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Human Bladder Cancer: Evidence for a Potential Irritation-induced Mechanism

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Introduction

This report discusses in some detail the role that irritation from calculi and infection may play in the causation of human bladder cancer. It serves as a backdrop to help interpret tumour findings in experimental animals as to their applicability to human disease potential. A full account of the causes of human bladder cancer will not be attempted; the subject has been ably discussed elsewhere (Cohen and Johansson, 1992; Jones *et al.*, 1992; Matanoski and Elliott, 1981; Silverman *et al.*, 1992).

The paper starts with some descriptive statistics on the occurrence of human bladder and other urinary tract cancers and delineates some of the differences between transitional cell and squamous cell neoplasms. Sections on stone formation and infection in humans set the stage for an analysis of their relationship to bladder and other urinary tract cancers by reviewing, first, the epidemiological evidence, then the clinical associations.

In 1994 approximately 51,000 persons in the United States were expected to develop cancer of the bladder, and about 11,000 died from it. Overall, the bladder cancer rate among males is three-fold higher than among females, with this cancer accounting for 6% of all new cases of cancer and 2% of cancer deaths among men, and 2% of cases and 1% of deaths among women (Boring *et al.*, 1994; Silverman *et al.*, 1992).

In the bladder, transitional cell carcinoma accounts for 93% of cases, squamous cell carcinoma for 2% and adenocarcinoma for 1% (Silverman *et al.*, 1992). In the renal pelvis and ureter, which are covered by urothelium as in the bladder, cancers are again mainly transitional cell and to a lesser extent squamous cell lesions.

In the United States, the age-adjusted incidence rate of bladder cancer is highest among white males (31.6 per 100,000), followed by black males, white females and black females, respectively (Ries *et al.*, 1994). Renal pelvis and ureteral cancer incidences among white males are 1.8 and 1.1 per 100,000, respectively, with both sites showing a two-fold excess of males to females. Incidence and mortality rates of bladder cancer risk increase sharply with age. About two-thirds of cases occur among persons 65 years of age and older. From 1969–71 to 1984–86, bladder cancer incidence rose 22% to 38%, depending on race and sex (Devesa *et al.*, 1990; Matanoski and Elliott, 1981).

There have been a number of risk factors identified for bladder cancer, the most substantiated factor being smoking. Moderate to heavy smokers typically show a two- to five-fold risk of bladder cancer compared with those who never smoked. It is estimated that cigarette smoking accounts for 25–60% of all bladder cancer cases in industrialized, developed countries (Cohen and Johansson, 1992). Occupational exposure to certain aromatic amines is associated with increased risk of bladder cancer and a variety of occupations have been associated with an increased risk of bladder cancer such as those in the leather, textile, rubber, chemical and clothing industries. Less established risk factors include ionizing radiation, cyclophosphamide use, and abuse of phenacetin-containing analgesics (Jones *et al.*, 1992; Matanoski and Elliott, 1981; Silverman *et al.*, 1992).

Epidemiological investigations

Bacterial and schistosomal infection and cancer

Bacterial urinary tract infections are among the most common urological conditions in humans (Smith, 1975). The differences in urethral anatomy and physiology predispose the sexes to different urological conditions. With a short urethra, females are generally much more susceptible to lower urinary tract infections, owing to ascending spread up the urethra. Foreign bodies can also be introduced into the urethra of females and lead to infection. Most of these infections are bacterial in origin, with the common invaders being Gram-negative rods from the colon as well as cocci.

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Abbreviations: CI = confidence interval; RR = relative risk.

The longer urethra in males usually decreases the likelihood of ascending urethral infections to the bladder during the younger years. However, infection may reach the bladder of males from a retrograde spread along the urethra from an infected prostate. In addition, with advancing age in males, vesical neck obstruction due to benign prostatic hyperplasia increases the risk of urinary stasis and incomplete bladder emptying. Stasis from any cause predisposes to infection. Bladder infections may ascend to the kidneys in patients with an inadequate ureterovesical valve. Urinary tract infections may also proceed in an anterograde manner, as a haematogenous infection of the kidney spreading down to the bladder.

In addition to bacterial invasion of the urinary tract, in Africa and the Middle East the bladder frequently becomes infected with the blood fluke *Schistosoma haematobium*. Flukes reside in a freshwater snail and are shed into water where they penetrate the skin of humans to enter the blood. Adult worms lodge in the venous plexus of the bladder wall. Eggs occlude the veins and result in surrounding tissue necrosis including the urothelium; eggs are shed into the bladder lumen. Healing is by scar formation. Secondary bacterial infections readily develop and become chronic, and stones not infrequently develop within the bladder.

Bacterial infection. Several case-control studies have demonstrated a significant association between acute bacterial urinary tract infection and bladder cancer (Table 1) (Claude *et al.*, 1986; Dunham *et al.*, 1968; Howe *et al.*, 1980; Kantor *et al.*, 1984; La Vecchia *et al.*, 1991; Wynder *et al.*, 1963), while two studies (Kjaer *et al.*, 1989; Piper *et al.*, 1986) found no association.

Table 1. Case–control studies of bladder infection and bladder cancer

Author	Infection: time before cancer diagnosis (yr)	Relative Risk	
		Males	Females
Wynder *et al.* (1963)	⩾2	4.4*	—
Dunham *et al.* (1968)	n.r.	2.4*	1.5*
Claude *et al.* (1986)	n.r.	1.6*	1.4
Piper *et al.* (1986)	⩾2	—	1.8
Howe *et al.* (1980)	⩽5	4.9*	2.8*
	>5	n.r.	n.r.
La Vecchia *et al.* (1991)	n.r.	3.4***	
	<5	5.1*	
	5–14	5.5*	
	⩾15	2.3	
	Bouts of acute infection		
	1	2.4(t)	
	2	2.0	
	3	2.9	
	4	4.7*	
Kantor *et al.* (1984)	1 or 2	1.5**	1.2
	⩾3	2.0*	2.1*
		SCC	TCC
Kantor *et al.* (1988)	1 or 2	2.0(t)	1.4*(t)
	⩾3	5.5*	1.9*

Asterisks indicate statistically significant increase (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$); (t) indicates statistically significant trend. n.r. = not reported. SCC = squamous cell carcinoma TCC = transitional cell carcinoma.

Kantor *et al.* (1984) found that the risk of bladder cancer significantly increased with the number of acute urinary tract infections: a relative risk (RR) = 1.5 was found with one or two bouts of infections, and a RR = 2.0 was noted for those with a history of three or more infections compared with those with no infections. La Vecchia *et al.* (1991) also found that the relative risk of bladder cancer increased significantly with the number of reported episodes of acute cystitis. Kantor *et al.* (1988) went on to show that the influence of infection on cancer was greater for squamous cell than for transitional cell cancer. Bladder cancer risks also increase with the amount of smoking, and an interaction between infection and smoking in influencing cancer risks was noted in the study by La Vecchia *et al.* (1991), but not in the larger study by Kantor *et al.* (1984).

