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Zoonotic aspects of filarial infections in man

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This article gives an account of the filarial parasites found in man and their potential transmissibility to and from other vertebrate animals under natural and experimental conditions.

Those species that are regarded as being primarily parasites of other vertebrates, but which also infect man, are then dealt with in greater detail. These include the subperiodic strain of Brugia malayi *and perhaps also* B. pahangi, *both of which are found in wild and domestic carnivores and monkeys, and* Dirofilaria *species of dogs and racoons.*

The Brugia *parasites develop to maturity with the production of microfilaraemia and clinical manifestations in man similar to those caused by periodic* B. malayi *in man. Human dirofilariasis, on the other hand, represents a transmission cul-de-sac for the parasite. Clinical manifestations are mild or absent and generally the worms do not mature and, even if they do, they rarely give rise to microfilaraemia.* D. immitis *causes pulmonary dirofilariasis, and* D. repens *and* D. tenuis *give rise to subcutaneous nodules in man. The diagnosis of dirofilariasis depends on an awareness of the infection in the animal reservoirs and of the possibility of man being exposed to bites of infected vectors.*

Filarial worms are viviparous and the young larvae they produce, which are known as microfilariae, eventually find their way into the peripheral blood or to the superficial layers of the skin of their vertebrate hosts. The microfilariae are eventually picked up by the appropriate intermediate host or vector. These vectors are most frequently mosquitos, although other arthropods such as blackflies, deer flies, midges, fleas, and even ticks and mites may also be vectors. The microfilariae reach the infective stage in the intermediate host after a period of about 7–14 days and the cycle is completed when the infected vector bites a susceptible vertebrate host.

Man is exposed to the bites of many of these arthropod vectors. Some of them carry filariae specific to man, and many others may carry larvae from animals that are potentially infective.

FILARIAE SPECIFIC TO MAN

Of the filarial worms infecting man, eight species can be considered as truly specific to him. These are *Wuchereria bancrofti, Brugia malayi* (periodic strain), *B. timori, Onchocerca volvulus, Loa loa, Mansonella ozzardi, Tetrapetalonema perstans* (= *Dipetalonema perstans*) and *T. streptocerca* (= *Dipetalonema streptocerca*).

Natural infections in animals with these species are rare, non-existent, or uncertain, although under laboratory conditions transmission may be achieved. For *W. bancrofti,*

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periodic *B. malayi,* and *B. timori,* natural infections have not been reported despite extensive search. Natural infections with *O. volvulus* have been reported in a gorilla in Zaire and with somewhat less certainty in a spider monkey (*Ateles geoffreyi*) in Mexico. For *Loa loa* there is inconclusive evidence that the human parasite may be found occasionally in the drill, *Mandrillus leucophaeus*; the common parasite of monkeys is considered to be a different subspecies, *L. loa papionis,* of larger size, with a nocturnal microfilarial periodicity and with different species of *Chrysops* as vector.

Infections with adult worms and microfilariae of *T. perstans* and *T. streptocerca* that are morphologically similar to those found in man, occur in chimpanzees and gorillas, and parasites similar to *M. ozzardi* have been found in neotropical monkeys. However, in none of these cases is there yet any certainty that the human and simian forms are the same species, or that transmission from man to a simian host or *vice versa* can take place. Although the exact relationships between the human and simian forms of these three relatively non-pathogenic parasites remain in doubt, one thing is virtually certain—that in all of them the human reservoir by itself is amply sufficient to maintain transmission.

Under experimental conditions, two of the parasites discussed may be readily transmitted to simian laboratory hosts. *O. volvulus* can be transmitted to the chimpanzee and *L. loa* to several genera of monkeys (*Mandrillus, Papio,* and *Erythrocebus*). *W. bancrofti* is the most difficult filaria to transmit, but recently workers[a,b] have succeeded in obtaining small numbers of adult worms and an occasional scanty microfilaraemia[a] after inoculating *Macaca* monkeys with the urban and rural strains of the nocturnal periodic form of this parasite.

Nocturnally periodic *B. malayi* and *B. timori* can be experimentally transmitted to cats and jirds but attempts to transmit *T. perstans, T. streptocerca,* or *M. ozzardi* to animals have not yet been successful.

