Successful control of schistosomiasis and the changing epidemiology of bladder cancer in Egypt

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INTRODUCTION

While bladder cancer is common and morbid in the USA and Europe, its toll has been far greater in Egypt. Until recent years, bladder cancer has been the most frequently diagnosed cancer and the most common cause of death in men aged 20–44 years in Egypt [2]. Bladder cancer epidemiology, its long history as a cause of morbidity and mortality, and the recent success in reducing its incidence are intimately related to the history of schistosomiasis in Egypt. In this review, we describe the phenomena that contributed to the schistosomal public health crisis, detail efforts to treat and prevent schistosomal infections (‘infestation’ is the correct terminology for a parasite–host interaction, but ‘infection’ is commonly used; we will use the two words interchangeably in this review), and discuss the relationship between urinary schistosomiasis and bladder cancer epidemiology in Egypt.

METHODS

We conducted a literature search of available English and Arabic language publications on schistosomiasis and bladder cancer. We searched the PubMed database and the holdings of the Eskind Biomedical Library at Vanderbilt University. We then used the bibliographies of these sources to expand our search. In addition, we searched the internet for published reports from governmental, non-governmental and international aid agencies involved in the effort to eradicate schistosomiasis and bladder cancer in Egypt.

A LONG HISTORY OF INFESTATION IN EGYPT

Urinary schistosomiasis has plagued Egyptians for thousands of years. Schistosomal ova have been found in mummies from 1200 BC, and hieroglyphics dating back to 1900 BC in the Kahun Papyrus depict haematuria related to the infection [3]. (Fig. 1). Medical papyri of the ancient Egyptians recognised the infection and several treatments for it, referring to it as aaa disease. In the Ebers, Berlin and Hearst Papyri, ancient Egyptians identified symptoms of haematuria, dysuria and frequency associated with the disease. They also describe a treatment mixture that includes sedatives and antispasmodics (Hyoscyamus), and even antimony [4–6]. With the fall of ancient Egyptian civilization, knowledge about this...
prevalent and lethal parasitic infection disappeared with it, until the 19th century.

The first Europeans to contract schistosomiasis did so in 1798 during the 3-year French invasion of Egypt. During the invasion, many soldiers are believed to have suffered, and even Napoleon was thought to have been infected [7]. The parasite responsible for the syndrome of haematuria, dysuria, anaemia, wasting and development of fatal bladder cancer was first identified in 1850, by Theodor Bilharz, a German pathologist who worked in Kasr Eleiny School of Medicine nearly 3000 years after the syndrome was first documented (Fig. 2). Bilharz died of typhus in Cairo 1862, and research about the disease died, temporarily, with him. The eponymous label of Bilharzia lives on, however, and is used today interchangeably with schistosomiasis.

IRRIGATION, DAMS, AND SNAILS

Snails (Biomphalaria and Bulinus species) are critical to the lifecycle of schistosomes, and serve as their intermediate host. The snails harbour sporocysts and release schistosomal cercariae into the water (Fig. 3). These cercariae penetrate human skin and migrate to the portal circulation and the liver, where they mature into adults. Paired worms then migrate to the venous plexus of the bladder and produce eggs that lodge within the bladder wall. Some of these are then released into urine, and find their way back to the water source. Therefore, the history of schistosomiasis is intimately related to the history of water management and sanitation in Egypt.

The Nile River has been virtually the sole source of that water for Egyptians, but until relatively recently has been subject annual cycles of floods and droughts. The need for dependable and reliable irrigation, along with improvements in engineering, allowed for the construction of dams and waterworks starting in the 19th century, providing year-round irrigation over a wider area. The largest dam, the Aswan High Dam, was completed in 1970 (Fig. 4).

These efforts resulted in more stable, year-round agriculture and hydroelectric power generation, but also slowed the flow of water through Egypt causing a dramatic increase in the snail population, and increased the contact of people with snail-infested water. Consequently, the prevalence of schistosomiasis soared. A study in 1930
suggested that perennial irrigation caused at least a 10-fold increase in disease prevalence [8]. Another study suggested increase prevalence from 1% to 3%, historically, to 60% to 70% with perennial irrigation [9].

**EARLY EFFORTS TO CONTROL INFECTION**

In the early 20th century, much was learned not only about the organisms themselves, but also about how to treat the infections they cause. Robert Leiper of the Royal Army Medical Corps discovered that two genera of snails (*Bulinus* and *Biomphalaria*) transmitted two species of schistosomes: *Schistosoma haematobium* and *S. mansoni*, respectively [10]. As the organism became better characterized, the prevalence of infection was recognised to be quite substantial. Reports from the Egyptian government in the early 1920s indicate that infection rates were as high as 70–80% [11]. At that time, the only treatment was the tartar emetic, an antimony compound administered as series of i.v. injections over a month with a severe side-effect profile, and only 50% efficacy for those able to complete a course of treatment [12]. However, the treatment only reduced disease prevalence marginally to ≈50%, and some treatment efforts were marred by the spread of Hepatitis B and C through re-use of needles.

