IMPORTANT PROTOZOAN-, HELMINTIC-, MYCOBACTERIAL- AND VIRAL INFECTIVE DISEASES IN THE TROPICS.

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Resumè

I have made this text after studying litterature about tropical medicine. I wanted to learn more about the diseases that dominate in the tropics. The tropics include vast geographical areas, and a large proportion of the people in the wold inhabit tropical countries. This part of medicine are little considered in the education of doctors in Norway. This special field has historically not been paid much attention to in the medical research. Hopefully the last years tendency of increased international focus on HIV and malaria, will give more attention to many tropical diseases that are imortant causes of mortality and morbidity on world basis. The problem is money for research and pharmacological companies are not very interested in the poorest communities in the world. Luckily, international organizations as WHO have recently decided to concentrate on combating some important tropical diseases. Tropical medicine differs from medicine in the western world due to both natural reasons; climate, echology and topography, and man-made reasons like echonomy, infrastructure and culture. Of course the tropics share many diseases with the west, but most of them play a different role in respect to prevalence and impact on the community. In the beginning I wanted to get an overwiew of the most important tropical diseases. Soon, I found out that this range was too big, and I decided to focus on a few concrete diseases which are ones of the most prevalent and most important in a socioechonomic wiev. Counciously, I have let out HIV, tuberculosis, gastroenteritis and malnutrition because they have been lectured in class. I have also considered malaria to a less extent in proportion to its impact on mortality and morbidity. This is because I already have made a work about malaria in my 2.year of medical scool in which I wrote more about the pathogenesis and ethiology.

1. Protozoan infections

1.1 Malaria

Malaria is acknowledged to be by far the most important parasittic tropical disease, causing great suffering and loss of life. Malaria in humans is caused by four species of protozoal parasites of the genus Plasmodium: P. Falciparum, P. Ovale, P. Vivax and P. Malariae. Of the four species, P. Falciparum is the most dangerous form of the disease, and accounts for most of the infections in Africa and for over one third of the infections in the rest of the world. Some 300 million people are believed to be infected with malaria parasites, with 90% of them living in tropical Africa.
Although virtually no reliable statistics exist on malaria morbidity and mortality in Africa, extrapolations from epidemiological studies suggest that the disease is probable responsible for no less than 500 000 to 1.2 millions deaths annually, mainly among children below the age of five years. Worldwide it is estimated that there are about 120 million clinical cases of malaria per year. The enormous total of lives and days of labour lost, the costs of treatment of patients, and the negative impact of the disease on development make malaria a major social and economic burden.
(I: Tropical Disease Research.
Progress 1991-92. Eleventh Programme report.)

Epidemiology

2.4 billion people in more than 90 different countries live in malaria areas, 300-500 millions have at any time malaria, and 1.5-2 million die from the disease every year. (II: Tidsskrift for den Norske Legeforening14, 2000; 1614)
90 % of the ones who dies are children in tropical Africa. (III: Tidsskrift for Den norske Legeforening 14, 2000; 120:1661-4)

Africa is hardest struck and the most dangerous of the species, falciparum, has its main site south of Sahara. The malaria situation is by no means under control. The occurrence increases especially in the perifery of big cities in the tropics, where the Anopheles mosquito finds its hatching place in the open sewerage system of the slum areas. The insect killing effect of the pollution of the city is also milder here.

In many countries the malaria situation is badly surveyed, one reason is that epidemiological researches are made on clinical diagnose. Diagnosis based on clinics is unreliable, especially in falciparumendemic areas, because falciparum malaria can have many different clinical disguises. Clinical suspect malaria should be confined by laboratory investigation, practically being micoscopy of special colored blood smears. Available now are also fast diagnose procedures based on circulating malaria antigens. The hope is making such tests available in malaria areas in lack of microscopes and diagnostic procedures.(II: Tidsskrift for den Norske Legeforening 14, 2000; 1614)

Pathogenesis

Malaria is transmitted when infected female mosquitoes inject 11-12 µm long sporozoites in the blood of human. These are found in the circulation for a few minutes until they reach and intrude liver cells. there, the primal schizogeny finds place, where the sporozoite after several replications turns into ca 10^4 merozoites , that liberates into the circulation. This stage lasts about 5 days for falciparum. The liberated merozooite promptly invades erythrocytes and start the erythrocytal schizogony, in which it via a trofozoite stage produces a multinucleated schizont. The mature schizont ruptures the erythrocyte, and the 16-32 daughter cells turn into merozooites, that invades other erythrocytes. During the disease, the sexual gametozytes develop in the erythrocytes, and they fertilize when they come into the female mosquito. There it becomes an ookinete, which produced a big number of sporozoites ready to infect the next human.

Diagnosis

Malaria always starts with fever, often followed by joint pain cold sensation and headache. In the first days the feverattacks come daily. Afterwards appears the typical fever tops ca. every 48th hour. This pattern is typical especially for Plasmodium vivax. Patients infected with P. falciparum also get the fever tops after a few days, with about the same interval. But the fever tops last longer and the diagnosis should rather be clear before it reaches this stage. Infections by the benign plasmodium species the desease continue with attack of fever and fever related symptoms in untreated patients in some weeks until it heals. In patients with P. falciparum infection the picture can develop in a more serious direction, and the patient can have affection of more organ systems with risk of fatal end. The clinical picture can sometimes imitate the picture seen in multiorgan failure due to bacterial sepsis.

Clinical suspect malaria should be confined by laboratory investigation, practically being micoscopy of special colored blood smears. Available now are also fast diagnose procedures based on circulating malaria antigens. (II: Tidsskrift for den Norske Legeforening14/2000, 1614) Thye diagnosis ought to be set from inspection f thin and thick blood smears. The finding of trofozoites (signetrings) or schizonts, the diagnosis is set. The finding of only gametocytes, it means that the patient recently had malaria, but is not a significant finding to set the diagnosis malaria. It is important to distinguish which species of malaria one has to treat. Often the area from which the patient is infected, can give a strong suggestion, but the final conclution can be verified from investigation of the smears, and preferably, the thin smears. The observation of both rings and banana shaped gametocytes, clearly gives the diagnosis of falciparum. Schizonts are seldom seen in smears because they stick in the microcirculation. In very ill falciparum malaria patients, though, schizonts can be found in the smears, containing a lot of nuclei and looking like P. vivax schizonts. The finding of only rings, make the diagnosing more difficult, but the observation of a lot of rings that are thin and gracile, erythrocytes containing two or more rings, or rings with two chromatin lumps indicates falciparum infection. (IV: Tidsskrift for Den Norske Legeforening 14, 2000; 1648-52)

Treatment

The treatment of benign malaria still is chloroquinephosphate plus primaquine. The most patients with falciparummalaria without problems can be treated with mefloquine.
Complicated cases, usually because of long latency between onset and diagnosing, reveals far reaching treatment, usually including parenteral treatment with quinine

Mefloquine is given in doses of totally 5-6 tablets for grown ups; three tablets instantly, two more after 6-8 hours, and if necessary one last after another 6-8 hours. Seriously ill patients should have quinine injection, or eventually a derivative of arthemisine parenerally.
Arthemeths are given intramuscularly and arthesunate can be given both i.m. and i.v. Both exist as tablets, and artesunate also as suppositories.
Severely ill falciparum infected patients should be in hospital, and might be in need of blood transfusion, treatment in respirator, or dialysis.
The treatment of benign malaria is ambulant, but short time hospitalisation can be preferable because the patients can throw up the medicine from nausea. The standard treatment is chloroquine, most often chloroquinephosphate a total of ten tablets in four doses. Suspicion to chloroquine resistant P. vivax, which exists in Southeast- Asia, suggests treatment with mefloquine. (IV: Tidsskrift for Den Norske Legeforening 14, 2000; 1648-52)

Control

In 950's and 60's it was tried to extinct malaria by chemical combating of the Anopheles mosquito, but after a while the mosquito developed resistancy against the insecticides. (II: Tidsskrift for Den norske Legeforening14/2000, 1614)
Prophylaxis includes prophylaxis against mosquito bites and chemoprophylaxis.
Prophylaxis against exposing, includes carefulness in the evening and night when the mosquito bites, covering clothes, anti-mosquito lotions in exposed areas, mosquito nets impregnated by anti-mosquito spray.
For the people living in the malaria endemic areas, the prophylaxis against exposing should be the only prophylaxis.

Medicaments for prophylaxis are chloroquinephosphate, proguanil, mefloquine and doxycycline. In areas of benign forms of malaria chloroquinephosphate should be sufficient, if any at all. Today the safest form of prophylaxis to falciparuminfection is mefloquine. The serum level of the drug rises slowly, and initiation of the medicament is recommended two to three weeks before exposure. This will also reveal possible serious side effects before departure. Doxycycline can be recommended in certain areas of Kambudcha where P. falciparum also is resistant to mefloquine. Doxycycline can also be an alternative where there are contraindications to the use of mefloquine. (IV: Tidsskrift for Den Norske Legeforening 14, 2000; 1648-52)

Newer Research

Klorproguanil-dapson.

A new drug, klorproguanil-dapson, have shown effective in the treatment of multiresistant falciparum malaria. A study from Tanzania where they followed 360 children under five years, it showed that after standard regimen treatment with pyrimetamin-sulfadoxin, 45% still had the parasite in the blood. 66% of these, developed clinically malaria. The half of them were treated again with the standard regimen, and the other half with klorproguanil-dapson. 61% in the first group still had parasitemia after one weeks treatment, while 15 % in the other group had. This combitation- treatment is cheap, 4-5 kroner per treatment, and it is recommanded by WHO for acute treatment of malaria in Africa. (V: Tidsskrift for Den norske legeforening 27/2001,3235).

A new pharmaceutic against malaria?

The malaria parasite is brought into the bloodstream as a sporozoite, and quicly finds itself way to the liver cells. There the first asexual formation finds its place. After thet, the parasites goe, now as merozoites, out in the blood, where they formate again. The clinical symptoms of malria come when the erythrocyte destroys, and a great amount of merozoites are let nout in the bloodstream. When the malaria parasite replicate asexually,the parasites synthezise membranes. A french research group have tested a new substance that bloqeate the synthesis of phosphatidylcholine and therefore also the synthesis of the membrane and the formation of the parasites. The mature parasite does not make membranes, and will therefore, in theory, not be affected. The preparate, called G25, have shown to impede growth of malariaparasites in vitro. Monkeys infected by Plasmodium falciparum got rid of the parasite after a few days' treatment and did not show residive two months later. Toxicological and other studies are necessary before G25 can be tried on human beeings.
(VI: Tidsskrift for Den norske legeforening 8/2002;871)

Dar es Salaam, 31 may (EFE): the spanish doctor Clara Menèdez, investigator at the medical faculty in the University of Barcelona, have given new hope in Tanzania for the prevention of malaria, which every year takes the life of more than 100. 000 people in this country. Menèdez started eight years ago the experimental work that has received the aprovement of WHO for its results, and now it is planned to extend the treatment to the areas most affected by malaria in Tanzania. A report from WHO indicates that the spanish investigator i 1994 introduced the vaccine SPS 66 in the

region Morogoro, 200 kilometres east of Dar es Salaam, where malaria is endemic. During these years, 701 children were vaccinated with the new pharmaceutical compound, which has obtained a reduction 56% in incidence and a reduccion of 30% of acute anemia in those infected. The project, leaded by the spanish fundation BBVA, USAID, the EU Center for Control of Tropical Diseases and the London Academy of Tropical Medicine and Hygiene, will be set in practise when the alarming reduccion in the effectivity of the current curative medicines is recognised by the Tanzanian authorities.
Because of the increasing number of deaths due to the recistancy of the paracites to the existing medicine available in the market, the government now is recommending the use of mosquitonets treated with insecticides.
Despite of this and because of the price of this medium, 6 dollars, inacessable for the majority of Tanzanians and especially in the rural communities, where the disease is of highest incidence, its use has not increased. This has facilitated the proliferation of the infection in the whole country.(VII: El periodico, may 31.02)

WHO defined in1998 malaria combating as one of the main targets for the organization. The unsatisfactory situation of today is mainly because that in the areas where the problem is greatest, the means and methods we dispose, are not used in a systematic and optimum way. The Roll Back Malaria program of WHO will put an effort in use and further develop the existing methods and continue the research that hopefully will reveal a vaccine and other means of combating the disease.

