Z Parasitenkd (1986) 72:13–28

Zeitschrift für
Parasitenkunde
Parasitology Research

Pathogenesis of lymphatic filariasis in man

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Invasion of man by lymphatic dwelling filariae *Wuchereria bancrofti, Brugia malayi* and *Brugia timori* provokes a variety of changes. In lymph nodes these changes have cell-mediated, humoral, and foreign body components. Our knowledge of the factors which modulate the sequence and intensity of these reactions is fragmentary, and based on very few direct observations of human tissue. Apart from Manson's earliest observations (Manson 1898) and three articles by O'Connor (O'Connor 1931; O'Connor et al. 1930; O'Connor and Hulse 1935) the pathology of filariasis provoked little interest until World War II. Then, 38000 American troups were exposed and within a year over 12000 infected (Beaver 1970). Studies on this cohort provide: (1) an accurate estimate of the incubation – 3 months minimum with peak manifestations at 8 months; (2) the concept of three main clinicopathologic features – lymphadenopathy, lymphangitis and inflammation of scrotal contents (King 1944) with detailed pathological studies of each (Wartman 1947); and (3) knowledge that with removal from endemic areas the patient's condition soon improved. Biopsy specimens from 64 of these patients are filed in the WHO Collaborating Centre for the Histopathology of Filarial Diseases in Man, and form the basis of our gradually expanding knowledge of the pathologic changes in filariasis.

Clinicopathologic features

Lymphadenitis. Epitrochlear, cervical, supraclavicular, axillary, antecubital, inguinal, pelvic and abdominal lymph nodes may be involved. Unusual sites include midhumeral, intercostal, popliteal, back, wrist, iliac crest and pectoral lymph nodes. Nodes enlarge, become tender, or painful and are discrete or matted but not attached to skin. They show bulging, moist grey-pink cut surfaces with intact capsules.

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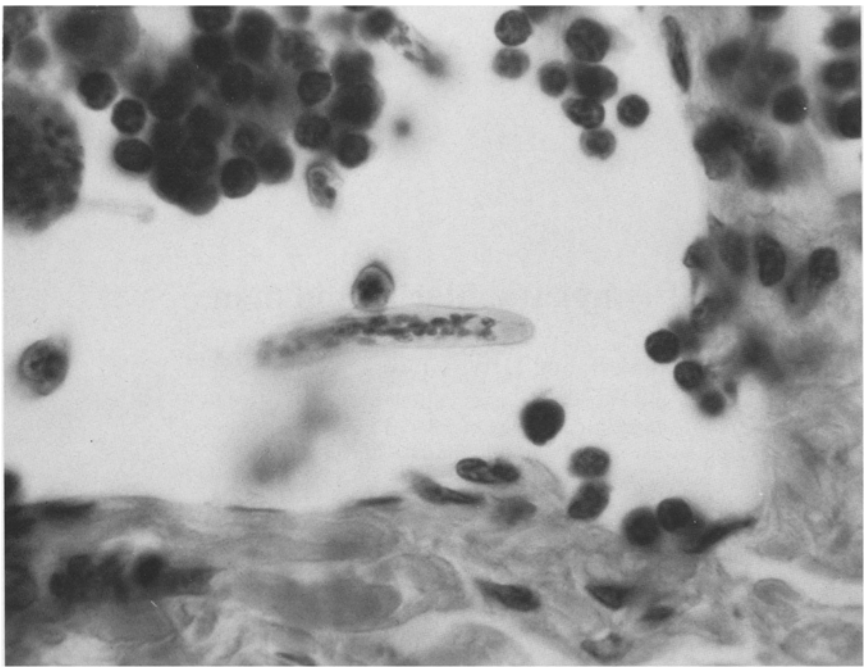

Fig. 1. Anterior end and cross section of a microfilaria of *Wuchereria bancrofti* in a dilated sinus in the medulla of a lymph node. The structures of taxonomic importance include a cephalic space of 6–11 μm length, two anterior nuclei side by side and an anterior diameter of 7 μm. HE, ×1080, AFIP photograph 71-12100

In man, the earliest stages of infection have not been studied; but in cats, following inoculation, it has been shown that infective larvae penetrate lymphatic vessels, migrate to the nearest node and provoke both cell-mediated and humoral responses (Ewert and El Bihari 1971). The larvae then descend through afferent lymphatics, molt, become adults and produce microfilariae (Fig. 1). In man, the earliest changes in lymph nodes are both inflammatory and reactive, but none is specific. When well developed, however, the combination is so characteristic and so rarely encountered in temperate zones, that a diagnosis of filariasis is strongly suggested.

Nodes without worms have distended sinuses containing histiocytes and eosinophils, septal fibrosis, thickened capsules traversed by dilated lymphatics, hyperplasia of follicles and increased numbers of paracortical lymphocytes. Sinuses may be enlarged to the point of forming "lake-like" expansions containing proteinaceous fluid (Michael 1944). Follicular hyperplasia has been emphasized, but in long-standing infections we have seen follicular atrophy – a paradoxical and unexplained phenomenon. Some nodes also have focal collections of histiocytes, epithelioid cells, and giant cells and these may also be in connective tissue adjacent to the node (Hartz 1944).

