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PROGRESS IN ASSESSMENT OF MORBIDITY DUE TO
SCHISTOSOMA HAEMATOBIIUM INFECTION: A REVIEW OF RECENT LITERATURE^a

schistosomiasis haematobia - ecc

CONTENTS

	<u>Page</u>
1. Introduction	2
2. Pathology	2
2.1 Pathogenesis	2
2.2 Worm and egg distribution in the human host	3
2.3 Factors influencing pathology	3
2.4 Disease in different organs	3
2.4.1 Urinary bladder	3
2.4.2 Ureter	4
2.4.3 Kidney	5
2.4.4 Genital organs	6
2.4.5 Gastrointestinal tract	6
2.4.6 Lung	6
2.4.7 Ectopic lesions	7
3. Clinical presentation	7
3.1 Early manifestations	7
3.2 Later stages	8
3.3 Urinary egg count	8
3.4 Haematuria and blood loss	8
3.5 Proteinuria and renal function	9
3.6 Bacterial infection of the urinary tract	10
3.7 Radiography, renography, ultrasound and computed tomography in morbidity studies of urinary schistosomiasis	10

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	<u>Page</u>
4. Effect of treatment on disease	12
4.1 Urinary egg excretion	12
4.2 Urinalysis	12
4.3 Disappearance or alleviation of symptoms and clinical disease	12
5. Bladder cancer and urinary schistosomiasis	13
5.1 Data in favour of the association between bladder cancer and urinary schistosomiasis	13
5.2 Data against a causal relationship between bladder cancer and urinary schistosomiasis	14
5.3 Possible basic mechanisms of carcinogenesis in urinary schistosomiasis	15
6. Conclusion	15
References	16
Tables	26

1. INTRODUCTION

Schistosoma haematobium infection is endemic in 53 African and Eastern Mediterranean countries including Jordan from where S. haematobium was reported in 1986. It is estimated that at least 180 million persons are exposed to the risk of infection and about 90 million persons are infected (155). However, the extent of morbidity due to S. haematobium infection has probably been underestimated. It is widely accepted that most infected individuals show no symptoms or signs upon physical examination, and only a small proportion develop serious chronic disease. The primary objective of the current strategy of control is the reduction or elimination of morbidity due to schistosome infection (156). To reach this objective, a thorough understanding of the morbidity due to S. haematobium is necessary. During the last decade considerable progress has been made in assessment of morbidity due to S. haematobium infection. This review emphasizes the scientific literature on this topic published, mainly but not exclusively, within the past 10 years.^a

2. PATHOLOGY

2.1 Pathogenesis

There are several different classifications for urinary schistosomiasis in the literature. Smith et al. (128), on the basis of an histological study using quantitative methodology, have suggested two stages for epidemiological, clinical and pathological studies: (a) active disease with significant egg excretion and (b) inactive disease with very few, mostly dead, eggs in the urine, or without eggs in the urine (5,128). Among infected persons the proportion of those with inactive disease increases with age. This classification is also supported by histopathological studies. Among 400 consecutive autopsies in Cairo, only 26% of S. haematobium infections were judged to be active at the time of death and the number of viable female S. haematobium worms decreased with age (28).

^a The reader would be well advised to familiarize himself with the older classic literature as reviewed in the special monographs Bilharziasis edited by F.K. Mostofi, Heidelberg, Springer-Verlag, 1967, and The urological aspects of bilharziasis in Rhodesia by R.M. Honey and M. Gelfand, In: Central African journal of medicine, 6: 1-259 (1960).

2.2 Worm and egg distribution in the human host

Quantitative pathological and parasitological studies of schistosomiasis at autopsy were carried out in Cairo by Cheever et al. (28). Adult schistosomes were recovered by perfusion and dissection; the tissue egg burden was estimated following hydrolysis of the tissues with potassium hydroxide. In 46 cases the distribution of S. haematobium female worms was: bladder, 48%; ureter and genitalia, 5%; mesenteric and portal veins, 47%; and pulmonary arteries, 0.2%. The organ distribution of S. haematobium eggs was: bladder, 42%; ureter, 7%; internal genitalia, 12%; intestines, 19%; liver, 5%; and lung, 16%. At autopsy more than half of the adult worms and eggs were found in the urogenital system. Considerable numbers of the worms were observed in the mesenteric and portal veins. A small proportion of S. haematobium worms was found in pulmonary vessels, but the lung tissue egg burden was high. The estimated geometric mean egg output was 600 000 eggs per S. haematobium worm pair, this being much higher than the estimated 15 900 eggs per worm pair for S. mansoni infection. Slower destruction of S. haematobium eggs in human tissue in comparison with eggs of S. mansoni was suggested to be the cause for this difference (28,106). Egg distribution is not random in the lower urinary tract. This is confirmed by the focal egg accumulation in histological studies at autopsy (28,34).

2.3 Factors influencing pathology

Evidence from clinical, epidemiological and pathological studies confirms that intensity of infection is a major factor determining development of the disease (3,29,67,69,75,103,106). Heavily infected persons are at risk of developing serious pathology. However, even at similar levels of intensity of infection, disease sequelae between individuals may vary widely. High focal tissue egg concentrations were observed in the ureters, at the ureteral orifice, interstitial ureter or ureterovesical junction, which may lead to urinary obstruction, yet the same density of eggs in the bladder is associated with little pathology (29).

Geographical variations in severity of the disease have been suggested by some authors. Clinical reports from Egypt and East Africa have indicated high morbidity and considerable mortality, while those from South and West Africa have not (57,80). However, the potential importance of different geographical strains of the parasite in the development of human disease remains speculative. Comparative experimental studies using different strains of S. haematobium are not available, and, even if such studies were performed, they may not elucidate the geographical variation of human disease (26,106). The human immune status and response to infection probably play an important role in the development of pathology.

2.4 Disease in different organs

2.4.1 Urinary bladder

2.4.1.1 Frequency of the lesions

This organ is the most frequently affected in S. haematobium infection. Clinically, pathological lesions were observed by cystoscopy in 45 Egyptian children between five and 12 years of age, infected with S. haematobium (3). The bladder lesions, in descending order of frequency, were: hyperaemia (100%), sandy patches (32%), granulomas (18%), ulcer (9%), nodules (7%) and polyps (7%). Hyperaemia and sandy patches were commonly associated with active infection. Multiple lesions were also observed in 22% of the cases. In a hospital study of 100 adults examined consecutively in Zambia, sandy patches were present in all cases, granulomatous lesions in 17 and ulcers in four (57).

On the other hand, sandy patches of the bladder were observed in all cases of severe urinary schistosomiasis at autopsy in Egypt, and schistosomal polyps and bladder ulcers were both seen in 4.3% of cases (131). In another autopsy series in Egypt, of 255 persons infected with S. haematobium, no typical bladder ulcers were found, although superficial ulceration of polypoid patches was common (29).