La Vecchai *et al.* (1991) suggested that urinary tract infections may have a late-stage effect on bladder cancer risk, because the relative risk for cystitis is elevated for 14 years since the first episode but decreases thereafter. An even shorter latency was found in a Canadian study where bladder and kidney infections preceded bladder cancer diagnosis by up to 5 years (RR = 4.9 and 3.0 for men and women, respectively); longer intervals were without effect (Howe *et al.*, 1980). In this study, 480 cases in males were matched with 480 controls, and 152 female cases were matched with 152 controls. Similar analyses of the temporal relationship between stone formation and bladder cancer have not been investigated in epidemiological studies, but they may shed light on whether stone formation is secondary to tumour development or whether it may be causative (see below). One case–control study of bladder cancer deaths among women less than 45 years of age showed a significant excess of paraplegia (odds ratio = 12.0, 95% confidence interval (CI) 1.46–99.7), a condition associated with long-term, persistent urinary tract infection (see section on patients with dysfunctional bladders, below) (Dolin *et al.*, 1994).

It is difficult to evaluate the reported associations of infection and bladder cancer reported in the studies above (Table 1). Because the dates of the bladder infections were not obtained in most of the reported studies, it is possible that the occurrence or diagnosis of infections may have been the consequence of early bladder cancer, rather than a cause of the disease (Silverman *et al.*, 1992). However, the presence of a tumour *per se* is not necessarily a predisposing factor for infection unless it leads to stasis and residual urine. Another problem in case–control studies, as La Vecchia *et al.* (1991) indicate, is recall bias, because patients with bladder cancer are possibly more sensitized towards recalling urinary tract conditions than patients admitted to hospital for other diseases (and population-based controls as well). However, this may not be a major

problem, because acute urinary tract infections produce significant symptoms in almost all cases and prompt such patients to seek medical attention. Selection (diagnostic) bias is also possible, because patients with recurrent cystitis are probably subjected to cystoscopy more than patients without it.

In contrast to the epidemiological studies and a number of clinical investigations (see below) in humans that have probed the relationship between bacterial infection and cancer of the urothelium, there is a paucity of experimental studies. Repeated implantation of bacteria (*Escherichia coli*) directly into the bladder of female rats leads to hyperplasia, lesions consistent with neoplasia and, in some cases, squamous metaplasia, von Brunn's nests, and calculi. Simultaneous implantation of bacteria and a stainless-steel wire into the bladder results in similar effects, but an increase in calculus formation (Davis *et al.*, 1984). Even a single implantation of bacteria into the bladder can result in chronic infection and tumour formation, especially in the renal pelvis, following initiation with *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) (Johansson *et al.*, 1987).

In studies using the heterotrophic bladder (Uchida *et al.*, 1989; Yamamoto *et al.*, 1992), repeated injection of live *E. coli* results in bladder inflammation and simple and papillary hyperplasia. Similar results are found following the injection of dead coliforms; effects are reversible following removal of the bacteria; repeated injection of dead bacteria results in tumour formation. Attempts to determine the components of bacteria that may account for the development of urothelial hyperplasia have focused on lipopolysaccharides of the cell wall (Uchida *et al.*, 1989; Yamamoto *et al.*, 1992).

Studies of urine from patients with chronic bacterial urinary tract infections have detected strains able to reduce nitrate to nitrite and seemingly to produce nitrosamines. Excretion rates of nitrite (mg/day) and volatile nitrosamines (μg/day) were noted in infected persons, but not in subjects free of infection (Tricker *et al.*, 1991).

In laboratory studies, as the time between initiation of the rodent bladder with *N*-methyl-*N*-nitrosourea and the beginning of injections of killed bacteria increases, the tumorigenic effect lessens, as if the bladder is able to repair genotoxic lesions produced by the nitroso compound before promotion by the bacteria (Kawai *et al.*, 1994). These findings may be relevant to human observations above, where infection often precedes the development of bladder cancer by not more than a few years.

In sum, these findings in the rodent bladder indicate that bacterial infection or bacterial cell components can produce inflammation, cellular proliferation and promotion activity, and contribute to tumour development; bacteria may also produce nitrosamines that could influence carcinogenesis. They support the observations in humans that infection may play a role in bladder carcinogenesis.

Schistosomal infection. Several researchers have reported an association between *Schistosoma haematobium* infection and bladder cancer, particularly squamous cell carcinoma. Gelfand *et al.* (1967) conducted a bladder cancer case–control study of Africans admitted to a hospital in Salisbury, Rhodesia and found that bladder cancers were associated with infestations that were severe and long-standing. Mustacchi and Shimkin (1958) found the risk of schistosomiasis was 2.1 times higher in patients who were found to have bladder cancer than in those who had negative results of cystoscopy.

Khurana *et al.* (1992) reviewed 254 consecutive urinary bladder biopsies in Saudi Arabia and found evidence of urinary schistosomiasis in 88 and malignant neoplasms in 60. Nine of the 60 cases had bladder schistosomiasis; the remaining 51 had no evidence of schistosomiasis. The authors noted that the distribution of bladder cancer [42 cases (70%) transitional cell carcinoma, 12 cases (20%) squamous cell carcinoma, five cases (8%) adenocarcinoma, and one case (2%) rhabdomyosarcoma] differed from that found in Western countries and in particular the incidence of squamous cell carcinoma was higher; this association of schistosomal infection and squamous cell carcinoma is like that reported in Africa. They also reported that the average age of their cancer patients was lower than that of Western countries, suggesting that schistosome-related bladder cancer tends to occur among younger patients than does transitional cell carcinoma. The authors did not estimate the odds ratios in their study, and the comparison of distribution and average age was made with relatively small numbers of cases. Thus, it is difficult to draw conclusions from this study.

Thomas *et al.* (1990) reported a positive geographical correlation between *S. haematobium* and the incidence of squamous cell carcinoma of the bladder in Zimbabwe. The ecological correlation was significant, but the methodology of the study prohibits one from making any definitive conclusion. In the rural agricultural areas of Egypt, 17–70% of people develop schistosomiasis because of contact with contaminated water, and schistosomiasis among squamous carcinoma patients in South Africa (68%) is much higher than among transitional cell carcinoma patients (19%). Although schistosomes have produced bladder cancer in a non-human primate model, there is a lack of prospective studies in humans relating the presence or absence of schistosomiasis with the development of bladder cancer (El-Bolkainy, 1983).

Several hypotheses have been provided as to the actual casual relationship between *S. haematobium* and bladder cancer, including local tissue damage, mechanical irritation, bilharzial toxins or secondary bacterial infection. Bacterial products include nitrate reductase capable of synthesizing nitrosoamines and β-glucuronidase enzymes (Tawfik, 1988). One of the arguments for a causal association of schistosomiasis

with bladder cancer is the specificity with squamous cell carcinoma. Another is the fact that where *S. haematobium* is endemic, bladder cancer incidence is elevated. Payet (1962) reported, however, that bladder cancer incidence rates are similar in areas of Africa where schistosomiasis is endemic, infrequent, or absent. Even with these complexities, the International Agency for Research on Cancer has judged that there is sufficient evidence to conclude that *S. haematobium* infection is carcinogenic to humans (IARC, 1994).

Bladder stones and cancer

Lithiasis, or stone formation, is a common disorder of the urinary tract. In the Western world, most urinary stones involve the upper urinary tract, while in previous times and in children today in developing countries such as India and China, bladder stones are more common (Scott, 1990; Streem, 1987). Stones form in the kidney from precipitation of inorganic and organic salts. The composition of stones has been well studied. Calcium oxalate stones are by far the most common in adults in developed countries. For example, in Japanese adults nearly 90% of stones are mixtures of calcium oxalate and calcium phosphate. Ammonium acid urate stones are generally found in children and have been decreasing in incidence in the United States and other developed areas, possibly due to changes in diet; however, they remain endemic in various Asian countries (Barratt and Ghazali, 1977).