Nodes containing worms may have any or all of the above changes in addition to focal reaction to the worms. Adult worms, male or female,

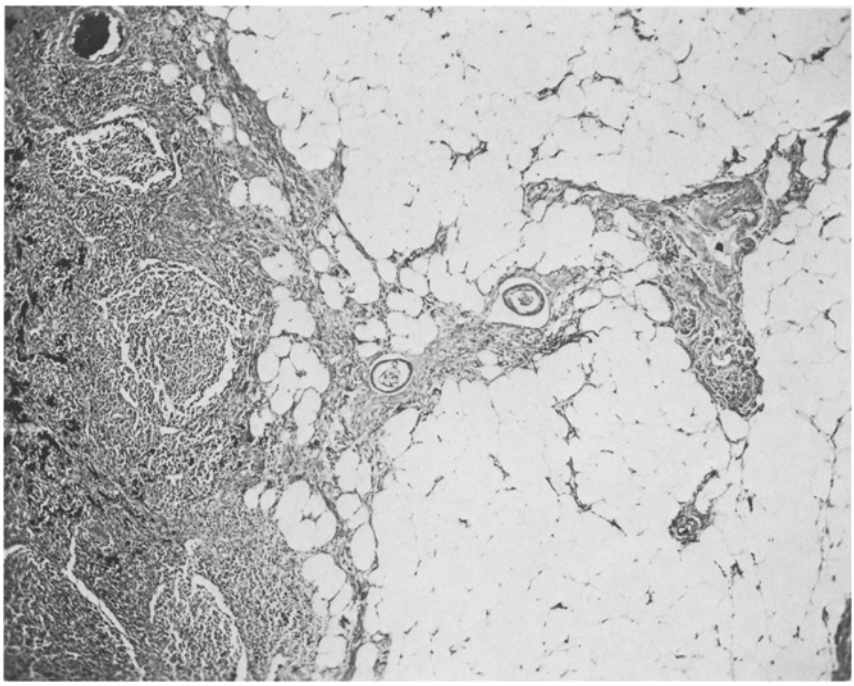

Fig. 2. Two cross sections of an adult *Wuchereria bancrofti* in a dilated lymphatic vessel in the connective tissue of the capsule and adjacent adipose tissue of a lymph node. HE, ×50, AFIP photograph 70-6690

dead or alive, lie in sinuses and in dilated lymphatic vessels of the capsule (Fig. 2). The worms are coiled and centered in necrotizing granulomas. There is a matrix of degenerating histiocytes against the worm and this is surrounded by viable histiocytes, a layer of epithelioid cells and giant cells, and finally scar tissue at the perimeter. The epithelioid cells are palisaded and supported by granulation tissue. Varying numbers of eosinophils, lymphocytes and giant cells of both foreign body and Langhans' type populate the outer portions of the lesion. Saponification and calcification begin within the worm, but spare the cuticle (Rogers et al. 1974). Eosinophils cluster in sinuses, in lymphoid cords and in connective tissues of the hilum. Eosinophils are especially prominent near and around adult worms and are usually the most conspicious inflammatory cell (Fig. 3). The inflammation may extend to adjacent tissue especially when the degenerating worm is in the capsule. The lesions resolve as compact scars. This spectrum of changes becomes more meaningful when correlated with the studies of humoral and cell-mediated responses in the nodes of cats infected with *Brugia pahangi* (Rogers et al. 1975).

In summary, the pain and the enlargement of the lymph nodes in filarial lymphadenitis have both humoral and cell-mediated components and are associated with the presence of one or more of at least six basic phenomena:

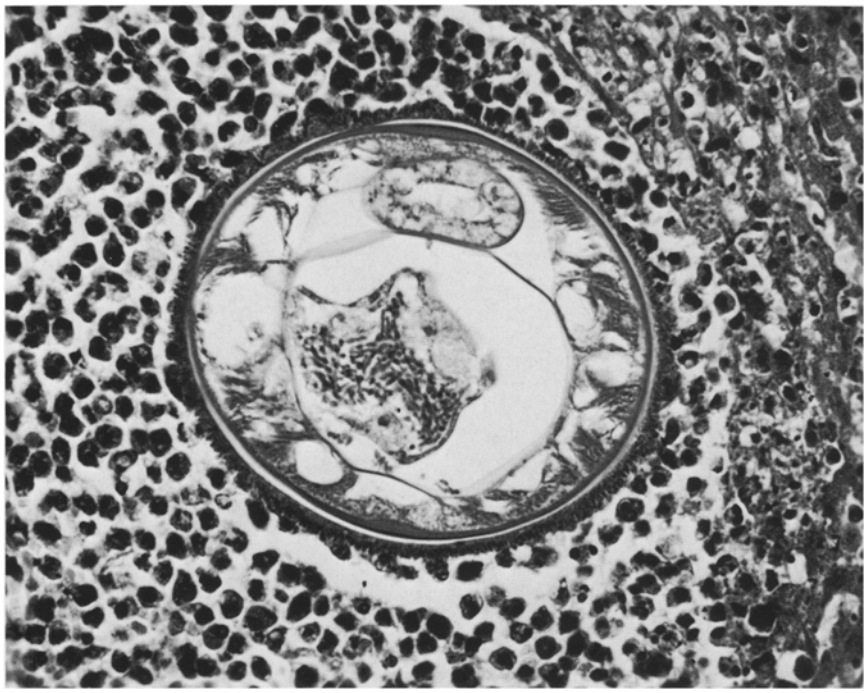

Fig. 3. A cross section of a male *Wuchereria bancrofti* in a lung of a patient from Boroku, New Guinea. The worm is surrounded by inflammatory cells, many of which are neutrophils and eosinophils. The worm's cuticle is covered by an eosinophilic layer of Splendore-Hoeppli substance. HE, ×525, AFIP photograph 71-6112

sinus histiocytosis, follicular hyperplasia, paracortical hyperplasia, edema, adult worm(s) and diffuse and focal granulomas.

