Schistosomiasis

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Extracts from the film 'The Human Blood Fluke' Wellcome Film Unit, 1952.

Colour
Duration: 00:27:43:18

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<Opening titles>

<Narration over film>

This film is based on the work of two research teams: one lead by Dr Owen Standen at the Wellcome Laboratories of Tropical Medicine in the early 50s and the other led by Dr Diane McLaren in the late 80s at the National Institute for Medical Research.

Dr McLaren's scanning and transmission electron micrographs of the schistosome are featured in our video. This is the image seen in the microscope which is enlarged still further when processed photographically. It should be appreciated that these electron micrographs represent a wide range of magnifications. For example this

adult male schistosome is magnified by about 35 times when viewed on a 50 cm television screen. His ventral sucker 500 times and this spiny inside edge of the sucker 7000 times. Some of our images are magnified around a quarter of a million times, like this section showing the outer surface of a larval schistosome.

It was with the aid of this electron microscope that Dr McLaren was able to unravel one of the most puzzling stages in the life-cycle of the schistosome: the crucial processes involved in the transformation from free-living organism to a parasitic way of life.

These happy children are playing in water that is more than likely to be infected by one of the world's most damaging parasitic diseases.

<Intertitle>

SCHISTOSOMIASIS

Schistosomes are parasitic flukes that live in the bloodstream of man. They cause the disease schistosomiasis, probably better known as bilharzia**,** a major health problem for hundreds of millions of people in many tropical and subtropical regions of the world.

A male schistosome is seen here with a female partly held in his gynecophoric canal. The male is about a centimetre long and uses the lateral folds of his body to form the gynecophoric canal with which he embraces the longer more slender female. Incidentally, the scientific name *Schistosoma* means cleft-bodied.

This is the anterior part of the cleft which surrounds the head end of the female. Here are the paired schistosomes in the portal vein of an experimentally infected hamster. The flukes migrate as far as they can into the mesenteric veins and the female extends out of the gynecophoric canal to deposit her eggs into the smaller blood vessels. The eggs then work through the tissues into the lumen of the intestine. In this species of schistosome, the eggs pass out later with the faeces. Here's an egg in a faecal smear.

The earliest records of urinary schistosomiasis are to be found in the Ebers Papyrus dated around 1900 BC. Although the ancient Egyptians did not know the cause of the disease, they recognised and clearly illustrated the urinary symptoms in their hieroglyphics. Calcified schistosome eggs have also been identified in the kidneys of mummies more than 3000 years old.

It was not until 1851 that German pathologist Theodor Bilharz identified *Schistosoma haematobium* as the causative urinary agent of schistosomiasis in Egypt. In 1904 Katsurada described the life-cycle of *japonicum* and in 1907 Sambon described *mansoni* as a separate species. In 1934, Fisher recorded the existence of *intercalatum,* and as recently as 1978 Voge, Bruckner and Bruce discovered *mekongi*. Today eighteen species are recognised; of these *mansoni, japonicum* and *haematobium* probably infect more people worldwide than any of the other species.

Mansoni lives chiefly in the veins of the large intestine and this part of the portal circulation is also infected by *japonicum.* The passage of eggs through the intestinal tissues causes ulceration, thickening and fibrosis of the bowel wall. Eggs can be seen in this much thickened region of the superficial layers of the intestine. Also at the bases of the villi. Those eggs which enter the lumen of the gut are discharged with the faeces.

Schistosoma haematobium differs from the other two species. It inhabits the blood vessels of the bladder and its eggs are discharged with the urine. The main clinical sign is haematuria but ultimately fibrotic lesions may develop throughout the whole of the urogenital system. Bladder cancer is not an uncommon development in advanced stages of the disease. Schistosomiasis is currently endemic in 75 countries. *Haematobium* is present in 53 countries, mostly in Africa but also in the Eastern Mediterranean. *Mansoni* shows a similar distribution except that it's also found in South America, notably Brazil, though it was probably carried with the slave trade. *Japonicum,* on the other hand, is confined to countries of the Far East: China, Indonesia and the Philippines. Japan, where the parasite was originally found, has

now been freed from the disease. *Mekongi* occurs in South East Asia. And *intercalatum* is found in Central and West Africa.