The situation in nature with regard to all the filarial parasites of man is summarized in Fig. 1. The worms that are specific parasites of man have been divided into 3 groups in the centre of this diagram:

(*a*) *W. bancrofti* and *O. volvulus,* for which, as pointed out earlier, no suitable laboratory model is at present available;

(*b*) *B. malayi* periodic strain, and *B. timori* for which laboratory models with microfilaraemia are available but for which natural infections have not yet been reported; and

(*c*) *Loa loa, M. ozzardi* and the *Tetrapetalonema* spp., formerly known as *Dipetalonema streptocerca* and *D. perstans,* where there is uncertainty whether the human and simian parasites are the same.

ZOONOTIC FILARIAE

The term zoonosis, as it was defined by the Joint WHO/FAO Expert Committee on Zoonoses in 1959 includes "those diseases and infections which are naturally transmitted between vertebrate animals and man", but G.S. Nelson has pointed out that in these instances it is essential to discuss the direction of transmission. It is of little value to know

[a] Cross, J. H. et al. Experimental transmission of *Wuchereria bancrofti* to monkeys. *American journal of tropical medicine and hygiene,* **28**: 56-66 (1979).

[b] Dissanaike, A. S. & Mak, J. W. Experimental infection of the long-tailed macaque, *Macaca fascicularis* (syn. *M. irus*) with *Wuchereria bancrofti* (rural strain). (Laboratory Demonstration). *South East Asian journal of tropical medicine and public health,***9**: 451-452 (1978).

that a particular organism is found in both man and animals; what one is really concerned about is the relative significance of man and animals as maintenance hosts of the particular infections.

The truly zoonotic filarial worms that infect man are of two types:

(*a*) First, there are the two parasites *B. malayi* (subperiodic) and *B. pahangi.* With the former both natural and experimental infections have been reported. The latter has so far been shown to infect man only experimentally, but it is presumed to infect man in nature. Both animal-to-man and man-to-animal transmissions can and probably do occur with both parasites.

(*b*) Secondly, there are animal parasites that may infect man following the bite of a vector carrying infective larvae. In such cases, man represents a cul-de-sac from the point of view of the parasite, since the worms very rarely develop to sexual maturity and even if they do, microfilaraemia is not observed. *Dirofilaria* parasites from domestic carnivores and perhaps other wild vertebrates fall into this class.

The truly zoonotic human filarial infections may thus be considered under two headings: (i) sylvatic animal filariasis, and (ii) domestic animal filariasis.

Sylvatic animal filariasis

The sylvatic animal filariae that can infect man include the subperiodic strain of *B. malayi* and perhaps also *B. pahangi,* as mentioned above (see Fig. 1). These two species are primarily parasites of monkeys and carnivores, and man has been experimentally infected from these sources. Subperiodic *B. malayi* has become an important zoonosis in which animal-to-man and even man-to-man transmission continues to occur in Indonesia (Java, Kalimantan, and Sumatra), Malaysia (Peninsular Malaysia), the Philippines, and Thailand. The topographical distribution of this parasite is limited to swamp forests and those areas immediately surrounding them. Here, man and domestic animals are particularly exposed to bites of mosquitos coming from the forest areas to feed. Women and children, being more confined to the villages are less likely to enter the forest and are not bitten so often. *Mansonia* vectors of subperiodic *B. malayi* will feed on several species of animal as well as man, and their feeding preferences are for cattle, man, goats, pigs, dogs, cats, and fowl, in that order. They feed mainly out of doors.

Epidemiologically, subperiodic *B. malayi* shows little host-specificity. It has been reported in leaf-monkeys, macaques, palm civet cats, wild cats, the pangolin, and domestic cats. In the swamp-forests of Malaysia, leaf-monkeys are the most abundant and important reservoir hosts and their infection rates can be as high as 70 %. In this part of the world, cats are very important household pets and also harbour the parasite. Control of this human infection is therefore difficult since animal-to-man transmission continues even after the human reservoir has been greatly reduced.

Subperiodic *B. malayi* has been experimentally transmitted from man to cats and to other animals including monkeys, the slow loris, civets, dogs, hamsters, and white rats and other rodents. It has also been transmitted from cats to man. The ability to develop in such a wide range of vertebrates shows its remarkable adaptability.