Metabolic stones arise from inborn errors of metabolism where increased amounts of various normal metabolites are found and precipitate in the urine; such conditions include uric aciduria/gout, cystinuria, hyperoxaluria, xanthinuria, and orotic aciduria (Watts, 1977). Materials that have been only rarely reported in stones include steatin, sulfonamides and indigo. Approximately 2.5% of the weight of adult stones consists of glycoprotein or mucoprotein matrix (Hesse *et al.*, 1977).

Generally, a stone that forms in the kidney moves to the ureter where it may lodge and cause pain. If a stone traverses the ureter to the bladder (those up to 0.5 cm in diameter), it is usually eliminated through the urethra unless there is some stricture to outflow from the bladder because the bladder neck is at the most dependent position of the bladder in humans. If a stone continues to obstruct urinary flow and causes pain, it is removed by extracorporeal shock lithotripsy or surgery. This is a very different history than that for most mammals that walk on all four limbs, where stones may be retained in the bladder (DeSesso, 1995). Unlike most stones in humans, those in a renal calyx or pelvis may be clinically silent and grow to a large size that conforms to the shape of the renal pelvis (staghorn calculus), coming to attention only after producing signs and symptoms of urinary tract infection.

Stones that form in the bladder *per se* are often secondary to some other inciting cause such as infection, the presence of a foreign body or, especially in children, may be secondary to pre-existing conditions such as inborn errors of metabolism (Rambar and Mackenzie, 1978). Persons with bladder neck obstruction due to causes such as prostatic hyperplasia, spinal cord injury or urethral stricture may have residual urine and be predisposed to infection. Infection also puts a person at risk for stone formation; if the infectious organisms split urea to ammonia and greatly elevate urinary pH, magnesium ammonium phosphate (struvite) stones often form. Today, about 7% of stones are associated with bacterial infection (Ohkawa *et al.*, 1992).

Stone frequency varies greatly within and among countries and appears to be related to diet, climate, race and sex (Broadus and Thier, 1979). Stones have been associated with diets deficient in vitamin B (Gershoff *et al.*, 1963) and are more prevalent during the summer months, possibly associated with dehydration and increased urinary concentration (Scott, 1990); heredity may play a role; they may also be associated with various pharmaceuticals such as methoxyflurane, allopurinol and corticosteroids (Cheng, 1980).

Many reports concerning the incidence of uroliths have relied upon hospitalization records that may underestimate the actual incidence because many diagnosed cases are not hospitalized. A study of Danish physicians found that 12% of males and 7% of females reportedly suffered from urinary stones in the past (Larsen and Philip, 1962). In questionnaires sent to 175,000 adults participating in a northern California prepaid health plan, 32.0/1000 men and 21.0/1000 women reported ever having been diagnosed by a physician as having a urinary tract stone (Hiatt *et al.*, 1982).

The age-adjusted annual incidence rate of renal stones in a group of outpatient or hospital-based patients in Minnesota presenting with pain, dysuria and haematuria was 1.23/1000 for males and 0.36/1000 for females (Johnson *et al.*, 1979). The female rates were stable over the 25 year period, but rates for males increased by approximately 50% over this time period, for unknown reasons. The peak incidence for a first-time upper urinary tract stone was 30–60 years, and recurrences were found in about one-half of the patients.

Although males are generally reported to have higher incidences of stone formation, a post-mortem survey (Larsen and Philip, 1962) found similar incidences of urinary tract stones (at any site) in males and females. Differences in the activity of hepatic glycolate oxidase, an enzyme related to testosterone metabolism, leading to greater oxalate production in males has been proposed to be a factor in the greater frequency of stone observation that is usually reported in males (Finlayson, 1977).

Although the incidences of bladder stones and of bladder cancer are known to vary significantly among countries, no citations were found that investigated

the relationship between these two variables. Within a geographical setting, however, several case–control epidemiological studies have examined the relationship between bladder stones and bladder cancer. Only two of seven studies indicate a significant association; these investigations are summarized in Table 2.

Among the epidemiological studies, a US hospital-based matched case–control investigation of patients with invasive cancer found a slightly increased, but not significant, rate of stones among male bladder cancer patients (RR = 2.2) (Wynder *et al.*, 1963). No significant association of stones and bladder cancer was found for females, either. This lack of an association was also true in a study in Milan, Italy where an RR of 1.2 was found for bladder or kidney stones among patients with transitional cell cancers of the bladder (La Vecchia *et al.*, 1991) and in studies from three Canadian provinces (Howe *et al.*, 1980) and from northern Germany (Claude *et al.*, 1986). In Copenhagen, Denmark, no relationship between bladder stones and bladder cancer was found in males (RR = 1.5) or in females (Kjaer *et al.*, 1989). A significantly increased risk was noted for kidney stones and bladder cancer in females (RR = 3.7) but not males. Tumours were histologically verified; about 90% were transitional cell tumours.

In a study of hospital patients in New Orleans (Dunham *et al.*, 1968) a significantly increased risk of stones among bladder cancer was found among males (RR = 2.8), but not among females. Persons with bladder papillomas were excluded. A statistically significantly increased risk (RR = 1.8) for bladder cancer and bladder stones also was found in a large study in the United States (Kantor *et al.*, 1984). However, a precise temporal relationship between stone formation and the development of bladder cancer was not possible; all that was recorded was that the stone had occurred at least 1 year before the time of cancer diagnosis. No relationship between bladder cancer and kidney stones was found. Interestingly, among those bladder cancer cases with squamous cell carcinoma, an increased (but not statistically significant) RR of 4.4 was found for a history of bladder stones. This study included only patients with histologically diagnosed cancer and matched 2213 males with bladder cancer with 4217 controls and 719 female cases with 1481 controls; 97% of the tumours were transitional cell tumours.

Table 2. Case-control studies of bladder stones and bladder cancer

Author	No. of cases of bladder cancer	No. of controls	Relative risk (95% CI)
Wynder *et al.* (1963)	300 M 70 F	300 M 70 F	2.2 (0.9–5.5) n.r.
Dunham *et al.* (1968)	334 M 159 F	350 M 177 F	2.8 (1.6–5.2) 2.1 (0.7–5.7)
Howe *et al.* (1980)	480 M 152 F	480 M 152 F	n.s. n.s.
Kantor *et al.* (1984)	2213 M 719 F	4217 M 1481 F	1.8 (1.1–2.8)*
Claude *et al.* (1986)	340 M 91 F	340 M 91 F	n.s. n.s.
Kjaer *et al.* (1989)	290 M 98 F	595 M 195 F	0.5 (0.1–2.4)*
La Vecchia *et al.* (1991)	303 M 61 F	336 M 111 F	1.0 (0.5–2.0)*†

n.r. = not reported; n.s. = apparently not significant or authors reported as not significant.
*Value is for both sexes combined.
†Stones in the bladder or kidney.