Worldwide, some 200 million people are infected with the schistosomes and 500 to 600 million are at risk. The highest infection rates are found in Brazil, Egypt and the Sudan.

Freshwater snails play an essential role in the transmission of the disease since each schistosome will spend part of its life-cycle in the tissues of a snail. Species of *Bulinus* are intermediate hosts for *haematobium*. *Biomphalaria* carries *mansoni,* and *Oncomelania* carries *japonicum*.

Wholesale destruction of the snail hosts with chemical molluscicides is one obvious method of reducing the incidence of schistosomiasis, but since the snails are hermaphrodite, possessing both male and female sexual organs, it needs only one individual survivor of a control programme of this kind for an entire area to be repopulated within a single season. Moreover, development projects such as hydroelectric schemes, like the gigantic Kariba Dam on the Zambezi, have created large bodies of water and consequently allow the snails to flourish in recent years.

Although most infected people carry only small numbers of schistosomes, treatment with an effective drug not only reduces the prevalence of the disease, it also reduces morbidity. Praziquantel is currently the drug of choice since a single dose affects all the main species of schistosomes that infect man and it produces high cure rates. Oxamniquine is also used for *mansoni* especially in South America, while metrifonate is valuable for the treatment of *haematobium.*

It's man's primitive habits with regards to urination and defecation which maintain the disease in the community. Obviously the separation of urine and faeces inhabited by the snails is vital in the control of infection. In the third world this is easier said then done. However, in Zimbabwe the Blair Research Laboratories have produced some interesting designs for simple water pumps and lavatories; this one is a strong shelter

built over a deep pit. It has an odour pipe, fly traps and is easy to keep clean. And here are some variations on the basic design.

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The Blair water pumps are ingenious. This one uses the pipe that delivers the water as the pump handle. In the playground of a village school, these girls are enjoying their swing pump. Official notices, pamphlets and posters are also used in an attempt to increase local awareness in endemic areas.

The most desirable control measure would undoubtedly be a one-shot vaccine and it's towards this goal that current research is mainly directed. All species of human schistosomes have essentially the same life-cycle. We've chosen *mansoni* for discussion here as it's the easiest to maintain and investigate under laboratory conditions. The flukes live paired in the hepatic portal of the mesenteric veins. The male is light in colour with a dark central line – the gut, just visible. The female, partly held in his gynecophoric canal, appears very dark in comparison because her gut is more obvious. The dark colour is haematin, a product of haemoglobin digestion derived from red cells of the host's blood which fills the double zigzag line of the gut. If you look closely, you'll see individual blood cells moving through the narrower passages.

This female has an egg in her uterus. Above the egg is the spiralled vitelline duct. The female is cylindrical and has a relatively smooth surface, but the dorsal surface of the male bears many spiny bosses or tubercles that are thought to anchor him in position by catching against the walls of the blood vessels. There are numerous pits between the tubercles which presumably serve to increase the absorptive surface area, while sensory organelles are abundantly distributed all over the entire body. These ensure that the schistosome is aware of minute changes in its microenvironment.

Each fluke has two suckers at the anterior end of its body. The ventral sucker is used by the fluke to attach itself to the walls of the blood vessels. The very spiny surface of the sucker ensures a firm grip. The oral sucker is important for feeding and is used to ingest the red blood cells of the host. The orifice is spiny and its outer margin is well endowed with sense organs. In this electron micrograph, we can see two blood cells inside the oral sucker. Here the well-anchored pair seem to be traversed by continuous peristaltic waves which are probably associated with the rate of blood flow.

