Schistosomiasis and Neoplasia

Napoleon’s troops are said to have referred to Egypt as the “land of menstruating males.” Hematuria from schistosomal cystitis was so common that the passage of blood in the urine was taken as an indication of puberty. Schistosomes are parasitic flatworms that are transmitted through freshwater snails. Adult worms of two of the three species commonly infecting man (Schistosoma mansoni and S. japonicum) live in mesenteric venules and produce pathologic changes mainly in the liver and colon. The third species, S. haematobium, resides mainly in venules of the bladder and ureters. The living adult worms provoke little reaction, and most pathologic changes are caused by host inflammatory reaction to eggs laid by the worms. Eggs retained in the tissues slowly release antigen into the surrounding tissues (1). However, the eggs live for only a few weeks, during which time the principal reaction to them takes place. The fate of dead eggs varies greatly depending on the species of both the worm and its mammalian host. In man, eggs of S. mansoni are rapidly cleared from the tissues, whereas eggs of S. haematobium tend to calcify and persist for prolonged periods (2). The pathogenetic significance of calcified eggs is not defined, but these eggs are probably inert. In endemic areas, schistosome infections are usually acquired at an early age and persist for many years. Although they continue to lay eggs throughout the infection, the worms do not multiply within the body. Infections may thus be light or heavy, and the pathologic changes vary accordingly. Under most epidemiologic circumstances, infection intensity in man peaks between the ages of 15 and 20 years. Immunity to superinfection is readily demonstrated in animals but has not been well documented in man (3, 4).

Schistosomiasis and Cancer of the Urinary Bladder

Does Schistosomiasis Cause Bladder Cancer?

The frequent association of S. haematobium infection with bladder cancer, the high prevalence of bladder cancer in some areas endemic for schistosomiasis, and the distinctive morphology of the bladder tumors led investigators at the turn of this century to postulate a causal association between schistosomiasis and bladder cancer in Egypt (5, 6). In contrast to other bladder cancers, those associated with schistomiasis are usually squamous cell in type, seldom originate in the trigone, and occur in relatively young individuals (7-9). A series of 229 cases recently reported from Egypt by El Boulkany et al. (10) is typical. Two-thirds of the tumors were squamous cell, less than 6% originated in the trigone, and the mean age of the patient at the time of diagnosis of the cancer was 47 years. Khafagy et al. (11) found multiple infiltrative primary tumors in 22% of 86 infected cases and carcinoma in situ in 41%. Ishak et al. (7) noted squamous cell carcinoma in situ in 31% of 49 bladders containing squamous cell carcinomas. Squamous metaplasia is common and occurs most frequently in bladders bearing squamous cell carcinomas. Cystitis cystica, cystitis glandularis, and colon metaplasia are also frequent (7). Rigorous statistical proof of the association between bladder cancer and S. haematobium infection has not been obtained, though most published data tend to confirm the association (12-14). In areas where S. haematobium infections are less prevalent and less intense than in Egypt, most authors note an association of squamous cell bladder cancer with schistosomiasis [(15-22) are the more recent publications], but conflicting reports also exist (23). In some localities in Africa other identifiable factors clearly are more important than schistosomiasis—for example, urethral stricture in Uganda is frequently associated with squamous cell carcinoma of the bladder, but these tumors most commonly arise in the bladder trigone (24).

The apparently overwhelming yet unproved association of schistosomiasis and bladder cancer has perhaps discouraged further studies of the problem. No epidemiologically oriented study of the association has been undertaken since the report of Mustacchi and Shimkin published 20 years ago (12). Thus, although our knowledge of the morphology and behavior of the tumors has progressed (7, 10, 11, 25, 26), our knowledge of the causal connection has not. A second potent deterrent to clarification of the problem is the great difficulty one may encounter in planning and executing a proper study. For example, common sense would lead one to expect bladder cancer to be more frequent in heavily infected patients. The lower prevalence of schistosome-associated bladder cancer in countries with less severe schistosomiasis suggests the same conclusion.

Abbreviation used: HbsAg=hepatitis B surface antigen.

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Editor’s note: Periodically, the Journal publishes solicited guest editorials as a means of transmitting to investigators in cancer research the essence of current work in a special field of study. The Board of Editors welcomes suggestions for future editorials that succinctly summarize current work toward a clearly defined hypothesis regarding the causes or cure of cancer.
as does the association of bladder cancer and occupational exposure to schistosome infection (9). However, meaningful determination of the intensity of infection is extremely difficult. The number of schistosome eggs passed in the urine probably reflects the intensity of infection (2), but, as previously noted, the mean age of infected individuals at the time of maximum egg passage is about 15 years. By the time cancer has developed, the schistosome infection is often inactive or minimally active. Masses of calcified eggs in the bladder often attest to the previous presence of heavy infection, though calcified eggs apparently persist in some individuals (2, 27) but not in others (27). Generally such calcified eggs are not passed in the urine where they could be detected or counted (28). For the pathologist to count the number of eggs in bladders removed for cancer is a simple matter, but to obtain similar data from a comparable population without bladder cancer is nearly impossible.