Attention was also turned to interrupting the lifecycle of the organisms by destroying their snail hosts, using copper sulphate. This was pioneered in El-Dekhela oasis in 1926–30 by Mohamed Khalil, Director of Chronic Disease at the Egyptian Ministry of Health, and results were promising [13]. An American named Barlow, a graduate of Johns Hopkins’ School of Hygiene, arrived in Egypt in 1929. He was convinced that the Khalil study was biased, and believed that the best method of controlling the snail population was by temporary drying of the canals and manual collection of the snails [11]. In 1937 and 1938, Barlow conducted large-scale experiments in which canals were dried and dredged every 2 months, and reported positive results, albeit with large investments of human capital [14]. The Egyptian government subsequently developed a Bilharzian snail control section with Barlow at the helm [13]. By 1950, the snail control programme employed ≈10 000 people [15].

Unfortunately, despite the enormous effort put forth during this era, most of the treated canals were still infested with snails. Several multinational efforts at snail eradication ensued. Despite all of these efforts, the prevalence of schistosomal infection in Egypt was still ≈50% in rural areas of Egypt in the middle of the 20th century [16].

**THE MODERN ERA OF INFECTION CONTROL**

By 1980, a new compound called praziquantel became available, and was found have >90% efficacy in eradicating human infection after only one dose. Moreover, its side-effect profile was minimal and it was inexpensive. Armed with this new agent, the United States Agency for International Development and the Ministry of Health and Population (MOHP) of Egypt collaborated to design and implement the Schistosomiasis Research Project (SRP). Designed by scientists from both countries, the project had two objectives:

1) to provide the Ministry of Health in Egypt with better tools with which to control schistosomiasis;
2) to build the capacity for Egyptian scientists to carry out biomedical research.

The SRP was instrumental on several fronts, from improving diagnostic techniques to implementing and monitoring treatment efforts. The SRP scientists developed rapid tests for *S. mansoni* and *S. haematobium*. The dipsticks are still used in newly irrigated areas of Egypt for screening purposes. For therapy, the SRP showed that mass treatment (i.e. treatment of all persons in an affected community) was efficacious, safe and well tolerated. In all, mass treatment turned out to be more effective than mass screening. It was also made much more palatable after the development of a paediatric suspension of praziquantel suitable for young children and others unable to swallow the large and very bitter tablet formulation [17].

In 1997, the Minister of Health and Population accepted the SRP recommendations and gave another programme, the National Schistosomiasis Control Project (NSCP), the ‘go ahead’ to begin mass chemotherapy against schistosomiasis in schools and high-prevalence villages (i.e. those found in earlier surveys to have >20% prevalence of schistosomiasis). The effort was bolstered with $27 million in funding from the World Bank. Later that year, all of ≈10 million school-children in rural Egypt and all residents of >500 villages considered to be at high risk of infection, were offered praziquantel. With success of the NSCP, the threshold for treatment was lowered from a prevalence of 20% to 10% in 1999, and then lowered again to 3.5% in 2002.

Public awareness about the disease soared during this time, in part because of treatment efforts, but also because of aggressive, targeted education efforts, including television messages. Health education classes about schistosomiasis were taught in schools. Limited outreach activities were also conducted using mosques and targeting agriculture workers. It was established that almost 100% of the population had seen the television messages, and that most understood the availability of free chemotherapy. The SRP also initiated and supported an epidemiological survey in nine governorates. Stool and urine from >70 000 individuals were examined in a representative sample of the villages in each of these governorates.

Snail elimination using niclosamide (superior to and less expensive than copper sulphate) became a supportive strategy rather than a primary strategy, as praziquantel use spread throughout the country. With success of this programme, the number of waterways treated decreased from 49 000 annually, to 1800 between 1997 and 2001. Similarly, the length of waterways treated decreased from 4400 km to 2900 km [18]. Nevertheless, the ‘snail team’ still surveyed all canals and drained them twice annually. Throughout Egypt, but particularly in the Delta, the potential for transmission is still widely present: between 5% and 30% of waterways still harbour snails [18].

The NSCP was closed in 2002, and the outcomes were overwhelmingly positive. Among the general population in the Delta, the prevalence of *S. mansoni* declined from 14.8% in 1993 (the first year of the project) to 2.7% in 2002 (when the project was closed) and continued to decline thereafter, reaching 1.5% in 2006. Similarly, the prevalence of *S. haematobium* declined from 6.6% in 1993 to 1.9% in 2002, then to 1.2% in 2006 [19]. Overall, national and international efforts to control schistosomiasis in Egypt have been remarkably effective over the past 30 years (Fig. 5).
The widening availability of modern sanitary infrastructure development and sustainability. Administrative and political obstacles have dogged the agency, but some progress continues to be made. New canals are now lined with concrete to guard against the establishment of snail colonies. Newly established villages have sufficient water supply and sanitation to keep the human risk factors for transmission at a minimum. All new immigrants to newly reclaimed areas are systematically screened and treated for schistosomiasis. These efforts take place in the setting of increasing urbanization of the Egyptian population, increasing literacy and the widening availability of modern sanitary equipment and clean water supply.