Lymphangitis. Inflamed, dilated and varicose lymphatics have been recognized as a feature of filariasis since Manson's first description but the enormity of the dilatation is best appreciated radiographically (Montangerand et al. 1965; Young 1976). Sixty percent of American troups had attacks of lymphangitis or lymphadenitis. Lymphangitis was usually preceded by lymphadenitis. The attacks began as red streaks with local edema and heat, then spread distally and resolved in a retrograde pattern. Regional lymph nodes became large and tender. Lymphangitis within the abdomen caused pain in the flank or abdomen, radiating to genitalia or thigh.

The distribution of lymphangitis in one study (Dickson et al. 1943) was:

Scrotum alone	128 (51%)
Arm alone	56 (22%)
Leg alone	7 (3%)
Scrotum and leg	6 (2%)
Scrotum and arm	49 (20%)
Arm and leg	3 (1%)
Scrotum, arm and leg	2 (1%)
Total	251 (100%)

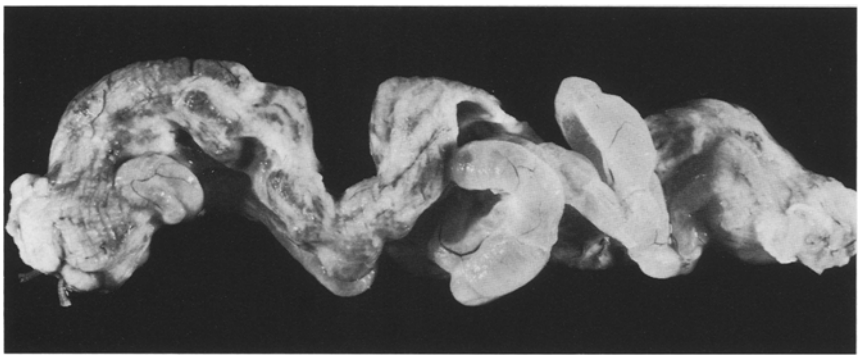

Fig. 4. An edematous and congested spermatic cord. The patient was 19 years old and from Belem, Brazil. The clinical diagnosis was filariasis. Microscopically the cord and pampiniform plexus were congested and lymphatics were greatly distended. The supporting connective tissues were edematous and chronically inflamed. Funiculitis – edema and inflammation of the spermatic cord – is probably the most common manifestation of filariasis in the adult male patient. Gross photograph, ×25, AFIP photograph 70-4284

Microscopically, the lymphatic vessel dilates and its wall thickens with edema and inflammatory cells, mainly lymphocytes, histiocytes and eosinophils; but neutrophils, plasma cells and giant cells may also be in the wall and in adjacent tissue. The endothelium thickens and may become heaped up in folds or polypoid masses. Segments of adult worm may be free or enclosed in lymphatic thrombi, which organize and recanalize. Splendore-Hoeppli substance has also been identified in the inflamed tissue reacting to the worm. Hemorrhage into lymphatics was a feature of one study (von Lichtenberg 1957). Degenerating worms in lymphatics provoke a necrotizing granulomatous response identical to that in lymph nodes. Filarial lymphangitis of animals is essentially identical to that in man (Ah and Thompson 1973).

Funiculitis. Filarial funiculitis is filarial lymphangitis of the spermatic cord (Fig. 4). It descends from the inguinal ring causing pain, swelling and nodularity. Microscopically the changes in the lymphatics are identical to those of peripheral lymphatics and surrounding tissues. The predisposition of lymphatics of the spermatic cord is seen also in experimental filariasis (Malone and Thompson 1975). In summary, filarial funiculitis is a filarial lymphangitis of the spermatic cord with secondary inflammation of adjacent connective tissues.

Epididymitis. Epididymitis usually accompanies funiculitis and both are primarily a lymphangitis. The epididymis becomes large, smooth, soft and tender. Microscopically there is interstitial edema and infiltrates of lymphocytes, plasma cells, eosinophils and histiocytes. The infiltrates surround lymphatics. Degenerating worms are common in lymphatics of the tunica vaginalis and in the fibromuscular tissue of the cord. The lymphangitis and the focal granulomas provoked by worms are identical to those already described (Fig. 5).

