Parasites in the Etiology of Cancer—
Bilharziasis and Bladder Cancer

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Bilharziasis, sometimes termed schistosomiasis, is a parasitic disease still prevalent in some parts of the world, such as Africa, Asia and South America. There are three common species: haematobia, which mainly affects the lower genitourinary tract; mansoni, which principally infests the inferior and superior mesenteric veins but migrates to the large intestine; and japonica, which invades the liver, lungs and central nervous system. Infection with the haematobia species in the urinary tract deserves special attention since, unlike bilharziasis of other organs, it causes a chronic form of cystitis that may ultimately be complicated by the development of bladder cancer. In fact, in Egypt, cancer of the bilharzial bladder is the most common cancer in males.

An association between urinary bilharziasis and bladder cancer has been described by the ancient Egyptians and, among others, by Ferguson in 1911. However, the precise role of the parasite in the development of cancer remains controversial. While experimental trials have failed to prove any direct relationship between bilharziasis and cancer, the presence of chronic bacterial cystitis, complicated by urethral strictures, calculi, diverticulae and paralytic stasis, has been known to induce epithelial changes in the bladder mucosa, which may progress to invasive cancer. Bilharzial cystitis is unique in that the initial parasitic infestation occurs early in childhood and persists for two-three decades or more. The exact incidence of cancer development in patients suffering from chronic bilharzial cystitis is unknown. Of 2,500 new cancer patients reported to the Cairo Cancer Institute every year, about 700 patients (27 percent) present with cancer of the bilharzial bladder. (Table.)

Also recently suspected as etiologic agents are the nitrosamines, which are widely and heavily used as soil fertilizers in Egypt. Thus, the water supply and largely vegetarian diet of the Egyptian farmer are rich in nitrate content. Some bacterial strains found in the urine of patients with chronic bilharzial cystitis are capable of forming nitrosamines from nitrates and nitrites. Results of preliminary studies are favorable.

Additional data are clearly necessary to delineate whether there is a direct causal relationship between bilharziasis and bladder cancer. However, the over-representation of cancer in a region where there is a high incidence of parasitic disease, and the unique characteristics of bilharzial bladder cancer, indicate the possibility that this parasite plays a role in the etiology of cancer.

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Bilharziasis

Epidemiology

The irrigation system in Egypt favors the year-round survival of snails, essential to the life-cycle of bilharziasis. The rural population in endemic regions is constantly exposed to the disease. Children are commonly infested as early as two-three years of age. Little is known at present about immunological resistance to the parasite, however, repeated infestations are common after eradicating the disease with drugs. The low socioeconomic and cultural standards of the Egyptian farmer stand as major obstacles against the various measures so far practiced to control bilharziasis.

Clinical and Pathological Manifestations

There is a direct correlation between the severity, persistence, repetition and lack of treatment of bilharzial infestations and the development of various manifes-
The urinary bladder and lower ends of both ureters are most heavily affected with bilharziasis. The deposition of ova provokes a cellular reaction of leukocytes, especially eosinophils, histiocytes, plasma cells and giant cells. Various degrees of fibrosis occur. The ova finally die and become calcified. These calcified ova lying underneath atrophic mucosal cells give rise to characteristic dirty yellow, sandy patches.

Almost all chronic cases of bilharziasis are associated with secondary intractable mixed bacterial infection. Gross patchy or, less frequently, diffuse leukoplakia is common. Signs of chronic bacterial cystitis may be present, such as cystitis glandularis. Other typical presentations include ulcers, granulomatous masses and polypi.

The bladder musculature undergoes atrophy and fibrosis. Muscular hyperplasia and fasculation are occasionally evident as a result of fibrotic bladder neck obstruction, even in young patients. Fibrotic strictures may develop in the ureters, causing hydronephrosis, pyelonephritis and pyonephrosis. Strictures and fistulae are not uncommon in the urethra. The seminal vesicles are particularly involved, resulting in fibrosis and enlargement, which may infrequently attain huge dimensions. The prostate is less commonly affected; fibrosis is the main feature. Stone formation in the ureters, urethra, bladder, kidneys and prostate is a typical complication. The areolar tissue surrounding the involved organs is transformed into masses of dense fibrofatty tissue.

Malignant Transformation
Metaplastic, hyperplastic and dysplastic epithelial changes may occur in the bladder mucosa. Squamous cell metaplasia is particularly common. Columnar cell metaplasia, frequently associated with mucus formation, is less common. All grades of dysplasia, including carci-
noma in situ and ultimately invasive cancer, may develop.