Clinical investigations

Clinically, transitional cell and squamous cell tumours differ significantly (Oyasu, 1995), which may indicate that these tumours arise by different means. Transitional cell carcinomas commonly occur in multiple sites in the same individual, whereas squamous cell carcinomas are not regularly multicentric (Rafla, 1975). For instance, of hundreds of cases of transitional cell carcinoma of the renal pelvis from multiple publications, about 40% developed a second such tumour in the other pelvis, a ureter or the bladder. Multiple cancers of the bladder are also a common finding. In contrast to these findings, multiple squamous cell carcinomas are very uncommon (≪1%) (Petersen, 1992).

Several hypotheses have been advanced to account for the finding of multiple urinary tract transitional cell carcinomas. One is that there is a 'field' effect where a given area of the urinary tract has altered cells that may develop into tumours. This hypothesis is supported by the very common finding of broad areas of dysplastic cells and the development of second tumours within the bladder of persons with primary bladder tumours (Wolf and Hojgaard, 1983). The other hypothesis is a 'drop' effect, where tumour cells from one site autotransplant to another site in the urinary tract. The finding of tumours of the same renal pelvis and ureter and bladder tumours near the opening of the ureter on the same side support this proposal (Harris and Neal, 1992; Petersen, 1992). Molecular analyses of urinary tract tumours demonstrate a monocional origin of all tumours within an individual (Harris and Neal, 1992; Sidransky *et al.*, 1992), which greatly supports the 'drop' hypothesis.

Clinicians have suspected an association between chronic inflammation from stones and infection and certain cancers of the urinary tract (Bessette *et al.*, 1974; Petersen, 1992; Utz and McDonald, 1957). Similar observations linking inflammation and tumours have been made in animal studies (Clayson, 1974; Johansson *et al.*, 1987; Kagawa *et al.*, 1992; Yamamoto *et al.*, 1992). In humans, the association between inflammation and tumours applies more often to squamous cell cancers, whereas in rodents most tumours are transitional cell neoplasms. Smoking and other known causes of human cancer are mainly associated with transitional cell cancer.

Various clinical findings are relevant to the potential role of infection and calculi in the carcinogenic process in humans. A direct approach is to look at

persons with a penchant for urinary tract infection (e.g. patients with dysfunctional bladders) or stone formation (e.g. persons with inborn errors of metabolism) to see if they are at risk for developing tumours. An indirect approach is to analyse several steps that may be part of the carcinogenic process and to combine them into an overall impression.

Bladder cancer among patients with dysfunctional bladders

Dysfunctional bladder patients include persons with spinal cord injury or spina bifida. In general, these persons have chronic infections of the urinary tract, and some have calculi. Many have been on long-term catheter drainage. Thus, there are several potential irritants in the bladder—infection, stones and catheter.

Among various studies (Table 3), Kaufman *et al.* (1977) reported that of 62 patients with long-term indwelling catheterization, 10% had diffuse squamous cell carcinoma; five of these patients were among 25 who had been on indwelling catheters for more than 10 years. Broecker *et al.* (1981) noted that of 50 patients who had indwelling urinary catheter drainage for at least 10 years, there were 11 cases (22%) of squamous metaplasia compared with four cases among 31 patients (13%) who had external urinary catheter drainage. No malignancies were seen in either group. Bickel *et al.* (1991) reported that eight of 2900 spinal cord injury patients seen at three medical centres in Louisiana developed bladder cancer, six with transitional cell carcinoma and two with squamous cell carcinoma. Bejany *et al.* (1987) reported on 11 male patients with spinal cord injuries who developed bladder tumours: seven were on chronic indwelling catheter drainage; two had defunctionalized bladders after ileal conduit urinary diversion; and two voided spontaneously and used an external collecting device. Nine of the 11 had squamous cell carcinoma, and two had transitional cell carcinoma.

These studies of spinal cord injury patients did not generally indicate such factors as how the patients were found within the populations studied, the duration of the spinal cord disorders, or the frequency of follow-up investigations. Thus, it is hard to determine such things as cancer incidence and death rates, although El-Masri and Fellows (1981) estimated that spinal cord injury increased the risk of death from bladder cancer by about 20-fold. In another study (Nyquist and Bors, 1967), there were seven urinary tract cancer deaths among 258 deaths among spinal cord injury patients (five bladder, one renal cell and one urethral carcinoma); the authors concluded that this was a 50-fold increase in cancer of the urinary system.

The reversal in the ratio of transitional cell to squamous cell cancer of the bladder cancer in spinal cord injury patients is noteworthy (Table 3). Normally there are about 49 cases of transitional cell cancer for each case of squamous cell carcinoma, but among the dysfunctional bladder patients there are about equal numbers of transitional cell and squamous cell carcinomas. Interestingly, in a case–control study of women dying with bladder cancer before the age of 45 years, at least four of six paraplegia cases had squamous cell carcinoma (Dolin *et al.*, 1994). Although patients with dysfunctional bladders develop transitional cell cancers, it appears that they are much more prone to developing squamous cell carcinoma than are most people who develop bladder cancer.

Table 3. Bladder tumour diagnoses among patients with dysfunctional bladders

Author	No. of persons	No. of cancer cases	
		SCC	TCC
Melzak (1966)*	3800	4	3
Kaufman *et al.* (1977)	62	6	—
Broecker *et al.* (1981)	1052	2	4
El-Masri and Fellows (1981)	6744	11	13
Locke *et al.* (1985)	25	2	—
Bejany *et al.* (1987)	300	9	2
Yaqoob *et al.* (1991)	14	3	1
Bickel *et al.* (1991)	2900	2	6
Total		35	26
US relative frequency		1	49

SCC = squamous cell carcinoma; TCC = transitional cell carcinoma.
*Did not use tumour frequency from this study in computing totals, because El-Masri and Fellows (1981) is a follow-up study.

Stone-forming inborn errors of metabolism

A number of human inborn errors of metabolism are associated with urinary stone formation, often beginning at an early age and persisting throughout life. Examples include such conditions as cystinuria, uric aciduria/gout, xanthinuria and hyperoxaluria. An attempt was made to identify literature relative to urinary tract cancer among these persons: not one citation was found. Given the intense propensity for these people to develop stones throughout their life, one cannot but be impressed by the lack of literature citations on urinary tract cancer.

Associations among infection/stones, squamous metaplasia and squamous cell carcinoma

An indirect approach to evaluate the relationship between inflammation and cancer is to analyse several components that may be part of the carcinogenic process and combine them to give an overall impression. The first is to investigate whether infection and stones can produce squamous metaplasia; the second is to investigate cases of squamous metaplasia as to whether infection and stones are antecedents and whether squamous cell cancer develops; the third is to look at occurrence of infection, calculi and squamous metaplasia among squamous cell carcinoma patients. In combination, these analyses lend support to the notion that inflammation plays a role in bladder carcinogenesis, and especially for squamous cell neoplasms.

Table 4. Leukoplakia: antecedent conditions and tumour development

Author	No. of cases*	Percent of cases: History		Tumour type†		
		Infection	Stones	SCC	TCC	Other‡
Morgan and Cameron (1980)	32	53	28	25	—	3
O'Flynn and Mullaney (1967)	20	25	20	10	—	—
Connery (1953)	45	56	n	16	—	4
Benson *et al.* (1984)						
(bladder)	78	58	10	28	8	6
(upper tract)	24	42	54	4	4	4
Widran *et al.* (1974)	450	15	0.4	2	—	—

n = not reported; SCC = squamous cell carcinoma; TCC = transitional cell carcinoma.
*Leukoplakia cases, except in Widran *et al.* (1974) which were squamous metaplasia; all diagnoses were in the bladder except Benson *et al.* (1984), which included renal pelvis and ureteral cases.
†Tumour diagnosed at time of diagnosis of metaplasia or subsequent to it.
‡Other: mixed types, anaplastic or not given.