2.4.1.2 Types of lesion

Hyperaemia is a clinical diagnosis and varying degrees of intensity are observed by cystoscopy in early and active infection. It is often associated with heavy infections and found most frequently near the ureteral orifices.

Sandy patches are the most common pathological lesions in the urinary bladder and are pathognomonic for S. haematobium infection. The sandy patches appear as yellowish/tan, with rough looking areas in the mucosa due to heavy egg concentration, reaching densities as high as 1 000 000 eggs per gram of tissue at autopsy (29). These same lesions have also been found in the ureters and rarely in the intestine (131). The trigone of the bladder and the proximity of the ureteral orifices are the most frequently affected sites.

Polypoid lesions of the bladder have been observed at all stages of the disease and are also related to heavy local tissue egg burden. Polyps of varying size may be either sessile or pedunculated. The majority are pea-sized, but polyps as big as 3 cm with multiple small satellite polyps have been reported (3). Smith et al. (132) made an analysis of bladder polyps excised by cystotomy from 18 patients with S. haematobium infection. The infections were all in an active stage except in three patients with inactive disease. The tissue egg burden of inactive polyps was higher than that of active polyps suggesting that the former were derived from active polyps with very heavy tissue egg burdens while small active polyps regressed naturally or after chemotherapy.

Vesical ulcers occur mainly on the posterior wall of the bladder. The ulcers were usually small with a heavy tissue egg burden in the ulcer site. High tissue egg density in the posterior wall has been considered to be a predisposing factor to ulceration. A series of bladder ulcerations in Egyptian patients with S. haematobium infections treated surgically were reported by Smith et al. (129). Among the 93 cases reported, two forms of schistosomal bladder ulceration were described: an acute form resulting from necrotic polypoid patches and a chronic form associated with heavy oviposition in the posterior midline and deep in the detrusor muscle.

Focal granulomas of the bladder are usually the size of a pin head, sometimes surrounded with dilated capillaries. At the centre of the granuloma there are schistosome eggs surrounded by layers of epithelioid cells, fibroblasts, and inflammatory cells. At a later stage necrosis, calcification or fibrotic tissue may replace the granuloma.

At autopsy bladder muscle hypertrophy was more frequently seen in cases with schistosomal obstructive uropathy than in those without, but no association with the presence of S. haematobium or with the intensity of infection was observed. However, the degree of diffuse, fibrotic constriction of the bladder was proportional to the bladder tissue egg burden (29).

Calcification of the urinary tract, predominantly the bladder, is a common sequela of urinary schistosomiasis. In a Zambian teaching hospital among 100 consecutive patients hospitalized with schistosomiasis, calcified bladders were present in 35 (57). In two other clinical series, 11 out of 26 (42.3%) and 94 out of 115 (81.7%) patients with active urinary schistosomiasis were shown to have calcified bladders in Egypt and Zambia respectively (81,145). However, these selective data tend to be biased towards the severe form of the disease which was the cause of hospitalization. In community based morbidity surveys only one out of 26 school-age children (3.8%) examined showed bladder calcification in Egypt (22) and 13 out of 124 adults (10.5%) in Liberia (85). Forsyth and Macdonald (68) reported in an earlier survey in Tanzania that 25 out of 358 (7.0%) infected schoolchildren had calcified bladders. Linear calcification of the bladder along the lines of deposited eggs rather than in the tissue itself usually occurs in its submucosa (106). Most of the calcified bladders retain normal elasticity. Only minor differences between the average capacity of calcified and non-calcified bladders were found in patients with schistosomiasis (29). Small urinary bladders have also been observed (120). Calcification of the bladder has been suggested as a risk factor towards the development of bladder cancer and its presence may be an indication of heavy infection as well as of other lesions or conditions (5,29). Carcinoma of the bladder in S. haematobium infection is reviewed in section 5.

2.4.2 Ureter

The ureters are less heavily and less frequently affected than the bladder. However, the pathological sequelae on ureters are no less important. Bilateral ureteral involvement in S. haematobium infection is the rule with lesions predominating more on one side than the other. In case of unilateral disease the left ureter is more often affected than the right according to some investigators (5,7,75,130,146). Abdel-Wahab (5) has suggested that this may be due to the richer venous anastomoses of the left ureter with the portal vein than

those of the right ureter. However, in a quantitative post-mortem analysis of 117 cases with urinary schistosomiasis, Smith et al. (128,131) found that the tissue egg burdens of the right lower ureter were markedly higher than those of the left, but unilateral obstructive uropathy occurred equally on both sides. Other reports have concluded that hydroureter as well as hydronephrosis were less frequently seen on the left side (127,154). Patients with bilateral schistosomal obstructive uropathy were found to have higher egg burdens than those with unilateral disease (154), although this conclusion was not confirmed in another study (29). Autopsy studies have generally confirmed the positive relationship between tissue egg burdens in the ureters and severity of the disease. Furthermore, tissue egg burdens of the ureters were much greater in cases with obstructive uropathy than in those without (128,131). In at least one study the presence, though not the degree, of the obstructive uropathy was related to the intensity of infection (29). Umerah (145) was the first to report that ureteral dilatation may not be associated with stricture caused by S. haematobium but is due to abnormal ureteral motility. This observation was confirmed by Abdel-Halim et al. (1). Severe schistosomal obstructive uropathy (hydroureter and hydronephrosis) has been frequently associated with ureteral stenosis, ureteral deformation and ureteral stone.

Pathologically, the lesions seen in the ureters are similar to those of the bladder including sandy patches, polyps, granulomas, ulcers, calcification and stones. Ureteritis cystica, a result of hydropic degeneration and dropout of the central cells of a urothelial cell nest, and ureteritis glandularis, containing mucus and lined with one or more layers of columnar cells, have been reported (5). Resolution of granulomas may result in ureteral fibrotic stenosis which, clinically, is most commonly seen in the interstitial ureter, and less frequently in the ureterovesical junction or lower third of the ureter. Ureteral calculi are common in urinary schistosomiasis (24,25,45). Smith et al. (130) reported that they produced obstruction in 24% of 155 cases with schistosomal obstructive uropathy treated surgically. Carcinoma of the ureter is rare in urinary schistosomiasis.

2.4.3 Kidney

Schistosomal granulomas in the kidney parenchyma are not clinically important and have been observed in 2% of the infected cases at autopsy (5). Significant renal lesions are mainly the sequelae of schistosomal obstructive uropathy. At autopsy two-thirds of cases with extreme hydronephrosis were associated with distortion of the ureteral orifices (29). Those with hydroureter combined with hydronephrosis were found to have higher egg burdens than those with hydroureter only (154). Hydronephrosis was found to be more common in boys than in girls (68,69).