1.2. African Trypanosomiasis

African trypanosomiasis is caused by parasites of the genus Trypanosoma. These organisms are flagellate protozoa. In Africa, the organisms responsible for human trypanosomiasis are Trypanosoma brucei, a complex of organisms transmitted to man by the bite of tsetse flies, Glossina. Trypanosomiasis in man is usually referred to as sleeping sickness, and is characterized by a range of symptoms which initially only affect the haemolymphatic system, but after varying periods of time following infection, also involve the central nervous system. The name sleeping sickness derives from the comatose, somnolescent state characteristic of patients in the terminal stage of the disease.

Epidemiology

Human trypanosomiasis is endemic only in the areas where Glossina species are found. The echological limit of Glossina distribution is a line from the northern fringes of the Kalahari and Namibian deserts. Sleeping sickness is endemic in 36 countries and, while 20 000-50 000 cases are recorded every year, this is believed to be an underestimate, particularly because surveillance has been reduced as public health service has been under economic constraints. The number of deaths has been estimated in the World Development Report to 55 000/year. Death from sleeping sickness is inevitable if the disease is untreated; for this reason, epidemics will cause serious disruption and economic loss to communities who are deprives of treatment because hospitalization is neither feasible nor available. Calculations of DALYS (disability of adjusted life years lost) have ranged sleeping sickness as the third most important contributor to the global burden of parasitic disease after malaria and schistosomiasis. Sleeping sickness is endemic throughout eastern and sout-eastern Africa, and the human is infected by the bite of Glossina spp. assosiated with woodland savanna habitats.

These are preferentally bovine feeders, and feed on humans only when other host are scarse. The classical wiew of the epidemiology of T. b. rhodesiense is that specific groups of people whose activities or occupations bring them in contact with savanna or thicket habitat where game animals are more abundant, are associated with infection.

Aethiology

Parasites are pleomorphic, extracellular in the blood and tissue and vary in length from 12 to 42 μm; they have a small subterminal kinetoplast and a free flagellum. Parasite multiplication is impaired by specific antibodies produced by the host, but some parasites escape the immune response by antigenic variation. The result is fluctuating parasitemia with progressive and multiple pathological changes which vary in pattern and intensity with the different parasite strains, host, population and individual characteristics. T. b. rhodesiense and T. b. gambiense are the causative agents of acute and chronic sleeping sickness respectively. Neither the frequency of hybridisation in the wild nor its significance in terms of epidemiology or drug resistance are yet known.

Pathogenesis

The parasite escapes the immune response by varying their glycoprotein coat, and by inducing generalized suppression of the immunological functions. The disease affects principally the haemolymphatic system, producing an increase of perivascular cellularity characteristic of an inflammatory process. This is associated with widespread haemorrhages and tissue oedema. These changes in T. b. rhodesiense disease can involve the heart as myocarditis, that can extend to fibrosis and myocytolysis, and secondary infections may contribute to the cardiac lesions. In the chronic forms of the disease perivascular infiltrations also become a marked feature of the CNS involvement with meningoencephalitis.

Diagnosis

Because chemotherapy causes a significant risk, particularly in the late stages of treatment when the parasite has invided the CNS, diagnosis of the stage of the disease is critical. Several immunodiagnostic procedures offer the possibility of examinig large groups of the at-risk population, from which positive suspects can then be examined by the more rigorous methods of parasite detection.
Detection of parasites can be made in freshly prepared wet blood films as a quick method, but stained thick films is more sensitive. Concentration methods has been developed because parasites may only be present in low numbers. A major problem is that trypanosomes may only be present in small numbers in the blood, both acute and chronic infections having fluctuating aparasitaemic periods. The parasites preferred environment is in the lymphoid and connective tissue spaces, where numbers do not necessarily correspond with parasitemia. Because the prognosis is significantly worse one the parasite has entered the CNS, accurate asseesment of the stage of the disease is necessary. Diagnosis isdependent upon direct analysis of CSF, which may be negative even though the blood-CSF and the blood-brain barriers have been broken.Centrifugation of the CSF must be taken rapidly (under 10 min.) because the parasites appear to be more fragile than those in blood. Widely accepted criteria are: The precence of trypanosomes; and /or leucocytes ≥5 cells/mm^3; and/or protein≥40 mg%. The sequential approach to serological andparasitological diagnosis of T. b. gambiense would be: card agglutination test for trypanosomiasis(CATT), gland puncture, thick blood

film, microhematocrit miniamine exchange column and quantitative buffy coat technique (QBC). In T.b. rhodesiense it would be wet film, thick film, microhematocrit and QBC.

Clinical symptoms and signs

Infection is characterized by initial intermittent fevers, gradual involvement of the reticuloendothelial sysem and the endocrine system, and later the develpoment of neurological symptoms.

The first stage in virulent T.b. rhodesiense disease is the chancre that develops in the biting site of Glossina, and lasts several weeks. As it progresses the skin becomes darkened and can remain so for years. The incubation period vary from hours to weeks and the clinical manifestations vary from case to case. The initial stage though, called the haematolymphatic stage, is subsequently characterized by relatively non-specific symptoms like irregular febrile episodes, headaces, malaise, weight loss, muscle and joint pains, pruritus, anemia and deep hyperaestesia. Facial oedema, endocrine disorders, cardiac abnormalities, enlarged lymphnodes, moderate hepatosplenomegalia and involvement of the digestive system are among the variety of other features which are associated with the disease. Owing to the clinical variation, differential diagnosis is of big importance.

Most cases of T.b. rhodesiense run an acute or subacute course which is fatal in a few months from damage to the heart or viscera; those due to T. b. gambiense frequrently extend to a chronic course of several years, leading to the extensive nervous system involvement and classic sleeping sickness. The early neurological changes as headace, irritability and mood changes correlate with the widespread meningeal inflammation which occurs in both forms of the disease. As the disease progresses the signs of neurological changes become more marked, with progressive mental deterioration, mood changes and the classical reversal of sleep patterns with daytime somnolence leading to permanent sleep, coma and eventually death. Motor function becomes seriously deteriorated with abnormal movements and altered gait. Speech is impaired. The profound neurological changes correlate with the progression from meningitis to encephalitis. More extensive in T. b. gambiense infection, with its natural duration of two years or more and involving a large variety of mental changes.

Treatment

Two drugs, suramin and pentamidine are currently used for the treatment of early stage-disease. Pentamidine is not effective in T.b. rhodesiense. The dosages are: 4 mg/kg body weight>10 daily injections i.v. or i.m. for pentamidine, and 20mg/kg body weight 5-7 injections i.v. every 5-7 days for suramin.

Melarsoprol is the drug of choice for the treatment of late stage sleeping sickness. It is administered at a dose of 3.6 mg/kg per day, and several different regimens of treatment are listed by WHO. The most feared side effect is arcenical encephalopathy, which is observed in between 5-10 %. Treatment using melarsoprol requires the patient to be under medical care in wiew of the problems associated with treatment; this also reqires additional facilities and skills as well as drug availability, good diagnostic facilities and methods for follow-up. The problems of provision of such facilities whithin the existing constraints on health sevices in Africa are clearly evident. The cost of treatment are a severe drain on African health care services. Such provision are only likely to be provided in future by external support or by private providers such as non-governmental organizations.

Melarsoprol-resistant cases can now be treated with eflornithine, a potent inhibitor af polyamine synthesis. The drug is administered at a dose of 100 mg/kg i.v. every 6 hours in an isotonic saline infusion for 14 days, followed at 21-30 days by an oral dose of 75 mg/kg every 6 hours. Even though eflornithine is clearly a safer drug than melarsoprol, the cost of eflornithine treatment is outside the capacity of national health sevices. Eflornithine is not effective alone in T.b. rhodesiense infections.

Nifurtimox, which is used for treatmant of Chagas' disease, has been used for treatmant of melarsoprol-resistant T. b. gambiense with some success.

The prognosis following treatmant with suramin or pentamidine is exellent , provided there is no CNS involved. Achivement of cure is lessened even with marginal CNS signs.
Nevertheless cure rates of at least 90% are achievable in severely advanced infections.

1.3. Leishmaniasis

Leishmaniasis is caused by parasites of the genus Leishmania. It is actually a complex of syndromes, which are widespread geographically, and represent zoonotic infection with variable penetration to man. They occur in various zoogeographical zones, each with their own biological complex of parasite, host and vector.
Leishmania has been very successful in adapting, so that its been established in many different ecological habitats. The several patterns of disease in human reflects this diversity of some extent, but is also affected by the host immune response.

Aethiology

Leishmania is transmitted between long-lived vertebrates by short-lived phlebotomine sandflies, and have a cylcle of development in each. In the vertebrate they are in the amastigote form, round or oval bodies with diameter of max. 2.5 - 6.8 μm, without a flagellum. In the sandfly and culture, they are in the mastigote form, long slender and motile bodies,10 - 20 x 1.5-3 μm, with an anterior flagellum.
There are at least 30 species of Leishmania, of which 12 named and several unnamed infect man.

Ingested amastigotes transform into promastigotes and pass into the gut of the sandfly. Over the next 4-7 days they migrate forward in the gut, developing into infective metacyclic forms. During this process tree molecules, which are thought to be important to the infectivity, are expressed o the surface membrane. One is lipophosphoglycan wich protects the promastigote from lysis by host complement. The others are the major glycoprotein gp63 and acid phosphatase. When sandflies feed, they tear tissue, and the promastigote enters macrofages in a way not yet certain. Parasitization of the macrophage reduces the expression of class II molecules of the macrophage surface and increases the requirement for interferonγ for microbial killing. There by it downregulates the hosts immune - response. The amastigote resists killing by oxygen radicals, but is killed by NO produced from L- arginine.

Reservoir hosts are usually wild animals; rodents, edentates or canines. Most natural reservoir hosts are well adapted to Leishmania, and develop mild lesions, most commonly on the skin.

Sandfly vectors breed in organic detritus in a variety of sites. It depends on temperature and rainfall. Thus transmission is often seasonal. Sandflies are fastidious in their requirements of temperature, humidity and still air. The majority of species bite at night.

Epidemiology

Some species of the parasite are more virulent than others. The behaviour of Leishmaniasis in a given areas reflects the behaviour of the human population in relation to the cycle of transmission. The population at risk will differ in each situation. The availability of the parasite to sandflies varies greatly. Zoonotic
Reservoirs usually represent a quite stable chronic source of infection.