Female schistosomes produce hundreds of eggs a day and these are deposited into a venule of the intestinal wall where they become tightly lodged. The eggshell is covered with hundreds of needle-like spines which abrade the tissue and enable the eggs to work their way across the bowel wall and through the villi. Here are two eggs in tissue at the bases of the intestinal villi. They're making their way towards and into the lumen of the gut. Later they'll pass out of the body with the faeces. Some eggs are inevitably swept back past the flukes and carried in the portal blood to the liver where they eventually provoke an immune reaction and become encapsulated in a granuloma. These granulomas are clearly visible as white spots on the liver of an infected mouse. An egg is at the centre of this mass of infiltrating leucocytes, mainly mononuclear cells and eosinophils. These cells ultimately destroy many eggs; they've already started to invade the shell of this one.

In severe chronic infections, the liver becomes filled with granulomas and this leads to portal obstruction, hypertension, ascites and massive enlargement of the liver and spleen. Compare the size of the organs in a normal mouse and a mouse harbouring a chronic schistosome infection. These features of pathology accurately mimic the clinical symptoms of the human disease.

Schistosome eggs are easily detected in faecal smears. They are about a seventh of a millimetre long and are comparatively large as helminth eggs go. The prominent lateral spine is the characteristic feature of *Schistosoma mansoni*. The spine is terminal in *haematobium,* and although lateral in *japonicum*, the spine is very small.

The *japonicum* egg is much rounder and is therefore easily distinguished from the oval-shaped egg of *mansoni*.

When passed in the faeces, each egg contains a fully formed miracidium whose surface is covered with hundreds of cilia. The miracidium also possesses two pairs of flame cells which can be recognised by their flickering movement. They form part of the simple excretory system and their activity shows that the organism is alive. In fresh water, the egg expands by osmosis and as its contents become diluted, the miracidium is stimulated into activity. The movements of its surface cilia set up currents in the liquid which appears to bubble. Suddenly the shell is fractured and the miracidium half emerges together with fluid from the egg, but the miracidium is still contained within the vitelline membrane which surrounded it in the egg and it has to struggle hard for a time before it finally manages to free itself. Then in a moment it's on its way in search of a particular species of snail.

The miracidia are propelled by vibrating the thousands of minute hair-like cilia covering their elongated bodies. This is a critical period for them; they must find their particular species of snail within a few hours or they'll die. The snail shown here is *Biomphalaria glabrata* from South America. The miracidia adhere to its exposed surfaces. They burrow their way in by a combination of enzymic digestion and mechanical movement. It takes about an hour for a miracidium to penetrate completely. Once this is accomplished, the miracidium transforms to a primary sporocyst which migrates towards the liver of the snail and begins a process of asexual multiplication. In this way, many secondary or daughter sporocysts develop independently and grow into long thin bodies that eventually become convoluted. They give rise to cercariae that bud off in continuous sequence. Finally, the liver tissue of the snail is almost completely replaced by sporocysts and free cercariae.

This is a secondary sporocyst which has been dissected out of the liver of an infected snail. It contains mature cercariae which are struggling to get out. They have developed in the sporocyst with their tails folded back along their bodies. This one is struggling very vigorously to free itself. Remember we are watching cercariae with

space around them. If they were still inside the snail, they would be tightly packed and their movements greatly restricted.

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At about four weeks after infection, the first cercariae emerge from the snail and they're soon escaping daily in swarms. They're about ½ mm long and are actively swimming organisms that travel through the water with characteristic movements, usually tail first. Their life is short – about 48 hours at the most, for they have no functional gut and their rapidly expended energy reserves cannot be replaced. The cercaria has an elongated body region and a long forked tail. It also has an oral and ventral sucker by which it adheres to any substrate.

The external surface of the cercariae is covered with spines that are backwardly directed. These help it to penetrate the skin of its next host since they ensure that the organism can only travel in a forward direction. Each cercaria has a secretory complex comprising of three types of unicellular glands which open through the oral sucker. This electron micrograph shows the folded gland openings. The glands contain powerful proteolytic enzymes which help the cercariae to digest its way through the skin of the host.

Here cercariae are penetrating the tail skin of a mouse. They attach with their suckers, digest and wriggle their way through the skin. Once the body is inside, the tail drops off but remains active. The parasite, now called the schistosomulum, is safely within its new host.