Evidence regarding the relation of S. haematobium infection to pyelonephritis or glomerulonephritis is conflicting. At autopsy, no association between pyelonephritis and either the presence or intensity of S. haematobium infection per se was found (29, 123). However, there is general agreement about the relationship between pyelonephritis and schistosomal obstructive uropathy; the factors predisposing to pyelonephritis in cases of schistosomal obstructive uropathy, such as stricture, renal stones, etc., are similar to those in cases without schistosomiasis. Based on a consecutive study of 246 autopsies in Cairo, Sadigursky et al. (123) concluded that glomerulonephritis was not related either to S. haematobium or to S. mansoni infection, nor were any mesangial pathological changes related to schistosomal infection. Nephrotic syndrome associated with a combined S. haematobium/Salmonella infection reversed after treatment with antischistosomal drugs (61). Glomerular lesions in the absence of schistosomal antigen were observed in S. haematobium infected adults (12). IgM, IgG, Clq and C3 were identified in the glomeruli of seven out of 13 patients whose clinical presentation was not suggestive of glomerular disease.

In renal biopsies from children with S. haematobium infection, Higashi et al. (84), using immunofluorescent microscopy, observed schistosomal antigen in mesangial areas of the glomeruli in four out of 13 children as well as extensive granular deposits of IgG, IgM and C3. The absence of clinical renal disease and lack of basement membrane changes suggested that such deposits may not be of functional significance. This was confirmed by normal renal function tests (84).

2.4.4 Genital organs

Genital organs may be secondarily involved since S. haematobium parasitizes the vesical plexus (121,131). However, the evidence of the functional consequences of these lesions remains conflicting. In one analysis the mean S. haematobium egg count per gram of seminal vesicle tissue was nearly 20 000 while egg distribution among other organs such as the upper ureter, rectum and appendix was lower in that order (131). As a result of heavy infection, seminal vesicle fibrosis, muscular hypertrophy and enlargement of the seminal vesicles were observed and at times, though rarely, were extensive or associated with calcification. Increased seminal vesicle weight and volume correlated well with obstructive uropathy; and determination of seminal vesicle enlargement by manual examination could be a simple method of screening for schistosomal obstructive uropathy, as suggested by Christie et al. (35). The prostate is less commonly affected and the eggs are concentrated in the ejaculatory ducts associated with fibrosis (58). S. haematobium eggs, with sometimes an associated inflammatory reaction, can be found in the testis, epididymis and penis. A direct correlation between these lesions and male fertility has not been proved.

The presence of S. haematobium eggs in the female genital organs is not uncommon. The sites of predilection are the vulva, vagina and cervix, while the internal genital organs, such as the ovaries, Fallopian tubes and body of the uterus, are less affected (76,77,121,153,157). Polypoid, ulcerating and nodular lesions may be found on the cervix or on the vaginal wall caused by cellular infiltration, granuloma and fibrosis. The histopathology of 176 clinical cases of gynaecological schistosomiasis in Malawi was reviewed (157). Gynaecological complications of schistosomiasis were considered to be a significant cause of female morbidity in Malawi, especially when the lower genital tract was involved; involvement of the upper genital tract was not a major cause of morbidity, but was difficult to diagnose clinically. In autopsies carried out in Nigeria the frequencies of infection in the cervix and vagina were similar, although higher tissue density of eggs was found in the vagina (52). S. haematobium eggs were found in 31% of ovaries in 34 women at death in Nigeria using a digestion method, while no eggs were seen in histological sections. Moreover, in a large series of 19 862 surgical biopsies in Ibadan S. haematobium eggs were found only in one specimen. Apparently, the low tissue density of eggs escaped routine histological examinations. Tissue digests of the Fallopian tubes and uterus showed S. haematobium eggs in 11% and 20% of cases respectively, but histologically no lesions were noted. In the majority of S. haematobium infections, Fallopian tube involvement was only incidental (70). Tiboldi (144), who reviewed publications on ovarian involvement in schistosomiasis during the past 70 years, found that big differences existed in the frequency of ovarian involvement among different countries or areas and that clinical disease of the ovaries due to focal S. haematobium egg deposits was rare. No causal association between infertility or ectopic pregnancy and schistosomiasis has been reported.

2.4.5 Gastrointestinal tract

The tissue egg density of S. haematobium increased from the proximal to the distal gastrointestinal tract with the egg concentration in the appendix being highest, much higher than that observed in the adjacent regions of intestine (131). Some authors consider that symptomatic appendicitis may be associated with heavy infections (121,128,154) and even cause obstruction (88). Others feel that this remains conjectural (52). At least one case of intestinal metaplasia with focal adenocarcinoma in S. haematobium infection has been reported (56). Polyps have been found, mainly in the rectosigmoid colon, in 6% of S. haematobium infected cases in a post-mortem study. The polyps were inflammatory lesions and, like those in S. mansoni infection, their surfaces were frequently ulcerated (29). Calcification of the colon detected by radiological examination in S. haematobium infection has rarely been reported (29,64). Of 510 South African schoolchildren who were excreting S. haematobium eggs in the urine, 388 (76%) also had eggs in rectal biopsy specimens (38).

2.4.6 Lung

S. haematobium egg granulomas are frequently seen in the lungs both of experimentally infected animals and of humans at autopsy (26,29,80,121,126). Although the concentration of S. haematobium eggs in the lungs is relatively high compared with S. mansoni eggs, both pulmonary arteritis and cor pulmonale are rare complications in S. haematobium infection. In experimentally infected animals pulmonary arteritis may be seen but cor pulmonale has not been reported. Among 159 autopsy cases with only S. haematobium infection in Egypt, focal

pulmonary arteritis was discovered only in one case with heavy infection and no cor pulmonale was observed in that series. Cor pulmonale was not related to the intensity of S. haematobium infection (29). In another pathological study of S. haematobium infection done in the Sudan, although a higher frequency of lung lesions was found, pulmonary arteritis was only seen in three cases associated with liver fibrosis due to S. mansoni infection (80). Few cases of cor pulmonale caused by S. haematobium infection have been reported in the literature within the past 10 years (13,91) although schistosomal cor pulmonale associated with S. haematobium infection was described earlier (5,126).

It has been suggested that collateral circulation is a prerequisite for eggs to reach the lungs and cor pulmonale to develop in S. mansoni infection. This hypothesis is based on the fact that the lungs usually become involved after the development of advanced hepatic fibrosis and portal-systemic collaterals. Many clinicopathological studies have confirmed this. However, in S. haematobium infections eggs from the perivesical plexus can pass through the inferior vena cava and directly to the lungs. Lung granulomas are quite frequent in urinary schistosomiasis at autopsy but pulmonary arteritis, as seen in S. mansoni infection, is not. Cheever et al. (29) suggested that intensive oviposition over a short period may be necessary for inducing cor pulmonale in S. mansoni infection, but in S. haematobium infection eggs are deposited in the lungs gradually. Although this seems unlikely, no other hypothesis has been proposed.