Two approaches to the study of infection intensity in patients with bladder cancer seem feasible. First, the "calcified bladder wall" in S. haematobium infection is not itself calcified but merely packed with calcified schistosome eggs (29). The shadow on the radiograph is related to the number of schistosome eggs in such bladders (28). The determination of the prevalence of cancer in groups with different infection intensity, judged from plain radiographs of the abdomen, is possible. Second, the transmission of schistosomiasis is often very focal, and to study otherwise similar groups of people in areas of high and low transmission is feasible when transmission is judged either from egg passage in younger patients or bladder calcification in older patients.

**How Important Is Schistosomal Bladder Cancer?**

No data exist that would allow one to reasonably estimate the morbidity and mortality caused by schistosomal bladder cancer. In two recent series of cases from Egypt (30, 31), about 2% of S. haematobium-infected patients seen at autopsy had bladder cancer. If all bladder cancers in infected patients are assumed to be fatal and to be caused by schistosomiasis, they would account for 16% of deaths related to S. haematobium infection in one series (30) and for 26% of deaths attributed to either S. haematobium or S. mansoni in the other (31). Twenty years earlier in the same hospital, bladder cancer was found in about 4% of infected cases (14). Much less sensitive techniques for the detection of schistosome infections were used in this earlier study. These data are from an urban university teaching hospital, and I have no idea what relation they may have to the mortality caused by schistosomal bladder cancer in the population at risk. Looked at from another point of view, bladder cancer is among the most frequent malignant neoplasms occurring in Egypt and Mozambique (8, 13, 32). Mustacchi and Shimkin (12) estimated that the relative risk of bladder cancer for patients with schistosomiasis in Tanta, Egypt, was 2.1-2.2, but they emphasized the need for better epidemiologic surveys. Whatever the past and present risk of schistosomal bladder cancer, the risk possibly will increase if exposure to other bladder carcinogens becomes more frequent.

**What Are the Etiologic Factors in Schistosomal Bladder Cancer?**

Chronic inflammation of the bladder and urinary retention were early noted as possible mechanisms by which schistosomiasis might predispose to bladder cancer. Inflammatory infiltrates and ulceration (usually microscopic) might decrease the effectiveness of the mucosal barrier to reabsorption of carcinogens in the urine (33). Urinary retention might also lead to increased absorption of carcinogens from the urine. A small amount of residual urine is frequently found in S. haematobium infection (27). Severe obstruction of the bladder neck is also described (34), though it is apparently infrequent (31). Elevated levels of urinary β-glucuronidase have been noted in S. haematobium-infected patients, and this enzyme may cleave glucuronides to yield carcinogenic products (35, 36). The urinary concentration of tryptophan metabolites, some known bladder carcinogens, was found to be increased in patients with S. haematobium infection (37, 38).

The possible presence of carcinogenic substances in the schistosome eggs has been little studied and has not been examined with more sensitive in vitro techniques such as cell transformation or mutagenic effects on bacteria. The effects of schistosome infection on the immune system might also affect carcinogenesis. The infections are prolonged with continued release of eggs and metabolic products into the circulation. Thus a major immune stimulus obviously exists. Immunodepression also exists but is generally specific, i.e., confined to reactions to the parasite and its eggs, but more generalized immunodepression has been described in some experimental situations. These findings and host immunity and hypersensitivity in general have been thoroughly reviewed by Phillips and Colley (4).

The interaction of bacteria in the urine with excreted chemicals must also be considered, e.g., the formation of nitrosamines from nitrites (39). Bacterial infection of the urine may be common in hospitalized patients with schistosomiasis, perhaps because of instrumentation of the urinary tract or because patients with bacteriuria are more likely to seek medical attention. However, with one exception (Laughlin L, Higashi G, Edman D, et al: Unpublished data), field studies have not shown increased bacteriuria in those individuals passing schistosome eggs in the urine (40-42). Salmonella bacteriuria is clearly more frequent in patients with S. haematobium infection than in those without (43), but again the prevalence of Salmonella bacteriuria outside of hospitals is low (44, 45). The low prevalence of bacteriuria in schistosome-infected patients does not rule out a role for bacteria in the pathogenesis of bladder cancer. One should also note that the field studies that have failed to link bacteriuria to egg excretion missed most patients with inactive schistosomiasis, and these individuals may
have severe damage to the urinary tract as the result of previous schistosome infection (30, 31).