Although *Brugia pahangi* has been found occasionally in leaf monkeys and the slow loris, it is essentially a parasite of domestic dogs and cats and of wild carnivores. In this respect, it is unlike subperiodic *B. malayi* which appears to be more a parasite of primates. Experimentally, *B. pahangi* has been transmitted from cats to man, in whom it may even produce low levels of microfilaraemia. However, no natural infections in man

have so far been reported and this is perhaps because, as in experimental human infections, *B. pahangi* causes similar clinical manifestations to *B. malayi*; and, more important, because it is not easy to distinguish the microfilariae except by special staining techniques and measurements, which are not practicable in routine surveys. The differential susceptibility of certain mosquito species to infection with these two parasites is another useful criterion for distinguishing between them. For example, *Armigeres subalbatus* is a good vector for *B. pahangi* but not for subperiodic *B. malayi.*

Recently, a technique for demonstrating acid phosphatase distribution in microfilariae has been found useful in distinguishing between species of the same genus.[c] The use of this technique to distinguish between *B. pahangi* and *B. malayi,* may well result in the finding of natural human infections with *B. pahangi* in Peninsular Malaysia in the near future.

Domestic animal filariasis

In the domestic environment (Fig. 1), it is clear that the mosquito vectors of filarial worms of domestic animals usually have greater chances of biting man than do those that usually feed on forest animals.

Here, the *Dirofilaria* spp. of dogs and cats are important in causing human infection. Being poorly adapted to the human host, they often cause obvious clinical manifestations and hence attract the attention of physicians, surgeons, ophthalmologists, dermatologists, radiologists, and general practitioners.

Since 1957, when *Dirofilaria* infection was first reported by E.C. Faust, numerous reports of human infection with *Dirofilaria* worms have appeared in the literature. These worms may be divided into two groups:

(*a*) Those belonging to the subgenus *Dirofilaria,* represented by *Dirofilaria (Dirofilaria) immitis,* found in the right heart and pulmonary vessels of the dog (the normal host), which are characterized by a relatively smooth cuticle.

(*b*) Those belonging to the subgenus *Nochtiella,* which are invariably parasites in subcutaneous tissues of their normal hosts. They have longitudinal ridges in the cuticle, with fine tranverse striations. *D. repens* is found in dogs and *D. tenuis* in the racoon.

In many of the earlier reports of dirofilariasis in man, the worms were labelled "*D. conjunctivae*" because they were often recovered from the eye region. Yet several were located in subcutaneous tissues quite distant from the conjunctiva, including the upper and lower limbs, the abdomen, chest wall, and even the penis. It has now become clear that "*D. conjunctivae*" includes several species of worm that are normally located in subcutaneous tissues or in the heart and pulmonary vessels of their hosts, but which are seen in subcutaneous sites when they infect an unnatural host such as man. The common subcutaneous worm of dogs which infects man in Africa, Europe, India, and Sri Lanka is *D. (Nochtiella) repens* which has been shown to cause lesions in the subconjunctiva and in subcutaneous tissues in practically all parts of the body. In the USA, it is *D. (Nochtiella) tenuis,* a parasite of racoons which often infects man in this way.

Dirofilaria infections in the USA were reviewed by P.C. Beaver, in 1965, who identified 35 subcutaneous cases (mostly from Florida) and 11 pulmonary cases. Since then, over 100 subcutaneous infections have been reported, mainly from USSR (over 30 cases), Italy (over 30 cases), Sri Lanka (12 cases) and smaller numbers from Central

[c] YEN, P.K.F. & MAK, J.W. Histochemical differentation of *Brugia, Wuchereria, Dirofilaria* and *Breinlia* microfilariae. *Annals of tropical medicine and parasitology,* **72**: 157-162 (1978).