2.4.7 Ectopic lesions

S. haematobium worms may migrate outside the genitourinary system and their eggs may cause ectopic lesions.

S. haematobium eggs deposited in the liver may cause granulomas, but Symmers' fibrosis was not seen in persons infected only with S. haematobium (89). Tissue reaction to S. haematobium eggs was considered to be less severe than that to S. mansoni eggs.

Cutaneous deposition of S. haematobium eggs has been recorded. They are usually seen in the genital and perigenital region (6,75). Papular lesions in the neck, chest, abdominal wall or periumbilical areas were also reported (86,98,108). Skin biopsies usually show viable eggs.

Ectopic deposits of S. haematobium eggs in the central nervous system (CNS) with clinical symptoms confirmed histologically were rare as compared with CNS involvement in S. mansoni and S. japonicum infections (101,125). However, S. haematobium eggs in the CNS without functional sequelae are not uncommon and were found in as many as 28 out of 50 persons with urinary schistosomiasis at death (125). Usually S. haematobium eggs in the CNS cause little or no histological reaction while elsewhere they may elicit inflammatory responses. The spinal cord is affected more often than the brain (125,154), although an adult S. haematobium worm was found in the choroid plexus (32).

3. CLINICAL PRESENTATION

3.1 Early manifestations

The earliest symptoms associated with penetration of the cercariae, or "cercarial dermatitis", are usually mild and marked by slight irritation with erythema or papular eruption at the site of penetration. The severity of the symptomatology tends to be correlated positively with the number of penetrating S. haematobium cercariae (40). Severe itching and dermatitis may also be induced by invasion of non-human schistosome cercariae. Since humans are not their definite hosts, they die in the epidermis provoking an allergic and inflammatory reaction manifest as highly pruritic dermatitis, lasting for several days (40,75).

Most S. haematobium infected persons are unaware of the early stages of infection, although a "toxic syndrome", similar to what is known as Katayama fever in S. japonicum infection, may appear in a few cases. The symptoms appear gradually, with the establishment of the infection and the start of oviposition. They include general myalgia, headache, low grade fever, malaise, abdominal pain and eosinophilia. In general, haematuria is the first sign of infection seen in children of endemic areas 10-12 weeks or more after S. haematobium infection. Similarly, the general symptoms in 29 patients infected with S. haematobium, who were white expatriates returning to Britain from Africa, were found to be no more frequent than in non-infected control subjects returning from endemic areas, whereas complaints of

gross haematuria, dysuria and increased frequency of micturition were pathognomonic among those with the infection (79).

3.2 Later stages

In accordance with clinical manifestations and pathology, two chronic stages have been identified: (1) an active stage in younger age groups with egg deposition in various organs associated with acute and subacute symptoms as well as eggs in the urine, and (2) an inactive stage in older age groups, in which urinary egg counts are low or absent but extensive and sometimes irreversible pathological changes are present. Symptoms may be minimal either in the active or in the inactive stage. Obstructive uropathy may be asymptomatic until well advanced (106).

3.3 Urinary egg count

Once S. haematobium female worms have begun oviposition, eggs can be found by urine examination. Urine egg count is one of the three main indices for estimating the intensity of infection; the other two, tissue egg burden and number of worm pairs, can only be determined at autopsy. In the active stage urinary egg excretion can be used as an indirect estimate of tissue egg burden and severity of the disease and is particularly relevant for epidemiological studies. In the inactive stage, few or no eggs may be present. Urine egg counts are of limited value in estimating the prevalence of severe disease in inactive cases or older populations (133).

In clinical studies a single egg count may not quantitatively reflect the activity of infection in an individual patient. A single negative examination of urine should never be accepted as conclusive evidence of the absence of infection. However, on a population basis, the intensity of infection as estimated by urinary egg counts correlates with various measurements of morbidity, i.e., haematuria, proteinuria (29,149).

When patients were classified into four categories according to the mean of nine daily egg counts, i.e., <1 (minimal), 1-100 (light), 101-400 (moderate) and >400 (heavy) per 10 ml urine, Warren et al. (148) found that a single urine examination correctly classified 75% of the cases by egg output level while the examination of two samples did so for 78%. This is sufficient for the classification of intensity of infection in an epidemiological study.

Cheever et al. noted in a post-mortem study that there appeared to be a threshold for intensity of infection below which urinary disease was less, and above which there was no clear relationship between intensity of infection and severity of disease (29). However, Forsyth et al. (68) and Warren et al. (149) held that there was no lower threshold as some lesions were detected in individuals with very low egg counts.

3.4 Haematuria and blood loss

Clinical haematuria of variable severity and duration has always been associated with urinary schistosomiasis in the older literature. Gross haematuria is often transitory or intermittent, but microscopic haematuria may continue to be present between episodes. It is usually seen at the end of urination, although haematuria throughout micturition may be seen in some severely infected cases (57). Without antischistosomal treatment it may continue for several years with declining severity.

In hospital-based studies, the prevalence of haematuria in S. haematobium infected patients is usually high. In community-based studies, although the complaint of haematuria may not be striking, the prevalence of haematuria among infected persons detected either by microscopic examination or by urinalysis reagent strips is high: the lowest percentage reported by Pugh et al. was 35.2% in Nigerian villagers, while the highest, 92.7%, was reported by Browning et al. in Egyptian students (Table 1) (22,38,103,116,142,152).

In several epidemiological studies nearly all children between ages 5-14 with more than 50 eggs per 10 ml of urine had blood in the urine detected by chemical reagent strips (105,142). However, differences in the rates of haematuria at similar levels of urinary egg outputs have been noted between endemic areas (105,142). In Nigeria high prevalences of haematuria were observed only with high urinary egg counts (54,116).