Vectors vary in their degree of anthrophilia and zoophilia. Vectors in cycles of transmission remote from man are less likely to infect man. See fig. 1 for geographical distribution for visceral leishmaniasis.

Pathogenesis

Leishmania multiply in cells of the mononuclear phagocyte system, wich includes blood monocytes, histiocytes, epitheloid cells, Kuppfer cells and cells of the reticuloendothelial system. Inoculated promastigotes are phagocyticed in the skin and form into amastigotes and start to divide. One of tree events follows:

1.Parasites are killed by successful immune response, and the person becomes immune to reinfection of that species.
2.A local infection is established until the host immune response eradicates it or is overwhelmed, permitting dissemination.
3.The infection metastazises to the bloodstream to the viscera, oronasal mucosa or skin.

Cutaneous Leishmaniasis

In an early lesion of cutaneous leishmaniasis, lymphocytes and plasma cells surrounds infected macrophages. One or more patterns, that reflect the nature of immune response, may develop. And the disease may develop to be self- healing, diffuse spreadindg, secondary mucosal infective, persisting, with little ulceration or crusting, or chronical, associated with development of a typical tuberculoid pattern.
Epidermal changes also reflect the type of immune response. The epidermis thickens, and pseudoepitheliomatous hyperplasia may be striking. Some lesions due to L. braziliensis are accompanied by fibrinous exudate and vasculitits.

Post- Kala- Azar dermal leishmaniasis

Indian PKDL is characterized by dermal infiltration with histiozytes, plasma cells and lymphocytes that is variable in distribution, intensity and extent. Epidermal changes are not marked and there is no ulceration. As a rule, viscera are spared.
In Africa PKDL is characterized by a tuberculoid histology, scanty parasites and a positive leishmanin test. It represents recognition and destruction of residual cutaneous parasites by the emergent cellular immune response.

Mucosal leishmaniasis

The early lesion is in the deep mucosa of the nose or mouth. An infiltrate of lymphocytes and plasma cells develop around small arterioles whose endothelial cells contain amastigotes. The inflammation extends towards the mucosal surface and may assume any of the histological patterns that are seen in CL. Cell mediated hypersensivity is strong, and the leishmanin test is positive.

Clinical features

The incubation period varies from few days to several months.
One or more lesions appear on uncovered parts of the body. At the site of inoculation a nodule appears, erythematous in pale skin. As it grows, a golden, brown or blood stained crust forms centrally. This may fall of, leaving an ulcer, which usually has a raised edge. The sore remains in this stage for a variable time before healing, leaving a depressed mottled scar.

Cutaneous Leishmaniasis

L. major
Incubation is from 1 week to two months. Lesions necrose rapidly, and tend to be inflamed and exudative wet sores. They heal within 3-5 months. Lesions are common on the limbs.

L. tropica
Incubation is from 2 - 4 months. The initial lesion may develop little satellite papules. It is crusting slowly, and heals within 10-14 months. Lesions are most common in the face, and children are often infected.

L. chagasi and L. infantum
Incubation period may exeed 1 year. The lesions are nodular, may never ulcerate, and may last 1-3 years. They are most common on the face.

L. ethiopica
Solitary lesions centrally in the face. Satellite papules accumulates to produce a spreading nodule, that may not crust, but heals slowly over 2-5 years.

L. brazilensis
Deep, usually single, rapidly developing ulcers with raised red edges, especially on the limbs. Most of the lesions heal in one year, but the infection is common, and many people have ulcers that last up to 10 years.

L. guyanesis
Lesions are often multiple, on the trunk and limbs, and the form is associated with spread in the lymphathic system.

Diffuse Cutaneous Leishmaniasis

Occurs in infection with L. aethiopica and L amazonensis, and is the rule with the parasite in The Dominican Republic.The primary lesion does not ulcerate, but spreads slowly locally and

through the bloodstream to other parts of the skin. It produces nodules, plaques and hypopigmented macules that may resemble lepromatous leprosy and make severe deformity. Spontaneous healing is rare.

Leishmaniasis residivans

Rare complication of L. tropica, where the infection persists in the face of a vigorous immune response.Red-brown or yellow-brown papules continue to reappear, ulcerate and heal around a scar of a heals sore, over many years. They may form a plaque, resembling lupus vulgaris.

Post- Kala- Azar dermal leishmaniasis

This is a sequel of infection with L. donovani. Patients often presents a history of self-healed or treated VL. In India the onset is insidious. Lesions tend to appear after an interval of 1-2 years, and diagnosis may be delayed for 20 years. Hypopigmented macules appear over many sites of the body. Consequently, nodules appears in a similar distribution. Clinically PKAL may resemble lepromatous leprosy, but peripheral nerves are not involved, and it fails to show acid resistant bacilli.
In East- Africa PKDL commonly occurs at the end of the course of treatment for VL, presenting a popular rash over face and forearms, or as a crop of well roundes papules, healing spontaneously over a few months.

American mucosal leishmaniasis

After dermal infection with L. braziliens, L. guyanensis or L. panamensis, some percent of the infected will develop metastatic mucosal lesions, often about the time the ulcer heals.
About 15% of ML, gives no history of previous skin lesion. The common sites affected, in order of frequency, are nasal mucosa, pharynx, larynx, and upper lip.
The initial lesion is a nodule, usually on the anterior septum, and the initial symptom is of nasal obstruction or epistaxis. The nasal cartilage may collapse, and the infection spreads to involve oronasopharyngeal mucosa. The infection spreads to the mucocutaneous junctions of the lips and nose, and may ulcerate, or hypertrofiate. Nasal, pharyngeal, or laryngeal obstruction are serious, even fatal complications. Death may also ensue from secondary sepsis, pneumonia, or starvation. Spontaneous healing is unusual.

Diagnosis

Parasitological diagnosis require that material from a lesion, is taken and inoculated on a culture media. It is used to make slit-skin smears on slides, which are stained.
For ML, biopsy and hamster-inoculation, are best.

Innounodiagnosis is performed by inoculation of leishmanin (a suspension of washed promastigotes in a solution of 0.5 % phenol in saline), into the forarm, and measuring the induration after 48-72 hours.
In ML, serology with detection of antibodies is useful in diagnosis.

Treatment

Physical methods include freezing, surgical exicion, curettage and heat. Chemical methods include careful infiltration of sodium stibogluconate or meglumine antimoniate into the edge and base of the lesion.
Systemic it may be given antimonials. A regimen is given for three weeks is usually adequate, but if response is slow, the treatment should be continued. Other drugs are less well established, but some has been successfully used in treatment, allopurinol against L panamensis in Columbia, ketoconazole against same species in Panama, and L. mexicana, and L. major in Sinai. Dapson cured 82% of CL sores in India.
Previously treatment with antimonials, given a relapse, leaves the parasite less likely to respond second treatment, Therefore it is important that the treatment continues a sufficient time to eradicate the last parasite.

Visceral leishmaniasis

Pathogenesis

In the endemic situation there are about 30-100 sublinical infections for every case of VL. Healing is associated with the development of tuberculoid granulomas in the liver, the transient appearance of antibodies, and acquisition of leishmanin positivity. Risk factors for development of VL are malnutrition and immune depression.

Established VL represents the failure of specific cell mediated immunity to control the infection. There is a general depression of cell-mediated immune responses, and this, together with malnutrition and leucopenia probably underlies the high rate of secondary infection that are the common causes of death in VL.

Parasites multiply in the visceral reticuloendothelial system. In the spleen infarcts are common. In the liver, Kuppfer cells are affected, and there may be venous congestion with patchy necrosis in groups of hepatocytes. But severe liver damage is unusual.
In other cases granulomas may form, and a fibrinogenic response may develop.
Lymph nodes show sinusoidal cell proliferation and parasitization and depletion of germinal centres.
Duodenal and jejunal mucosa is thickened because the submucosa is infiltered with parasitized immune cells. The villi are blunted.
The bone marrow is usually hyperplastic.
Three quarters of patients coming for biopsy shows interstitial pneumonitis with mononuclear cells containing amastigotes or leishmanial antigen.

Clinically there are found raised mean values of IgG and IgM . Some of these immunoglobulins are antileishmanial antibody, some are autoantibodies reflecting B-cell polyclonal activaton. Complement is activated, and complement levels are reduced. Immune complexes present in high titre, and seldom give raise to uveitis and nephritis.
Liver enzymes are normal, but plasma albumin is raised.
Pancytopenia is the rule. Immune lysis and ineffective erythropoiesis may contribute to the anemia.

Clinical features

The established disease presents a fairly unifrm pattern but the onset tends to differ between indigenous and expatriate individuals. Incubation period range from 3 weeks to over 2 years. In expatriates and early in epidemics, the onset is usually acute with the sudden appearance of fever and rigors in 96 %. Malaise, headache, dizziness, anorexia, cough or diarrhoea may occur early in a few patients, but there are no specific symptoms, and the differential diagnosing is difficult.
In the indigenous patient in an endemic area the onset is insidious, and the delay in seeking medical help may be up to one year.
Physical examination early reveals splenomegaly in over 90% of patients, and hepatomegaly in 75%.
Abdominal pain is usually due to the enlarged spleen. Cough and diarrhoea may indicate intercurrent infection. Epistaxis is common and occasionally severe, but other form of haemorrhage is rare. Oedema may be part of a syndrome comprising hair and skin changes, resembling kwashiorkor.
In India most patients develop darkening of the skin (kala-aza r= black sickness). This is also seen in a proportion of Africans.
Retinal haemorrhage and uveitis are seen occationally.

Gradually patients become exhausted and emaciated, and the abdomen extended by spleen and liver. Intercurrent infections supervene. Untreated 80-90 % die. Teated, only severely sick people die.

Diagnosis

Parasitological diagnosis may be obtained by investigation of pararasite from samples of tissue or blood. Splenic aspiration is the most sensible method. The spleen and liver can be palpated engrossed.
Bone marrow aspiration is commonly used, and so is also lymph node aspiration.
Immunological diagnosis can be made on detection of specific antibodies by ELISA method.

2. Helminthic infections

2.1. Schistosomiasis

Schistosomiasis is the second most prevalent disease and a leading cause of severe morbidity in several foci in Africa, Asia and South America. Depending on the type of schistosomiasis, the clinical manifestations of the disease involve liver/intestinal(S. Mansoni, S. Intercalatum, S Japonicim or S. Mekongi), and urinary complications(S. Haematobium) resulting from reactions to Schistosome eggs lodged in the tissues of infected people.
It is estimated that around 200 million people are infected by one or another form of Schistosoma. Because infection follows contact with waterbodies contaminated with infected water snails, the level of transmission and the intensity of infection are dependent of the contact patterns, and vary greatly among communities. Studies of lesions resulting from chronic infection indicates that there are tens of millions of people with serious chronic schistosomal illness in the world.

Mortality is low, but the disease can cause premature death , for example through the rupture of enlarged collateral blood vessels. Available information on the social and economic importance of schistosomiasis is controversial, partly because the studies they are based on were undertaken in communities of different endemicity.(I: Tropical Disease Research. Progress 1991-92. Eleventh Programme report.)
The term human schistosomiasis referres to a complex of acute and chronic parasitic infections caused by mammalian blood flukes; Shistosoma. These infections are transmitted by specific aquatic or amphibious snails in a wide variety of freshwater habitats. Of the 16 species known to infect man or animals, only five are responsible for the overwhelming proportion of human infections: S. haemabiotum, S. intercalatum, S. mansoni, S. japonicum and S. mekongi.

