Schistosomiasis: The Possibility of Control by Immunisation
The Scientific Basis of Medicine

Presented by Professor George Nelson.
Introduced by Dr Ian Gilliland.

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<Opening titles>

<Gilliland to camera>

Professor Nelson is Professor of Medical Helminthology at the London School of Hygiene and Tropical Medicine. He has had a great deal of experience in that subject, being a senior parasitologist in Nairobi and also a medical officer in Uganda. He is the author of numerous publications on filariasis and bilharzia. And the subject of today's intriguing discourse is Schistosomiasis: the Possibility of Control by Immunisation. Professor Nelson.

<Nelson to camera>

Thank you Dr Gilliland. As you say, the title of my talk today is Schistosomiasis and the Possibility of Control by Immunisation, but I think first of all we want to know what

is schistosomiasis and why is it necessary to introduce immunisation procedures for the control of this disease.

Schistosomiasis or bilharziasis was discovered by Dr Bilharz in Egypt in 1860. We now know that there are at least 200 million people infected with one or other of these parasites somewhere in the world and it is one of the most formidable of all infectious diseases. Unlike other infectious diseases which are being controlled, schistosomiasis is increasing in prevalence and its increasing in severity in many parts of the world.

There are three parasites that are of major medical importance: *Schistosoma haematobium* which causes the bladder bilharziasis or schistosomiasis, and *Schistosoma mansoni* and *Schistosoma japonicum* which mainly affect the liver. Now I have three charts showing the distribution of these three parasites in the world. First of all *Schistosoma haematobium.*

<Nelson refers to chart with indicator stick>

Schistosoma haematobium is mainly confined to Africa. It occurs in Egypt where it was first discovered, in West Africa, in South Africa and in Madagascar. It is also an important problem in parts of the Middle East and there's one small focus of the disease in India. *Schistosoma mansoni* originally was confined to Africa and it is still a very major public health problem in many parts of Africa and in Madagascar and in the Middle East. But unlike *haematobium,* it managed to get across the Atlantic with the slaves and it is now a major public health problem in Brazil and in Venezuela and in parts of the Caribbean. That is *Schistosoma mansoni.*

The third parasite is *Schistosoma japonicum*, named originally because of its discovery in Japan, but this is a major disease problem of China, particularly in the Yangtze Basin. But it also occurs in the Philippines and it extends as far south as Indonesia. There is a possibility that there may be a serious *japonicum* problem in the Mekong Delta area where there are new major developments in irrigation.

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<Nelson sits down and to camera>

The schistosomes are trematode worms <*insert of projected still from film*> and I'd like you to see a film which illustrates the worms – the way in which a male carries the female.

<Nelson narrates over projected film>
Now here are the worms that have been removed from the body. You can see the large male and the small female inside it. And in the background there you can probably see some of the eggs that are laid by the female. These are worms, living worms, in the portal vein.

<Nelson refers to chart>

Now this is a life-cycle chart of the life-cycle of *Schistosoma mansoni*, the parasite that we've just seen in the portal vein of an experimental animal. In man the eggs are passed in the faeces. They must find water and they must find water fairly soon, and when they get into water, they hatch. And out of the egg you get the miracidium which is a small creature which swims about vigorously in the water for up to 24 hours until it finds the appropriate snail host. And there is a different snail for each species of schistosome. In this case the snail host of *Schistosoma mansoni* is Biomphalaria. Inside the snail you get the development of sporocysts. These sporocysts produce thousands and thousands of cercariae. And the cercariae come out into the water, the snail producing cercariae everyday, often for many weeks. And the cercariae penetrate directly through the skin of man – when he puts his feet in the water, when he goes bathing, when he washes himself; the cercariae can penetrate through the skin very rapidly.

Once they get through the skin they convert into schistosomules. These schistosomules go up through the lymphatics into the lungs, stay there for a few days, then come down to the liver, and from the liver they migrate into the hepatic

portal vessels. *Schistosoma haematobium*, they migrate to the vesicular blood vessels. Once they get there, in a period of about 6 weeks, they reach maturity and start producing eggs. And that is the cycle of *Schistosoma mansoni*, very similar for *haematobium* and very similar for *japonicum.* The stage of a parasite that we are particularly interested in from an immunisation point of view is cercariae and the schistosomules.