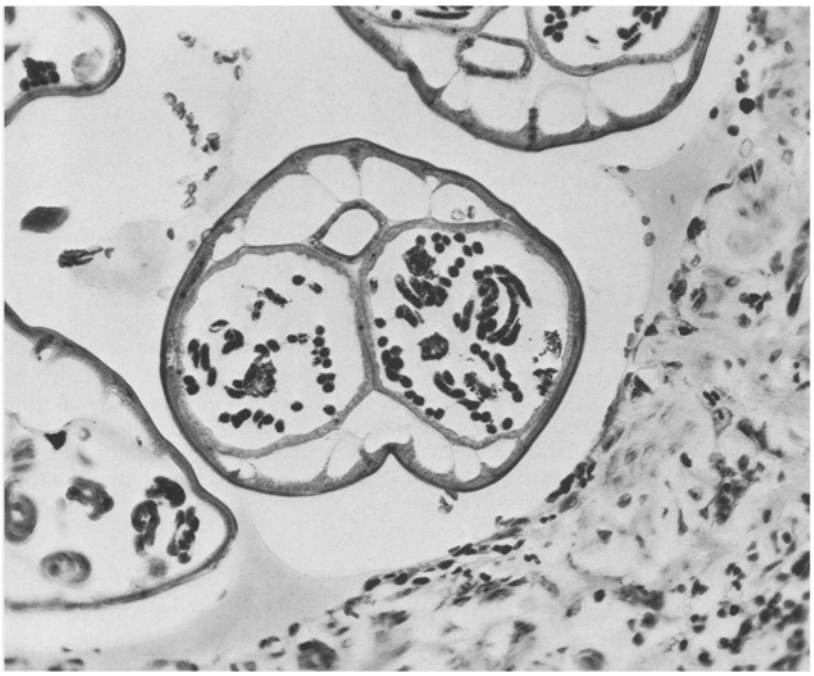

Fig. 5. Cross section of a gravid *Wuchereria bancrofti* from the epididymis of a patient from Paramaribo, Surinam. Note the thin cuticle, body cavity, thin muscle layer, digestive tube and paired uterine tubes containing microfilariae. Movat stain, ×305, AFIP photograph 70-8650

Orchitis. Filarial orchitis is characterized by swelling and pain sometimes radiating up the cord. A boggy edematous testis is characteristic – probably from edema and inflammation of the tunica and adventitia rather than inflammation of the testis. In one series, however, three of six testes had acute interstitial orchitis, characterized by edema, a scattering of leukocytes, mostly eosinophils, but with "little damage" to the germinal tubules (von Lichtenberg 1957).

Lymphedema and elephantiasis. Filarial lymphedema is usually localized and self-limited but in some patients may progress to elephantiasis (Fig. 6). Clinical and experimental evidence suggests that only repeated infections cause the progressive damage that leads to elephantiasis (Rogers et al. 1975). Upper and lower limbs, external genitalia and breasts are common sites. The incidence of elephantiasis ranges from 1% to 3% in endemic areas and tends to increase in older age groups. The first excised scrotum described by Manson had exudation of lymph from the skin and a viable worm protruding from the cut surface. Scrotums we have studied have verrucous changes of epidermis over moist, homogeneous white tissue. Microscopically this white tissue is interlacing bundles of smooth muscle interspersed with loose connective tissue containing dilated lymphatics and clusters of inflam-

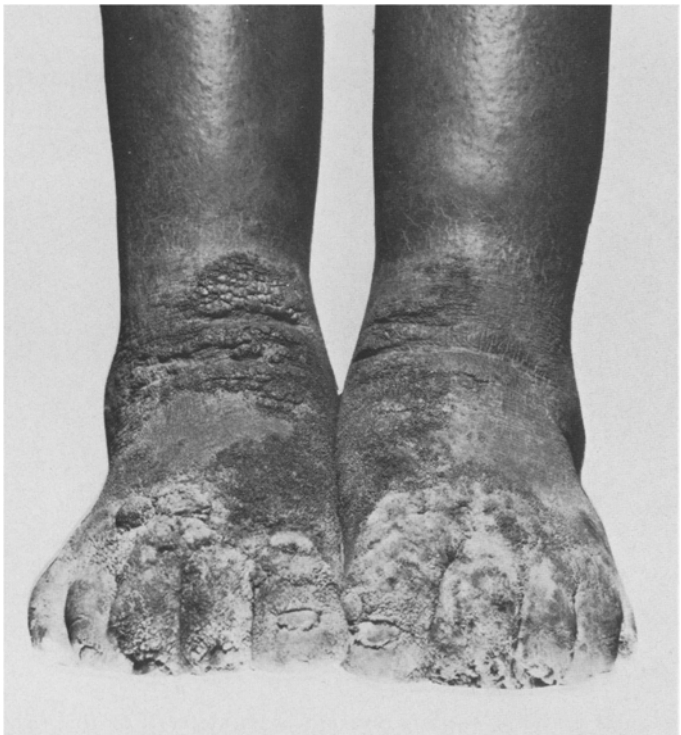

Fig. 6. Mossy foot in a 30-year-old Ziarian with filariasis. The characteristic changes include a crusty warty skin, lymphangitis and lymphedema. Gross, AFIP photograph 84-7549

matory cells, especially plasma cells. The cause of this enormous increase of smooth muscle is unexplained but it probably represents hypertrophied and hyperplastic cremasteric fibers.