Aethiology

S. mansoni, S. japonicum and S. mekongi inhabit the precolonic venules whithin the distribution of the portal venous system. They produce 'intestinal' or 'rectal' schistosomiasis. S. haemabiotum inhabits the terminal venules in the wall of the bladder, the genitourinary system and the pelvic plexus whithin the distribution of the inferior vena cava and it cause 'urinary' or 'vesical' schistosomiasis. Less is known on human infection with S. intercalatum., but it produces the clinical syndrome of a lower bwel colitis, i.e. lower abdominal pain with either dysentery or diarrhoea.

Life cycle

The life cycle of all schistosome infecting man has a common pathway from a sexual generation of adult schistosomes within the vascular system of the definitive host, an asexual phase in the freshwater intermediate snail host and a return to man via cercarial invesion of the skin or mucosa on a host's exposure to cercarial infested fresh water. Adult schistosomes, living as pairs within capillary blood vessels, the slender filiform females held in the gynaecophoric canal of the males, producing eggs daily thoughout their lives. Eggs are laid intravasculary toward the peripheral branches of the capillary venules. Partly mature at oviposition, some eggs pass through the vessel wall into the lumen of the genitourinary tract or the boweland reach the external world in the excreta. Other eggs which are the immune stimulating and pathogenetic agents in the tissues, embolize from their intravascular origin to liver, lung and many other sites. When excreted viable eggs reach fesh water, in a suitable environment, the larvum whithin, becomes active. The egg hatches and the miracidium emergesand are infective to snails during 8-12 hours. Usually one or two miracidia undergo further intramolluscan develpoment, producing a sacculate mother sporocyst which in turn produces daughter sporocysts. This is followed by migration to digestive gland of the snail and subsequent cercarial developmant. After an incubation period in the snail, cercariae escape from the daughter sporocysts and emerge from the snail.
Free swimming fork-tailed cercariae, about 1mm length, penetrate human skin or mucosa when man are exposed to infected water and after passage through the tissues as scistomsomula, will develpoe into a male or female schistosome.
After migration of scistomsomula to the portal vascular system, further growth occurs in the intrahepatic vessel. Pairing of male and female schistosome takes place on sexual maturity with futher migration to the preferred sites of egg deposition.

Epidemiology

Transmission is influenced by numerous variables, the major ones being:

1. The distribution, biology and population dynamics of the intermediate snail hosts.
2. The patterns and extent of environmeltal contamination with human excreta which in turn depend on the prevalence and intensity of human infection and the socioeconomic and hygienic background.
3. Human water contact activitie, pattern and duration.
4. The host-parasite relationship in man and the role of protective immune mechanisms.

Of all the parasitic infections of man, schistosomiasis is one of the most widespresd. It is the most prevalent water-borne disease and is most common in rural areasof developing countries, with an estimated 200 million infectes globally in 76 countries. Children are particularly important as reservoirs of infection because of their undescriminate excretory habits, and their unrivalled opportunities for water contact in hot climates.

The infectionmay also occur from movements of infected people into refugee camps where endemic foci may be initiated.

Mayor factors associated with the spread and intensification of schistosomiasis are its links with water development projects, particularly man made lakes and irrigation schemes since these are often sites of population immigrations for farming and fishin, so much feature of the present tropical scene.

Prevalence and intensity of infections with S. Haemabiotum and S. Mansoni peaks between 10 and 24 years, and reduces with increasing age.

Pathogenesis

The lesions occuring during this long lived infection are caused largely by schistosome egg. Adult worms are impervious to th eimmune system of the host and by themselves cause no or little pathology.

Slightly less than the half of the eggs are laid into the lumen of the gut or urinary tract. The remainder are laid in the walls of the organ or embolize into the portal portal radicles or lung arterioles. Collateral vascular bypasses enable eggs to reach many other organs in the body.

Sluble egg antigens (SEA) induce an acute host hypersensivity response. The immunopathology of scisosomiasisis considered to be due to granuloma formation around tissue-deposited eggs and is a manifestation of delayed hypersensivity through a T-cell mediated immune response.

During an active infection, a range ot early, mature and involuting granulomas are present. In primary infections large fluorid granulomas occur with some central necrosis, consisting of the egg surrounded by cellular aggregates of eosinophils, mononuclear phagocytes, lymphocytes, neutrophils, plasma cells and fibroblasts. Fibroblasts throughout the lengthy involution process tends to replace other cell types.

After the acute phase of some 3 months, modulation of the hosts immune response results in relatively small granuloma.

The pathology of schistosomiasis results from collections of granulomas, from fibroblastic lesions obstructing vessels and fibroinflammatory swellings containing millions of eggs. Unlike early granulomas, these late obstructive and fibrous lesions respond poorly to chemotherapy.

Clinical features

With the exeption of haematuria in urinary schistosomiasis there is no one diagnostic symptom or sign; even the commonly described various symptoms are rarely pahognomonic. Many are symtom free or ignore their symptoms and are only discovered on purposive surveys or during investigations for some unrelated complaint.

Cercarial dermatitis are seldom decribed in indiggenous habitants of endemic areas, only rarely on non immune visitors, but more commonly on exposure to avian cercariae. Arising within a few minutes of exposure and receding within 24-72 hours, itching and sometimes accompanied by erythema.

Acute schistosomiasis. The incubation period is not known accurately. The clinical picture is one of an acute pyretical illness; continuing fever is a prime characteristic; the patient feels ill and may have rigors, sweating, general myalgia and headache. An urticarial skin rash may appear and lymphadenopathy or other non-specific signs may occur. Anorexia, nausea, abdominal discomfort and loose stools or diarrhoea, sometimes with mucus or blood are not rare. The liver and spleen are frecuently slightly enlarged and tender. A cough is frequent and an intense eosinophilia is almost always present. Cerebral symptoms may appear and the occurrence of of spinal chord syndromes is an indication for urgent investigative measures.

Urinary schistosomiasis (S. Haematobium) gives as the cardinal complaint recurrent painless haematuria.Other urinary tract symptoms may precede or be associated; burnig on micturation,frequency, suprapubic discomfort. Bladder involvement may lead to precipitancy, dribbling or incontinence. Chronic bladder lesions may produce persistent urinary dribbling and occasionally multiple fistulas in the perineum. In the later stages of obstructive uropathy, hydronephrosis may developand cause renal parenchymal dysfunction which, often added to urinary tract infection, leads to impaired kidney function.
Intestinal or urinary schistosomiasis (S. Intercalatum). Clinical symptoms are usually mild or absent and is not regarded as a serious public health problem. The usual clinical presentation is one of diarrhoea, often with blood in faeces and lower bowel discomfort. Yet some cases may present with haematuria.

Intestinal schistosomiasis (S. Mansoni, , S Japonicim or S. Mekongi) has a wide spectrum of clinical presentetions. Many of the patients infected by S. Mekongi are symptom free or have minimal symptoms. In a portion of heavy infections clinical features are chronic or intermittent diarrhoea with blood in the stools, abdominal discomfort or pain and colicky cramps. Severe dysentery occur. Secondary symptoms of fever, weakness, fatigue, anorexia and weight loss are frequent.
Hepatomegaly, often in the left lobe and splenomegaly are frequent. In the later stages of infection, there occurs a chronic catarrhal state of the intestine with swollen, granular mucosa and loose stools with blood and/or mucosa and an intermittent dysenteric syndrome.
The primary complications of polyposis produces a chronic dysentery with blood and proteimn loss. Intussusuception and/or rectal prolapse may occur.
Hepatosplenomegalic schistosomiasis is often symptom free, presents as upper abdominal pain or swelling. Physical signs include a firm enlargement of the liver, often with splenomegalia. The spleen may become very large, sometimes extending into the left iliac fossa. Acites may be present.In advanced cases, endocrine changes due to hypopituitarism may be found.

A not uncommon presenting signof hepatosplenic disease is haematemesis from gastro-oesophagal varices. In many cases melena follows and this acute episode may precipitate ascites and/or peripheral oedema.

S.japonicum/ S.mekongi. While the infections with the oriental schistosomes follow a broadly similar clinical cource to S.mansoni, several distinct differences emerge. In general infection with S.mekongi is milder than with S. japonicum. Hepatosplenomegaly is common but cerebral and cardiopulmonary complications are not reported. In the acute phase of cerebral schistosomiasis the presenting symptoms and signs are those of a meningoencephalitis with pyrexia, headache, vomiting, blurred vision and disturbed conciousness. In the established phase of infection, neurological presentations are recognized as as epilepsy and signs suggestive of space occupying lesion or stroke.

Diagnosis

The clinical picture of the disease varies in the different infections of scistosomiasis, and in the different stages. Differential diagnosis must be made from several other diseases, like: typhoid, brucellosis, malaria, leptospirosis, trichinosis, tropical eosinophilia, visceral larvae migrans, renal tuberculosis, hemoglobinurias cancer of the urogenital tract, peptic ulcer, biliary disease, pancreatitis, various forms of dysentery, ulcerativecolitis and various causative diseases for hepatosplenomegaly.

A definitive diagnosis is made by the direct visual demonstration of the eggs of the parasite in body excretions or secretions or alternatively from biopsies from liver or surgically removed tissue.

A recent addition to direct diagnostic tecniques is the detection of scistosome antigens in serum or urine. They are detected by enzyme immunoessay and have high specificity and sensitivity.

Treatment

The drugs of choice are chemotherapeutics. The primary objective of chemotherapy is the cure of the individual patient by eradication of the infection from which he suffers. Cure leads to cessation of egg deposition, the pathogenic agent in the tissues, and this prevents additional organ damage; existing lesions will, in the vast majority of cases, regress. In lerge-scale community based treatment, where compromises must be made on dosage, the main aim is to reduce the community agg load. Individual cure may or may not occur.

Antischistosomal drugs can be divided into two groups:

1. The one drug effective against all species of all species of schistosome infecting man, praziquantel.
2. The monospecific drugs effective against only one species of schistosome, i.e. oxamniquine, effective only against S. mansoni.

Control

Both prevention and control depend on an area specific, species-specific and epidemiologically-specific mixture of intervention methods. An accurative measure of these variables, quantitative when possible, is necessary before entering into preventon and control programmes. Prevention is directed toward health education and the provision of adequate sanitation and water supplemented by environmental improvements. Control includes the

administration of chemotherapeutic drugs and molluscicides. Integration of these interventions is essential for success.

A lot of research aimed at the production of vaccines against schistosomiasis has been done. Advances in molecular biology has led to findings of a vast amount of antigens, and progress in human vaccination studies has lagged behind those in animal models. Anyway, one view emerging is that a vaccine, even with long term protective effect, would probably be insufficient as a sole control mechanism, but would need to be given in conjunction with other control mechanisms.

2.2. Filariasis

The filariases result from infection with vector-borne tissue dwelling nematodes called filariae. Depending on the species, adult filariae may live in the lymphatics, skin, blood vessels, connective tissue or serous membranes. The female produces larvae (milcrofilariae) which live in the blood stream or skin. The transmission of human filariae is confined to warm climates. See fig. 2 for general life cycle for filariae.

Lymphatic filariasis

Lymphatic filariasis results from infection with filarial worms. Three species, Wucheria bancrofti, Brugia malayi and B. timori cause the infection in man.

