

CANCER AND SCHISTOSOMIASIS

The role of schistosomiasis in the aetiology of cancer is controversial. *Schistosoma mansoni* has been associated with the follicular lymphoma of the spleen,³ colorectal cancer³⁵ and hepatocellular²⁴ and bile duct⁶⁴ carcinoma. *Schistosoma japonicum* has been linked with hepatoma^{103,108} and *S. intercalatum* has been associated with induced bladder cancers.^{25,94} The majority of available information, however, involves *S. haematobium* which has been associated with a number of malignancies including hydronephrosis,¹¹⁰ ovarian teratoma⁶⁴ and bladder cancer.^{69,72,88,90,93,95,102,104,117}

Attention was first drawn to the correlation between schistosomiasis and bladder cancer by Ferguson.⁴⁶ Subsequent studies have confirmed this association.^{7,13-15,31,33,42,43,56,79,101,112,116,121} The peak age of schistosomal cancer patients is younger than that of bladder cancer patients without schistosomiasis.^{39,91,111} The histogenetic aspects of tumours in schistosomal bladders, specifically the increased frequency of squamous bladder carcinoma as opposed to transitional cell carcinoma, promotes a causal link between the two diseases.^{2,6,40} Inflammatory proliferative lesions of squamous epithelium leading to squamous metaplasia of the urothelium can be caused by chronic irritation due to the presence of *S. haematobium* eggs.^{36,99,120} Squamous metaplasia is a progenitor of squamous cell carcinoma in most cases although the sequence of events is not fully elucidated.^{39,62,99}

Numerous explanations have been proposed for the association of schistosomiasis and cancer. These include: fibrotic reaction in the bladder to schistosome eggs resulting in foreign-body tumorigenesis,¹⁰⁰ the presence of schistosomal toxins,¹³¹ reduced immune surveillance,²¹ chronic inflammatory reaction of the mucosal barrier to carcinogens,³⁶ bladder stasis resulting from fibrosis permitting longer contact between mucosa and toxic agents,³⁶ alkaline sepsis,¹⁰⁰ and the presence of endogenous or exogenous carcinogens in schistosomal bladders,^{36,52} most notably nitrosamines.^{37,38,40}

Several of these explanations may contribute to a complete understanding of the carcinogenic process, but the explanations proposing a possible role for carcinogens are particularly intriguing. Endogenous or exogenous carcinogens may be introduced into the schistosomal bladder from many sources. Disordered tryptophane metabolism occurs in schistosome infections.^{19,28} This could result in the increased production of carcinogenic metabolites.^{19,28,123} Natural factors associated with the worms or eggs may also prove carcinogenic. These include surface and somatic antigens or concomitant bacterial infections.^{8,22,96} Bacterial clinical isolates from schistosomal bladders have been found to excrete a mutagenic substance into general growth medium.^{114,115} Nitrosamines are formed by bacterial catalysis of the nitrosation of secondary amines with nitrates or nitrites and could be carcinogenic to the bladder mucosa.^{74,77,80-82} Neoplastic transformation of the urothelium was initiated by low, sub-carcinogenic doses of N-nitroso compounds in *S. haematobium*-infected hamsters⁷¹ and baboons.⁷⁵ It has been suggested that schistosomiasis provides the proliferative stimulus necessary to accelerate cancer growth from latent tumour foci produced by carcinogen exposure.⁷⁰ Although the aetiological significance of this finding for humans is only now being investigated further, nitrosamines have been found in urine samples from Egyptian schistosomal bladder cancer patients and from United Kingdom paraplegic patients with chronic urinary tract infections.^{74,75} Evidence against this explanation, however, has come from a study using the Ames *Salmonella*/microsome test which failed to detect significant mutagen responses when comparing urine from patients with carcinoma of the schistosomal bladder, individuals with atypical bladder cytology but without malignancy on cytology, subjects with urinary schistosomiasis but without bladder cancer, and subjects without either schistosomiasis or bladder cancer.⁴⁵

The alteration of host metabolism of carcinogens may also play an integral role in the carcinogenic process. Schistosome-infected patients are known to have elevated enzymatic activities associated with serum and urine.^{1,10,11,44} One enzyme, β -glucuronidase (BG) is particularly enhanced.⁴⁸⁻⁵¹ At present there is little evidence regarding the source of the increase in activity in individuals suffering from schistosomiasis. It may originate from

the worms, bacterial infections or the disintegration of the cellular contents of parasite-induced bladder lesions.⁵⁰⁻⁵¹ However, irrespective of the source of BG in the schistosomal bladder, it is possible that an increase in BG concentration may release an active carcinogen by its hydrolytic action on an inactive carcinogen glucuronide. The parasite may induce neoplasia increase by secreting or excreting a precarcinogen metabolite that is inactive like the glucuronide but becomes active when freed by the hydrolytic action of the enzyme in the bladder lumen.⁴⁹ Although the data of Everson et al.⁴⁵ argue against this concept, it is feasible that schistosomal bladders could be exposed to an environmental carcinogen which may be affected by BG. Gentile et al.⁵⁷ have shown that *S. haematobium*-infected Syrian hamsters have elevated urinary BG activity and that the metabolic activation of the bladder carcinogen 3,3'-dichlorobenzidine (DCB) is significantly enhanced in the presence of this urine, a mammalian activating system (S-9) and BG.