The sequence is now repeated in diagram: a cercaria attaches and makes a hole in the epidermis. It deepens the aperture and enters it by elongating its body. Shedding its tail, it migrates through the dermis and fat layer where it turns, seeking a blood vessel. On finding one, it enters and starts its journey round the body of the host. It's carried in the bloodstream, first to the lungs. By this time it's become longer and considerably more slender and lost its mid-body spines, although spines are retained

at both ends. The spines, together with rhythmic activity, enable it to migrate along the tiny lung capillaries which are often smaller in diameter than the larva itself.

The flukes leave the lungs through the pulmonary veins and pass via the left side of the heart to the liver. The earliest migrants arrive in the liver six to eight days after infection. They become short and squat, begin to feed, and their intestines fill with dark haematin pigment. Two to three week old juvenile flukes are now more recognisable as schistosomes but they have a convoluted system of folds and ridges on the surface. By week four, however, these folds are less conspicuous and dome-shaped elevations appear on the dorsal surface of males. They clearly represent early stages in the development of surface tubercles. Male and female flukes pair at around week five and the male tubercles take on their characteristic spiny appearance. The paired flukes migrate through the portal vein to the mesenteric veins and egg laying begins. That completes the life-cycle of the schistosome.

We now have some observations on one of the most intriguing features of the life-cycle: the transition from free-swimming cercariae to parasitic schistosomulum. The cercaria has to adapt very rapidly to its move from fresh water to body fluid, a temperature change of about 20 degrees <*centigrade on intertitle*> and a hostile environment. The most dramatic changes take place at the outer surface of the cercariae.

This is a diagrammatic section through a cercaria. The surface is spiny and totally covered by a typical three-layered membrane. The outer layer is the glycocalyx. This is an electron micrograph for the three-layered membrane. Under the membrane is the tegument, a syncytium with no cell walls. Its nuclei are located in deeper cell bodies joined to the tegument by narrow, twisted connections. These are layers of muscle cells. This is how the section appears under the electron microscope.

When the cercaria enters the tissues of its new host, large numbers of membranous secretion granules are synthesised in the subtegumental cells and pass up into the tegument. The bodies join together and then connect with the surface of the larva to liberate their membranes to the exterior. The original tri-laminate membrane and the

glycocalyx are cast off in a mass of microvilli. This action not only serves to distract the host's immune system, it also sensitises the host against subsequent schistosome infection.

The parasite rapidly covers itself with a new seven-layered membrane derived from the membranous bodies. The larva further confuses the host by disguising its surface with proteins derived from the host's red blood cells. At an early stage of infection, it's also thought that the host produces a class of antibodies which attach to the invading parasites. Their function is rather puzzling in that they're not aggressive towards the parasite. Furthermore, they serve to block the killing of the parasite by other toxic antibodies. Later there's a switch, so that the toxic antibodies predominate. This could explain the finding that young children playing in infected water have no resistance to schistosomiasis and may become heavily infected. But as they get older, they develop an effective immune response that kills newly invading parasites and thus limits the number of schistosomes they carry.

Because man eventually develops this partial immunity, concerted efforts are being made in many research laboratories to analyse the mechanisms responsible for killing the flukes, and to characterise the parasite antigens against which the host responses are directed. Present research gives hope that it will be possible to design and produce a vaccine for human use. It would be an acceptable and desirable first step in disease control if the vaccine could reduce the debilitating pathology caused by schistosome eggs.

Schistosomes, like many other parasites, have a variety of ways of avoiding the lethal effects of immunity: shedding of microvilli, using host protein as a disguise and the development of blocking antibodies. These are but three of their many tricks. A really successful vaccine will have to be several jumps ahead of these highly sophisticated, evasive strategies.

Until that time comes, we must rely on improved standards of hygiene to break the life-cycle of the parasite and drugs to reduce the infection. But the problems of expense, the need for repeated drug administration and the ever-present threat of

drug resistance mean that researchers are working against the clock to develop an effective vaccination programme.

<End credits>

<In addition to those listed at beginning>

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