

## THE INCIDENCE OF BLADDER CANCER IN PARAPLEGIA

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**Incidence and Pathogenesis in Non-paraplegic Subjects.** Carcinoma of the bladder is of world-wide interest. Sandrey (1953) said that the most important problem confronting the urologist today is that of effectively controlling cancer of the bladder. Bladder cancer is on the increase, especially among men in cities. Egypt and other African countries appear to have a high incidence of bladder cancer. Makar (1955) found 44 per cent. of bladder cancer cases among 3872 patients with cancer in various organs. It is suggested that this high percentage is due to high incidence of bilharziasis in Africa. In the U.S.A., in 1961, bladder cancer accounted for 12.2 per cent. of total incidence of cancer among males and 4.9 per cent. in females. Deaths from bladder cancer in U.S.A. in 1961 accounted for 3.8 per cent. of all cancer deaths among males and 2 per cent. among females. Survival percentage is higher than in cancer of lungs and stomach. In 1958-1959, death rate among males was 6.5 per 100,000 of population and 2.2 among females. Wallace (1964) reports that in this country there are about 6000 cases of bladder tumours every year and 3000 registered deaths from bladder tumours.

It is now established that bladder cancer may result from occupational exposure to aromatic amines, derivatives of aniline:  $\beta$ -naphthylamine, benzidine or xenylamine (4-amino-diphenyl) (Case *et al.*, 1954). The manufacture of aniline dyes had started in Germany in 1860. Thirty-five years later Rehn (1895) described bladder cancer in men who had worked with aniline for 15 to 29 years. It became later recognised that aniline derivative: 2-naphthyl-amine, 1-naphthyl-amine, benzidine, and 4-aminobiphenyl can cause bladder cancer in men working with these products.

Investigations initiated by British Chemical Manufacturers show that exposure to aniline alone was not associated with increased risk of bladder cancer. It showed clearly, however, that contact with benzidine,  $\alpha$ -naphthylamine and  $\beta$ -naphthylamine was associated with bladder cancer. This is in agreement with American evidence. The use of renal tract carcinogens in the manufacture of rubber was abandoned in this country some years ago (Ministry of Labour communication, 1966). Since 1962 the Federal Dyeing Administration, U.S.A., has produced rigid specifications to exclude any toxic ingredients in medical and surgical products. Active carcinogens are released locally, probably by enzymatic hydrolysis of excreted metabolites. These active carcinogens, ortho-aminophenols and aryl hydroxylamines, would account for bladder cancer in men exposed to aromatic amines.

Clemmensen (1962) reports that smoking is statistically correlated to bladder cancer. Reports from U.S.A., France and Denmark all indicate that cancer of the bladder is seen about twice as often in smokers as in comparable non-smokers.

Wyder, Onderdonk and Mantel (1963) report a positive association between bladder stones and bladder cancer. They suggest possible association between cystitis and bladder cancer. (*See addendum.*)

The fact that infection of the urinary tract is still very common in paraplegics

and tetraplegics makes it worth while to examine the incidence of bladder cancer in these patients and the purpose of the present paper is to give a survey of the observations made on this problem.

**Clinical Material of Paraplegic and Tetraplegic Patients.** At the National Spinal Injuries Centre, 11 cases of bladder cancer were observed out of 3800 paraplegics, *i.e.* 0.28 per cent. There were nine men and two women. Ten cases were traumatic due to vertebral fracture or gun-shot injuries, and in one (Case 5) the cause of paraplegia below T<sub>5</sub> was syphilis. As far as the spinal cord level was concerned, one was cervical, five were thoracic lesions, five had cauda equina lesions. Eight were complete and three incomplete transverse spinal or cauda equina lesions; four were spastic and seven flaccid. The bladder cancer was diagnosed a considerable time after the onset of paraplegia: earliest after 13 years, latest after 42 years. The youngest patient in whom bladder cancer was diagnosed was 37 years old, the oldest was 68 years old and the average age was 51 years.