The clinical severity of S. haematobium infection varies greatly in different countries and in different areas within each country. Many differences appear to be caused by varied exposure to infection with resulting variation in intensity of infection. However, strains of S. haematobium from different areas also have distinctive behavior in both snails and experimentally infected mammalian hosts (46). The possible importance of the strain of schistosome for the production of bladder cancer is unknown, and genetically determined differences between patients who develop bladder carcinoma and those who do not have also not been investigated.

What Are Suitable Experimental Models of Schistosomal Bladder Cancer?

Experimental studies of schistosomal bladder cancer have been hampered by the lack of suitable experimental hosts. S. haematobium develops well in Syrian golden hamsters, in which bladder involvement is irregular. Other rodents tested have proved to be unsuitable hosts. Several nonhuman primate species are good hosts (47). Papillary and nodular transitional cell hyperplasia of the bladder can be produced with some regularity in capuchin monkeys. On the basis of the marked increase in thickness of the epithelium and the fusion of papillary growths, we believed these to be morphologically equivalent to grades I-II papillary bladder tumors of man. However, the tumor cells were well differentiated, and these lesions have not infiltrated the bladder wall or metastasized (48, 49). Several tumors, from which biopsy specimens were taken at cystotomy, have regressed, and in these animals the schistosome infection in the bladder had become inactive or minimally active (49). Increased levels of tryptophan metabolites in the urine of infected monkeys paralleled those found in infected persons (50). C-type virus particles were seen in a tumor from one monkey (51). Similar papillary and nodular epithelial hyperplasia was seen in talapoin monkeys (48), gibbons (52), and opossums (53). Talapoin monkeys and gibbons are not available commercially, and further experiments with opossums led to only irregular involvement of the bladder by the schistosome infection (54). In addition, spontaneous bladder tumors occur frequently in opossums.

A superficially infiltrative cancer of the bladder was produced in 1 cynomolgus monkey infected with a related schistosome species, S. intercalatum (55). However, this has proved not to be a reproducible phenomenon (Kuntz RE: Unpublished data). Cynomolgus monkeys are not appropriate hosts for S. haematobium, which produced only abortive infections with minimal production of eggs (Cheever AW, Duvall RH: Unpublished data). S. haematobium infection and N-methyl-N-nitrosoare apparent have additive effects on the hamster bladder, and similar studies have begun with baboons (56). Cocarcinogenic effects of S. haematobium and 2-acetylaminofluorene were reported for the mouse bladder by Hashem and Boutros (57), but the schistosome infection did not involve the bladder and the authors did not state whether the mice became infected by the schistosome larvae to which they were exposed.

Injection of dead schistosomes, their eggs, or concentrated urine from schistosome-infected patients into experimental animals has not produced lesions of importance (58-60).

Models of schistosomal bladder cancer in experimental animals inevitably will remain more complex than models based on the administration of chemical carcinogens. The carcinogenic stimulus presumably includes the deposition of schistosome eggs in the bladder. The sites and rate of egg laying are influenced by the varied and perhaps changing relationships between the mammalian host and the parasite. However, if a tractable model of schistosomal bladder cancer can be found, it will offer unusual opportunities to compare the human disease with a "natural" experimental counterpart.

**SCHISTOSOMIASIS AND HEPATOCELLULAR CARCINOMA**

S. mansoni and S. japonicum infections may produce hepatosplenomegaly and portal hypertension. Although clinically similar to cirrhosis in some respects, hepatocellular function is usually well preserved. The changes in the liver are characterized by pathognomonic portal fibrosis (Symmers' clay pipestem fibrosis) with maintenance of lobular architecture (61). Regenerative parenchymal nodules are seen in the late stages but they are generally confined to the subcapsular area (61). Hepatomas were equally frequent in uninfected and schistosome-infected patients in autopsy series from Brazil (62), Puerto Rico (63), Egypt (64), and Mozambique (32). In Japan, both hepatoma and circulating HbsAg were significantly more frequent in autopsied patients with S. japonicum than in those without, but most autopsied patients with schistosomiasis and hepatoma also had post-hepatitis cirrhosis (65). In Brazil, HbsAg carriers were significantly more frequent among patients with hepatosplenic schistosomiasis mansoni than among either uninfected patients or those with S. mansoni infection but without hepatosplenic disease (66). However, in this same hospital neither schistosome infection nor hepatosplenic schistosomiasis was related to cirrhosis or to hepatoma (62).