The question as to whether blood or iron loss in S. haematobium infection is sufficient to cause anaemia has been a subject of discussion in the literature for many years. One of the first studies of blood and iron loss during the active stage of infection reported that nine out of 18 patients had severe haematuria and lost from 2.6 to 126 ml blood and from 0.6 to 37.3 mg iron daily, as measured by in vivo red blood cells labelling with ⁵⁹-Fe (60). However, among the nine persons with severe haematuria, six had daily blood loss below 10 ml. There was no detectable blood loss in the other nine patients with occasional terminal haematuria and clear urine. In another clinical study, five out of eight patients in early stage of infection who complained of haematuria lost from 0.9 to 6.0 ml of blood daily (99). In a recent study with an uninfected control group, Stephenson et al. recorded that mean iron loss in children with high S. haematobium egg counts (200-1194 eggs/10 ml urine) was about 0.65 mg daily and these children were losing approximately 0.50 mg more iron in their urine per 24 hours than those of the uninfected group. The iron losses in S. haematobium infected children when averaged over a month were comparable to menstrual blood loss in women. It was suggested that heavy infections by themselves, if untreated, can cause or aggravate iron deficiency anaemia (139). In association with other factors causing iron deficiency, such as malnutrition and other parasitic infections, S. haematobium infection would potentiate anaemia (53,78). In Niger the risk of anaemia was 30% greater among infected children between 5 and 14 years of age than among non-infected children in the same age group. In addition, the haemoglobin level was 1 g lower than in the non-infected children. No differences between the infected and non-infected women were observed (20). On the other hand, community-based studies have usually shown that neither the presence of nor the intensity of S. haematobium infection correlates with anaemia. In general gross haematuria seldom persists for more than a few days, thus the intermittent blood loss is too small to cause a significant decrease in haemoglobin (54,85). The correlation between blood loss due to S. haematobium infection and anaemia has yet to be conclusively demonstrated on a population basis. Individuals with severe haematuria, whose blood losses are considerable, especially those suffering simultaneously from other blood loss disease, are at greatest risk of developing clinical anaemia (138,151).

3.5 Proteinuria and renal function

Like haematuria, proteinuria is also a recognized sign of S. haematobium infection. The origin of urinary protein has been the subject of few clinical studies. Evidence regarding the relation of proteinuria in urinary schistosomiasis to the renal function is conflicting (see also section 4.3).

Ezzat et al. (59) reported that moderate or heavy proteinuria was observed in about half of all the men in endemic villages in Upper Egypt of whom over 96% of those with moderate or heavy proteinuria had S. haematobium infection. In a control village without schistosomiasis in the same area only one person with heavy proteinuria was observed. In the same report the prevalence of S. haematobium in patients with nephrotic syndrome in the hospital was greater than in their matched controls. The authors concluded that S. haematobium infection was a risk factor for nephrotic syndrome.

The evidence that proteinuria is possibly of glomerular origin due to immune complex glomerulonephritis is conflicting (12,36,84,123). Some authors have cited the reversibility of proteinuria after treatment to support the renal origin of proteinuria (36,62). On the other hand, a large number of epidemiological, clinical and post-mortem studies failed to show an association between proteinuria in S. haematobium infection and nephropathy (5,48,116,122,123,127,131,152). On the contrary, all these studies have suggested that proteinuria is related to lower urinary tract pathology due to schistosomiasis.

The level of proteinuria correlates positively with the intensity of S. haematobium infection (38,103,136,152). Heavy proteinuria has usually not been associated with significant impairment of renal function and in a follow-up survey it was found to respond well to antischistosomal chemotherapy (116). Urinary protein levels were reduced rapidly one month after treatment. However, even in the absence of eggs in the urine one month after metrifonate or praziquantel treatment, previously heavily infected persons (median: 84 eggs/10 ml of urine) continued to have low levels of proteinuria (48). It is suggested that proteinuria in heavily infected patients may not be caused only by lesions associated with egg penetration but also by chronic tissue lesions which reverse more slowly.

Recently, urinary protein was analysed qualitatively according to molecular weight to determine its origin. Sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE) showed an excretion of albumin, transferrin and IgG consistent with a post-renal pattern of proteinuria (48). Up till now, there has been no direct evidence concerning involvement of immunological mechanisms in proteinuria of S. haematobium infected subjects as is seen in S. mansoni infection.

Renal function in most of the S. haematobium infected cases was normal except in those with obstructive uropathy and superimposed urinary bacterial infection (110). Thus impairment of renal function is most likely associated with obstructive uropathy. In these persons the renal medulla is decreased and functional deficit is correlated with reduction of medullary tissue as seen radiographically. Reduction in concentrating ability is frequent (94). Phenolsulfonphthalein (PSP) excretion rate may be low. However, in the presence of obstruction of the urinary tract, abnormal PSP excretion could not be attributed definitely to renal dysfunction. Glomerular filtration rate and tubular functions are usually normal in patients without bilateral obstruction or bacterial infection. In community-based studies, minimal renal functional impairment was evidenced by several reports from Egypt and Nigeria. Glomerular function is less influenced than is the tubular function (22,81,115,116). In a study of 61 hospitalized patients of S. haematobium infection in Cairo no impairment of urine acidification, total hydrogen ion excretion or creatinine clearance was observed in patients with hydronephrosis due to schistosomiasis without urinary bacterial infection (159).

3.6 Bacterial infection of the urinary tract

Urinary tract pathology due to S. haematobium infection and subsequent obstructive uropathy has been postulated to increase the risk of secondary bacterial infection.

Several epidemiological surveys in Egypt, Gambia, Nigeria and Niger revealed significant differences among rates of bacterial urinary tract infection in patients with schistosomiasis or in communities endemic for urinary schistosomiasis in comparison with rates in control groups without schistosomiasis or in comparable non-endemic areas (19,92,134,150). In Egypt, bacteriuria was found in 20 out of 390 (5.1%) school boys in an endemic area with a prevalence rate of 66% which is more than 10 times greater than that observed in the non-endemic control area (92). In an endemic community in Gambia, prevalence of bacteriuria in males under 25 years of age was 6.6% (10/152) while in a comparable but non-endemic area it was absent (0/153) (150). In Nigeria significant bacteriuria was observed in 3.2% of males in an endemic area as compared to 0.5% of those of the control group (134). The rate of urinary tract infections in an endemic village in Niger was five times higher than in a control village (19). In hospital studies, due to the high frequency of obstructive uropathy, the association between bacteriuria and schistosomiasis is usually significant (5). The predominant organisms isolated from urine in urinary schistosomiasis were Escherichia coli, Staphylococcus albus, Streptococcus faecalis, Proteus species, Pseudomonas, Klebsiella and Salmonella (2,5,134).

On the other hand, rates of bacteriuria have also been reported to be negligible or absent in some endemic populations or among infected individuals. In a Nigerian community where 3097 urine specimens were examined by culture for bacteria and for eggs, no significant difference was found in the rates of bacteriuria between infected and uninfected groups (117). Similar results were also recorded by other community-based studies in Nigeria, Liberia and Egypt (22,85,134). Two consecutive autopsy studies in Egypt suggested no association between histological pyelonephritis and urinary schistosomiasis per se (29,131).

Patients with S. haematobium infections have high urinary leukocyte counts (15,49,65) most of which are eosinophiles (15). In contrast to patients with bacterial urinary tract infections, patients with urinary schistosomiasis and leukocyturia tend to have normal peripheral leukocyte counts.