These epithelial changes appear many years before malignant transformation and are generally well manifested in the surrounding mucosa of most established lesions, especially those of the squamous cell variety.

**Cancer of the Bilharzial Bladder**

Cancer of the bilharzial bladder differs from non-bilharzial bladder cancer in many significant areas: age at diagnosis, site, tumor type, degree of lymph node involvement and clinical manifestations.

**Incidence**

Bilharzial bladder cancer is the most common cancer in Egyptian males. It is also found in certain districts of Iraq, Yemen, Saudi Arabia, Sudan and several other African countries, though the incidence is less than in Egypt. This could be attributed to the lower degree of endemicity, intensity and persistence of bilharziasis in these regions.

Cancer of the bilharzial bladder affects males five times more frequently than females, primarily because males are exposed to bilharziasis as they work in the fields. The usual age at diagnosis is the fifth decade, followed by the sixth, fourth, third and seventh. This younger age incidence is remarkable compared to the standard age at diagnosis of non-bilharzial bladder cancer.

**Tumor Site and Type**

Tumors may arise in the vault, anterior, lateral or posterior walls of the bladder. A nodular, fungating, infiltrating tumor, which may attain considerable size, is the most common type of bilharzial bladder cancer, accounting for 80 percent of lesions. A verrucous variety that may present as a fibrillary, filamentous or mammiliated growth or as a mixed lesion, comprises another five percent of cancers. Tumors of the trigone are rare (two percent), but the area may be involved through direct spread of advanced disease. Papillary lesions are also rare (two percent), in contradistinction to non-bilharzial cancer. Malignant penetrating ulcers and diffuse, infiltrating growths account for the remainder of lesions. Multiple tumors are present in about 25 percent of patients.

Squamous cell tumors predominate (75 percent), a characteristic feature of bilharzial bladder cancer. (Fig. 2.) The transitional cell variety comprises about 20 percent of cancers and adenocarcinoma approximately five percent. Leiomyosarcoma and other sarcomas are rarely encountered. The grade of malignancy is usually low (80 percent). Cellular differentiation and excessive keratinization are very marked.

Most patients report with advanced disease, T3 and T4 clinically and P3 and P4 pathologically. At the time of surgery, deep muscle invasion is almost always present and extravasal infiltration is common. Lymph node involvement, generally confined to the pelvis, is found in 27 percent of patients. Blood stream dissemination is unusual. Compared to non-bilharzial bladder cancer, the degree of lymphatic and blood stream involvement is relatively limited, despite the depth of invasion and size of the lesion at presentation. The low grade of malignancy, the associated vesical, perivesical and perivascular fibrosis and, probably, an as yet unknown immunological mechanism, may explain this phenomenon.

**Clinical Aspects**

Various manifestations of cystitis are the main clinical feature in all stages of bilharzial bladder cancer, unlike the classic picture of gross hematuria encountered with non-bilharzial bladder cancer. This may be attributed to the solid nature and keratinized surface of most tumors, compared to the soft, friable, vascular, papillary lesions that characterize non-
bilharzial neoplasms. Microscopic hematuria is always present, however, and macroscopic hematuria is an occasional complaint. The passage of whitish shreds of keratinized, fibrinous and necrotic tissue is common. Clot retention may sometimes occur. A white clot, formed of keratin, fibrin and necrotic tissue, is frequently the result of a verrucous, low-grade squamous cell carcinoma. A red clot, on the other hand, is usually a complication of a highly malignant anaplastic lesion. Most patients present with a palpable mass, which is easily felt without anesthesia.

The calcified outline of the urinary bladder, the lower ends of the ureters and occasionally the seminal vesicles may be demonstrated on plain radiography. Interruption of the calcified outline of the urinary bladder and the presence of irregular finger-print opacities due to calcific deposits on the tumor surface may also be shown on plain X-ray film.

Extensive cytological studies of the urine of patients with bilharzial cystitis and established cancer have been carried on at the Cairo Cancer Institute for the last five years. (Fig. 3.) Cytology has not yet been used for mass screening of the population in endemic areas, but some projects have recently been started.