Equivocal increases in the frequency of hepatoma have been reported in experimental animals infected with S. mansoni. In mice given injections of 2-amino-5-azotoluene, hepatomas occurred earlier and much more frequently in those infected with S. mansoni than in those uninfected (67), though toxic fine structural changes in hepatocytes were less frequent and less severe than in the uninfected mice (68). Infected mice treated with a single dose of the antischistosomal compound hycanthone also developed hepatomas, whereas treated, uninfected mice did not (69). The cocarcinogenicity of S. mansoni infection in mice is thus a well-established fact, and under the proper circumstances a similar effect may occur in man. A marked difference exists in liver...
lesions in human and murine schistosomiasis. The average 2-cm² slide of liver from many, perhaps most, persons infected with *S. mansoni* contains no eggs, whereas the mouse liver is packed with them. Of approximately 200 human cases that I have examined quantitatively, only 2 had infections of intensity comparable to that in a mouse infected with a single pair of *S. mansoni* (70).

**SCHISTOSOMIASIS AND LYMPHOMA AND LEUKEMIA**

A striking association of giant follicular lymphoma of the spleen and hepatosplenic schistosomiasis was found in Brazil, 8 cases of splenic giant follicular lymphoma being found in a series of 863 surgically removed spleens (71). None of these patients showed peripheral lymphadenopathy, although nodes at the splenic hilum showed giant follicular lymphoma in 4 cases. One patient subsequently developed a reticulosarcoma. Another died shortly after surgery, and no residual lymphoma was found at autopsy. Several series of autopsy cases suggest an association of either lymphoma, leukemia, or both with schistosomiasis, but the nature of the association varies in the different reports (30, 31, 72). A suggestion of a positive association remains, and in the study from Nigeria of Edington et al. (72), lymphoreticular tumors were present in 16% of infected individuals and 5% of uninfected individuals.

**SCHISTOSOMIASIS AND CARCINOMA OF THE COLON AND OTHER SITES**

Inflammatory polyps of the colon have been frequently reported from Egypt and occasionally from elsewhere, and there is no doubt of their causal relation to schistosome infection, most frequently with *S. mansoni*. The polyps usually regress after treatment of the schistosome infection (73). *S. haematobium* infection frequently involves the colon and also causes inflammatory polyps (30, 31). The polyps do not show adenomatous changes, and cancers of the colon are not associated with schistosomiasis infections or with schistosomal polyposis of the colon (30, 31, 74). Surprisingly, schistosomal polyps of the colon are rare in Brazil (62).

Numerous case reports of coincidental schistosomiasis and colon cancer have been published, but never with evidence to indicate that cancer was more frequent in infected individuals. Extensive colon lesions occur in experimental animals infected with any of the three species of schistosome, but tumors have not been reported.

Cancers of the ovaries, uterus, and numerous other organs have also been attributed to schistosomiasis, but no evidence of more than a coincidental association has been provided.

**CARCINOGENIC EFFECTS OF DRUGS USED TO TREAT SCHISTOSOMIASIS**

I noted previously the cocarcinogenic effects of schistosome infection and a single dose of the drug hycanthone, a thioxanthone derivative, in the production of hepatomas in mice (69). In a second laboratory, no carcinogenic effect was observed (75). In yet a third laboratory, in which multiple drug injections were given, a carcinogenic effect was noted, but no differences were found between infected and uninfected mice (76). Hycanthone also has a marked mutagenic effect in the Ames test and in host-mediated mutagen assays. Using clorindazole analogs of hycanthone, Hulbert et al. (77) were able to dissociate the chemotherapeutic and mutagenic activities of the drug. Several other schistosomal drugs show lesser mutagenic activity (78). Hycanthone has been used extensively in the treatment of schistosomiasis in recent years, and a related drug, lucanthone hydrochloride, was commonly used previously. Niridazole, another drug still widely used in the treatment of schistosomiasis, has been shown to produce tumors in mice on prolonged feeding. The tumors produced included transitional cell carcinomas and smooth muscle tumors of the urinary bladder (79, 80). Hycanthone and niridazole continue to be used in clinical practice, principally because they are much more convenient to administer than the antimonials, which are also effective, and because they produce less immediate toxicity. The chemotherapy of schistosome infections has been recently reviewed by Katz (81).

**CONTROL OF NEOPLASIA CAUSED BY SCHISTOSOME INFECTION**

The control of schistosomal bladder cancer will probably be achieved through the control of schistosomiasis. Advances in the knowledge of bladder cancer are less likely to be important for the infected population than are advances in antischistosomal chemotherapy, snail control, engineering, and public health. These would have the important advantage of decreasing other morbidity and mortality caused by the infection. However, control of schistosomiasis, like the control of smoking, has proved elusive. In the meantime, better diagnosis and treatment of existing cases of schistosomal bladder cancer are important goals. Such diagnosis and treatment are not now possible for more than a small fraction of affected individuals. The annual budgets for health in developing countries are frequently 1 or 2 dollars per capita, and for the foreseeable future one cannot justify undue emphasis on treatment of the individual with bladder cancer. Elucidation of the mechanisms by which schistosomiasis causes bladder cancer will provide knowledge of great importance and general applicability, and populations exposed to *S. haematobium* infection form high-risk groups of unusual research interest.

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