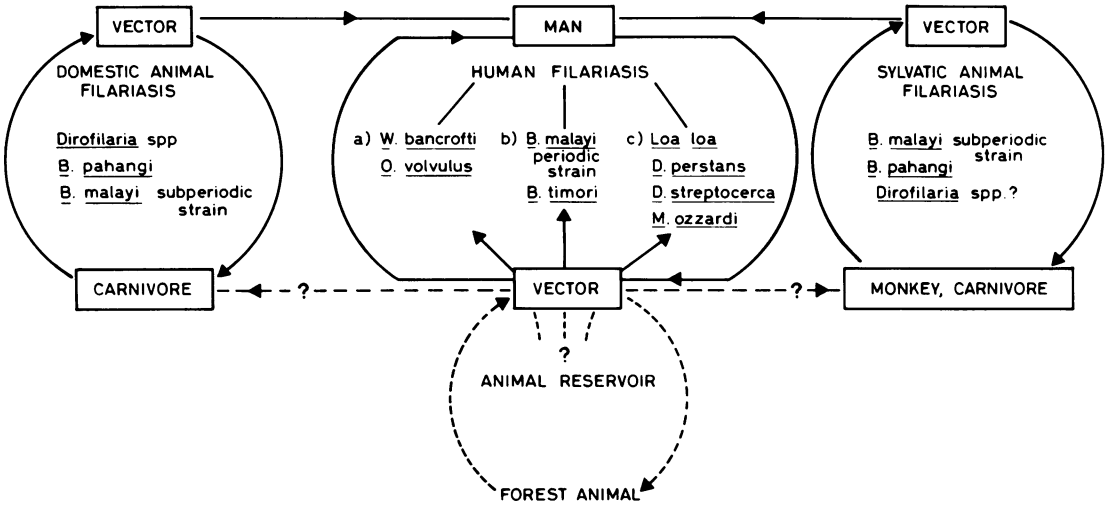

Fig. 1. Chart showing zoonotic aspects of filarial infection in man.

Africa, Argentina, Brazil, Canada, Egypt, Equatorial Guinea, France (including Corsica), Federal Republic of Germany, Greece, Hungary, India, Israel, Republic of Korea, Romania, Senegal, Spain, Thailand, Turkey, and the USA.

Sixty-eight cases of pulmonary dirofilariasis have so far been reported, but only from the USA (47 cases), Australia (20 cases), and Japan (1 case). *D. immitis,* the only parasite incriminated so far, has also been seen in other sites, such as the subcutaneous tissues (in Japan), the vitreous body of the eye (in a suspected case in Malaysia) and in the anterior chamber of the eye in two cases in Australia.

Clinically, the subcutaneous infections usually present as a lump or nodule in or around the eye or in the skin over any other part of the body. They may appear as shifting areas of swelling and redness which finally localize, often after treatment with diethylcarbamazine. Sometimes an associated secondary infection draws attention to the lesion. Identification and diagnosis is usually made after surgical removal of worms, or after biopsy of a cystic swelling or nodular mass (Fig. 2). A subcutaneous infection was found in a 6-month-old infant in Sri Lanka and it appears that any age group may be affected. The longitudinal striations in the cuticle are clearly seen in tranverse sections of the worm (Fig. 3).

In pulmonary dirofilariasis, more than 70% of reported cases have been symptomless, the lesions having been accidentally discovered during radiography. Sometimes chest pain and cough may occur, followed occasionally by haemoptysis, fever, chills, and malaise. Radiologically, lesions appear as solitary, circumscribed areas 1–2 cm in diameter, i.e., "coin-lesions" (Fig. 4). Systemic eosinophilia is not common. A granulomatous response is characteristic (Fig. 5). Microscopically, infarction vasculitis and eosinophilia are present. The infarct is caused by occlusion of an arteriole where a thrombus forms around impacted dead worms (Fig. 6). The worms are invariably immature and hence microfilariae are not found either in sections or in the peripheral blood.

Recently, a single case of *Dirofilaria immitis* infection with microfilaraemia has been reported in a case of systemic lupus erythematosus, but this was a transient happening

and too rare to be of epidemiological significance. *D. tenuis,* on the other hand, the subcutaneous parasite of the racoon, is probably a parasite better adapted to man, and gravid females with microfilariae have been demonstrated in two patients in the USA.

It is evident from all the published reports of human cases, both of subcutaneous and of pulmonary dirofilariasis, that infection is probably much more widespread and common than the number of reported cases indicates. In those countries with the most reported cases, an awareness of the infection has been mainly responsible. Many cases, especially of the pulmonary type, go unnoticed unless radiologists, thoracic surgeons, and physicians look out for them. For this reason, it would be an advantage to have available a serodiagnostic test for these infections which is both sensitive and specific.

TREATMENT

In all cases of human zoonotic filariasis, the only specific treatment available at the moment is the administration of diethylcarbamazine (DEC). In dirofilariasis, the evidence suggests that DEC has little effect on the adult worm. Local treatment will depend on the site and nature of the lesions. "Coin lesions" are detected in the lungs during life and can be misdiagnosed as early bronchial carcinoma. At present no specific tests are available to prove that these lesions are due to filarial worms. A careful study of the history and an explanation to the patient may be necessary before a lobectomy is performed, which is the only way of confirming the benign nature of the granulomata and demonstrating the worm in tissue sections. Subcutaneous lesions, whether cystic or otherwise, are usually removed surgically for diagnosis. Sometimes the worm, while still alive, may be teased out of a cystic swelling in the subconjunctival or other superficial site.