Hydrocele. The incidence of hydrocele may be high (Aruba et al. 1980). The fluid is amber and contains lymphocytes and eosinophils but no flocculi. In some series microfilariae were not present, but in others they were common (Gratama 1966). Fluid reaccumulates after aspiration and appears to persist longer in patients who have repeated aspirations. One hydrocele suddenly enlarged following treatment with diethylcarbamazine (DEC) (Robinson 1968).

Varicocele. Varicocele commonly develops after an attack of acute funiculitis but its relationship to filariasis is uncertain. Furthermore, a varicocele could be mistaken for the dilated thick-walled and tortuous lymphatics of filariasis. In one microscopic study of veins associated with filarial lymphangitis, filarial phlebitis could not be established (von Lichtenberg 1957).

Tropical pulmonary eosinophilia. Eosinophilic lung, a rare manifestation of filariasis, is characterized by cough, asthma, pulmonary infiltrates, amicrofi-

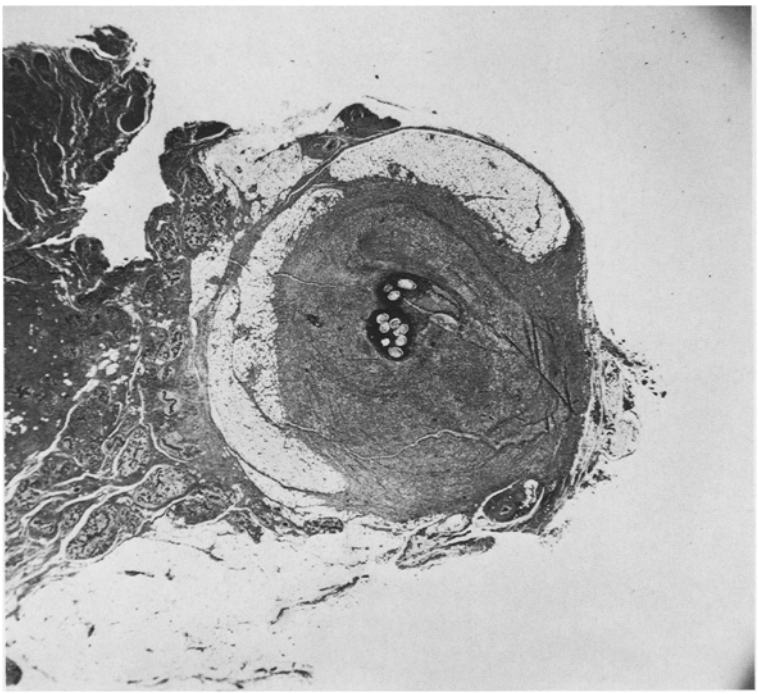

Fig. 7. Cross section of a coiled gravid *Wuchereria bancrofti* in an abscess from the right breast of a woman from Sierra Leone, West Africa. The worm is surrounded by an inflammatory exudate. In endemic areas filarial worms frequently cause masses in the female breast. HE, × 6, AFIP photograph 73-13064

laremia, eosinophilia and high levels of IgE and anti-filaria antibodies (Neva et al. 1975). Lung, lymph node and spleen contain microfilariae centered in foci of eosinophils (Webb et al. 1960). Patients are relieved with DEC. This is a hyperimmune response, which has a parallel in animals (Wong 1964; Crandall et al. 1982); it is a consequence of tissue invasion by microfilariae (Lie 1962) which probably invokes the allergic pathway described and summarized by Buisseret (1982).

Breast. Filarial granulomas of the female breast are firm solitary inflammatory masses and are well recognized in endemic areas (Figs. 7 and 8). The involved breast is excised if cancer is suspected. The inflammation is provoked by adult worms in lymphatics of the breast or in the axillary tail. Microscopically the lesions resemble those already described in lymph nodes. A series of 131 filarial granulomas of the breast was recently reported from Eastern China (Yuehan and Qun 1981).

Eye involvement. Serous conjunctivitis with photophobia has been described in patients with filariasis (Michael 1944; Fogel and Huntington 1944). Other ocular manifestations include adult *W. bancrofti* in the anterior chamber

