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THE PREVENTION OF BLADDER CANCER:
AN INTEGRATED APPROACH THROUGH THE CONTROL OF SCHISTOSOMIASIS¹

Identification of specific causes of cancer and their prevention is of global concern for cancer control efforts. The geographical distribution of urinary schistosomiasis and cancer of the bladder supports an aetiological relationship between these two diseases. The association of bladder cancer and schistosomiasis is a unique combination of a cancer which can be identified at an early stage at the community level and an aetiological agent which is susceptible to specific treatment. Now more than ever before the feasibility of the control of bladder cancer through control of urinary schistosomiasis in endemic countries should be carefully examined.

1. SCHISTOSOMIASIS

Schistosoma haematobium infection or urinary schistosomiasis is endemic in 52 African and Eastern Mediterranean countries. This disease is an occupational hazard affecting the poor agricultural rural populations of these countries. It is estimated that at least 180 million persons are at risk of infection and about 90 million persons are infected (WHO, 1980; Iarotski & Davis, 1981).

The highest prevalence and the major proportion of heavy infections are observed in school-age children. In most rural endemic areas, extensive and frequent water contact of this age-group is associated with heavy infections. The excretion of blood and protein in the urine of infected children, as well as adults, is directly correlated with the number of S. haematobium eggs in the urine (Mott et al., 1983). These clinical manifestations are related to severe focal lesions of the bladder which may develop into chronic disease including carcinoma of the bladder 20-30 years after infection begins.

For many years it has been known that the bladder lesions due to S. haematobium infection in children may be reversible with antischistosomal treatment. The older antischistosomal drugs were highly toxic and their large-scale use was limited, particularly in children. A turning point has been reached now that safe oral antischistosomal drugs, praziquantel and metrifonate, can effectively stop the progress of and reverse the morbidity due to S. haematobium infection (WHO, 1980; Iarotski & Davis, 1981; Mott et al., 1983).

2. BLADDER CANCER

Bladder cancer, one of the 12 most common cancers, is estimated to occur in over 173 000 persons per year (Parkin et al., in press). Among males, bladder cancer is ranked as the eighth most common cancer and is the twelfth most common cancer in females. Two types of bladder cancer may be distinguished clinically, pathologically and epidemiologically.

Transitional cell bladder cancer is frequently observed in the western developed countries and is related to industrial exposure to known carcinogens. Squamous cell bladder cancer occurs in African and Eastern Mediterranean countries, such as Kenya, Malawi and Egypt,

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following very closely the geographical distribution of *S. haematobium* infection. Almost all of the reported series of cases of bladder cancer with urinary schistosomiasis are of the squamous cell type, predominantly in males in agricultural occupations. The comparative characteristics of these two types of cancer of the bladder are summarized in Table 1.

TABLE 1. COMPARATIVE CHARACTERISTICS OF BLADDER CANCER WITH AND WITHOUT SCHISTOSOMIASIS

Characteristic	With schistosomiasis	Without schistosomiasis
Age (median)	40 years	65 years
Male:female ratio	9:1-5:1	2:1
Estimated latency after initial infection or exposure	20-30 years	30-40 years
Occupational risk	Farming	Industry
Cell type	Squamous (75-95%)	Transitional (95%)
Location	Bladder wall (98%)	Trigone (21%)
Number of sites	Single mass	Multiple (up to 25%)
Metastases	Rare	Frequent

In Malawi, Mozambique and Zambia, where *S. haematobium* prevalences are particularly high among agricultural workers, the overall incidence rates of squamous cell cancer of the bladder are about eight times as high as those found in the United States of America and the United Kingdom. In certain areas of Southern Malawi, where *S. haematobium* infections are particularly severe, the total incidence of bladder cancer is about four times as high as in the United States of America or the United Kingdom but the incidence rates of the squamous cell type is 35 times as high (Lucas, 1982).

The bladder cancer associated with schistosomiasis is the most frequent of all cancers in males in Egypt.

In Uganda, cancer of the bladder has not been associated with schistosomiasis but rather with urethral stricture of unknown aetiology. On the other hand, squamous cell, rather than transitional cell bladder cancer is observed. No consistent experimental animal model for bladder cancer of either cell type has been developed (Hicks, 1983).

Experimental evidence from various animal studies suggests that the biogenesis of bladder cancer observed in developed countries is a multistage phenomenon. A carcinogen appears to initiate these events followed by promotion and propagation of tumour growth by other factors which are not necessarily carcinogens *per se*. The proven chemical bladder carcinogens act on the urothelium from its urinary face.

3. RELATIONSHIP BETWEEN SCHISTOSOMIASIS AND BLADDER CANCER

A causal association between *S. haematobium* infection and cancer of the bladder was suggested over 100 years ago. In countries endemic for urinary schistosomiasis, the high frequency of squamous cell bladder cancer compared to the transitional cell type has been consistently reported (Cheever, 1978). Surveys in hospital outpatient clinics in Egypt indicate that squamous cell cancer of the bladder occurs in 10 of every 1000 infected adults as compared with 0-3 cases in every 1000 adults without *S. haematobium* infection (Halawani & Tamani, 1955). In a cross-sectional village survey in Egypt, using an exfoliative cytology

technique, 2.5% of males above age six with S. haematobium infection compared with 0.3% of uninfected males were diagnosed as having bladder cancer. Amongst females, the bladder cancer rates were 1.1% and 0-2% respectively (Dimmette et al., 1955). No large-scale prospective population or cohort epidemiological studies on bladder cancer within endemic areas have been undertaken.

