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PATHOGENESIS OF LYMPHATIC FILARIASIS IN MAN

by

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*Pathol / course  
Lymphadenoma -  
Lymphangitis -  
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Introduction

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 (1,2) and 3 articles by O'Connor (3,4,5) the pathology of filariasis provoked little interest until World War II. Then, 38,000 American troops were exposed and within a year over 12,000 infected (6). Studies on this cohort provides: 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 (7)--with detailed pathological studies of each (8); and 3) the knowledge that with removal from endemic areas the patient's complaints soon abated. Biopsy specimens from 64 of these patients are filed in the WHO Collaborating Centre for the Histopathology of the Filarial Infections of Man, and form the nucleus of our gradually expanding knowledge of the pathology of filariasis.

Lymphadenitis

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

In man the earliest stages of infection have not been studied, but in cats following inoculation, it has been shown that infective larvae penetrate a lymphatic vessel, migrate to the nearest node and provoke both cell mediated and humoral responses. (9) The larvae

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then descend through afferent lymphatics where they mature and produce microfilariae. 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. (10) 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. (11)

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, dead or alive, lie in sinuses and in dilated lymphatics of the capsule. 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, then 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. 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 conspicuous inflammatory cell. 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. (12)

In summary the pain and enlargement of filarial lymphadenitis has both humoral and cell mediated components and is associated with one or more of at least six basic changes: 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. (13,14) Sixty percent of US troops had attacks of lymphangitis - 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 (15) 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%)

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Microscopically the lymphatic vessel dilates and its wall thickens with edema and inflammatory cells that are 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. (16) 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. (17)

#### Funiculitis

Filarial funiculitis is filarial lymphangitis of the spermatic cord. 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. (18) 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.

#### 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 3 of 6 testes had acute interstitial orchitis, characterized by edema, a scattering of leukocytes, mostly eosinophils, but with "little damage" to the germinal tubules. (16)

#### Lymphedema and Elephantiasis

Filarial lymphedema is usually localized and self limited but in some patients may progress to elephantiasis. Clinical and experimental evidence suggests that only repeated infections cause the progressive damage that leads to elephantiasis. (19) 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 inflammatory 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. (20) 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. (21) Fluid reaccumulates after aspiration and appears to persist

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longer in patients who have repeated aspirations. One hydrocele suddenly enlarged following treatment with DEC. (22)

### 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. (16)

### Tropical Pulmonary Eosinophilia

Eosinophilic lung, a rare manifestation of filariasis, is characterized by cough, asthma, pulmonary infiltrates, amicrofilaremia, eosinophilia and high levels of IgE. (23,24) Lung, lymph node and spleen contain microfilariae centered in foci of eosinophils. (25) Patients are relieved with DEC. (26) This is a hyperimmune response, has a parallel in animals (27, 28) is a consequence of tissue invasion by microfilariae (29) and probably invokes the allergic pathway recently described and summarized by Buisseret. (30)

### Breast

Filarial granulomas of the female breast are firm solitary inflammatory masses and are well recognized in endemic areas. 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. (31)

### Eye Involvement

Serous conjunctivitis with photophobia has been described in patients with filariasis. (10,32) Other ocular manifestations include adult *W. bancrofti* in the anterior chamber, (33,34) adult *Brugia* sp. in the conjunctiva, (35,36) and microfilarial uveitis caused by *B. malayi*. (37)

### Hepatomegaly

A patient with hepatomegaly, pleural effusion and obstruction of the inferior vena cava has been described. (38) 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 (29) and routinely at autopsy. (39) These granulomas are discrete and comprised

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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. (40)

#### Glomerulonephritis

Some reports relate filariasis to glomerular damage. One patient had glomerulonephritis and nephrosis characterized by facial swelling and dyspnea. The glomeruli contained microfilariae, eosinophils, IgG and C<sub>3</sub>. (41) Another patient with filariasis for 25 years developed nephrosis and had a proliferative glomerulitis with deposits of C<sub>3</sub>. (42) 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. (43) Focal interstitial nephritis has been produced experimentally. (44)

#### 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 loiasis. (45) 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 lymphatics and blood vessels. (10) 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. (45) 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 (46) has summarized the evidence that chronic filariasis causes amyloidosis in natives of New Guinea. Amyloidosis has been noted also in experimental filariasis. (44)

#### Unusual Sites

Fortuitous microfilariae have been identified in a vaginal smear (47) and in bone marrow. (48) 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. *B. malayi* causes elephantiasis of the lower limbs in Northern Sumatra 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 one week. Edema of the foot recurs and increases with each attack. (49,50). Experimental infection of three volunteers caused tenderness and swelling at the sites of inoculation followed by swelling of regional nodes and lymphangitis.

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