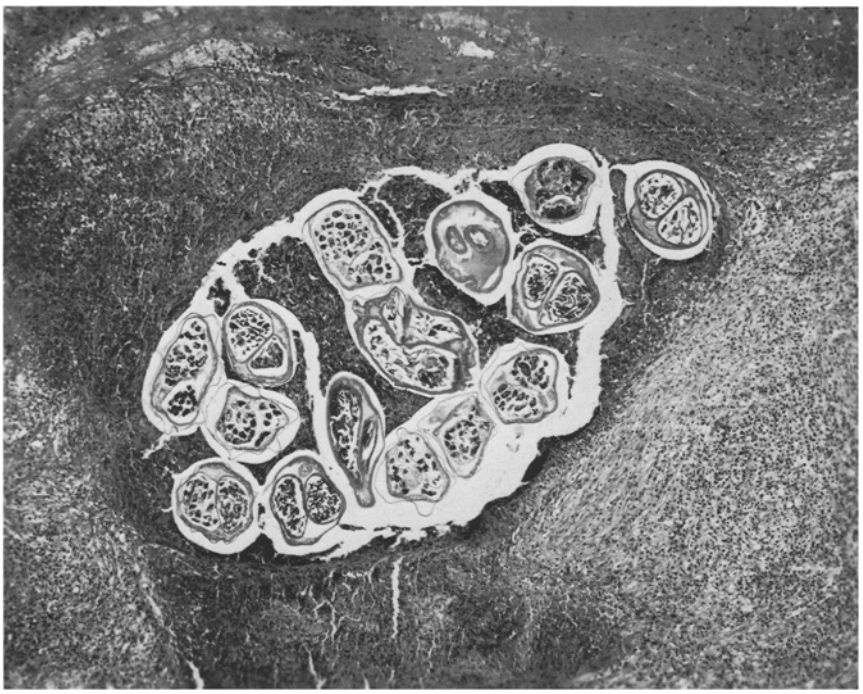

Fig. 8. Another mass in the breast caused by a coiled gravid *Wuchereria bancrofti*. The patient lived in China. The worms are in a mass of necrotic tissue surrounded by edematous and inflamed connective tissue. The filarial worms probably migrate to the breast through the lymphatics but all traces of the lymphatic vessel are destroyed. HE, × 60, AFIP photograph 81-13400

(Fernando 1935; Chatterji 1954), adult *Brugia* sp. in the conjunctiva (Dissanaike 1974; Mak and Boo-Liat 1974), and microfilarial uveitis caused by *B. malayi* (Anandakannan and Gupta 1977).

Hepatomegaly. A patient with hepatomegaly, pleural effusion and obstruction of the inferior vena cava has been described (Sanjeeva et al. 1980). Microfilariae of *W. bancrofti* were in hepatic sinusoids. The patient improved with DEC.

Splenic granulomas. Although rarely sought, splenic granulomas have been found in patients with pulmonary eosinophilia (Lie 1962) and routinely at autopsy (Dhayagude and Amin 1942). These granulomas are discrete and comprised of eosinophils, histiocytes and giant cells around degenerating microfilariae. They also have been identified in a variety of animals infected experimentally including the silvered leaf monkey (Palmieri et al. 1982).

Glomerulonephritis. Some reports relate filariasis to glomerular damage. One patient had glomerulonephritis and nephrosis characterized by facial swell-

Fig. 9. Inguinal lymph node from a silvered leaf monkey which contains a coiled cluster of adult *Wuchereria kalimantani* in a dilated lymphatic in the capsule. Gross, × 12, AFIP photograph 78-9064

ing and dyspnea. The glomeruli contained microfilariae, eosinophils, IgG and C_3. Another patient with filariasis for 25 years developed nephrosis and had a proliferative glomerulitis with deposits of C_3 (Yap et al. 1982). Another patient with filarial chyluria and treated by disconnection of lymphatics from the renal pelvis had glomerulonephritis and deposits of immune globulin and complement in the glomerulus (Waugh et al. 1980). Focal interstitial nephritis has been produced experimentally (Klei and Crowell 1981).

Hypersensitivity reactions. Patients with acute filariasis may have urticaria. Transient swellings of limbs, trunk, eyelids and forehead have a counterpart in the fugitive swellings of loaiasis (Englehorn and Wellman 1945). These resemble erythema multiforme, may appear before, during or after attacks of filariasis and tend to involve tissues around lymphatics. Microscopically they are "typical allergic phenomena" with congestion, edema and infiltration of inflammatory cells around lymphatic and blood vessels (Michael 1944). Parasites have not been identified in these specimens.

Filarial abscesses. Filarial abscesses have been described among natives and soldiers in the South Pacific. They are common on the medial aspects of the upper thigh and under the rectus fascia of the lower abdomen (Englehorn