At autopsy the chronic sequelae of urinary schistosomiasis have been correlated directly with the number of S. haematobium eggs in the tissues. Up to 26% of deaths associated with schistosomiasis are due to cancer of the bladder (Cheever, 1978). In summary, the epidemiological association whereby cancer of the bladder is caused by urinary schistosomiasis has been consistently supported by clinical and pathological studies (Cheever, 1978; Halawani & Tamani, 1955; Dimmette et al., 1955; Brand, 1979).

Experimental research tends to support this causal relationship (Gentile, 1983). The cancers of the bladder induced in non-human primates after experimental S. haematobium infection do not have all the same characteristics as the human bladder cancers (Hicks, 1982, 1983). Attempts to produce cancer of the bladder in non-primate animals by schistosomal infection or direct incorporation of schistosome eggs have been unsuccessful (Dimmette et al., 1955).

Observations from experimental animal studies indicate that infection with S. haematobium supplies the proliferative stimulus necessary to accelerate the development of visible latent tumour foci from cells initiated or converted by exposure to low doses of bladder carcinogens. Urinary schistosomiasis might therefore be expected to increase the incidence of clinically symptomatic bladder cancer in exposed populations for any particular age-group (Hicks, 1983).

The predisposition to secondary bacterial infection of the urinary tract, particularly recurrent cystitis, due to pathological changes caused by chronic S. haematobium infection is a contributing aetiological factor for bladder cancer. The role of nitrosamines caused by bacterial infections, particularly in children, has been emphasized. Abnormal hepatocellular function in severe chronic schistosomiasis due to concomitant S. mansoni infection may contribute to the formation of abnormal tryptophan metabolites which are incriminated as cocarcinogens. Synergism between tobacco-smoking and schistosomiasis has also been suggested.

4. BASIS FOR BLADDER CANCER PREVENTION

In endemic countries, it has long been recognized that control of bladder cancer would probably be achieved through control of schistosomiasis (WHO, 1980; Cheever, 1978). Past pessimism regarding the control of schistosomiasis is unwarranted in view of the achievements of intensive programmes using efficient low-cost quantitative parasitological diagnostic techniques and safe, effective oral antischistosomal drugs.

Even without multiple interventions for schistosomiasis, treatment alone could be expected to reduce the risk of development of bladder cancer. If associated with an early detection programme, morbidity and mortality of bladder cancer as well as of schistosomiasis could be seriously affected.

4.1 Phases of intervention

The integration of schistosomiasis control and detection of bladder cancer does not permit distinction between primary and secondary prevention in the classical sense. The natural history of the two diseases presents opportunities for intervention at three stages:

- (1) during early S. haematobium infection and prior to development of disease;
- (2) after disease caused by S. haematobium is detectable and before the development of bladder cancer;
- (3) after development of the malignancy.

The first stage of intervention is the treatment of urinary schistosomiasis in entire endemic populations which causes:

- the elimination and cure of the infection in a high proportion of the infected population;
- in persons who remain infected, substantial reduction of the intensity of infection;
- reduction of the risk of development of severe disease and the sequelae, formerly associated with heavy infections;
- a surprisingly long period of reduced prevalence and intensity of infection in spite of exposure to reinfection.

At the second stage, treatment of urinary schistosomiasis is important as is treatment of concomitant urinary tract infections.

At the third stage, early detection by cytology screening is now feasible in endemic populations (El-Bolkainy et al., 1982).

4.2 Monitoring of high-risk groups

Within the health care system including primary health care, diagnosis and early detection and treatment of urinary schistosomiasis and bladder cancer may be provided. High-risk groups to be monitored include:

- school-age children may be monitored by systematic urine examinations;
- adults in agricultural occupations should be screened for both schistosomiasis and cancer of the bladder;
- individuals with haematuria in endemic areas may be identified for treatment of schistosomiasis and screened for cancer of the bladder.

5. AN APPROACH

The large-scale use of new effective antischistosomal chemotherapy within integrated control programmes provides a unique opportunity to assess the impact of this intervention on the incidence or repeated point prevalence measurements of bladder cancer. In view of the available information on the association between bladder cancer and schistosomiasis, it is of importance to monitor the effect of treatment of schistosomiasis on cancer rates in defined populations. The methodology for urinary cytology and quantitative parasitological measurements is technically feasible, relatively inexpensive, and has been tested in large-scale surveys acceptable to the population. The parasitological techniques are used routinely in national control programmes.

SUMMARY

The concept of the prevention of squamous cell cancer of the bladder in countries endemic for urinary schistosomiasis in Africa and in the Eastern Mediterranean Region is supported by epidemiological, clinical, pathological and experimental data. The association of bladder cancer and urinary schistosomiasis is a unique combination of one of the 12 most common human cancers which can be identified at an early stage in the community and a common parasitic infection, the aetiological agent, which is susceptible to specific treatment.

Further experimental research into the mechanisms of this relationship is to be encouraged. An evaluation of a large-scale community-based antischistosomal treatment programme to reduce the prevalence and incidence of bladder cancer is suggested.

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