



Egyptian farmers working by the River Nile are at risk of schistosomiasis, which can lead to bladder cancer.

EGYPT

# The flatworm's revenge

How Egyptian men swapped one type of bladder cancer for another.

BY LOUISE SARANT

Since the dawn of the Egyptian civilization — and probably long before that — parasitic flatworms of the species *Schistosoma haematobium* have lurked in the River Nile. They grow inside river snails and emerge into the water looking for their next home. When a worm encounters a human, it burrows through the skin and travels through the blood vessels to the liver, where it turns into a fluke. It then heads to the bladder, where it mates and the females lay eggs. The eggs cause acute inflammation of the bladder wall, which results in haematuria — blood in the urine. The eggs are then passed out of the body in the urine, and any that reach fresh water will hatch and look for a snail to infect.

Eggs of *S. haematobium* have been found in the urinary tract of a mummy from the twentieth dynasty, which began in 1189 BC. Of the ten known ancient-Egyptian medical papyri, five, including the Ebers Papyrus from 1550 BC, describe urological problems such as enlarged prostate, bladder stones, cystitis and urinary frequency. Many archaeologists believe that the pharaonic term used to describe these

urinary problems — *aaa* — might well refer to *S. haematobium* infection, known today as urinary schistosomiasis.

To stop *aaa*, the ancient Egyptians were encouraged to avoid polluted water, and fishermen, farmers and others in regular contact with the river were advised to wear penile sheaths made of linen. But the advice failed to curb the infection rates. Haematuria was so common in Egyptian men that French physicians with Napoleon's campaign in 1798 described Egypt as the only country where men menstruate.

Schistosomiasis is also known as bilharzia after Theodor Bilharz, the German parasitologist who first described *S. haematobium* in 1851. If untreated, the infection can lead to dysuria (painful urination), haematuria, anaemia and wasting, and is a major risk for bladder cancer, specifically squamous cell carcinoma. This type of bladder cancer is rare worldwide, but it was Egypt's most common cancer at the start of the twentieth century. Because of the health consequences of chronic schistosomiasis, Egyptian health officials spent decades trying to eliminate the parasite. But while the government was focused on controlling schistosomiasis, and hence squamous cell carcinoma, it failed

to notice the rise of other chronic diseases, including different forms of bladder cancer. Now Egypt has another battle on its hands.

## SNAIL'S PACE

In the 1920s, approximately 70% of the Egyptian male population was infected with *S. haematobium*. Starting in the 1930s, the Egyptian government made several attempts to eliminate the parasite at different stages of its life cycle. The first attempt targeted the snails, which are the parasite's intermediate host. Government workers drained river-fed canals so the snails could be collected manually. They tried killing the gastropods with copper sulfate or niclosamide. "It was a terrible idea," says Hussein Khaled, a medical oncologist at Egypt's National Cancer Institute at Cairo University. The chemicals, diluted by the large volume of fresh water in the Nile, had little effect on the snails. The 'snail team' treated more than 4,000 kilometres of the river's waterways, but progress was limited: the infection rate was still around 50% in the middle of the century.

The treatment of infected individuals was slightly more successful. From the 1950s to the 1980s, officials conducted Egypt's largest ever

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River snails are the intermediate host of *Schistosoma* parasites.



public-health campaign, offering free treatment for schistosomiasis.

In those days, the only available cure was tartar emetic, a compound of antimony that was administered as 12–16 injections given once a week. It had severe side effects and low efficacy, but it did decrease schistosomiasis. However, the re-use of contaminated glass syringes and poor sterilization led to millions of people being inadvertently infected with the hepatitis B and C viruses.

In the early 1980s, an oral drug, praziquantel, became available that could kill blood flukes in one dose with minimal side effects. Between 1982 and 1988, Egypt's health ministry used praziquantel only in some particularly high-risk regions and for certain age groups, but it soon became the standard treatment. In 1988, the ministry began providing praziquantel free of charge nationwide to people diagnosed with schistosomiasis, using a strategy of population-based selective chemotherapy.

The government also tried to change the behaviour of the highest-risk section of the population: its farmers. The health ministry broadcast an effective TV health campaign in the 1980s. Starring beloved actor Mohamed Reda dressed as a farmer, it encouraged agricultural workers to take their oral medication and to “turn their back to the canal” — a message to stop urinating in the Nile, as this was releasing the parasite to restart its life cycle.

Eventually, the campaigns had the desired effect. By 1993, the prevalence of urinary schistosomiasis had fallen to less than 7%.

## RISK FACTORS

Despite tackling schistosomiasis, Egypt still faced huge problems with bladder cancer. “We thought that if people stopped polluting the water, schistosomiasis would disappear and bladder cancer would be eliminated,” says Amal Ibrahim, an epidemiologist at the National Cancer Institute at Cairo University. “The problem is: it did not happen.”