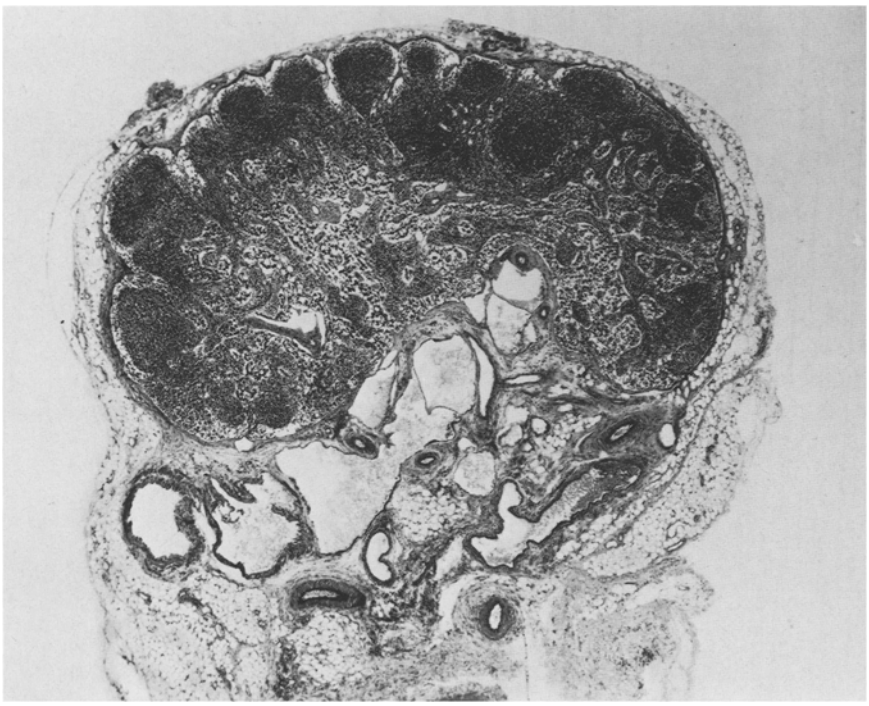

Fig. 10. A portion of a lobulated inguinal lymph node from a silvered leaf monkey infected with *Wuchereria kalimantani*. Note the dilated lymphatics of medulla and hilum. There is also thickening of the capsule and marked histiocytic hyperplasia. HE, × 25, AFIP photograph 85-5123

and Wellman 1945). They develop and resolve slowly and are associated with fever, prostration and local pain. They are usually deep to the fascia and do not point to the skin. Incision and drainage reveals communicating pockets.

Amyloidosis. McAdam (1978) has summarized the evidence that chronic filariasis causes amyloidosis in natives of New Guinea. Amyloidosis has been noted also in experimental filariasis (Klei and Crowell 1981).

Unusual sites. Fortuitous microfilariae have been identified in a vaginal smear (Leong 1976) and in bone marrow (Pradhan et al. 1976). In neither location was there evidence of reaction.

Special features of the different species. Definitive studies on the pathology of *Brugia timori* are not available. In northern Sumatra *B. malayi* causes elephantiasis of the lower limbs but apparently not the other complications of bancroftian filariasis such as scrotal elephantiasis, chyluria and hydrocele. Clinically *B. malayi* causes attacks of disabling fever associated with painful and enlarged inguinal nodes, followed by red streaks – resolving in about

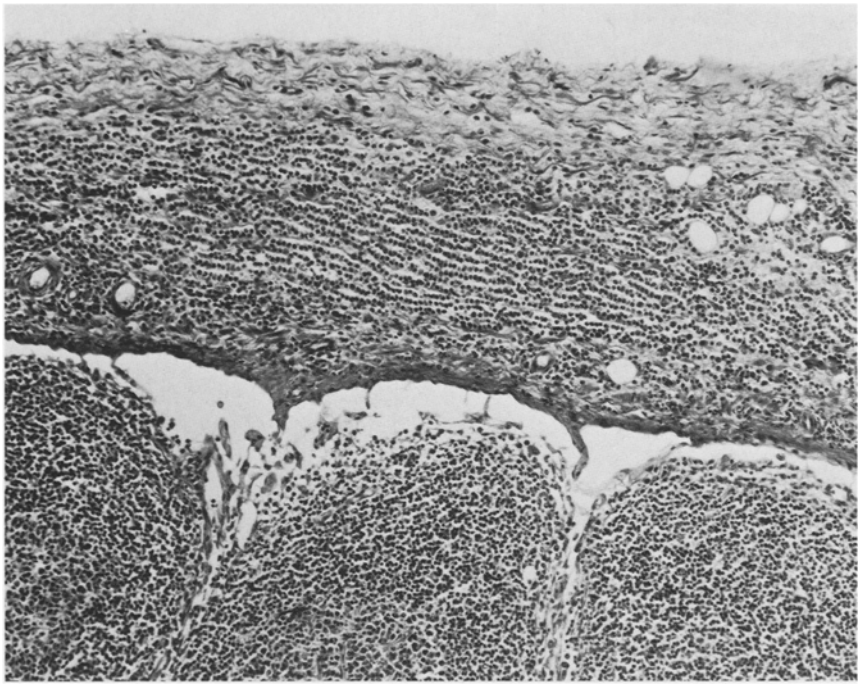

Fig. 11. An inguinal lymph node with a capsule thickened by inflammatory cells – many of which are neutrophils – from a silvered leaf monkey infected with *W. kalimantani*. The subcapsular sinuses are dilated and contain histiocytes. HE, ×100, AFIP photograph 85-5120

one week. Edema of the foot recurs and increases with each attack (Dassanayake 1938; Denham and McGreevey 1971). Experimental infection of three volunteers caused tenderness and swelling at the sites of inoculation followed by swelling of regional nodes and lymphangitis.

Suggestions for future studies in lymphatic filariasis

During the past few years there have been several important advances in the field of filariasis. These advances are destined to shape the future of filariasis. Recently the WHO has published its fourth report by the WHO Expert Committee on Filariasis (TRS-702, 1984) which deals with lymphatic filariasis. Some of these advances are:

Taxonomy. The Timor microfilaria is now characterized with descriptions of all developing stages and has been named *Brugia timori*. A new species of *Wuchereria, W. kalimantani*, infected 35% of silvered leaf monkeys (*Presbytis cristatus*) in South Borneo, although *W. kalimantani* has not been identified in people in that region (Fig. 9).