SCHISTOSOMIASIS AND BLADDER CANCER

A.R. Ferguson [20], in 1911, was the first scientist to posit a connection between chronic schistosomal infection (with S. haematobium) and bladder cancer, based on a series of 40 cases. As Egyptians are exposed to other carcinogens (tobacco, pesticides) at rates that exceed those seen in other countries, this association was not immediately recognized as aetiological by the whole scientific community. However, over the century since the Ferguson paper [20], his hypothesis has been confirmed in the laboratory and in epidemiological studies.

Mechanistically, there are several factors that may contribute to the oncological potential of schistosomiasis infection. Bilharzial ova deposited in the bladder provoke an intense inflammatory reaction, associated with the production of oxygen-derived free radicals, which may induce genetic mutations or promote the production of carcinogenic compounds (such as N-nitrosamines and polycyclic aromatic hydrocarbons) [21–23], leading to malignant transformation. Shokeir [24] showed that schistosomiasis is often accompanied by chronic bacterial super-infection, which may in itself predispose to squamous cell (SC) neoplasia. Bacteria found to accompany schistosomiasis can promote the formation of N-nitrosation of amines, adding to those from other sources such as the diet.

In addition to the laboratory data linking schistosomiasis infection with Bilharzial bladder cancer are epidemiological studies, which show that changes in the epidemiology of schistosomiasis are reflected in the changing epidemiology of bladder cancer [25,26]. In the 1970s, bladder cancer is thought to have accounted for about one third of solid cancers in Egypt, making it the most common solid cancer among men in Egypt and second only to breast cancer in women [27]. In 2002, even as schistosomal infection control efforts were taking hold, the incidence of bladder cancer was the highest in the world, at 37 cases per 100 000. Between 1999 and 2001, bladder cancer still accounted for 16.2% of all cancers among men in Egypt [28]. By contrast, bladder cancer is the ninth most common cancer worldwide. In the USA, it is the fourth most common cancer among men, accounting for 7% of non-skincancer malignancies, and is 12th most common among women [26,29].

Besides incidence, there are other epidemiological differences between Bilharzial bladder cancer and the urothelial cell (UC) bladder cancer commonly seen in the West. The median age at presentation for patients with Bilharzial bladder cancer is 61.6 years, as opposed to 72.9 years in patients with UC carcinoma of the bladder in the USA [28]. The predominant cell type is SC (>80%), compared with Western series where UC is found in 90–95% of patients with bladder cancer. About 95% of cases are muscle-invasive at the time of presentation and, in absence of effective systemic therapy, these cases are often fatal. In fact, until recently, Bilharzial bladder cancer has been the most common cause of death among men aged 20–44 years [28]. Another distinction from UC carcinoma of the bladder is that the male predominance is more pronounced in Bilharzial bladder cancer (about 5 : 1 vs 3.5 : 1).

With the reduction in schistosomiasis due to control efforts over the past 30–40 years, the epidemiology of bladder cancer in Egypt has shifted dramatically. This is exemplified by a recent study from Gouda et al. [27] in which they reviewed 9843 patients treated for bladder cancer by Egypt’s National Cancer Institute (NCI) in Cairo between 1970 and 2007. The authors identified a dramatic decline in the proportion of patients with bladder cancer who had schistosomal ova on pathological evaluation (82.4% vs 55.3%) and in the proportion of patients with cancer treated for bladder cancer (from 27.6% of patients treated for cancer to 11.7%). They also describe an increase in the median age at presentation (from 47.4 years to 60.5 years), a decrease in the male to female ratio (from 5.4 to 3.3) and a decrease in the proportion of patients with SC histology (from 75.9% to 33.0%) (Fig. 6). A similarly designed study from the Egyptian NCI in Cairo showed that patients treated for bladder cancer in 2005 had a six-fold increased risk of UC carcinoma of the bladder (vs SC carcinoma) compared with patients treated in 1980 [30]. They also evaluated the incidence of Bilharzial bladder cancer at several other institutions in Egypt during this period and showed no rise in incidence at other institutions as the incidence decreased at the NCI. Although such retrospective study designs are limited, the NCI-Cairo is the nation’s largest tertiary referral centre and cystectomy is rarely performed in the community. Furthermore, these epidemiological trends have also been documented in nation-wide tumour registries [28].

Thus, the receding tide of schistosomal infection has resulted in a victory against the deadly SC (Bilharzial) variant of bladder cancer.

CONCLUSION

The coordinated environmental health efforts of the Egyptian government and multinational organizations have met with overwhelming success in the battle against schistosomal infection and, in turn, bladder cancer. These efforts have included public works, ground water projects, public health education, screening, treatment, infrastructure development and sustainability. The control of schistosomiasis has led to a shift in the epidemiology of bladder cancer in Egypt, characterized by lower incidence,
higher age at diagnosis, lower male predominance, and lower proportion of SC histology.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: MOHP, the Ministry of Health and Population; SRP, Schistosomiasis Research Project; NSCP, National Schistosomiasis Control Project; SC, squamous cell; UC, urothelial cell; NCI, National Cancer Institute (Egypt).