Treatment
Radiotherapy
Many modalities and techniques of radiotherapy have been attempted in the past 40 years, but the results so far are generally disappointing. Because of the tumor’s advanced stage at diagnosis, the presence of extensive fibrosis and resistant pyogenic infection, long-term survival with radiotherapy as the sole thera-
peutic modality could not be achieved, although limited palliation is sometimes obtained.

Postoperative irradiation after limited resection is almost always followed by local and/or metastatic recurrence, as well as the typical complications of bladder fibrosis, contracture and telangiectasia. Preoperative cobalt irradiation using limited fractionated dosages (2500-4000 rads) is now under trial at the Cairo Cancer Institute. Available data suggest that this method may be of some value in patients with anaplastic lesions, T4 disease or when conservative surgery has been recently attempted. Preoperative radiotherapy with a hemostatic limited dosage is usually beneficial in patients with persistent, severe hematuria.

**Surgery**

Endoscopy and conservative surgery have little or no place in the management of bilharzial bladder cancer, because of its advanced stage, large size, multiplicity of tumors and the frequency of associated, generalized precancerous lesions involving the bladder mucosa.

Segmental resection has been and still is practiced by some urologists. However, only limited palliation is offered, and local and lymphatic recurrences usually follow.

Radical cystectomy (anterior pelvic exenteration) is still the only modality that can provide long-term survival. Pelvic lymph nodes are widely and thoroughly dissected, and removed with the excised organs. Total destruction of one kidney, limited invasion of the small intestines, colon, uterus, vagina or muscles of the abdominal wall, and superficial adhesion to the back of the pubic bone are not contraindications for radical surgery. Wider resections are then carried out. Invasion of the lower part of the rectum is usually associated with diffuse infiltration of the pelvic cellular tissue, and the results of total pelvic exenteration have been extremely disappointing.

The ureters are implanted into an isolated ileal or colonic segment to form a conduit. This technique has proven to be the most satisfactory, provided that the patient is able to manage the conduit. Some patients, especially those who come from far districts and whose social and economic conditions are very low, are faced with considerable inconveniences and difficulties, such as regularly obtaining collecting bags. Under these circumstances a rectal bladder with a terminal colostomy, or a rectal bladder combined with a perineal transanal colostomy have proven, over the last 10 years, to be convenient. The mobilized terminal segment of the colon is brought out through a space dissected between the internal and external sphincter ani, and fixed to the perianal skin. Provided that little damage is done to the anal musculature and that the blood supply of the mobilized colonic segment is adequate, satisfactory control for both urine and stools is obtained, especially in younger men who represent the vast majority of patients.

Our experience with more reconstructive techniques, such as subtotal cystectomy, ileo- or colocoloplasty, total cystectomy, cystoprostatectomy and uretero-ileo or colo-urethral anastomoses have been found less favorable. Late renal damage is a common complication, generally resulting from stricture formation at one or some of the multiple anastomotic sites or from persistent patency and reflux in the absence of adequate sphincteric mechanisms.

However, radical cystectomy is associated with high morbidity and mortality rates, which may be prohibitive especially in the elderly, and should be confined to highly specialized centers; our experience during the last 30 years clearly demonstrates this fact. In the Cairo Cancer Institute the average mortality rate is about 10 percent. The figure
Recurrence

Recurrence after surgery usually occurs locally in the pelvis, and is frequently manifested during the first or second postoperative years. Metastases in the pelvic bones, lungs and liver, respectively, may develop. Irradiation may offer marked palliation for bony lesions. In our experience, postoperative irradiation to reduce the incidence of local recurrence has been disappointing. Nevertheless, trials are now underway employing preoperative irradiation, radical surgery, followed by external or interstitial irradiation to localized fields of suspected residual tumor tissue. It is still too early to assess the results.

The value of various chemotherapeutic agents is also very limited, although short periods of palliation are occasionally obtained.

Long-Term Survival

- The overall five-year survival rate for different groups of patients subjected to radical surgery between 1949-1969 (1,007 patients) was 27.3 percent. The five-year survival rate was 18 percent when pelvic lymph nodes were involved and the lesion was localized to the obturator and/or the external iliac nodes on one side. When other groups were involved, there was no long-term survival.

- The five-year survival rate was 10-15 percent when loops of small intestine and/or colon were locally involved and resected, and when the lesion was superficially adherent to the back of the pubic bone, which was partly chiseled off.

- There was no long-term survival after extensive surgery when muscles of the pelvic floor were invaded and the prostate and/or the lower part of rectum were deeply infiltrated.

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