Animal reservoirs of lymphatic dwelling filariae. In Southeast Asia both the macaques (*Macaca* spp.) and leaf monkeys (*Presbytis* spp.) are important

Fig. 12. Inguinal lymph node from a silvered leaf monkey infected with *Wuchereria kalimantani*. Adult worms are in dilated pericapsular lymphatic vessel. Note the capsular fibrosis, dilated subcapsular sinuses and histiocytosis. HE, ×60, AFIP photograph 85-5129

reservoirs of zoonotic brugian filariasis. One of us (JRP) has shown, contrary to popular belief, that the domestic cat is not as important a zoonotic reservoir of *Brugia malayi* as once thought. Surveys are needed to ascertain the ecological areas of subperiodic *B. malayi*, the proportion of subperiodic *B. malayi* transmitted to man from non-human reservoirs and whether a non-human reservoir of *W. bancrofti* exists. In addition surveys are needed to determine whether *B. pahangi* infects man in areas where it is endemic in monkeys, cats and other wild and domestic animals.

Pathology. Much basic research on filarial diseases is needed. Research on pathogenesis must go forward together with immunological and clinical studies and trials. The more that is known about the inflammatory and immune responses of man and animals, the more likely it will be that new approaches to control and treatment will develop. Efficient and practical animal models must be used to compare lesions of *Brugia* and *Wuchereria* species infecting man. These must be studied as a first step toward the establishment of animal models for evaluating filaricidal drugs and filarial vaccines.

Immunodiagnosis. Immunodiagnostic techniques to detect parasitic antigens or other products of parasites must be developed to diagnose active infec-

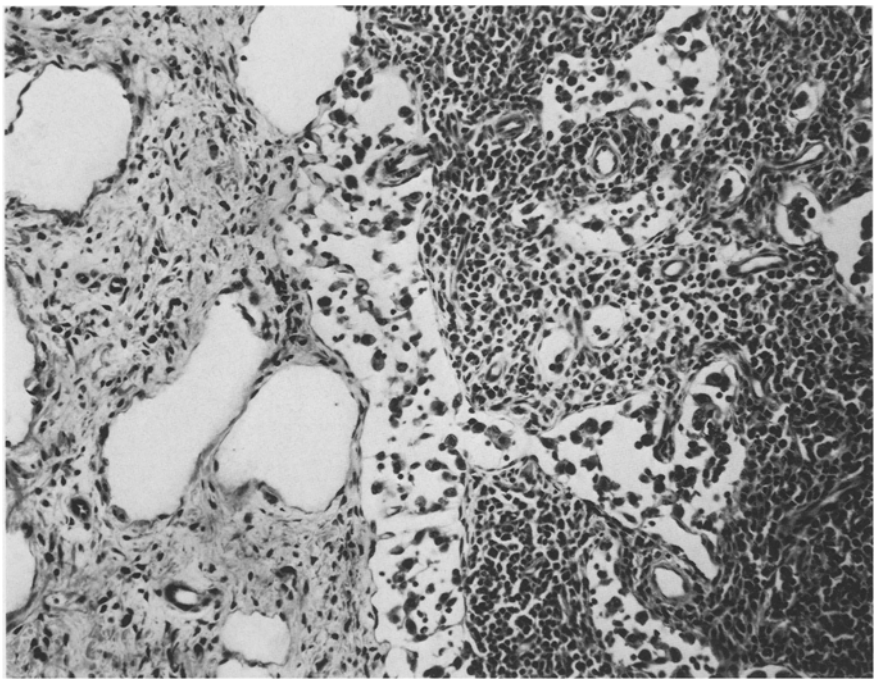

Fig. 13. A lymph node from silvered leaf monkey infected with *Wuchereria kalimantani*. The lymphatic vessels and medullary sinuses are dilated. The sinuses are distended by histiocytes and a scattering of other inflammatory cells. HE, ×250, AFIP photograph 85-5121

tions, prepatent infections and to evaluate intensity of infections. This is a WHO priority. Monoclonal antibodies are necessary to provide reagents of high and reproducible specificities. These will have great potential in development of immunodiagnostic techniques, immunodiagnostic probes and reagents, antigen synthesis, and simple immunodiagnostic skin tests for recognition of specific antigens.

Animal models (transmission studies). Leaf monkeys (*Presbytis* spp.) have been infected with *W. bancrofti*. The lesions appear identical to *W. bancrofti* infections in man (Figs. 10–13). In rodents (although not as successfully as in the leaf monkey model) it has been possible to maintain *W. bancrofti* for up to 3 months. Attempts to passage *W. bancrofti* through *Presbytis* to attain an adaptive strain should be encouraged.

Culture. Although still in an early stage, the development of techniques for culturing infective (third stage) larvae to adult worms and the development of filarial cells lines of the various filariae would be valuable for in vitro screening of drugs against the various stages of filarial parasites.

Filaricides. Several new drugs showing antifilarial activity include Levamisole, Mebendazole, Centderazine, Furapyrimidone and Ivermectin. Studies

are necessary to determine their usefulness as prophylactic treatment in preventing lymphatic filariasis in both man and zoonotic reservoirs.

Acknowledgements. This work was supported in part by the World Health Organization (WHO), Geneva, Switzerland. The specimens and records are in the WHO Collaborating Centre for the Histopathology of Filarial Diseases in Man, in the Department of Infectious and Parasitic Disease Pathology at the Armed Forces Institute of Pathology. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the WHO, the Department of the Army, or the Department of Defense.

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Accepted May 30, 1985