Life cycle and transmission

The adult worms reside in the lymphatics of the human host. Sheated microfilariae are produced from the ova in the females uterus and appear in blood after a minimum of 8 months in W. bancrofti and 3 months in B. malayi. Microfilariae are ingested by the vector female mosquito during a blood meal, exsheat in the mosquito stomache, and penetrate the stomach wall. They then migrate to the thorax muscles where they develop into the infective third stage larvae. Mature larvae migrate into the mouth parts of the mosquito and enter the skin of the human host, probably through the puncture site when the vetor takes its meal. The larvae migrates to the lymphatics and develop to adult worms where they might live and produce microfilariae for more than 20 years.

Clinical features

Lymphatic filariasis manifest in both acute and chronic forms and may be with or without fever. The onset is usually sudden.

Bancroftian filariasis

Lynphangitis and adenitis

Episodes of acute lymphangitis and adenolymphangitis, accompanied by fever and chills, become recurrent, occuring several times within a year. In most endemic areas groins and male genitalia are frequently affected. Glands are often matted together and have a soft rubbery appearance.

Funiculitis and hydrocele

Recurring attacks of funiculitis or epididymoorchitis may lead to hydrocoele formation.

Other lesions of the spermatic cord include lymphocele, lymphangiectasis and lymphadenovarix.

Abcess formation
Sterile abcesses may form deep to the rectus fascia in the lower abdomen. Infected lymph nodes may suppurate. Painful lumps may occur due to granulomatous reactions around worms.

Lymphoedema and elephantiasis
Lymphoedema progressing to elephantiasis most commonly affect the lower limbs. The upper limbs, scrotum, penis, vulva and breasts may also be affected. Early attacks are characterized by adenitis and pitting oedema. Following initial attacks the limb returns to normal. Over several years the oedema becomes non-pitting with thickening and loss of skin elasticity. Further progression leads to evident elephantiasis with dermatosclerosis and papillomatous lesions. The development of elephantiasis may be arrested at any stage. It commences on one leg but often becomes bilateral.

Chyluria
Chyluria, the presens of chyle in the urine, follows the rupture of lymphatics into the urinary tract. The obstruction of lymph flow is due to blockeage of the retroperitoneal lymph nodes below the cisterna chyla. Retenton of urine due to chylous or blood clots may be the first symptom. Apart fronm chyluria, chylous reflux may produce chylocoele, lymphadenovarix of the spermatic cord, scrotal dermal chylorrhoea, chylous ascites and chylous diarrhoea.

Monoarticular arthritis
The knee joint is most commonly affected, followed by the ankle.

Occult filariasis
Referres to the endemic zones where the classic lymphatic pathology is not present and where milcrofilariae are not found in the blood, but in which any larval stages may be seen in the tissues.

Tropical pulmonary eosinophilia
TPE is characterized by clinical and immunological hyperresponsiveness. Patients presents with paroxysmal cough and wheezing that is worse at night, low grade fever, scanty sputum production but occationally haemoptysis, adenopathy and extreme blood eosinophilia. There is radiological evidence of diffuse miliary lesions.

Brugian filariasis
The main difference in the clinical manifestations between brugian and bancroftian filariasis is the rarity of hydroceles and other genital lesions for B. malayi. In brugian filariasis the elefantiasis is confined to below the knee, whereas in infection with bancroftian filariasis, the thigh as well is often affected.

Diagnosis

A sudden onset of fever, acute groin pain with swollen tender lymph glands and oedematous swelling of the legs distinguishes an acute attack of filiaial elephantiasis from the many other causes of fever and adenitis that occur in tropical countries.

Parasitological diagnosis is usually based on recovery of microfilariae from the patients blood. Amicrofilariae does not exclude filarial disease. The sample of blood should be taken at a time when the peak concentration of microfilariae is expected to be, and a counting chamber tecnique is often used. In areas where more species of filariasis is endemic, stainig tecniques are recommended.
The diethylcarbamazine provocative test includes the provocing of nocturnal periodic microfilariae of W bancrofti and B malayi, to enter the periferal blood in daytime. This occurs by administrating DEC, and taking the blood sample after on. Because of the risk of a severe Mazzotti reaction the test is contraindicated in onchocercasis endemic regions.
Immunological diagnosis can be made based on the fact that filiarial worms create a range of immmune reactions in the host. Several immunodiagnostic tecniques, including the indirect fluorescent antibody test(IFAT) and ELISA, have been developed for lymphatic filariasis. Immunodiagnosing may be useful in diagnosing visitors to endemic areas who develop symptoms of lymphatic filariasis but have no microfilaremia.

Treatment

The treatment of filariasis mainly consists of of chemotherapy and /or symptomatic treatmaent. A new surgical tecnique utilizing lymphovenous drainage procedures shows promise for the treatment of elephantiasis.
In chemotherapy the drug most commonly used is diethylcarbamazine citrate. It is a microfilaricidical agent also capable of killing adult W. bancrofti, Brugia malayi and B. timori. DEC is administered orally and the daily recommended dosage is 6 mg/kg body weight daily, in three divided doses after food, for 12 days. Drug reactions due to dying parasites may commence a few hours after start of treatment. Side effects are reduced when treatment is spaced.
DEC treatment may prevent development of chronic obstructive disease. Treatment can be repeated every six months or as long as the patient has symptoms or remains microfilaremic.
Ivermectin for the treatment of lymphatic filariasis is currently being evaluated. Preliminary results have shown that a single dose of ivermectin effectively removes microfilariae of W. bancrofti, but there is no evidence of a macrofilaricidal effect and microfilariae reappear in blood faster than after a treatment with DEC. Should further investigation confirm low toxicity, in particular low neurtoxicity, ivermaectin may soon be commonly used for the treatment of lymphatic filariasis.

In conjunction with DEC therapy symptomatic treatment; analgesics, antipyretics and bed rest are useful for treating filarial fever and lymphadenitis. Elevation of the affected limb, special massage and the application of an elastic bandage or stocking and prevention of superficial ifections assist in the management of lymphadenomatous limb.

Surgical treatment can be indicated in some cases. Chronic hydrocoeles require excision and eversion of the sac. In scrotal elephantiasis, surgical removement of the grossly elephantoid skin and scrotal tissue with preservation of penis and testicles have proved very worthwhile. Surgical treatment of limb elephantiasis have generally proved to be unsuccessful. In chyluria, when surgery is indicated this may include disconnection of the renal hilar lymphatics by nephropexy.

Control

The diversity of the disease in vector, parasite and disease parameters as well as community differences makes the need for a control programme to be adjusted to the targeted population. The main methods used in control are chemotherapy and mosquito control. To achieve success in a controll programmeit is necessary for the community to be actively involved. Community leaders should be given adequately health education, insuing their co-operation in a preparatoty phase.

Therapy with DEC to a community may consist of selective or mass treatment. In selective treatment , DEC is given only to those testing positive, and is necessarily preceeded by a large scale screening. In mass treatment costs are reduced, and treatment is given to the whole tolerant population. The dosage in mass treatment may be given in the normal intensive regimens, in lowered dose, in spaced doses or even added to salt.

Mosquito control rapidly reduces the transmission in a community, but slowly affects the prevalence, and should therefore always be preceeded by or combined with chemotherapy. The main antivector measures that have been used in the control of filariasis are environmental control of breeding sites, larviciding and the use of insecticides against mosquitoes.

2.3. Onchocerciasis

Onchocerciasis (river blindness) results from infection with Onchocerca volvolus. Man is the natural host and the vectors are species of blackflies.
The life cycle is common with that of other filariae. Transmission of infective larvae occur when the fly takes its blood meal. Larvae penetrate the skin, and develop over several months to adult worms. The gravid female releases microfilariae whidh are found in the skin after a prepatent period of 7-34 months after the introduction of infective larvae. Adult worms live in subcutaneous nodules or free in the skin. The adults are slender white worms, males mesuring 2.5 cm x 0.2 mm, and the female 35-70 cm x 0.4 mm. Microfilariae are mainly found in the upper dermis and in nodules but may also appear in any blood fluid, particularly after treatment with DEC. They are common in the eye, the entering route being directly from skin, through the blood stream or the cerebrospinal fluid along the optic cord.

Clinical features

The main clinical manifestations are dermatitis, eye lesions and nodule formation.

Dermal changes occur when the microfilariae are undergoing destruction and vary from papules to extensive pigmentary and chronic athrophic changes of presbyderma.
Sowda is arabic for black, and describes the dermal darkening, swelling and coverage of scaly papules. It is characterized by intense scratching, and usually involves only one limb. It is common in Yemen, Sudan and West Africa, and involves a strong immune response.

Nodules are subcutaneous granulomas resulting from tissue reaction around adult worms. They are painless, round to oval and measure from a few mm to several cm.
Eye lesions include many changes both in the anterior and the posterior segment of the eye. Punctate keratitis is an acute inflammatory response around microfilariae, and are reversible

lesions. In sclerosing keratitis, vascular infiltrates pass inwards, resulting in exessive scarring of the cornea which causes blindness. Posterior segmental lesions include optic nerve atrophy, choroidorenitis, both which may lead to blindness.

Diagnosis

Clinically differencial diagnosis must be made from many other causes of pruritic dermatitis. The nodules of onchocercomas are cahracterized by painlessness, firmness and extreme mobility. Anyway the picture may vary, and nodules must be distinguished from i.e. lyphadenomas, lipomas and neurofibromas. Deep unpalpable nodules can be detected by ultrasonography.
The oral administration of DEC, after which an intense pruritis following death of microfilariae, diagnoses an infection (Mazotti test).
The recommended first test is parasitological diagnosis froma skin snip. Two or four snips are taken from the optimate site of the body depending on the geographical area. They are immersed in isotonicsaline, and microfilariae that have escaped after 15 minutes are microscopically counted.
Immunodiagnostic tests can also be made, based on IFAT or ELISA techniques, but are of little practical use due to low sensivity and specificity. The test cannot distinguish between present and past infections, and cross-reactions are common. The tests can however be valuable in detectind infection in people from non-endemic areas who have visited an endemic area.

Treatment

Because of the severity to some of the adverse reactions to DEC, macrofilaicide now now has replaced DEC as the drug of choice in onchocerciasis. Ivermectin in a single dose of 150 µg/kg body weight causes rapid elimination of microfilariae from the skin. The disappearance from the eye is much slower, and retreatment may be necessary. Follow up skin snips should be examined 6-12 months after the initial treatment.
The single dose regimen has no known long lasting effects on mature worms. Suramine, although largely used as a macrofilaicide, has had fatal outcomes because of drug toxicity, and its use is not recommended. A potential macrofilaicidal activity of higher doses of ivermectin needs further investigation. A new macrofilaicidal drug, Amocarzine, is presently undergoing clinical trials.

Nodulectomy have only limited use because some worms reside outside the nodules, and some nodules are not palpable. Head nodules should be exiced because their precence increases the risk of eye lesions.

Control

Antivector control, particularly larviciding of breeding sites, has been the main control measure used in onchocerciasis. The emergence of recistance to larvicides and the reinvasion of the ares treated, are problems that can be supervined by treating larger areas and applying alternating larvicides. Another big problem which needs to be taken to account is the echological impact that is made by wide distribution of larvicides.
To date all the macrofilarial drugs have been too toxic for mass druf treatment. Ivermectine shows promise of being of value both in mass chemotherapeutic regimens and as a clinical

profylactic. It reduces microfilarial burden and thus transmission in the community. Currently a dosage of 150 µg/kg body weight every six months or once a year is being encouraged.