<Nelson narrates over projected film>

These are the living cercariae swimming around in the water. They produce proteolytic enzymes which allows them to penetrate through the skin of man and animals. And, here's a cloud of cercariae that have been produced for experimental purposes.

<Nelson to camera>

The snails that transmit schistosomiasis are all freshwater molluscs that are found in streams and dams and in irrigation systems throughout the endemic areas. Major developments in agriculture, major developments in irrigation are in many ways responsible for the increased prevalence of schistosomiasis throughout the world. It is becoming a manmade disease.

<Nelson narrates over projected slides>

One of the most important developments which has caused the increase of schistosomiasis is the building of big dams. This is the Aswan Dam in Egypt which has produced an enormous increase in schistosomiasis because it's converted the Nile Valley from an area where there was annual irrigation depending on the Nile flood and now you have perennial irrigation with water all the year round. And with water being available all the year round, the snails that transmit the disease are available all the year round to carry on transmission. The Volta Dam in Ghana, which is the largest manmade lake in the world, is also already infested with *Schistosoma haematobium* and it's becoming a major problem for Ghana.

Schistosomiasis is an ancient disease, although it's spreading now, it has been in existence for a very long time and we have evidence of this from the examination of mummies in the British Museum. Work that was done in 1910 by Ruffer showed that mummies dating back to 2000 BC contained eggs of *Schistosoma haematobium*.

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<Nelson to camera>

Schistosomiasis is also a disease of the army, a disease of military importance. It was a disease which was probably responsible to some extent for Napoleon's retreat from Egypt, because his troops complained that they were menstruating when they started passing blood in their urine. It was also said to be responsible for the failure of mainland Japanese to invade Formosa, because the training ground for several divisions of troops that were going to invade Formosa was heavily infected with *Schistosoma japonicum.*

In the 14-18 war, schistosomiasis was an important cause of disease amongst British and Australian troops operating in the canal region in Egypt. And it was during that war that Professor Leiper, who was one of my predecessors in the London School of Hygiene and Tropical Medicine, was sent out to find out how the disease was transmitted. It was Leiper who discovered the two types of snails responsible for the transmission of *Schistosoma mansoni* and *Schistosoma Haematobium.*

He not only discovered the method in which the disease was transmitted but he suggested methods of control which are still applicable today – the control of the snails using molluscicides, the control of the parasite using various forms of chemotherapy, the control of the disease by preventing people from entering infected water or from preventing them from contaminating water where snails exist. All this was worked out at the time of the 14-18 war.

But despite all of this, the disease is just as common in Egypt as it ever was, probably more common now as a result of the building of the High Dam, and the disease is spreading throughout many other parts of the world.

There's been some success in the control of the disease – a little. In Japan the disease has practically disappeared because of the very wealthy rapid economic development of Japan. They've been able to convert the irrigation ditches which harboured the snails into cement canals which are inhospitable to the snails, and therefore the disease has disappeared due to snail control.

In mainland China, there are claims for widespread control of the disease due to health education inspired by Chairman Mao himself who has produced a very nice poem about schistosomiasis. The people there are cooperating in the control of the snails; they cooperate by subjecting themselves to mass treatment by antimony drugs and they cooperate in community development projects to make the land inhospitable to the snail by burying and filling in ditches, and also by conserving human faeces and sterilising it before it's put on to the land.

In the Middle East there has been some success. And we have a short extract of a film showing the spraying of snail infested water in Iran using one of the modern molluscicides, which are effective in concentrations as low as one part of molluscicide to two million parts of water.

<Nelson narrates over film>

The film is an example showing snail control in Iran using either Frescon or Bayluscide. It is essential to treat every single body of water where the snails may be found. Drip feed methods can be used on large irrigation schemes. This is an enormous saving in labour provided that the water carries the molluscicide throughout the scheme as it does here in Tanzania on a large sugar estate. Similar methods are being used in Sudan in the Gazira irrigation scheme.

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<Nelson to camera>

In the long term, the most effective method of controlling schistosomiasis is obviously to avoid infected water. But this means providing alternative sources of clean water and this is often very expensive. And in any event, it's very difficult to prevent children from swimming in infected water or for agricultural workers from actually working in irrigation ditches and from working in paddy fields.

<Nelson narrates over projected slide>

It's even difficult to prevent the more sophisticated and educated members of the community from bathing or enjoying aqua sports like waterskiing in infected waters.