CONTROL

The control of subperiodic *B. malayi* infection, poses the greatest problem of all the zoonotic filarial infections. Mass treatment of the human population with DEC, so effective for periodic *B. malayi* and *W. bancrofti,* does not suffice because the large animal reservoir remains untouched. The leaf monkeys in Peninsular Malaysia, for instance, can hardly be controlled and moreover the *Mansonia* vectors which breed in forest swamps, are virtually impossible to eliminate. The treatment of domestic cats for this infection is frought with difficulties owing to the severe reactions to DEC that may develop. Hence, much research is needed to find means of tackling the problem of the control of human infection with subperiodic *B. malayi.*

With regard to dirofilariasis, prevalence data on *Dirofilaria* infection in dogs and other animals should be collected in all parts of the world so that the infection can be anticipated and prevention and control instituted where necessary. Treatment of infected dogs and avoidance by man of infective mosquito bites would seem to be the obvious preventive measures.

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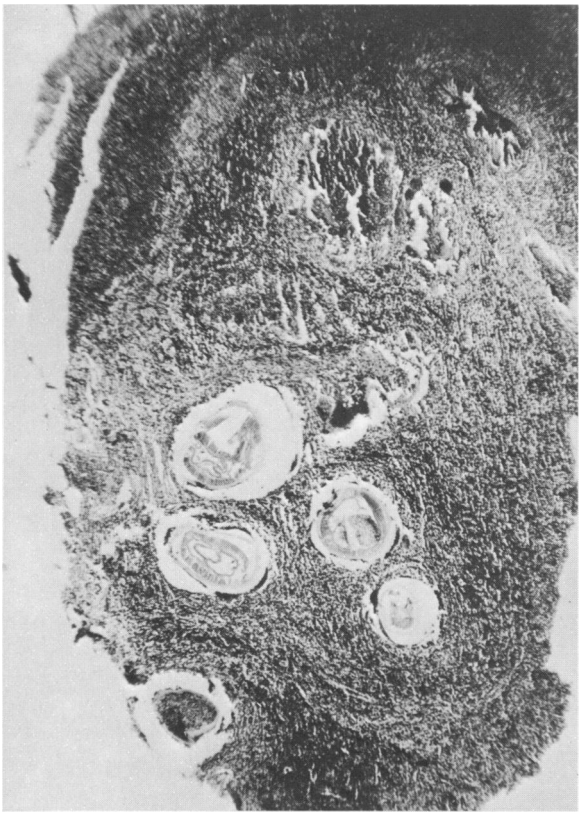


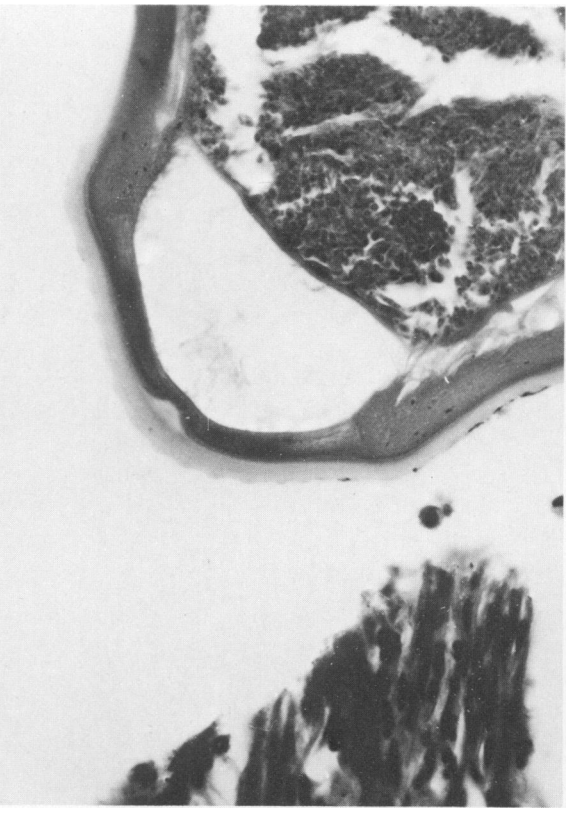


Fig. 2. Section of granulomatous lump removed from the cervical region of a patient, showing dead female *Dirofilaria* (*Nochtiella*) surrounded by numerous eosinophils.