It is fair to say that there is considerable controversy as to the pathogenesis of squamous cell carcinoma in the urinary tract and whether it proceeds by way of squamous metaplasia (Oyasu, 1995). Although this controversy has not been settled, most authorities consider that at least some forms of squamous metaplasia can develop in the face of inflammatory or other stimuli.

Squamous metaplasia has different manifestations. One form, squamous metaplasia of the vaginal type, is a normal variant in postmenarcheal females, involving the trigone and bladder neck; it is not involved in cancer. Squamous metaplasia may also exist in localized areas in a non-keratinized state, or it can have a keratinized layer on its surface that gives a whitish sheen on gross examination (leukoplakia). Clinical studies have reported that keratinized lesions frequently involve several areas of the bladder, may be quite extensive or may even involve essentially all of the mucosal surface (Morgan and Cameron, 1980; O'Flynn and Mullaney, 1967); these lesions may be of significance for cancer development. Although non-keratinized squamous metaplasia and squamous metaplasia of the vaginal type are common lesions, leukoplakia is rare in the absence of intercurrent urinary tract disease (Shirai *et al.*, 1987; Widran *et al.*, 1974; Wiener *et al.*, 1979).

Cytology of persons with infection or stones. Studies of exfoliated cells from persons with infections and stones often show abnormal cellular forms. Among people with chronic urinary tract infections, cytology of bladder washings showed squamous metaplasia in 12 of 14 patients; many of these were confirmed by biopsy (Polsky *et al.*, 1976). Urinary cytology of 216 cases with urinary calculi resulted in diagnoses of malignancy or of suspected malignancy in 6–18% of a total of 216 cases (Beyer-Boon *et al.*, 1978; Highman and Wilson, 1982). Persons with long-term urinary stones, especially staghorn calculi of the renal pelvis, showed squamous cells in the urinary sediment suggestive of squamous metaplasia. All cellular abnormalities disappeared when the stones were removed, which suggests the potential for reversibility of effects.

Antecedents and tumour development among persons with squamous metaplasia. Several studies have examined patients with squamous metaplasia as to antecedent urological conditions and development of urinary tract tumours (Table 4). Most authors used the designation leukoplakia to describe the metaplastic lesions. In these cases 25–58% of metaplasia subjects reported a history of infection, while in 10–28% of bladder cases and 54% of upper tract cases a history of calculi was reported. In another study (Widran *et al.*, 1974) with a significant proportion of females (88%) with squamous metaplasia of the vaginal type, a history of infection and stones was reported in only 15 and 0.4% of cases, respectively.

Urinary tract tumours were noted at the time of diagnosis of leukoplakia or subsequent to that time in a significant proportion of metaplasia cases (10–42% of cases in the bladder and 12% in the upper urinary tract); most of the tumours were squamous cell carcinomas (Table 4).

Infection, calculi and squamous metaplasia among cases of squamous cell carcinoma. Several clinical investigations have reported the association of various conditions in persons diagnosed as having carcinoma of the urinary tract. Reports of calculi among bladder cancer patients with transitional cell carcinoma are uncommon; however, about 16% of squamous cell bladder cancer patients have accompanying stones and about 50% have an infection (Table 5). Little information exists as to the length and pattern of occurrence of the inflammatory lesions

Table 5. Urinary conditions accompanying squamous cell carcinoma of the bladder

Author	No. of cases	No. with: Stones	Infection
Sakkas (1966)	47	5	33
Newman *et al.* (1968)	84	n	17
Bessette *et al.* (1974)	75	14	14
Johnson *et al.* (1976)	90	n	84
Rous (1978)	17	n	8
Totals	313	19 (16%)	156 (50%)

n = not reported

prior to diagnosis of cancer. In the upper urinary tract, calculi are reported in 43% of renal pelvis and 25% of ureteral squamous cell carcinoma patients (Table 6). An association between calculi and transitional cell carcinoma also seems to be present, but it is less impressive than for squamous cell carcinoma. In addition, among cancer patients, squamous metaplasia was reported in about 16% of renal pelvis patients (Petersen, 1992) and 18% of bladder cancer patients (Bessette *et al.*, 1974; Johnson *et al.*, 1976; Richie *et al.*, 1976).

Assessment of the role of inflammation in bladder cancer

The overall contribution of inflammation from bacterial infection and stones in human urinary tract cancer is difficult to assess. Experimental animal studies involving bacterial urinary tract infections and stone formation are consistent in showing a relationship between the inciting inflammatory stimulus and later tumour development. However, no long-term linkage and evidence of causation between infection/stones and cancer has been established in humans. Epidemiological and clinical studies show some relationship between bacterial infection and bladder cancer, especially squamous cell cancer. There seems to be an increasing risk of cancer with increasing number of acute bacterial urinary tract infections and for times after infection up to 4–14 years.

Bacterial infections are the most common urological conditions among females. For instance, 35% of female college students reported at least one urinary tract infection, and 6% had four or more (Remis *et al.*, 1987). In addition, acute cystitis occurs in about 1–2% of all pregnancies, but in excess of 10% of teenage pregnancies (Hediger *et al.*, 1991). Given these findings, if urinary tract inflammation through bacterial infection were truly a major risk factor for bladder cancer, one might expect that (1) tumours would be more common in females than in males, (2) squamous cell carcinoma would be a common bladder tumour type, and (3) tumours might occur at a relatively early age. However, this is not the case: bladder tumours are about three times more common in males than females; squamous cell tumours constitute only about 2–5% of all bladder cancers in developed countries, and the bulk of the tumours occur in persons of an advanced age. Even with these problems, physicians take the finding of keratinizing squamous metaplasia seriously when associated with urinary tract infection and advocate frequent follow-up because of the potential for squamous cell carcinoma formation (Benson *et al.*, 1984; Bessette *et al.*, 1974; Hertle and Androulakakis, 1982; Petersen, 1992).

Table 6. Calculi in persons with upper urinary tract transitional cell carcinoma (TCC) and squamous cell carcinoma (SCC)*

		No. of		Overall percentage with calculi
		Studies	Subjects	
Renal pelvis	TCC	8	502	7
	SCC	12	252	43
Ureter	TCC	13	2000	10
	SCC	20	43	25

*From Petersen (1992).

Investigations of persons with dysfunctional bladders and with schistosomiasis are consistent in finding some relationship between infection and cancer. However, both groups commonly have multiple sources of bladder inflammation. Cases of spinal cord injury usually have chronic, not acute, urinary tract infections; they often have chronic indwelling catheters and stone formation is common. In chronic schistosomiasis, the parasite occludes the venous plexus of the bladder wall and leads to necrosis of surrounding tissue, including the urothelium. Chronic bacterial urinary tract infections and stones may also form. In both the dysfunctional bladder cases and those with schistosomiasis, there is a disproportionate finding of squamous cell carcinoma.