<Nelson to camera>

This happens in places like Nairobi and in Rhodesia and on the Cariba Dam. It's obviously going to be more difficult to prevent people in the worst areas, in the underdeveloped areas of the world, from coming in contact with infected water. And it's for this reason that we believe that the final and most effective method of control of schistosomiasis will probably come through immunisation procedures.

Helminths and other parasites behave in much the same way in stimulating an immune response in the host but there is a difference. Helminths, unlike bacteria and viruses and protozoa, don't multiply in the host, and the disease in the individual can be controlled without necessarily having to get rid of the last worm. What we're aiming at is an amelioration of the disease by reducing the worm burden and interrupting re-infection as a result of an immunisation procedure. We're not necessarily aiming at getting rid of the last worm in the individual patient.

There's a good deal of epidemiological evidence suggesting that man develops a natural immunity to schistosomiasis. If he didn't, he'd hardly survive in many of the areas where infection rates in snails are enormous. There is also an enormous

accumulation of experimental evidence – work in mice and monkeys and baboons and domestic animals which indicates that there is the development of a strong resistance to re-infection. Perhaps the most outstanding work in this field is that of Dr Ron Smithers and his colleagues in the Medical Research Council Laboratories at Mill Hill, where they've been showing, by a series of very elegant experiments, that Rhesus monkeys will develop a complete resistance against reinfection as a result of the stimulation by adult worms of the production of antibodies. The adult worms not only stimulate the host to produce antibodies which will kill all the infected stages of the parasites as they enter the host, but they will have this remarkable facility of defending themselves against the attack of the host. This has been demonstrated by a simple experiment illustrated in this diagram.

<Nelson refers to diagram with indicator stick>

We have one of Dr Smithers's Rhesus monkeys, which if you transplant worms from a mouse – *Schistosoma mansoni* from a mouse – to the mesenteric vessels of the monkey, these adult worms will be a little sick for a few days, then they will recover and produce eggs just like normal worms. But if before you transplant worms from a mouse to a monkey, you immunise the monkey with mouse cells so that you make this monkey an anti-mouse monkey, and then transplant worms from a mouse to the mesenteric vessels of the monkey, the monkey will eliminate the worms.

Smithers and his colleagues have gone on now to show by in vitro culture techniques and by electron microscopy of the worms, that the adult worms are capable of taking on to their cuticle host antigen which disguises them and prevents the host from recognising them as foreign. But at the same time, the adult worms can stimulate an immunity which prevents the cercariae and the schistosomules from developing in the Rhesus monkey.

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<Nelson to camera>

They are hoping that they will be able to identify the antigens, they'll be able to identify the lethal antibodies – the protective antibodies – that by doing this, they will eventually get round to the development of a dead vaccine based on the antigenic characteristics of the worm which are responsible for resistance. But they are a very long way away from doing this and nobody so far has been able to produce any immunity at all against schistosomiasis in an experimental system using a dead antigen to stimulate the immunity.

Adult worms are not the only part of the life-cycle responsible for an immune response. We've known for a long time that cercariae and probably schistosomules can also produce an immunity. Irradiated cercariae which have been attenuated by irradiation so that they cannot survive in the host to reach adulthood and don't produce eggs, if administered to a Rhesus monkey can be used to immunise it against a subsequent infection. This principle has been used by veterinarians for quite a long time. In fact, there are two commercially available vaccines against helminth parasites of livestock, one against dictyocaulus which produces lungworm disease in cattle and sheep; the irradiated infected larvae can be used as a vaccine and are used very extensively as vaccines throughout the world. Another vaccine has recently been developed using the same principle against hookworm infection in dogs in the United States of America.

Now we've approached this subject in a slightly different way and it's based on, first of all, clinical observations in Kenya.

<Nelson narrates over slide>

We noted that in areas where man was simultaneously exposed to the schistosomes of cattle and wild animals that he was less severely affected in these areas where there were no cattle schistosomes, or no schistosomes in wild animals. For instance, in this area of East Africa, schistosomiasis is much less severe where all these cattle are infected with *Schistosoma bovis* than it is in Egypt where there is no *Schistosoma bovis* or in South America where there are no animal schistosomes.

<Nelson to camera>

Really what we were observing was rather reminiscent of what Jenner had observed more than a hundred and fifty years ago when he noted that dairymaids were protected from the virulent smallpox virus by previous exposure to the cowpox virus. You probably all know the old nursery rhyme which maybe was the thing that gave the hint to Jenner about this particular phenomenon of protection by natural exposure to a non-virulent organism against subsequent infection with a pathogenic and more virulent organism.