Furthermore, consensus regarding the association between urinary bacterial infection and urinary schistosomiasis is that only patients with significant schistosomal obstructive uropathy, such as hydronephrosis, hydroureter, urolithiasis and bladder outlet obstruction, are predisposed to bacterial superinfection (127,154).

Association of Salmonella with Schistosoma infection in man has long been known. Scanning electron microscopic observations revealed that Salmonella adhered by its pili to the surface tegument of S. haematobium. The association of Salmonella and Schistosoma may therefore contribute to the persistence of Salmonella infection (147). Persistent bacteraemia may accompany Salmonella bacteriuria. The schistosome may play a role as both the source and vehicle of the bacteria. Even without antibiotics, after treatment of schistosomiasis, a reduction of Salmonella carriers has been reported (5). Both antibiotics and antischistosomal drugs are recommended in treatment of prolonged E. coli bacteraemia associated with S. haematobium infection (63).

3.7 Radiography, renography, ultrasound and computed tomography in morbidity studies of urinary schistosomiasis

3.7.1 Radiography

Typical lesions demonstrated radiologically in S. haematobium infection are hydronephrosis, hydroureter, stricture and distortion of the ureter, ureteral calcification polyps, urethrolithiasis, calcified bladder, bladder filling defect caused by granuloma, polyps or carcinoma, reduction in bladder capacity, irregular contraction of the bladder wall or dilated bladder due to bladder neck fibrosis, and delayed dye excretion (5,74,81). A greater prevalence of urinary tract disease was observed radiologically in those with higher intensities of infection by many investigators (30,66,68,69,81,102,119,122,148). However, one report suggested that the intensity of S. haematobium infection did not correlate with the presence of bladder calcification which was seen with equal frequency in both young and older age groups (115). Recently, Cooppan et al. (38) also reported from South Africa that no relationship could be demonstrated between the intensity of the infection and structural damage of the urinary tract as shown radiologically.

Pollack et al. (114) reviewed the causes of bladder calcification and concluded that worldwide, S. haematobium infection is the most common cause of bladder wall calcification. Calcification of the bladder constitutes an important radiographic manifestation of urinary schistosomiasis and occurs in a significant proportion of the cases. Generally, two types of radiological presentation have been described: homogenous opacity and linear rim calcification. Other types also reported were amorphous and curvilinear forms (57,95,145). The different radiological presentations of bladder calcification are at least in part related to the degree of bladder distension with urine. Reversibility may occur after chemotherapy and even spontaneously following the decline in disease transmission in a community (75,118). It was demonstrated that grossly sandy radiopaque areas contained between 500 000 to 1 000 000 eggs/gram and that as few as 100 000 per cm² cast a shadow which could be detected radiologically (30). In other reports calcific tissue egg burden exceeding 20 000 eggs per gram of tissue could be detected in a X-ray film (127,154).

3.7.2 Renography

Few reports on radioisotope renography in patients with urinary schistosomiasis are available (110,111,160). In general, renographic abnormalities that persist after a waterload were more common in infected than in uninfected children. In children with a high intensity of infection and abnormal pyelograms, renographic abnormalities were also common. However, children with abnormal pyelograms may also have normal renograms and those with abnormal renograms may have normal intravenous pyelograms (110,111). Thus the two tests can be mutually complementary. In several children treatment with niridazole restored the renograms to normal within three weeks, much more quickly than structural recovery demonstrated by pyelogram which took several months (96). In another study, significant improvement was noted in 10 patients between 10 to 30 years of age with urinary schistosomiasis in both the renogram and tubular function test after niridazole treatment while the degree of obstruction, as determined by urography, remained essentially unchanged (158).

3.7.3 Ultrasonography

Ultrasonography was first used by Abdel-Wahab (5) to identify structural changes of the urinary tract due to schistosomiasis. Ultrasound was used for detection of schistosomal bladder and kidney lesions in a community-based study of 349 persons in Tanzania. The technique was validated in a small subsample examined by intravenous pyelography and

cystoscopy by Degrémont et al. (44). Major or minor congestion and hydronephrosis of the kidney, and thickened and irregular wall and tumour of the bladder could be found by ultrasonography. The ultrasound findings correlated positively with those of intravenous pyelography for dilatation of the renal pelvis and calices. In the Congo, Doehring et al. (47) showed that ultrasound abnormalities of the urinary tract were more frequent in children than in adults. The severity of the abnormalities correlated positively with the urinary egg counts as well as other measures of morbidity, i.e., haematuria, proteinuria, and leukocyturia. In another study, Burki et al. (23) reported that sonographic findings correlated well with those of intravenous pyelography and cystoscopy. Ultrasonography is probably less sensitive in detecting bladder calcification than X-ray study (23,44). The authors of both these studies suggested that ultrasonography was a valuable tool for rapid mass surveys of S. haematobium related morbidity (23,44). Furthermore, as ultrasound requires relatively simple instrumentation and is not invasive, it can be expected to be used increasingly for field surveys on schistosomiasis.

3.7.4 Computed tomography

Computed tomography (CT) is sensitive in detecting calcification of the urinary tract and delineating its location (87). Two unsuspected cases of urinary schistosomiasis were diagnosed by Aisen et al. (7) and Lautin et al. (93) by using CT in the United States. The calcified bladder and ureters were easily demonstrated by CT. The authors recommended that non-contrast CT be performed initially.

4. EFFECT OF TREATMENT ON DISEASE

Currently metrifonate and praziquantel are recommended for large-scale treatment of urinary schistosomiasis. Since their first clinical trials (42,43), their effect on morbidity has been shown as well. Praziquantel has even been used safely in a patient with chronic renal failure due to S. haematobium infection (112). Although surgical approaches to the urinary tract sequelae of S. haematobium infection are well established, the availability of effective antischistosomal drugs which may reverse these sequelae indicates that chemotherapy should be used initially (39).

4.1 Urinary egg excretion

Treatment of infected persons with metrifonate or praziquantel causes the disappearance or reduction of S. haematobium egg excretion and hence reduced contamination and transmission in a community.

Metrifonate in an oral dose of 10 mg/kg body weight given three times at 14 day intervals usually cures from 60% to 90% of those treated. In a review of 2061 persons with S. haematobium infection treated with different doses of praziquantel cure rates ranged from 72% to 100% (41). In another review, the cure rates achieved with praziquantel six months after treatment ranged from 83% to 100%. Treatment is also beneficial to persons who are not cured as their egg output was reduced by more than 95% (8). In a recent report, an overall cure rate of 60% and a 92% reduction in egg count were recorded after praziquantel treatment with either 30 or 40 mg/kg body weight in Ghanaian patients at six-month follow-up (105).