Epidemiological studies relating bladder stones and bladder cancer have not been as indicative of an association as have those for infection and cancer. Two case–control studies have shown a significant risk (Dunham *et al.*, 1968; Kantor *et al.*, 1984), whereas five others have not. Of special note is the total absence of literature citations concerning urinary tract cancer among persons with inborn errors of metabolism that have a life-long predilection for stone formation. Even with this, clinical studies of persons with stones, metaplasia and/or cancer often give some indication that stones may be a factor in the carcinogenic process at various sites in the urinary tract.

The response of rodents (especially rats) to infection and stones usually differs from that of humans, with an early and significant proliferative response of the urothelium and transitional cell tumour development among a significant proportion of treated animals (Clayson *et al.*, 1995; Oyasu, 1995). Humans seem to be less responsive to these stimuli; to the extent that they do respond, some may develop squamous metaplasia and squamous cell cancers.

If bladder stones in humans were viewed as a risk factor for bladder cancer, what kind of impact might they have? There is no direct way to evaluate this role, but using some of the epidemiological information and the associations that have been noted in clinical studies, very crude estimates can be developed for squamous cell carcinoma (see Appendix); estimates for transitional cell cancer, to the extent that they might occur; were not attempted. One estimate indicates that the chance of squamous cell cancer, given a bladder stone, is about 6%. The other indicates that stones may essentially account for all cases of squamous cell carcinoma of the bladder. Given the existing epidemiological and clinical information,

both estimates appear to exaggerate the significance of stones in bladder cancer.

Admittedly, both of the above crude estimates of the influence of stones do not include adjustments for factors that may greatly affect these estimates, including (a) the proportion of bladder stones that remain in the bladder long enough to induce pathological effects, (b) the size and shape of the stone that may influence the severity of induced effects, (c) the duration of time the stone is in contact with the urothelium, and (d) confounding factors such as smoking. Intuitively it would seem that owing to our erect posture most stones would be passed in the urine or would lead to obstruction, pain and/or infection that would eventually result in their removal (DeSesso, 1995). Therefore, only a small proportion of stones may actually persist long enough to influence cancer formation. Furthermore, factors other than stones (e.g. infection, smoking) influence the development of squamous cell carcinoma. Therefore, the two risk estimates should be regarded as significant overestimates of the influence of stones on bladder cancer development.

Summary

Bladder cancer is one of the most common human cancers, constituting about 6% and 2% of all cancers among males and females, respectively. Over 90% of all bladder cancers are transitional cell carcinomas, with most of the remainder being squamous cell carcinomas. Smoking and occupational exposure to aromatic amines and other agents are most prominent among the risk factors identified.

Inflammation of the bladder, largely by infection but also by stones or a combination of the two, may play some role in human bladder cancer development. The association between inflammation and cancer appears to be stronger for squamous cell than for transitional cell carcinoma. Stones and infection can be important factors in the development of bladder tumours in rodents, but the tumours are predominantly transitional cell rather than squamous cell carcinomas.

REFERENCES

Barratt T. M. and Ghazali S. (1977) The actiology of renal stones in children. *Postgraduate Medical Journal* **53**, 35–40 (Suppl. 2).

Bejany D. E., Lockhart J. L. and Rhamy R. K. (1987) Malignant vesical tumors following spinal cord injury. *Journal of Urology* **138**, 1390–1392.

Benson R. C., Jr, Swanson S. K. and Farrow G. M. (1984) Relationship of leukoplakia to urothelial malignancy. *Journal of Urology* **131**, 507–511.

Bessette P. L., Abell M. R. and Herwig K. R. (1974) A clinicopathologic study of squamous cell carcinoma of the bladder. *Journal of Urology* **112**, 66–67.

Beyer-Boon M. E., Cuypers L. H. R. I., deVoogt H. J. and Brussee J. A. M. (1978) Cytological changes due to urinary calculi: a consideration of the relationship between calculi and the development of urothelial carcinoma. *British Journal of Urology* **50**, 81–89.

Bickel A., Culkin D. J. and Wheeler J. S. (1991) Bladder cancer in spinal cord injury patients. *Journal of Urology* **146**, 1240–1242.

Boring C. C., Squires T. S., Tong T. and Montgomery S. (1994) Cancer statistics, 1994. *CA: A Cancer Journal for Clinicians* **44**, 7–26.

Broadus A. E. and Thier S. O. (1979) Metabolic basis of renal-stone disease. *New England Journal of Medicine* **300**, 839–845.

Broecker B. H., Klein F. A. and Hackler R. H. (1981) Cancer of the bladder in spinal cord injury patients. *Journal of Urology* **125**, 196–197.

Cheng L. (1980) Urinary tract calculi in man and laboratory animals: incidence, composition and etiology. *Journal of Environmental Pathology and Toxicology* **4**, 317–349.

Claude J., Kunze E., Frentzel-Beyme R. I, Paczkowski K., Schneider J. and Schubert H. (1986) Life-style and occupational risk factors in cancer of the lower urinary tract. *American Journal of Epidemiology* **124**, 578–589.

Clayson D. B. (1974) Bladder carcinogenesis in rats and mice: possibility of artifacts. *Journal of the National Cancer Institute* **52**, 1685–1689.

Clayson D. B., Fishbein L. and Cohen S. M. (1995) Effects of stones and other physical factors on the induction of rodent bladder cancer. *Food and Chemical Toxicology* **33**, 771–784.

Cohen S. M. and Johansson S. L. (1992) Epidemiology and etiology of bladder cancer. *Urologic Clinics of North America* **19**, 421–428.

Connery D. B. (1953) Leukoplakia of the urinary bladder and its association with carcinoma. *Journal of Urology* **69**, 121–127.

Davis C. P., Cohen M. S., Gruber M. B., Anderson M. D. and Warren M. M. (1984) Urothelial hyperplasia and neoplasia: a response to chronic urinary tract infections in rats. *Journal of Urology* **132**, 1025–1031.

DeSesso, J. M. (1995) Anatomical relationships of urinary bladders compared: their potential role in the development of bladder tumours in humans and rats. *Food and Chemical Toxicology* **33**, 705–714.

Devesa S. S., Silverman D. T., Mclaughlin J. K., Brown C. C., Connelly R. R. and Fraumeni J. F., Jr (1990) Comparison of the descriptive epidemiology of urinary tract tumors. *Cancer Causes and Control* **1**, 133–141.

Dolin P. J., Darby S. C. and Beral V. (1994) Paraplegia and squamous cell carcinoma of the bladder in young women: findings from a case–control study. *British Journal of Cancer* **70**, 167–168.

Dunham L. J., Rabson A. S., Stewart H. L., Frank A. S. and Young J. L. (1968) Rates, interview, and pathology study of cancer of the urinary bladder in New Orleans, Louisiana. *Journal of the National Cancer Institute* **41**, 683–709.

El-Bolkainy M. N. (1983) Schistosomiasis and bladder cancer. In *The Pathology of Bladder Cancer*. Vol. 1. Edited by G. T. Bryan and S. M. Cohen. pp. 57–89. CRC Press, Boca Raton, FL.

Ellwein L. B. and Farrow G. M. (1988) Urinary cytology screening: the decision facing the asymptomatic patient. *Medical Decision Making* **8**, 110–119.

