vectors, particularly the larval stages in its niches.

Reduction in man-vector contact is difficult in endemic areas. *Mansonia* spp. mosquitoes have been known to bite both at night, early dawn and even during the daytime in the shade (Wharton, 1962). Research studies are needed to find out what protective measures can be introduced to reduce man-vector contact in endemic areas.

d. Social science studies are important component of integrated disease control especially with new methodology of control measures through community participation are introduced.

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