3. Mycobacterial diseases
3.1. Leprosy

WHO' estimate of the prevalence of leprosy in 1994 was 10-12 million cases, but case diagnosis and definition are not always clear in many regions of the world. Since 1985 there has been a steady decline in the number of registered cases for treatment of 69%. Despite of a lot of insecurity of such data, it seems like the situation has improved the recent years, partly because of the introduction of multidrug treatment.

Aethiology

The aethiologal agent in leprosy is Mtchobacterium Leprae. In size and shape it closely resembles M. tubelculosis. It occurs in lesions of lepromatous leprosy, intracellular and extracellular masses, globi, which consists of clumps of bacilli in capsular material.

Many of the manifestations of leprosy, inclusing reactions of the erythema nodosum type- which follow initial treatment, mustn be due in part to the antigens from dead organisms rather than living bacilli. We therefore need drug which will help the body to dispose of dead leprosy bacilli.

The only known reservoir of infection of leprosy is the human being, and the largest load of bacilli carried by lepromatous cases. The portals of exit are the skin and the nasal mucosa, and it has been showed that the organisms are able to survive up to 36 hours outside the human host. The portal of entry into the human body is not completely known, however the skin and the upper respiratory tract are believed to be routes.

Despite of the fact that there is no immunological test to identify subclinical infection with sufficient sensivity and specificity, evidence from tests for cell- mediated immuity, like ELISA, indicates that subclinical infection occur.

The minimum incubation period for leprosy is estimated to be a few weeks, and the maximum as long as 30 years.

The exact mechanism of transmission of leprosy is not known, but the belief is that disease is transmitted by contact between persons with leprosy and healthy persons. The degree of "contact" necessary is not known, but skin to skin, and even the respiratory route are possible routes.

There is evidence that not all people who are infected with M. leprae, develop leprosy. Factors determinating clinical expression after infection are genetic factors, route of infection, reinfection, prior infection with other mycobacteria and human immunodeficiency virus.

Classification of leprosy

Classification may be done on the basis of the pathological reaction of the tissues and the number of bacilli contained in them. If the bacilli obtain a foothold in the host, the defence

mechanisms may create an early reaction calles "indeterminate", because the lesion is too immature to be classified. This may persist for months, years, or go to complete healing, or to one of the clearly cut forms of leprosy. In the tuberculid form of leprosy the hosts immune response is high, and in the lepromatous form, the resistance is low. Between these two poles, there is a borderline form which may show some characteristics of tuberculoid and some of lepromatous leprosy. Regularly five classifications are used, though, based also on number of bacilli present: TT: tuberculoid(none seen in granuloma): BT: borderline tuberculoid(0-3 seen in granuloma); BB: borderline(3-5+ seen in granuloma); BL: borderline lepromatous(5 or 6+ seen in granuloma); LL: lepromatous(5 or 6+ seen in granuloma).

Patholology

In very early infection the bacilli proliferate in the fixed cells of the dermis and thereafter monocytes migrates towards the bacilli, engulfing and disintegrating them. Leprosy bacilli may also enter nerves, causing focal damage related to the blood vessels near the site of entry into the nerves. They spread along the fine nerves of cutaneous nerve twigs and are carried centripetally, multiplying and bursting into the endoneural spaces where they are phagocytosed by histiocytes. Clinically this stage is marked on the skin by wheal-like papules or pink macules. This is the indeterminate stage.

In lepromin negative persons (whose resistanse is poor) the histiocytes gradually change into lepra cells which in more severe cases become foamy; the ingested bacilli are not destroyed. In lepromin positive persons (whose recistance is good) the histiocytes change into epitheloid cells after ingesting the bacilli which they destroy. The number of lymphocytes in tuberculoid and borderline lesions in the skin are significant indications of the degree of resistance to the infection.

The change from indeterminate to tuberculoid leprosy involves the appearance of groups of epitheloid cells inside fine nerve twigs and the formation of sharply circumscribed foci of these cells in the dermis, often surrounded by a zone of lymphocytes, which are numerous. The epitheloid cells often coalesce to form giant cells. The nerve bundles in the skin are swollen by proliferation of Schwann cells, which develops into epitheloid cells. The nerves become difficult to recognize, they occationally undergo caseation.

Borderline leprosy is characterized by large hypopigmented patches, usually with loss of sensations of touch and temperature. There is an inflammatory reaction in the superficial layers of the dermis; it consists of small roun cells, histiocytes and lumps of epitheloid cells but no giant cells. Nerves may resemble those in lepromatous or tuberculoid disease.

In lepromatous leprosy large areas of the dermis are converted into continous sheets of chronic inflammatory tissue containing enormous numbers of basilli in slabs of lepra cells, derived from histiocytes, interspersed with groups of mononuclear and plasma cells. Lymphocytes are scanty. The subepidermal zone is clear of infiltrate. The disease is now systemic, the bacilli being transported by blood to lymph nodes, liver, spleen and bone marrow, where miliary lepromas and even large lepromas may be found. The mucous membranes of the upper respiratory tract is heavily infiltrated in advanced lepromatous leprosy. It is oedematous, thickened and ulcerated and the nasal cartilages may be perforated..

Clinical features

The majority of those that become infected, will overcome whithout symptoms or signs of the disease.
An early lesion may occur as a vague ill-defined hypopigmented patch with some anaesthesia. Spontaneous healing may take place in a high proportion of early lesions of childhood, however a definite diagnosis is an indication for treatment. The chief characteristics is the absence of toxicity, a huge amount of bacilli may be present in the body with few signs. The local inflammatory reaction may be localized in a small skin area, or its main nerve supply. Other cases show involvement of almost the whole body, but the patient is not neccesarily ill. At any stage during invasion sudden exanthemathous reactions may appear, accompanied by fever and general symptoms.

The chronic onset is so insidious that the disease has advanced to a considerable extent before any abnormality is evident. There may be paresthesies of an area, and discoloration of the skin.

In acute onset, which is much less common, there are occationally multiple lesions with less diffused margins, which tend to spread rapidly and which contain numerous bacilli.The first noticable sign may be a rash.

lepromatus leprosy

In lepromatus leprosy is seen in persons with a negligible resistance. The skin lesions are multiple, small and symmetrically distributed; they take form of macules, plaques, papules and nodules. Nodules and infiltrations may undergo superficial necrosis and ulceration and large ulcers may form on the lower legs, thinning of the eyebrows and eyelashes is common and may progress to complete loss. In one specific type of skin involvement, namely the pure diffuse type, the skin of the whole body becomes diffusely infiltrated, rendering it stiff and smooth.
Nerve involvement includes nerve thickening and associated sensory or motor dysfunction can usually be demonstrated as the disease progresses. A sensory loss is iften more pronounced muscle wasting and the skin suffers much damage from repeated trauma, owing to insensivity to pain. Nerve thickening, is found in those peripheral nerves which are superficial in some parts of its course, the thickening is found in the superficial portion. Loss of posision sense, vibration sense and tendon reflexes may occur. Involvment of autonomal nerves manifest itself in the early stages by slight oedema of hand and feet.

Nails are affected with digits, and appear dry, lustreless, narrowed and longitudinally ridged.

Mucous membranes involvement may involve nasal discharge, possibly bloodstained, and airway blockage due to hyperemia, swelling and nodules in the mucosa. The nasal cartilage may undergo destruction, and the nose obtain a "saddle-nose" deformity. Nodules may also occur on the lips, tongue, palate and larynx, leading to ulceration. Laryngeal involvement gives rise to hoarse cough, husky vioce and stridor.

Visual impairment and blindness occur frequently in leprosy patients. The complications leading to blindness are corneal changes, iris involvement and cataract. Leprosy is the third leading cause of blindness worldwide.

Bone changes due to lepromatous leprosy includes the skull and limbs. The causative factors are deposition of bacilli, repeated trauma resulting from analgesia, disuse owing to paralysis and contractures, secondary infection from thropic ulceration and general osteoporosis of hormonal origin.

Lymph nodes are generally enlarged and of soft rubbery consistance, the reticuloendothelial elements of the abdominal viscera are invades by bacilli, especially in the spleen and liver, and the red marrow. Lymphoedema of the lower limbs may give rise to elephantiasis in neglected cases.

Testicular athrophy may occur, resulting in sterility and gynaecomastia.

Glomerulonephritis, interstitial nephritis and pyelonephritis may occur. Renal amyloidosis is a prevalent complication in some geographical areas.

Tuberculoid leprosy

This type of leprosy may be purely neural or combined neural and dermal. The infection is never widespread but is localized to one area or to a few areas asymmetrically. Affected nerves are thickened, sometimes irregularly, and there are associated sensory or motor changes depending on the type of nerve involved.

Skin lesions take the form of macules or plaques. It is erythematous on fair skinsand hypopigmanted on dark ones, has a dry rough surface, well defined edges, and it is anaesthetic.Thickened nerves may be palpatd in the vicinity of the lesions, but tissues other than skin and nerves are not involved directly. The eye may suffer indirectly from corneal ulceration when there is damage either to facial or trigeminal nerve. Bone changes may occur as a result of disuse, loss of sensation and due to trophic ulceration, but are never symmetrical. Trophic ulcers on feet are common.

Borderline leprosy

The infection is neither as strictly localized as in tuberculoid leprosy nor as widespread as in lepromatous leprosy, but is somewhere between the two. Skin lesions are macular, infiltred or both and have a predilection for the back. Careful investigation will reveal imairment of sensation in some of the lesions. Infiltrated lesions have distinct festures in which the characteristics of the two polar types are merged. They are moderate in number and are invariably anaesthetic. Nerve involvement can always be demonstrated in borderline leprosy, and neurological symptoms such as paraesthesiae and hyperalgesia often precede the onset of skin manifestations.

Diagnosis

The diagnosis of leprosy rests upon three cardinal signs and an awareness of the disease:

1. Palpable thickened nerves.
2. Demonstration of anaesthesia.
3. Demonstration of M.leprae in skin, nasal mucosa or biopsy.

Bacteriological examination is carried out from a series of smears from the lesions, which are fixed and stained with Ziehl-Nielsen technique. Biopsy of the skin is essential for correct classification as it enables the histological changes in the skin to be studied.

Treatment

Multidrug therapy is now the standard treatment of leprosy. Most cases can be treated on an out-patient basis. Lapromatous patients need not be kept isolated as they are not discharging any viable bacilli with rifampicin treatment.
Several drugs are available for treatment and two or more are given concurrently as standard treatment. Examples of the mostly used drugs:

1. Dapsone is slowly bactericidal. The dose is 6-10 mg/kg weekly. Rifampicin is a strongly bactericidal drug. It is effective given monthly in dose of 600 mg every 4 weeks on an empty stomach.
2. Clofazamine has a remarcable effect on lepromatous leprosy. It has been found effective in doses of 50 mg daily supplemented by a mothly dose of 300 mg. It should be given for a short as possible period, and only under close supervision because of its toxical side effects.
3. Thioamides are given in doses of 250-500 mg daily. They kill M. leprae faster than Dapsone but more slowly than Rifampicin. It can be hepatotoxic, and its use is therefore recommended only in exceptional cases.