An additional way by which carcinogen metabolism may be altered by schistosomiasis is by a modification of metabolic regimes of a specific host organ. Using a laboratory mouse as a host, Gentile & DeRuiter⁵⁸ investigated the *F. hepatica*-aflatoxin B₁ (AFB₁) relationship. Mutagenic activity of AFB₁ was followed in the Ames *Salmonella*/microsome test using liver from uninfected and *F. hepatica*-infected mice. Liver S-9 preparations from infected mice were capable of inducing significantly greater AFB₁ mutagenic activity than liver S-9 preparations from either uninfected mice or Aroclor 1254-induced mice. Similar types of metabolic phenomena have been shown to occur with schistosome infections. The administration of a single dose of the antischistosomal drug hycanthone to mice infected with *S. mansoni* produced significant increases in hepatic neoplastic lesions while no hepatomas were produced when the same dose of the drug was given to noninfected mice^{65,66} although no differences were found with hamsters.^{16,18} Domingo et al.³⁴ observed that low doses of the hepatocarcinogen 2-amino-5-azotoluene produced a much higher incidence of hepatomas in mice infected with *S. mansoni* than in noninfected mice. Although the role of *S. mansoni* in these investigations is not clear, hycanthone and a less genotoxic antischistosomal agent (IA-4-N-oxide) have been shown to induce liver neoplasms when given following partial hepatectomy.¹²⁴ These results could be interpreted on the basis of cellular proliferation. It has been shown that carcinogens such as urethane, 7,12-dimethylbenz(a)anthracene, N-methyl-N-nitrosourea and DMN induce liver neoplasms or preneoplastic lesions when coupled with partial hepatectomy^{29,30} or when administered to newborn or very young animals in which the liver cells were still rapidly proliferating.⁵³ Vandewaa et al.¹²⁶ have shown that liver S-9 prepared from mice following partial hepatectomy is more capable of metabolizing AFB₁ into a mutagen than liver S-9 prepared from normal liver tissue. Furthermore, liver S-9 from *S. haematobium*-infected Syrian golden hamsters is more competent than liver S-9 prepared from uninfected hamsters at metabolizing DCB into a mutagen.⁵⁵ The data from this last study are intriguing in that accelerated cellular division is known to occur in the livers of infected animals in granulomas surrounding eggs deposited in that organ.²⁰ This rapid cell division may be similar to the type of cell division that occurs in regenerating tissues.

Although the precise role of liver cell proliferation and cell injury is not well defined, considerable evidence is available showing that the liver is most susceptible to the development of putative neoplastic lesions induced by several carcinogens when exposed during late G1 or early S-phase of the cell cycle.^{23,109} This probably reflects differences in susceptibility through unknown metabolic transformations or through DNA replication. Data using fluke-infected organisms suggest that the net production of carcinogenic metabolites is intimately dependent upon the balance between activation and inactivation in the host organisms. It is tempting to speculate that trematode-infected individuals either have an induced enzymatic profile in selected organs or have enzymes that cleave normally stable carcinogenic metabolite complexes. Clearly, the presence of parasites and transient enzyme kinetics coupled with diffusion problems of highly reactive carcinogens lead to complexly determined phenomena.

SUMMARY AND CONCLUSIONS

The data associating schistosomiasis and neoplasia are overwhelming, but explanations for this association remain speculative. Ultimately, the control of schistosome-associated cancers might best be accomplished through the control of schistosomiasis. Several older antischistosomal agents, including hycanthon and niridazole, are genotoxic^{67,68,104,105,112} and carcinogenic in test animals.^{86,124,125,130} Considering the substantial amount of supportive evidence for the cocarcinogenic effects of schistosomes, concern for the neoplastic potential of these older agents in infected individuals is certainly justified. The current antischistosomal drugs used for treatment of urinary schistosomiasis, metrifonate and praziquantel, are relatively non-toxic.^{132,133} The past pessimism towards control is no longer warranted in view of a better understanding of the epidemiology of schistosomiasis and of the availability of safe effective antischistosomal drugs and simple quantitative diagnostic techniques.¹³⁴ Elucidation of the mechanisms by which schistosomiasis augments neoplasia will provide knowledge of a fundamental nature as well as knowledge of general applicability. Situations such as these must be explored in order to appreciate more fully the impact of multiple, seemingly unrelated factors on disease prevalence in a human population.

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