Instead, Egypt shifted to a more Western pattern of bladder cancer. “We started to notice this change in the mid-1990s,” recalls Ibrahim. Egyptians tend to be heavy smokers, “so instead of having squamous cell carcinoma, we now have high rates of urothelial bladder cancer caused by smoking,” he says. Consequently, most bladder cancers in Egypt today are the urothelial type, which originates in the cells of the inner lining of the bladder. But a substantial proportion of squamous cell carcinomas are still attributed to chronic schistosomiasis infection. “This is caused by the 10–15-year lag period between schistosomiasis infections and the onset of bladder cancer,” explains Khaled.

For the past decade, Christopher Loffredo, who studies cancer prevention at the Georgetown Lombardi Comprehensive Cancer Center in Washington DC, has led several projects on bladder cancer in Egypt. Loffredo sees the shift in the type of bladder cancer as an effect of the country's rapid industrialization. “When countries transition, infectious diseases tend to lose ground and give way to chronic diseases,” he says. This is because diets change, lifestyles become more sedentary, and harmful behaviours such as smoking escalate. The use of pesticides, herbicides and insecticides also tends to increase.

To assess the risks posed by these changes, Loffredo and his colleagues conducted a large study<sup>1</sup> of Egyptian male farmers between 2006 and 2011. They found that smoking cigarettes and water pipes is the biggest risk factor. “Tobacco smoking increases the risk for bladder cancer by about two- or threefold compared to those who never smoked,” says Loffredo. In addition, exposure to pesticides increases the odds of getting bladder cancer in a dose-dependent manner, and this association is stronger for urothelial cancer than for squamous cell carcinoma. The health risks posed by pesticides, Loffredo says, are exacerbated by the farmers' poor education and limited financial resources. “If a farmer can't read the label of a product, there is a risk of overuse of certain harmful products.” He adds that most farmers do not have the means to purchase the masks and protective clothing they need to limit their pesticide exposure.

Although smoking and pesticides might be assumed to increase lung cancer, the lungs are not as badly affected as other organs. “It is not surprising that the cells located in the inner layer of the bladder are exposed and affected by the breakdown products of tobacco smoke and occupational chemicals,” says Loffredo. These products, he explains, are filtered from the blood by the kidneys and then sit in the bladder, often for hours at a time.

Loffredo's research has also exposed a third, quite surprising, risk factor. About half of the farmers with urothelial bladder cancer had a history of schistosomiasis. When combined with the other risk factors, the repeated irritation and inflammation of the tissue lining in the urinary tract caused by the schistosomiasis eggs is more likely to result in urothelial bladder cancer than squamous cell carcinoma.

## NEW CHALLENGE

The cancer situation in Egypt is complex. To further confuse the situation, for a long time Egypt had no official agency to collect data and

analyse them, so the burden of cancer remained unclear. In 2007, Ibrahim proposed that Egypt establish the National Cancer Registry. “Cancer is a monster,” he told representatives of the Ministry of Health and Population. “If you are fighting a monster, you need to know how big it is.” He received the necessary funding and started to collect population-based data from centres and hospitals across the country. A handful of these centres had developed small-scale, localized cancer registries in the 1990s, with the help of the Middle East Cancer Consortium, an intergovernmental organization established in 1996 with the primary goal of helping countries in the region set up national cancer registries.

Egypt's cancer registry covers 21% of the population, from the country's most populated regions, including rural areas, and extrapolates from these data to cover the burden of cancer in the entire population. Its 2014 report<sup>2</sup> revealed that there are 115 new cases of cancer in every 100,000 people each year. Bladder cancer affects 13 men per 100,000 (11%), which makes it the second-most-common cancer in men after liver cancer. Women have fewer risk factors because they smoke less and tend not to have occupations that put them in contact with the river. Not surprisingly, they are less likely than men to get bladder cancer — their incidence rate is only around 3 per 100,000. But because the population is growing and ageing, the prevalence of bladder cancer in both sexes is expected to increase more than threefold by 2050.

Despite the progress in data gathering and analysis, tackling bladder cancer does not seem to be at the top of Egypt's health agenda. The hepatitis fallout from the early schistosomiasis campaigns means that “bladder cancer lives in the shadow of liver cancer”, explains Ibrahim. The government has been attacking hepatitis C and hepatocellular carcinoma “very energetically” by providing free or low-cost treatment to a large section of the population. “They are now widening the scope of diagnosis and treatment by targeting students, workers and military recruits,” he adds.

Ibrahim says these actions should massively lower the incidence of liver cancer. He thinks that if the government put as much effort into targeting the smoking epidemic, rates of bladder cancer could also fall significantly. “But controlling smoking is more difficult than controlling hepatitis C,” he says.

Khaled agrees with this assessment. Egypt, he says, has one successful story: the control of schistosomiasis. “But we have a failure story, which is smoking.” ■

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1. Amr, S. et al. *Arch. Environ. Occup. Health* **70**, 19–26 (2015).
2. Ibrahim, A. S., Khaled, H. M., Mikhail, N. N. H., Baraka, H. & Kamel, H. J. *Cancer Epidemiol.* **2014**, 437971 (2014).