Treatment of complications makes a important part of the handling of lepromatous patients. The main therapeuthic weapons are steroids, clofazimine and thalidomide.

The prognosis of leprosy is usually good. In its milder forms it is a self-healing and also curable. Of those who become infected, only a small proportion develop overt signs. With modern treatment, including drug treatment, surgery and physiotherapy, much deformity can be avoided or relieved.

Relapse may occur. Clinically, a relapse shows itself by the appearance of new skin lesions, erythemathous papulonodules, and these are accompanied by the prescence of morphologically normal leprosy bacilli in skin smears and sections from the lesions in nasal mucus.

Control

The strategy of leprosy control involves essentially secondary prevention through early detection of cases and treatment of patients with effective drugs so that the reservoirs of infection can be eliminated and transmission of infection interrupted. There is no primary preventive strategy for leprosy, although BCG itself is known to have some protective effect. The efforts in control of leprosy must be put in: right treatment with multidrug therapy, case finding, patient and community education, distribution of the BCG-vaccine and research in developing new and more effective vaccines.

4.Viral infections

4.1 Arbovirus infections

These viral infections are usually spread by the bites of blood sucking arthropods, but some can also be transmitted by other means (milk, excreta or aerosols). They multiply to produce viremia in the vertebrates. The names by which these viruses are known are of mixed origin. Some are dialect names for the illnesses they cause (chikungunya, o'nyong-nyong), some are place names (Weat Nile, Bwamba) and some derives from clinical characteristics (Western equine encephalitis, yellow fever).

Aethiology

Most arboviruses are spherical RNA viruses. Many circulate in a natural invironment and do not infect man. The arboviruses of clinical importance belong to the Togaviridae, the alphaviruses, flaviviruses, the Bunyaviridae, nairoviruses, phleboviruses and other subgroups.

Epidemiology

The hosts are maintenance, link, incidental and amplifier hosts. Maintenance hosts lives in symbiosis with the viruses and they do not cause disease. They are primarily birds, other viruses, rodents and insectiovores. Incidental hosts become infected but transmission from them does not occur with sufficient regularity for stable maintenance. Man is usually an incidental host. Link hosts bridge a gap between maintenance and link hosts. Amplifier hosts increase the weight of infection to which man is exposed, for instance pigs, which act between man and bird in JE.

Invertebrate hosts include mosquitoes, sandflies and ticks and also Culicoides. After these vectors have imbibed virus from a vertebrate in a state of viremia, the virus undergoes an incubation period whithin the arthropod, known as the extrinsic incubation period.

Transmission

Transmission by arthropods involves several processes:

- Ingestion by the arthropods of virus in the blood or tissue fluids of the vertebrate hosts.
- Penetration of the viruses into the tissue of the arthropods.
- Multiplication of the viruses in the arthropod cells.

Stage 2 and part of stage 3 represent the extrinsic incubation period of the disease.
Some arboviruses can be transmitted in other ways, f.ex. by drinking milk of infected goats, contact with excreta of infective rodents and by aerosol.

Clinic features in general

After the virus enter the body it reaches the lymphathic system where it multiplies and from which it is released into the blood and thence to the organs affected.
Most arbovirus infections are inappearent or mild, producing fever and occationally a rash.

If clinical manifestations appear after infection they do so after en intrinsic incubation period lasting from a few days to a week or more. Some arboviruses damage the endothelial lining of the capillaries, increasing permeability, which allows the virus to pass the blood –brain barrier, causing meningoencephalitis. Others damage the parencymatous organs by direct damage to the cells in which they are situated, while with others damage is caused by the immune system of the host from the formation of antigen-antibody complexes and disordered complement formation wich damage the renal tubules and alter the coagulation and fibrinolytic systems of the body, causing haemorrhage.

The onset of clinical manifestations is usually abrupt, generally occuring after the onset of viremia. Fever is usual and is sometimes the only sign. In many cases recovery whithout any sequelae follows the viraemic phase. In other cases there can be remission, short or long. If long, the disease is biphasic. After this fever returns, with signs indicating localization of the virus in certain organs. If the period of viraemia has been without symptoms and the virus locates in the CNS, encephaliltis appear to be primary. All degrees of involvement may be observed in a single epidemic, but some arboviruses cause generally mild disease, others tend to severity.

Systemic febrile illnesses

This is the largest group and the mild forms of all arbovirus dieases are of this kind. The course may be biphasic and the infection may go on to the more serious haemorraghic or encephalitic forms.

In addition to fever, the following symptoms may occur:

- Anorexia, with nausea and vomiting, or respiratory symptoms may predominate(Tahyna).
- A rash with congestion of face and neck, inflammation of the palate, vesicles on the feet(Sindbis), or even petecchiae.
- Conjunctivitis, with photophobia and orbital pain or even cental renitis and choriorenitis(Rift Valley).
- Epidemic polyarthritis(Ross Riverin Australia).
- Arthralgia (o'nyong-nyong, chikungunya) or myalgia (especially in dengue) which can be severe ('break-bone disease').
- Inflammation and enlargement of the lymphatic glands ~(o'nyong-nyong, chicungunya, West Nile).
- Leucopenia, which is common, and thrombocytopenia (Colorado).

Diagnosis

Diagnosis can be based on serology or virology. Blood should be taken as soon as possible after the onset of the disease for isolation of the virus and for serological tests, and if there are meningeal signs the serebrospinal fluid may be used for isolation. Cells may be sedimented and examined by the fluorescent antibody technique.

Chikingunya (chik)

This virus is widespread in Africa and is also present in Saudi-Arabia, Borneo, Malaysia and the Philippines, Thilan, Cambodia, Burma, Sri Lanka and India.

It is an acute self-limiting febrile disease with an incubation period of 2-4 days, and has no haemorrhage or CNS-complications. There are no chronic sequela but a crippling arthralgia may occur intermittently for up to 4 months.

O'nyong-nyong

ONN is present in Uganda, Kenya, Tanzania and Nothern Sudan. It is an acute self-limiting disease which is a purely human infection. The incubation period is 8 days. Onset is abrupt with rigor and epistaxis; the fever settles rapidly and recovery takes place whithin a week but joint pains may persist.

Large epidemics occur when there are enough susceptible subjects, in which 70 % of the population may be affected.

Ross River fever

Ross River fever occurs annually in epidemics in northern and eastern Australia, and epidemically Fiji, American Samoa, Cook Island and New Caledonia.

It is an acute self-limiting infection with arthritis lasting a week, mainly a human infection. The incubation period is 3-9 days Onset is abrupt with fever, myalgia and arthralgia. Knees, ancles and wrists are painful and swollen.

Sindbis

Sindbis virus causes a self-limiting disease in South Africa, with fever, diffuse papular rash and, in severer cases, vesicles on the feet.

Oropouche virus (ORO)

Oropouche virus is a major cause of disease in the Amazon region of Brazil. Short lived infection with flu-like symptoms and photophobia. There are aseptic meningitis in some cases, but no fatalities.

Sandfly fever (phlebotomus fever, pappataci fever)

Sandfly fever is widespread throughout the Mediterranean and Middle East, Malta, Aegean Islands, Egypt and Iran, North Africa, Red Sea and Arabian Gulf; in Asia in the Caucasus and Himalayas.
The sandfly responsible for transmission is Phlebotomus pappataci.
The disease is acute and self- limiting lasting 2-4 days, with complete recovery and immunity to further attacs, and no mortality. The incubation period is 3-6 days. The onset is abrupt with high fever, congested face and neck stiffness and stiffness of limbs. Ocular symptoms with intense supraorbital pain and injected conjunctivae are marked.

Viral haemorrhagic fevers

Viral haemorrhagic fevers are caused by a number of agents which may be of arboviruses, arenaviruses or filaviruses. The pathogenesis may be caused by one or by a combination of a

number of factors. These factors are vascular damage, disorders of coagulation, immunopathology or direct damage of organs(e.g. hepatic necrosis in YF).
Most of the viruses causes mild infections but all of them can cause severe and fatal disease with haemorrhagic manifestations, and some has caused devastating epidemics in South America and the Far East. Incubation period less than 3 weeks.
Symptoms are pharyngitis, conjunctivitis, vomiting, diarrhoea, abdominal pain and haemorrhagical manifestations and shock.

Diagnosis

Specimens to be collected immediately are:

- A throat swab.
- A clean mid stream urine specimen.
- Venous blood for antibody studies and virus isolation. Virus is identified from blood specimens. Extreme care must be taken because the blood is highly infective.

Verification of the diagnosis must exclude other non VHF causes. A blood smear for malaria parasites is absolutely necessary.

Treatment

The most important part of treatment is that care must be taken of fluid and electrolyte balance. Treatment in aspect to shock is oxygene, restorage of fluid and electrolytes with infusioon of 15 % dextrose in half strength normal saline, at the rate of 100 ml/body weight daily is recommended. Plasma can be given to combat chock or in hypovolemia with packed cell volume in spite of replacement of fluids; 10-20 ml/kg per hour. Blood transfusions are not recommended in the hypotensive phase but can be given after recovery if the patient shows signs of severe haemorrhage.
In the hypotensive phase, hydrocortisone 50-100 mg daiøy, or aldosterone 0.1 mg/kg daily in conjunction with the infusion fluid may reduce mortality.

Curative treatment has been obtained with transfusion of immune plasma obtained from a patient who has recovered. It must be administered early in the illness, preferably in the first week. Ribavirin has proved beneficial if administered in the first week in Lassa fever and Rift Valley fever.

Immunization with vaccination is available only for YF, Rift Valley fever and Omsk haemorrhage fever.

Dengue

Dengue has a worldwide tropical and subtropical distribution between 30°north and 40°south.
After inoculation the virus reaches the regional lymph glands and disseminates to the reticuloendothelial system in which it multiplies and seeds the blood.
The onset is sudden with high fever which is biphasic. Severe muscle pains("brake bone fever"), headace and prostration are characteristic.An erythemathous rash followed by a morbilliform rash on the extremities accompanied by general lymphadenopathy appears after a few days.

Rift valley fever (RVF)

The pathology is not clear but is believed to be due to direct effect on cells of virus with increased virulence, or a sensitization similar to that of dengue, or a synergism between the virus and endemic Schistosomiasis.
RVF is a short acute febrile illness with complete recovery in the majority of the cases, but in less than 5% complications, haemorrhagic and encephalitic, can occur with fatal outcomes. See fig. 3 for geographical distribution of Rift Valley fever.

Clinical features

The incubation period is 3-7 days. The onset is abrupt with fever, headace, joint and muscle pain and photophobia. In the few, severe cases, there is onset of haemorrhagic manifestations and liver failure. Other complications are meningoencephalitis and ocular complications eventually with blindness.

Dengue haemorrhagic fever (DHF)

Geographical distribution is South-East Asia, Cuba, Caribbean and Pacific.The athiollogy is most likely immunologically severe response involving the complement system to a secondary infection with the agent. The pathological changes includes increased capillary permeability leading to rapid shifts of extracellular fluid, haemoconcentration, hypovolemia, reduced tissue perfusion and oxygenation, acidosis with widespread cellular damage leading to shock. There are pathological changes due to cell damage in liver, kidneys, reticuloendothelial system and bone marrow.