Fig. 3. Section of a male *Dirofilaria* (*Nochtiella*) worm from the penis of a child in Sri Lanka, showing characteristic longitudinal striations of cuticle seen in tranverse section of worm.

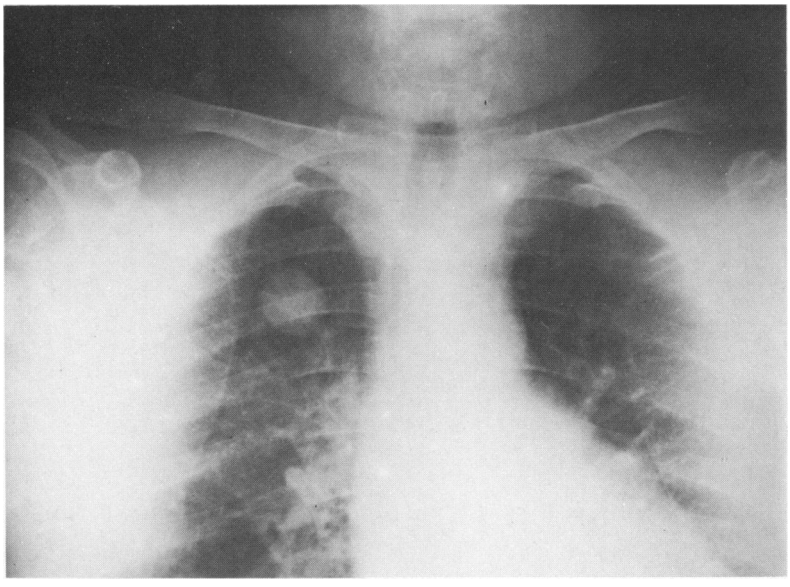
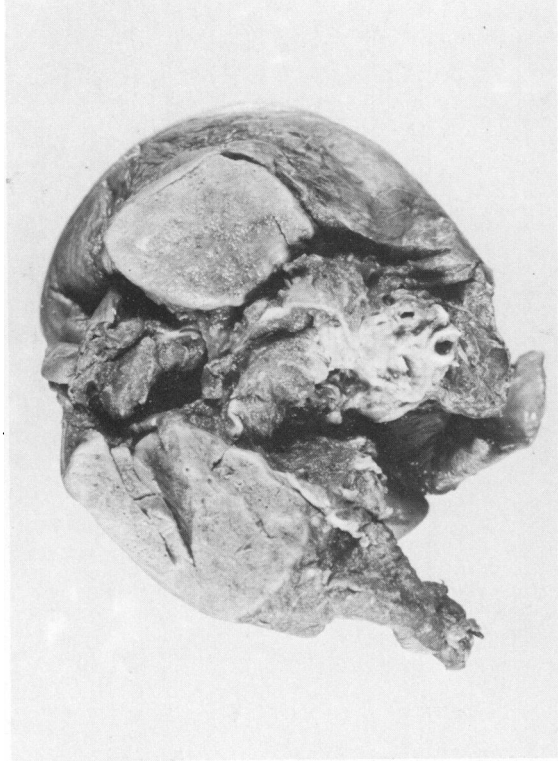


Fig. 4. Radiograph of a "coin lesion" resulting from *D. immitis* infection (illustration kindly provided by Dr D.E. Moorhouse).