<Nelson stands and recites over displayed poem with indicator stick>

The nursery rhyme:
“Where are going to my pretty maid?”
“I’m going a-milking, sir,” she said.
“What is your father, my pretty maid?”
“My father’s a farmer, sir,” she said.
“What is your fortune, my pretty maid?”
“My face is my fortune, sir,” she said.
She was a diary maid, her father was a farmer, she was exposed to milking cows and she had a pretty face, and an unusual pretty face, because it wasn’t marked by the pock marks of smallpox which were so common in the days of Jenner.

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<Nelson to camera>

In the same way we believe that if man is previously or simultaneously exposed to constant bombardment by non-pathogenic schistosomes – from cattle, from sheep, and from wild animals – this will in some way protect him from the more virulent schistosomiasis. To focus attention on this particular phenomenon, which has been sadly been neglected by epidemiologists and by immunologists ever since Jenner’s day, we coined the name zooprophylaxis.

<Nelson narrates over slides>

The definition of zooprophylaxis is as follows: The prevention or amelioration of disease in man as a result of previous exposure to heterologous infections of animal origin.

This is a very widespread phenomenon and probably of fundamental importance in protecting man from many of the virulent organisms in his environment. One or two examples are illustrated in the next slide.

We have the cowpox protection against smallpox. This isn't exceptional in viruses; there are probably many other viruses that protect against yellow fever for example. Bovine tuberculosis protecting against leprosy; it's notable that cattle owners in areas where bovine tuberculosis occurs very rarely suffer from leprosy. And in Kenya, one parasite that I worked on at one time was kala azar, *Leishmania donovani*. There is epidemiological evidence that exposure to previous lizard leishmania or non-pathogenic rodent leishmania confers some immunity against kala azar. And then finally, we have the animal schistosomes versus the human schistosomes.

<Nelson to camera>

Now this epidemiological evidence is suggestive but very difficult to prove that there is a significant amelioration of the disease in man as a result of previous exposure to schistosomes from animals. But we have now accumulated a great deal of experimental evidence in support of this particular hypothesis using a wide variety of schistosomes of animals and a wide variety of animal hosts; we've shown that one species of schistosome almost invariably confers some degree of protection against infection with another species of schistosome. This can be illustrated in the following slide:

<Nelson narrates over slide>

[…] which illustrates a comparison of homologous immunity to *Schistosoma mansoni* in baboons – these are all illustrations of what happens in baboons which very closely simulate the infection as seen in man. In homologous infections with *Schistosoma mansoni* in baboons, using a single exposure against a single challenge, you get a reduction in the worm count, the adult worm count of 22%, as against a reduction in egg count of 23%.

Using a heterologous infection to immunise the animals, either *Schistosoma rodhaini* or *Schistosoma bovis* we had a much better result. And neither of these parasites reaches maturity in the baboon. Like the irradiated cercariae, they die off before adults, but from these experiments it is suggestive that they produce quite a strong immunity against subsequent challenge with the virulent *Schistosoma mansoni.*

At the bottom we have illustrations of immunisation using hybrids between *Schistosoma mattheei* and *Schistosoma haematobium* against *mansoni*; and hybrids of *rodhaini* and *mansoni* themselves. At present they have been rather disappointing.

<Nelson to camera>

Ideally what we are looking for is a parasite which is highly infective, non-pathogenic and at the same time highly immunogenic. And we had great hopes for the hybrids. For example the hybrid between *Schistosoma mansoni* and the *Schistosoma rodhaini*.

<Nelson refers to chart>

The chart shows that if you infect baboons with *Schistosoma mansoni*, you can produce massive numbers of eggs in these animals and you can easily kill baboons if you give them too many of *Schistosome mansoni* cercariae. If you give them *Schistosoma rodhaini,* it doesn't matter how many you give them. You can give them thousands and thousands of cercariae – they'll never produce eggs so they will never produce pathology and they can be used on their own for immunising against *mansoni*.