4.2 Urinalysis

A semi-quantitative measurement of haematuria and proteinuria by reagent strips has been widely used for morbidity surveys of S. haematobium infections in recent years (21,49,55,65,106,116,143). It has also been applied to evaluate the effect of chemotherapy. Reagent strip urinalysis pre- and post-treatment showed a significant reduction of the number of patients with haematuria and proteinuria after metrifonate (49,51,55,65,136) or after praziquantel (46,50,104). However, some of the patients, usually those with heavy infection before treatment, still presented haematuria and proteinuria for a relatively long period although eggs were not found in the urine (55). Nevertheless, after treatment, leukocyturia and urinary iron loss were usually reduced.

4.3 Disappearance or alleviation of symptoms and clinical disease

Gross haematuria usually disappears after chemotherapy, as do dysuria, frequency of micturition and suprapubic or abdominal pain. The disappearance of bladder granulomas

following niridazole, metrifonate or praziquantel chemotherapy with subsequent relief of obstruction and resolution of hydronephrosis and hydroureter have been confirmed by a number of authors (4,46,50,57,62,95,96,107,118). Along with the improvement of the obstructive uropathy, the renal function deficiency as shown by maximal urine concentration, PSP excretion, and creatinine clearance were also improved (62). Even if the degree of obstructive uropathy showed little change in some severe cases by pyelography, renographic studies using ¹³¹I-iodohippurate as well as other renal function tests revealed significant improvement after chemotherapy (158). In general the pathological lesions of the urinary tract in children may be reversed by treatment; however, in adults the severe changes with bladder calcification may not regress.

Recently, Stephenson et al. reported a series of investigations with regard to the effect of metrifonate treatment on S. haematobium infections. After treatment, adult male patients gained weight, and fitness scores increased; in children, improvement of their anthropometric indices was recorded as judged by increase in weight, height, arm circumference, triceps and subscapular skinfold thickness; with the decrease of urinary iron level their haemoglobin levels increased; their general health and physical fitness improved, in comparison with control or placebo groups, especially in areas where protein malnutrition, hookworm infection and anaemia are common (135, 137-141).

5. BLADDER CANCER AND URINARY SCHISTOSOMIASIS

Bladder cancer associated with urinary schistosomiasis is a significant cause of mortality in some endemic countries (73). The relationship between S. haematobium infection and bladder cancer has been extensively reviewed by a number of investigators (10,18,27,31,58,71,97,113,124,154) during the last 10 years and the etiological significance of schistosomiasis in bladder cancer has been the subject of controversy.

5.1 Data in favour of the association between bladder cancer and urinary schistosomiasis

(a) Geographical correlation: In Egypt where S. haematobium infection is hyperendemic, cancer of the schistosomal bladder ranks first among all types of cancer recorded. Among 11 626 cases of cancer diagnosed at the Cairo Cancer Institute between 1970 and 1974, 3212 (27.6%) were bladder cancer (58). In these areas clinical and surgical management of bladder cancer due to schistosomiasis remains a challenge (11,72). Bladder cancer is the third most important malignancy in Zambia accounting for 8.3% of all malignancies (14). In some highly S. haematobium endemic areas of Malawi, the incidence of bladder cancer is four times as high as that in the USA and the United Kingdom (97). Regionally, as in Egypt, coastal Kenya, Malawi, Ghana, etc., there seems to be a correlation between the occurrence of bladder cancer and the prevalence of schistosomal bladder calcifications (16,18,97).

(b) Age at diagnosis: Schistosomal bladder cancer is found in a comparatively young age group, usually in the fifth decade (58). Among 1095 Egyptian patients with bladder cancer, the average age at diagnosis in the schistosome egg-positive group was 46.7 years, significantly younger than that in the egg-negative group (53.2 years) (17).

(c) Original tumour site: In schistosomiasis cases cancer may be found throughout the bladder. The tumour rarely originates in the trigone (2%) as is seen frequently in non-schistosomal cancers (18, 58).

(d) Histopathology: Squamous cell tumours predominate in schistosomiasis bladder cancer ranging from 43.9% in Sudan to 82.3% in Zambia (10, 14, 17, 33, 58, 100) (Table 2). This is in striking contrast to the figures reported from countries free of schistosomiasis, where squamous cell carcinoma of the bladder is a rarity (31).

In reviewing the epidemiological and pathological data in the literature from Iraq, Sudan, Nigeria, Tanzania, Mozambique, South Africa, Kenya, Egypt, Zambia and Malawi, Lucas (97) analysed the ratio of squamous cell carcinoma to transitional cell carcinoma of the bladder in relation to the proportion of egg-positive specimens. He concluded that the higher the intensity of infection, the greater the proportion of squamous cell cancers and the less that of transitional cell cancers; and he argued that squamous cell carcinoma of the bladder, but not transitional cell carcinoma, is etiologically associated with S. haematobium infection.

About 80% of schistosomal bladder cancers are large with a nodular, fungating and infiltrating appearance and often with a firm, keratinized surface; papillary lesions are rare. In contrast, most non-schistosomal bladder cancers present soft, friable, highly vascularized papillary lesions (18,58).

(e) Differentiation and metastasis: Unlike transitional cell cancer which predominates in non-endemic areas and has a tendency to metastasize, 70% to 80% of the squamous cell cancers in schistosomiasis cases are well or moderately well differentiated. Cancer of the schistosomal bladder usually spreads directly through the bladder wall. Lymphatic spread is less frequent and occurs later than in non-schistosomal cancer. Blood stream metastasis is rare. In contrast to non-schistosomal tumour, schistosomal bladder cancer is largely an indolent, localized disease process (31, 58).

(f) Experimental cancer in animals: Kuntz et al. (90) reported in 1972 that lesions of papillary transitional cell carcinomas of the urinary bladder were found in a talapoin monkey (Cercopithecus talapoin) and a capuchin monkey (Cebus apella) five to 12 months respectively after infection with S. haematobium. The absence of reports of spontaneous bladder cancers in monkeys suggested that the lesions were induced by schistosome infection. Hicks et al. (82) induced bladder cancer in four out of 10 baboons infected with S. haematobium and simultaneously treated with a low dose of a bladder carcinogen N-butyl-N(4-hydroxybutyl) nitrosamide (BBN) weekly for up to 30 months while none of the three control group baboons, infected with S. mansoni, or S. haematobium, or treated with BBN only, showed evidence of urothelial cancer. The authors postulated that S. haematobium supplied the proliferative stimulus necessary to accelerate cancer growth from latent tumour foci by exposure to a low dose of the bladder carcinogen.

5.2 Data against a causal relationship between bladder cancer and urinary schistosomiasis

The evidence for an etiological relationship has been questioned by several investigators (10,127).