Clinical features

On the second to fifth day of classical dengue fever the patient deteriorates rapidly, with development of shock syndrome. Restlessness, sweating and hypotension appear coincident with a positive torniquet test, petecchiae, ecchymosis and spontaneous haemorrhage. There can be tender enlargement of the liver, hypoproteinemia, hyponatremia, mild elevation of the liver enzymes and some nitrogen retention.

Yellow fever (YF)

YF is found in the tropical forest areas of Africa and South America.
The virus affects highly specialized epithelial or myocardial cells only . The changes are toxic, beginning with cloudy swelling and going on to degenerative fatty changes and coagulative necrosis. There is no inflammatory response. The organs affected are liver, kidneym heart, brain, digestive system and lung. Patients who recover show complete replacement of lost tissue by direct regeneration and hypertrophy of surviving cells.

Clinical features

In the majority of cases the infection is short and sharp with full recovery. Inappearant infections are common especially in endemic areas. In a minority infection is severe with biphasic fever, jaundice and severe haemorhages leading to the black vomit with a high mortality. Regarding to the organ affected, the patient has several symptoms related to affection of these.

Omsk Haemorrhagic fever (OHF)

OHF occurs in the Omsk area of Siberia.
The pathology of fatal cases is that of VHF with haemorrhage in tissues and necrotic areas in the liver. The infection gives usually an acute self-limiting disease with fever, papulovesical eruption on the soft palate followed by haemorrhagic features, epistaxis, melaena and uterine haemorrhage. The fever lasts five days, sometimes the fever is biphasic, recurring for 2-3 days. Fatality is 1-3 %.

4.2 Arenaviruses

Arenaviruses are a group of 14 of which only 5 are human pathogens; lymphocytic choriomeningitis (LCM), Lassa, Junin, Machupo and Guanarito. The four last are transmitted to man by contact with rodent excreta.

Lassa fever

Lassa fever is confined to West Africa and Central Africa. Recent estimates suggest that there are 100 000 cases annually with 5000 fatalities.
The mecanism of pathological changes is the same as for other VHF`s, with formation of antigen-antibody complexes as well as a direct effect of the virus on capillaries causing an increase in permeability. Pathological changes are found in liver, spleen, lungs, kidneys, heart and CNS.

Clinical changes

The incubation period is 3-16 days, and the natural course is complete recovery without sequelae. In a minority of cases there is a severe deterioration in condition after the first week, with death from haemorrhagic shock. The onset is insidious with fever, malaise and pain in limb muscles. On the seventh day there can be severe deterioration with a severe fall in blood pressure, vomiting, sore throat, continuou troublesome cough with chest pain, headache and diarrhoea. Clinical signs are inflamed pharynx with white patches on the tonsils, oedema of the eyelids and face, occationally maculopapular rash, low blood pressure and bradycardia. There is a leucopenia with albuminuria and casts in the urine. Convalescence is from the second to fourth week with extreme weakness for several weeks.

Junin virus (Argentinian Haemorrhagic fever-AHF)

Endemic- epidemic area 100 000 km north- west of Buenos Aires. The virus causes direct capillary damage and there is no evidence of an immunopathological response.

Clinical changes

Infection of man causes severe disease, with a high mortality and death between the eight and tenth day. The incubation period is 8-12 days and there is a slow insidious onset with chills, headache, myalgia, retro-orbital pain and nausea. This is followed by fever, conjunctival injection, oedema of face, neck and upper thorax with a petechial rash in the axilla and general lymphadenopathy. On the sixth to eight day there is sudden deterioration, with haemorrhage, haematemesis, melaena, haematuria and oligouria proceeding to anuria.

Neurological disturbances occur and death from hypovolaemic shock. There is a heavy albuminuria with leucopenia, trombocytopenia and altered clotting factors. (VIII: Manson's tropical diseases).

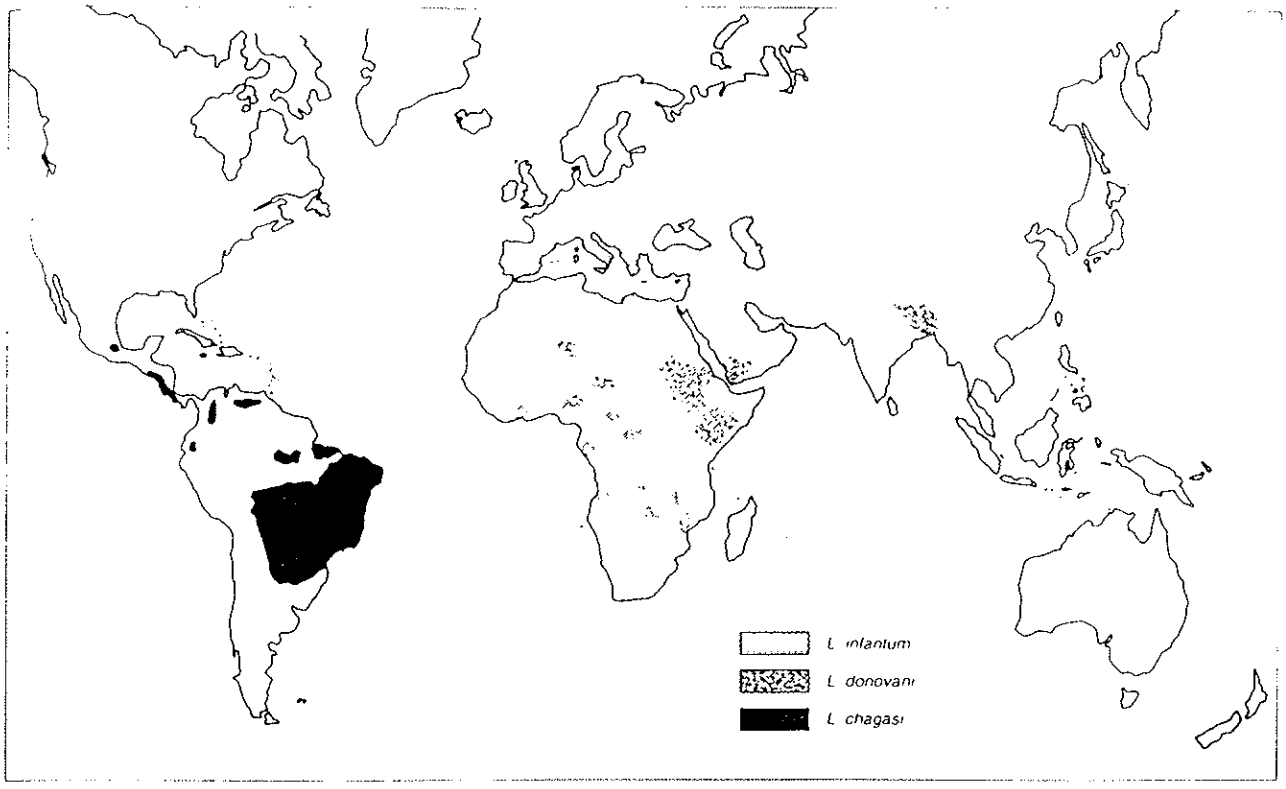

Fig 1. geographical distribution for visceral leishmaniasis.
(map, page 1217, Manson's tropical diseases).

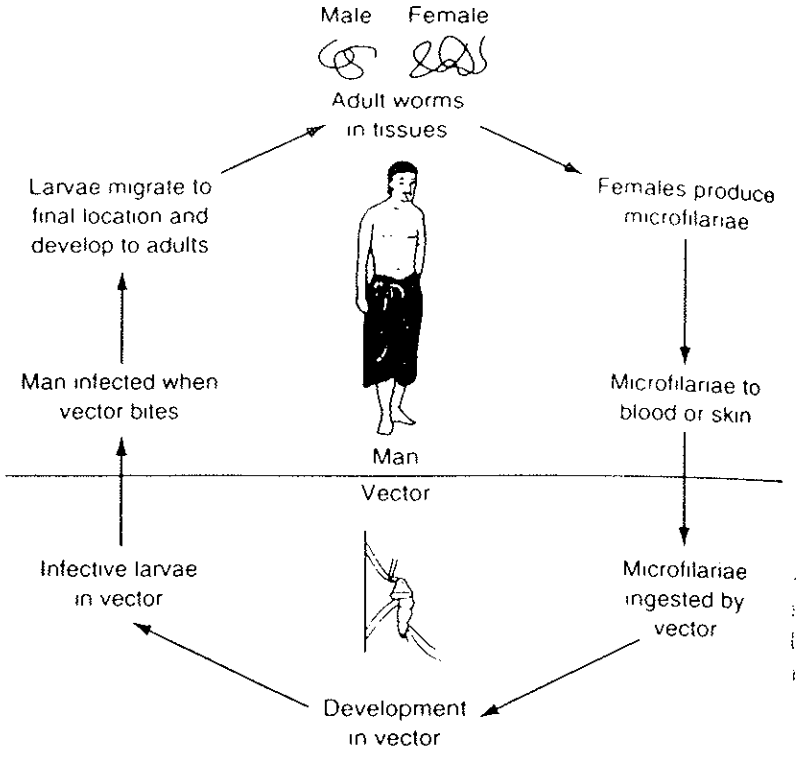

Fig.2. general life cycle for filariae
(figure, page 1322, Manson`s Tropical Diseases).

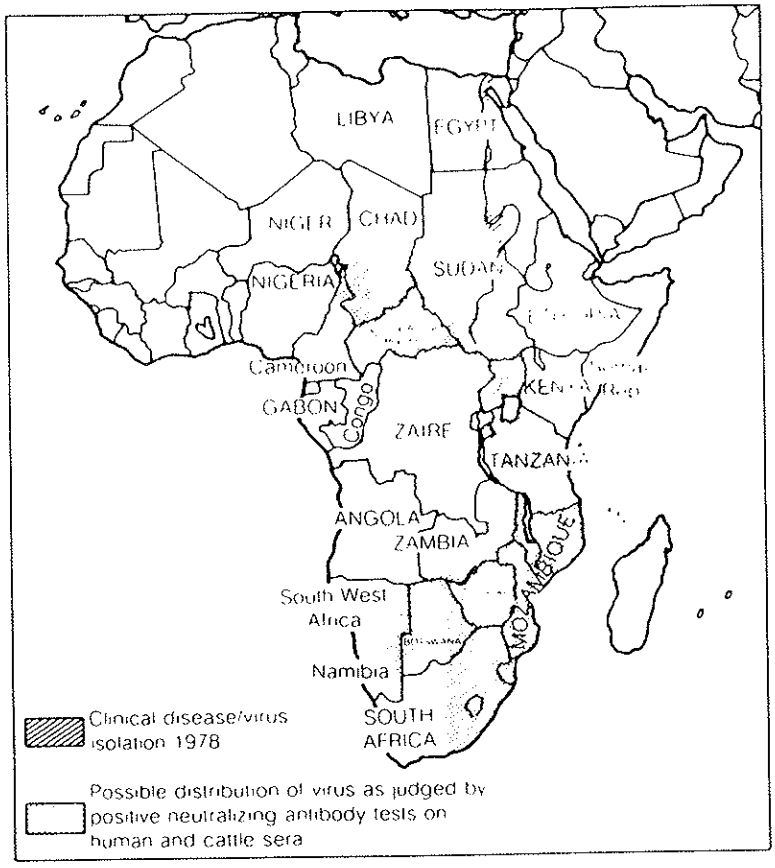

Fig. 3 geographical distribution of Rift Valley fever.
(Map, page 635, Manson`s Tropical Diseases).

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