But if Smithers and his colleagues are right, then we want more than just the schistosomula stage of *rodhaini* to promote the immunity. We would also like adult worms, so Dr Martin Taylor in my laboratory has hybridised *mansoni* with *rodhaini* – he's hybridised many other species – to try and produce the ideal schistosome. And the hybrid is infective, does produce adult worms and does produce only very, very few eggs. So in this sense, it was reaching the type of ideal that we were aiming at. Unfortunately so far, none of the hybrids have shown that it is as protective as the parent species – the non-pathogenic parent species like *Schistosoma rodhaini*.

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<Nelson narrates over film showing operation on monkey>

As we've seen in the table showing the results of the baboon experiments, the measurement of resistance is based on the percentage reduction of the adult worms and the percentage reduction of the eggs in the tissues. It's a fairly laborious process to actually count the worms in a large animal like a baboon or in a sheep or a cow. And it's based on the perfusion of the animal with saline citrate through the thoracic aorta, and then the collection of the worms which have been pushed out through the mesenteric vessels into the portal vein and collected by aspiration from the portal vein.

Here we have the opening of the portal vein. You can see the worms in the blood being sucked up into the tube and as the perfusion fluid goes through the mesenteric vessels and the liver, you'll see the liver going pale. Just by the tube there, you'll see the liver suddenly goes quite pale as the blood and worms are being pushed out into the tube.

The worms are collected on a bolting silk screen in this filtration apparatus and then they're counted in a Petri dish.

<Nelson to camera>

We have evidence suggesting that cross-immunity operates in both directions. Experiments that we've been doing in cattle and sheep indicate that the cattle and sheep can be protected from the major pathogenic effects of their own parasites by previous exposure to the human parasites. This can be seen in the next slide.

<Nelson narrates over slide>

Here we immunised calves with *Schistosoma haematobium*, the human parasite, and then challenged them with what we expected to be a lethal infection with *Schistosoma bovis.* And we had a considerable reduction: a 40% reduction in the adult worms and a 62% reduction in the egg count.

We did several experiments but another one that is illustrated here is immunisation of sheep with *Schistosoma mansoni* against *Schistosoma mattheei*, a parasite which is often fatal in sheep. And here we had an even better result, a 66% reduction in adult worms and a 49% reduction in eggs. And finally here – an interesting parasite *Schistosoma turkestanicum,* which is a parasite of economic importance in the Middle East in cattle. *Schistosoma haematobium* confers some protection against subsequent infection with *Schistosoma turkestanicum.*

<Nelson to camera>

Now these are heterologous experiments in cattle and sheep; we've also been doing homologous experiments using attenuated irradiated cercariae.

<Nelson narrates over slide>

The next slide shows that sheep that have been vaccinated with irradiated homologous *Schistosoma mattheei* can be protected, and can be protected quite well against subsequent infection with this parasite: a 74% reduction in worms and an 80% reduction in eggs as the result of the use of an irradiated cercarial vaccine. In

fact, it was much better in this particular experiment than the use of heterologous *Schistosoma mansoni.*

00:35:01:18

<Nelson to camera>

Now one of the big problems of this whole field of immunisation with schistosomes, which doesn't occur with the nematodes which are tough creatures, is that the cercariae live only for a short period of time, 20 to 40 hours, and they can't be kept in culture in vitro. So the logistics of actually taking snails, producing cercariae, irradiating cercariae in the field and then immunising with them, poses so many problems that it's unlikely that a cercarial vaccine will ever be developed which is of practical value until we have methods of preserving the cercariae. We've been trying to get round this problem by using the next stage of the parasite – the schistosomule.

You can convert the cercariae into schistosomules in vitro and you can culture the schistosomules in vitro and you can maintain them in vitro for several weeks. They will grow in vitro; they will grow to adults in vitro but you can suspend development. We're hoping that maybe we will be able to develop not a cercarial vaccine, but a schistosomula vaccine.

It's a very long way before we get a vaccine that will be of any value in human medicine, but we're optimistic that we can develop a vaccine which will be effective against schistosomiasis of veterinary importance such as occurs in the Sudan.

<Nelson narrates over slide>

This slide illustrates what happens in a natural infection with *Schistosoma bovis* in an area where the livestock industry is of vital importance.

<Nelson to camera>

This cow was dying of *Schistosoma bovis*. In South Africa and Rhodesia, sheep die of *Schistosoma mattheei* infections. We're hoping as a first step, of what is now a very long programme, that we will produce a vaccination procedure using a living parasite to immunise cattle and sheep against this severe disease. And then later, much later, we hope to develop a vaccine which may be of value in human medicine.

<End credits>