(a) Geographical correlation: Supporting evidence comes mainly from Egypt while elsewhere the evidence is less convincing. In South Africa, bladder cancer is no more common than in countries where S. haematobium is not endemic (75). A report with control groups showed no differences in groups with and without S. haematobium infection (37). In Nigeria, the age-specific rates of bladder cancer per 100 000 per year are no higher than the figures from the USA (75). Since these countries are endemic for schistosomiasis and the incidence of bladder cancer is no higher than the expected rates, there seems to be no etiological association between schistosomiasis and bladder cancer in these countries.

(b) Age at diagnosis: Generally cancer occurs in a younger age group in tropical areas than in temperate regions (10).

(c) Tumour types: Some reports from schistosomiasis endemic regions could not find an association between schistosomiasis and squamous cell carcinoma while some reports from an area free of schistosomiasis (Jamaica) or from one with a low prevalence rate (Uganda), have recorded high rates of squamous cell carcinoma of the bladder (9,10,29). Attah et al. (10) considered that patients from areas with poor medical facilities might present with advanced disease and that advanced transitional carcinoma of urinary bladder could be expected to present as squamous cell carcinoma.

(d) Histopathology: Two large consecutive autopsy series in Cairo showed no significant differences in the frequency or type of urothelial malignancies between patients with and without urinary schistosomiasis (29,131).

Although the opposite opinion for the etiological relationship may not be as strong and convincing as the opinion in favour of the association a consensus regarding the etiological association between S. haematobium and bladder cancer has not yet been reached. Further studies of the relationship have been suggested by Pike (113) and Cheever (27), in particular the use of case-control methods for the determination of the prevalence of cancer in groups with different intensities of infection, as judged by calcified bladder from plain abdominal roentgenograms.

5.3 Possible basic mechanism of carcinogenesis in urinary schistosomiasis

Several hypotheses have been proposed to explain the etiological role of schistosome infection in the development of bladder cancer. None have been confirmed.

(a) Fibrotic foreign body reaction: Brand (18) considered that chronic fibrotic foreign body reaction in the bladder wall against schistosome eggs is of etiological importance. Fibrosis induces epithelial proliferation and abnormal hyperplasia and metaplasia which lead to a genetic error in the disorganized epithelial cell.

(b) Egg-induced inflammatory response: Inflammation surrounding the egg might decrease the effectiveness of the mucosal barrier to reabsorption of carcinogens in the urine (27). Later, fibrotic tissue contracture may cause blockage of lymphatics and allows carcinogenic substance to accumulate (58). Christie et al. (33) found that schistosomal bladder cancer arose in the regions of the bladder with the highest egg burden regardless of overall egg burden and concluded that inflammation due to S. haematobium eggs seemed to act as a tumour promoter.

(c) Bacterial infection: Chronic bacterial infection in schistosomal obstructive uropathy was considered to be an important etiological factor by several authors (17, 31). Urinary bacteria produce nitrosamines, which are well-known to be carcinogenic to the bladder, from their precursors in urine. High levels of nitrosamines have been found in the urine of S. haematobium infected cases with bladder cancer (83). In Uganda, where schistosomiasis is not associated with bladder cancer, the common bladder malignancy is still squamous cell carcinoma. Urethral stricture in association with bacterial infection is considered to contribute to the development of bladder cancer through squamous cell metaplasia (97).

(d) Urinary stasis: Urinary retention would allow concentration of some endogenous carcinogens, expose the bladder epithelium to prolonged stimulation of these carcinogens, and also lead to more absorption of the carcinogens from urine (14,27).

(e) β -glucuronidase: The enzyme has been detected in miracidia and adult schistosomes and may be present in bacterially infected urine or come from disintegrated bladder cells (71,75). A higher level of urinary β -glucuronidase activity was demonstrated in schistosomiasis patients than in controls (31). Elevated urinary β -glucuronidase levels would liberate carcinogenic amines from glucuronide in urine (97); thus, the damaged urothelium would be exposed to the carcinogen.

(f) Reduction of immune surveillance: Generalized immunodepression by the infection has been described (27). Reduced immune surveillance might also affect carcinogenesis.

6. CONCLUSION

S. haematobium infection affects primarily the urinary tract and leads frequently to obstructive uropathy. The severity of the disease depends mainly on the intensity of infection. Morbidity might be negligible in a community with a low prevalence rate and low intensity of infection. With moderate to heavy infections a higher proportion of patients show considerable damage to the urinary tract and suffer from obstructive uropathy. The prevalence of the infection is markedly higher at young ages. Active disease is usually found in children while inactive disease is more commonly seen in adults. The clinical manifestations of S. haematobium infection are protean and in endemic areas should be considered in differential diagnosis. During the past decade progress has been made in assessment of the morbidity, especially by using quantitative egg counts, reagent strips or dip sticks, and ultrasonography. However, a better understanding of the morbidity of S. haematobium infection is still desirable. The current antischistosomal drugs effectively reduce or eliminate active infections and reduce the risk of disease. In spite of all the recent information, more clinical studies assessing morbidity due to S. haematobium and its response to treatment are needed.

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TABLE 1. PREVALENCE OF HAEMATURIA IN S. HAEMATOBIIUM INFECTED SUBJECTS

Country	Subject	Method of examination	No. with <u>S. haematobium</u> infection	No. with haematuria	Prevalence of haematuria (%)	Reference
Egypt	Students	Microscopic	41	38	92.7	Browning et al. (22)
Gambia	Villagers	Reagent strip	1 078	585	54.3	Wilkins et al. (152)
Ghana	Villagers	Reagent strip	Children 215 Adults 157	171 89	79.6 56.7	Mott et al. (103)
Liberia	Village children	Dip stick	189	129	68.3	Tanner et al. (143)
Nigeria	Villagers	Reagent strip	930	327	35.2	Pugh et al. (116)
South Africa	Students	Reagent strip	455	418	91.9	Cooppan et al. (38)
Tanzania	Village children	Dip stick	162	139	85.8	Tanner et al. (142)

TABLE 2. HISTOLOGY OF SCHISTOSOMAL BLADDER CANCERS IN AFRICA
REPORTED DURING THE LAST 10 YEARS^a

Country	Squamous	Transitional	Other	Total	Reference
Egypt	691(76.6%)	103(11.4%)	108(12.0%)	902	El-Bolkainy et al.(17)
Egypt	28(80.0%)	5(14.3%)	2(5.7%)	35	Christie et al.(33)
Egypt	(75%)	(20%)	(5%)	3 212 ^b	Elsebai(58)
Nigeria	25(75.7%)	3(9.1%)	5(15.2%)	33	Attah et al.(10)
Sudan	(43.9%)	(3.2%)	(47.1%)	49	Malik et al.(100)
Zambia	116(82.3%)	11(7.8%)	14(9.9%)	141	Bhawandeen(14)

^a Based on Pike (113).

^b All bladder cancer specimens including those without S. haematobium infections.

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