El-Masri W. S. and Fellows G. (1981) Bladder cancer after spinal cord injury. *Paraplegia* **19**, 265–270.

Finlayson B. (1977) Calcium stones: some physical and clinical aspects. In *Calcium Metabolism in Renal Failure and Nephrolithiasis*. Edited by D. S. David. pp. 337–382. Wiley, New York.

Gelfand M., Weinberg R. W. and Castle W. M. (1967) Relation between carcinoma of the bladder and infestation with *Schistosoma haematobium*. *Lancet* **i**, 1249–1251.

Gershoff S. N., Prien E. L. and Chandrapanonda (1963) Bladder stones in Thailand. *Journal of Urology* **90**, 285–288.

Harris A. L. and Neal D. E. (1992) Bladder cancer—field versus clonal origin. *New England Journal of Medicine* **326**, 759–761.

Hediger M. L., Scholl T. O., Stefenelli G. E., Shearer J. W. and Ances I. G. (1991) Urinary tract infections during pregnancy in adolescence. (Abstract) *American Journal of Epidemiology* **134**, 727.

Hertle L. and Androulakakis P. (1982) Keratinizing desquamative squamous mataplasia of the upper urinary tract: leukoplakia–cholesteatoma. *Journal of Urology* **127**, 631–635.

Hesse A., Dietze H. J. and Berg W. (1977) Spectrophotometric trace element analysis of calcium oxalate uroliths. *European Journal of Urology* **3**, 359–365.

Hiatt R. A., Dales L. G., Friedman G. D. and Hunkeler E. M. (1982) Frequency of nephrolithiasis in a prepaid medical care program. *American Journal of Epidemiology* **115**, 225–265.

Highman W. and Wilson E. (1982) Urine cytology in patients with calculi. *Journal of Clinical Pathology* **35**, 350–356.

Howe G. R., Burch J. D., Miller A. B., Cook G. M., Esteve J., Morrison B., Gordon P., Chambers L. W., Fodor G. and Winson G. M. (1980) Tobacco use, occupation, coffee, various nutrients and bladder cancer. *Journal of the National Cancer Institute* **64**, 701–713.

IARC (1994) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 6. Infection with schistosomes (Schistosoma haematobium, S. mansoni and S. japonicum)*. pp. 45–119. International Agency for Research on Cancer. Lyon.

Johansson S. L., Anderstom C., von Schultz L. and Larsson P. (1987) Enhancement of *N*-(4-(5-nitro-2-furyl)-2-thiazolyl) formamide-induced carcinogenesis by urinary tract infection in rats. *Cancer Research* **47**, 559–562.

Johnson C. M., Wilson D. M., O'Fallon W. M., Malek R. S. and Kurland L. T. (1979) Renal stone epidemiology: a 25 year study in Rochester, Minnesota. *Kidney International* **16**, 624–631.

Johnson D. E., Schoenwald M. P., Ayala A. G. and Miller L. S. (1976) Squamous cell carcinoma of the bladder. *Journal of Urology* **115**, 542–544.

Jones R. F., Debiec-Rychter M. and Wang C. Y. (1992) Chemical carcinogenesis of the urinary bladder—a status report. *Journal of Cancer Research and Clinical Oncology* **188**, 411–419.

Kagawa M., Yamamoto A., Ogawa K., Shitai T. and Fukushima S. (1992) Uracil-induced urolithiasis in the urinary tract is irritation dependent. *Toxicology Letters* **61**, 21–26.

Kantor A. F., Hartge P., Hoover R. N. and Fraumeni J. F., Jr (1988) Epidemiological characteristics of squamous cell carcinoma and adenocarcinoma of the bladder. *Cancer Research* **48**, 3853–3855.

Kantor A. F., Hartge P., Hoover R. N., Narayana A. S., Sullivan J. W. and Fraumeni J. F. (1984) Urinary tract infection and risk of bladder cancer. *American Journal of Epidemiology* **119**, 510–515.

Kaufman J. M., Fam B., Jacobs S. C., Gabilondo F., Yalla S., Kane J. P. and Rossier A. B. (1977) Bladder cancer and squamous metaplasia in spinal cord injury patients. *Journal of Urology* **118**, 967–971.

Kawai K., Kawamata H., Kemeyama S., Rademaker A. and Oyasu R. (1994) Persistence of carcinogen-altered cell population in rat urothelium which can be promoted to tumors by chronic inflammatory stimulus. *Cancer Research* **54**, 2630–2632.

Khurana P., Morad N., Khan A. R., Shetty S., Ibrahim A. and Patil K. (1992) Impact of schistosomiasis on urinary bladder cancer in the southern province of Saudi Arabia: review of 60 cases. *Journal of Tropical Medicine and Hygiene* **95**, 149–151.

Kjaer S. K., Knudsen J. B., Sorensen B. L. and Moller Jensen O. (1989) The Copenhagen case–control study of bladder cancer. *Acta Oncologica* **28**, 631–636.

Larsen J. F. and Philip J. (1962) Studies in the incidence of urolithiasis. *Urologia Internationalis* **13**, 53–64.

La Vecchia C., Negri E., D'Avanzo B., Savoldelli R. and Franceschi S. (1991) Genital and urinary tract diseases and bladder cancer. *Cancer Research* **51**, 629–631.

Locke J. R., Hill D. E. and Walzer Y. (1985) Incidence of squamous cell carcinoma in patients with long-term catheter drainage. *Journal of Urology* **133**, 1034–1035.

Matanoski G. M. and Elliott E. A. (1981) Bladder cancer epidemiology. *Epidemiologic Reviews* **3**, 203–229.

Melzak J. (1966) The incidence of bladder cancer in paraplegia. *Paraplegia* **4**, 85–96.

Morgan R. J. and Cameron K. M. (1980) Vesical leukoplakia. *British Journal of Urology* **52**, 96–100.

Mustacchi P. and Shimkin M. B. (1958) Cancer of the bladder and infestation with *Schistosoma haematobium*. *Journal of the National Cancer Institute* **20**, 825–842.

Newman D. M., Brown J. R., Jay A. C. and Pontius E. E. (1968) Squamous cell carcinoma of the bladder. *Journal of Urology* **100**, 470–473.

Nyquist R. H. and Bors E. (1967) Mortality and survival in traumatic myelopathy during nineteen years, from 1946 to 1965. *Paraplegia* **5**, 22–48.

O'Flynn J. D. and Mullaney J. (1967) Leukoplakia of the bladder: a report on 20 cases, including 2 cases progressing to squamous cell carcinoma. *British Journal of Urology* **39**, 461–471.

Ohkawa M. Shuji T., Nakashima T., Yamaguchi K., Orito, M. and Hisazumi, H. (1992) Composition of urinary calculi related to urinary tract infection. *Journal of Urology* **148**, 995–997.

Oyasu R. (1995) Epithelial tumours of the lower urinary tract in humans and rodents. *Food and Chemical Toxicology* **33**, 747–755.

Payet M. (1962) Mortality and morbidity from bladder cancer in West Africa. *Acta Unionis Internationalis Contra Cancrum* **18**, 641–642.

Petersen R. O. (1992) *Urological Pathology*. 2nd Ed. pp. 182–197, 227–241, 271–277, 312–331. Lippincott, Philadelphia.

Piper J. M., Matanoski G. M. and Tonascia J. (1986) Bladder cancer in young women. *American Journal of Epidemiology* **123**, 1033–1042.