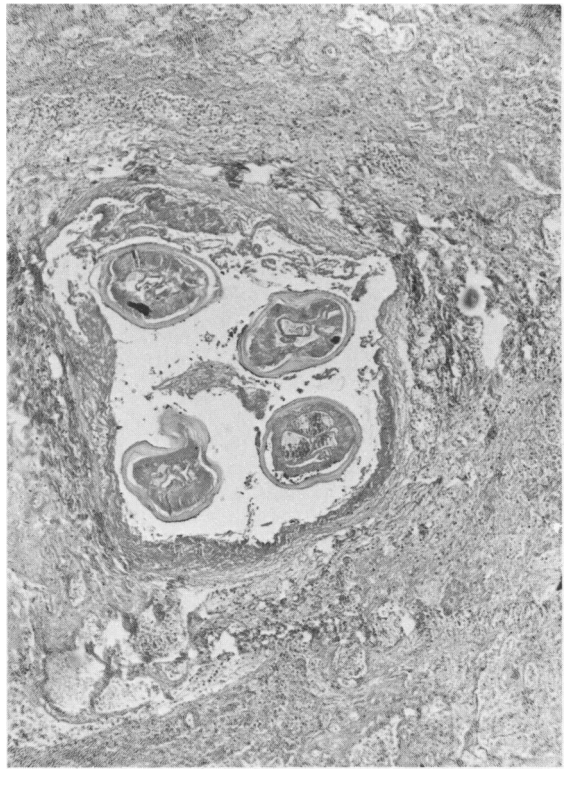


Fig. 5. Part of right lobe of human lung, bisected, showing well circumscribed, infarct-like lesion.[a]

Fig. 6. Tranverse section through worm in pulmonary artery at level proximal to a thrombosis, × 40.[a]

[a] The illustrations in Fig. 5 and Fig. 6 are taken from: Beaver, P.C. & Orihel, T.C. *American journal of tropical medicine and hygiene*, **14**: 1010-1029 (1965), and are reproduced by kind permission of the editor.

DL8 (Fig. 3 and Fig 4) and for permission to reproduce them; to Dr D. E. Moorhouse who kindly lent me the lung radiograph showing a "coin" lesion; and to Dr B.O.L. Duke who reviewed the manuscript before publication.

RÉSUMÉ

Incidence chez l'homme d'infections filariennes se rattachant aux zoonoses

Les zoonoses se caractérisent par la possibilité d'une transmission naturelle entre l'homme et l'animal, mais il est important de savoir, pour chaque type d'infection filarienne, si le réservoir principal du parasite est l'homme ou l'animal. Les infections considérées ont donc été classées en deux groupes selon qu'elles sont spécifiques de l'homme (il s'agit notamment, comme le montre la fig. 1) de celles causées par *Wuchereria bancrofi,* par la souche périodique de *Brugia malayi* et par *Loa loa* ou qu'elles atteignent principalement les animaux, soit sauvages, soit domestiques. Ceci étant, on constate chez l'homme des infections filariennes dues à des parasites infectant habituellement les animaux, et le présent article traite en détail de ces infections.

Dans le voisinage des forêts humides du Sud-Est asiatique, le moustique vecteur pique hommes et bêtes, leur transmettant *B. malayi* de souche subpériodique, qui infecte normalement les animaux carnivores et le singe mais est apparemment extrêmement adaptable. Quant à *B. pahangi,* sa transmission expérimentale du chat à l'homme a pu être réalisée et l'on pense qu'il peut y avoir aussi une transmission naturelle, mais il était difficile, jusqu'à présent, de distinguer les microfilaires respectives des deux parasites et les manifestations cliniques qui leur sont associées sont très semblables.

D'autre part, *Dirofilaria,* qui infecte les animaux domestiques — notamment les chiens et les chats — est un parasite fréquemment transmis à l'homme, chez qui les manifestations cliniques sont d'autant plus apparentes que cette espèce est mal adaptée à l'homme. Des manifestations sous-cutanées ont été signalées dans de nombreuses parties du monde et chez tous les groupes d'âge; elles affectent souvent l'œil ou la région de l'œil. *D. immitis* est cependant aussi à l'origine de dirofilarioses pulmonaires diagnostiquées chez l'homme par radiographie aux Etats-Unis d'Amérique, en Australie et au Japon. Dans l'infection humaine, les vers n'atteignent pas la forme adulte et on n'observe pas de microfilarémie; l'homme représente donc un cul-de-sac pour le parasite. Il est probable que l'infection est plus commune que ne l'indique le nombre des cas signalés, et la mise au point d'une épreuve sérologique spécifique serait utile. En outre, la collecte de données relatives à la prévalence de la dirofilariose chez les chiens et les autres animaux domestiques dans toutes les parties du monde faciliterait la prévention de l'infection chez l'homme.

Dans tous les cas d'infection filarienne humaine d'origine animale, le seul traitement possible est l'administration de diethylcarbamazine (DEC). Quant à l'endiguement, il pose un gros problème dans le cas de *B. malayi* de souche subpériodique car il est difficile de lutter efficacement contre un très vaste réservoir animal et le vecteur *Mansonia* est pratiquement impossible à éliminer.