Polsky M. S., Weber C. H., Jr, Williams J. E., III, Nikolewski R. F., Barr M. T. and Ball T. P., Jr (1976) Chronically infected and postdiversionary bladders. *Urology* **7**, 531–535.

Rafla S. (1975) Tumors of the upper urothelium. *American Journal of Radiology* **123**, 540–551.

Rambar A. C. and Mackenzie R. G. (1978) Urolithiasis in adolescents. *American Journal of Diseases of Children* **132**, 1117–1120.

Remis R. S., Gurwith M. J., Gurwith D., Hargrett-Bean N. T. and Layde P. M. (1987) Risk factors for urinary tract infection. *American Journal of Epidemiology* **126**, 685–694.

Richie J. P., Waisman J., Skinner D. G. and Dretler S. P. (1976) Squamous carcinoma of the bladder: treatment by radical cystectomy. *Journal of Urology* **115**, 670–672.

Ries L. A., Miller B. A., Hankey B. F., Kosary C. L., Harris A. and Edwards, B. K. (1994) *SEER Cancer Statistics Review, 1973–1991: Tables and Graphs. NIH Pub. No. 94-2789*. National Cancer Institute, Bethesda, MD.

Rous S. N. (1978) Squamous cell carcinoma of the bladder. *Journal of Urology* **120**, 561–562.

Sakkas J. L. (1966) Clinical pattern and treatment of squamous cell carcinoma of the bladder. *International Surgery* **45**, 71–76.

Scott R. (1990) The epidemiology of urolithiasis. In *Renal Tract Stone: Metabolic Basis and Clinical Practice*. Edited by J. E. A. Wickham and A. C. Buck. pp. 19–28. Churchill Livingstone, New York.

Shirai T., Fukushima S., Hirose M., Ohshima M. and Ito N. (1987) Epithelial lesions of the urinary bladder in three hundred and thirteen autopsy cases. *Japanese Journal of Cancer Research* **78**, 1073–1080.

Sidransky D., Frost P., von Eschenbach A., Oyasu R., Preisinger A. C. and Vogelstein B. (1992) Clonal origin of bladder tumors. *New England Journal of Medicine* **326**, 737–740.

Silverman D. T., Hartge P., Morrison A. S. and Devesa S. S. (1992) Epidemiology of bladder cancer. *Hematology/Oncology Clinics of North America* **6**, 1–30.

Smith D. R. (1975) *General Urology*. 8th Ed. pp. 200–207. Lange Medical, Los Altos, CA.

Streem S. B. (1987) Bladder calculi. In *Stone Disease: Diagnosis and Management*. Edited by S. N. Rous. pp. 335–345. Grune and Stratton, New York.

Tawfik H. N. (1988) Carcinoma of the urinary bladder associated with schistosomiasis in Egypt: the possible casual relationship. In *Unusual Occurrences as Clues to Cancer Etiology*. Edited by R. W. Miller *et al.* pp. 197–209. Japanese Science Society Press, Tokyo.

Thomas J. E., Bassett M. T., Sigola L. B. and Taylor P. (1990) Relationship between bladder cancer incidence, *Schistosoma haematobium* infection, and geographical region in Zimbabwe. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **84**, 551–553.

Tricker A. R., Stickler D. J., Chawla J. C. and Preussman R. (1991) Increased urinary nitrosamine excretion in paraplegic patients. *Carcinogenesis* **12**, 943–946.

Uchida K., Samma S., Rinsho K., Warren J. R. and Oyashu R. (1989) Stimulation of epithelial hyperplasia in rat urinary bladder by *Escherichia coli* cystitis. *Journal of Urology* **142**, 1122–1126.

Utz D. C. and McDonald J. R. (1957) Squamous cell carcinoma of the kidney. *Journal of Urology* **78**, 540–552.

Watts R. W. E. (1977) Metabolic causes of renal stone formation. *Postgraduate Medical Journal* **53** (Suppl. 2), 7–21.

Widran J., Sanchez R. and Gruhn J. (1974) Squamous metaplasia of the bladder: a study of 450 patients. *Journal of Urology* **112**, 479–482.

Wiener D. P., Koss L. G., Sablay B. and Freed S. Z. (1979) The prevalence and significance of Brunn's nests cystitis cystica and squamous metaplasia in normal bladders. *Journal of Urology* **122**, 317–321.

Wolf H. and Hojgaard K. (1983) Urothelial dysplasia concomitant with bladder tumours as a determinant factor for future new occurrences. *Lancet* ii, 134–136.

Wynder E. L., Onderdonk J. and Mantel N. (1963) An epidemiological investigation of cancer of the bladder. *Cancer* **16**, 1388–1407.

Yamamoto M., Wu H. H., Momose H., Rademaker A. and Dyson R. (1992) Marked enhancement of rat urinary bladder carcinogenesis by heat killed *Escherichia coli*. *Cancer Research* **52**, 5329–5333.

Yaqoob M., McClelland P., Bell G. M., Ahmad R. and Bakran A. (1991) Bladder tumors in paraplegic patients on renal replacement therapy. *Lancet* **338**, 1554–1555.

APPENDIX

Two indirect estimates of the role of stones in the development of squamous cell carcinoma (2% of all bladder cancers) are developed. The paucity of relevant statistics severely limits the ability to make valid projections. Therefore, these estimates should be construed to be nothing more than range-finding values that may help to give an appreciation of the influence of stones.

For the first estimate, if the chance that a white male develops bladder cancer over a lifetime is 3% (Ellwein and Farrow, 1988), then 0.0006 would be the lifetime chance of developing a squamous cell carcinoma. If 12% of males have a history of a urinary tract stone (Larsen and Philip, 1962) and 10% of stones are in the bladder (Hiatt *et al.*, 1982), then about 0.01 persons would have a bladder stone, a value about 17-fold higher than the frequency of squamous cell carcinomas among men. If it assumed that every bladder stone has the potential of producing bladder cancer and that all squamous cell cancers are due to stones, then the risk of a cancer from a bladder stone would be 0.06.

As a second estimate, if we take the age-adjusted incidence rate for bladder cancer in white males as about 30/100,000 (Silverman *et al.*, 1992), then the incidence rate for squamous cell carcinoma would be about 0.6/100,000. If the age-adjusted incidence rate for upper urinary tract stones among males is about 110/100,000 (Johnson *et al.*, 1979), then the frequency of bladder stones would be about one-ninth that rate. It is not known how frequently bladder stones lead to squamous metaplasia; however, it has been reported that it is a common event in regard to staghorn calculi of the renal pelvis (Beyer-Boon *et al.*, 1978); the effect of stones in the bladder may be less than in the renal pelvis. As a default, one can use 15% as an estimate, because among persons with squamous metaplasia (leukoplakia) of the bladder, about 15% (10–28%; see Table 4) had a history of stones. Likewise, among persons with squamous metaplasia, about 25% (10–28%; see Table 4) were diagnosed with squamous cell carcinoma. By combining these values, a rough estimate of the incidence of bladder squamous cell carcinoma from bladder stones is about 0.5/100,000 ($110/100{,}000 \times 1/9 \times 0.15 \times 0.25$). This estimate is very close to the incidence of bladder squamous cell carcinoma in the male population (0.6/100,000).