*Urinary Tract Pathology prior to Bladder Cancer.* Four patients (Cases 1, 3, 4, 5) had automatic bladders and seven atonic bladders. In all 11 cases there was a chronic urinary infection from the onset of paralysis. Suprapubic cystostomy was present in eight cases, for a period of 2 months to 20 years (Cases 1, 2, 4, 6, 7, 8, 9, 10). In 10 cases indwelling catheterisation was used for a period of up to seven years (Cases 1, 2, 3, 4, 5, 6, 7, 9, 10, 11). In two cases, suprapubic catheterisation was left permanently because of hydronephrosis in one man (Case 8) and constant urethral leaking in one woman (Case 4). Bladder calculi were found in five cases (Cases 6, 8, 9, 10, 11), in four of whom there were also renal calculi (Cases 6, 8, 9, 11). In Case 10, calculi were removed twice over a period of seven years. In case 8, bladder calculi were repeatedly removed nine times over a period of 18 years. In case 7 there were calculi in left kidney three times. In five cases no calculosis was observed. Three patients (Cases 6, 7, 10) had orchitis and in Case 11 an undescended testicle was removed 31 years before the bladder cancer. In four cases, there was reflux (Cases 6, 7, 9, 10), and in five cases hydronephrosis (Cases 2, 6, 7, 9, 11).

The Table gives clinical and histological details of the patients.

*Bladder Cancer Symptoms.* Haematuria was observed as the first symptom in seven cases (Cases 2, 3, 4, 5, 7, 8, 11). In the eighth case, the mucosa easily bled during cystoscopy. Cystography showed filling defects only in two cases—Case 5 and Case 7. Figure 1 shows two cystograms of a patient (Case 7) who suffered from cauda equina lesion after a gun-shot injury in 1944, and a suprapubic cystostomy was performed at once. He had a chronic urinary infection and developed right orchitis and calculi in the right kidney (three times), he also had hydronephrosis. Cystogram performed on 29.7.1947 showed a round bladder of 12 ounces capacity with no diverticuli or reflux. Suprapubic cystostomy was closed on the 18.11.1947. The patient was discharged home and was employed at De Havilland factory as a driller. He had regular check-ups and treatment for sores and urinary infection, and removal of calculi from the right kidney. He was admitted on the 12.9.1957 and cystoscopy revealed a polypoid mass in the bladder wall. Cystogram performed on the 8.10.1957 revealed a marked filling defect in the bladder, left ureteric reflux with hydroureter and fistula into the large bowel. Biopsy revealed cancer with transitional and squamous cells. Urinary diversion by bilateral abdominal ureterostomy and a colostomy were performed. The patient died on 19.10.1957.

TABLE  
Clinical and Histological Details

Case	Initials	Sex	Age	Cause	Level and type of cord or cauda equina lesion		Severity of lesion	Urinary tract pathology	Ca. diagnosis years after spinal lesion	Histology of bladder cancer
1	T. M.	M	54	Subluxation C7	C7	Spastic	Incomplete	Chronic cystitis. Supra-pubic drainage 2 mths. Positive cytology of urine for cancer cells.	20	Transitional and squamous cells
2	A. W.	M	56	Fracture T12	T1 (R) T8 (L)	Flaccid	Complete	Chronic cystitis. Supra-pubic drainage 3 yrs 4 mths. Hydronephrosis left. Haematuria.	19	Squamous cells
3	J. T.	F	38	Fracture T6	T6	Spastic	Complete	Chronic cystitis. Indwelling urethral drainage 7 yrs. Haematuria.	15	Transitional and squamous cells
4	M. C.	F	48	Fracture T6	T6	Spastic	Complete	Chronic cystitis. Supra-pubic drainage 19 yrs. Indwelling urethral drainage 7 yrs. Bloody and pussy discharge from supra-pubic tract. Haematuria. Carcinoma in supra-pubic scar.	26	Transitional cells

Clinical and Histological Details (*continued*)

Case	Initials	Sex	Age	Cause	Level and type of cord or cauda equina lesion		Severity of lesion	Urinary tract pathology	Ca. diagnosis years after spinal lesion	Histology of bladder cancer
5	W. N.	M	39	Meningomyelitis luetica	T6	Spastic	Complete	Chronic cystitis. Indwelling urethral drainage. Haematuria. Filling defect in bladder.	20	Squamous cells
6	J. D.	M	53	Fracture T12/L1	T11	Flaccid	Complete	Chronic cystitis. Supra-pubic drainage 16 mths. Indwelling urethral drainage 5 yrs. Calculi both kidneys and bladder. Bilateral orchitis. Bilateral hydronephrosis. Right ureteric reflux. Bloody and pussy discharge from supra-pubic scar.	13	Transitional cells
7	R. D.	M	37	G.S.W.	L2	Flaccid	Incomplete	Chronic cystitis. Supra-pubic drainage 3 yrs 4 mths. Right orchitis. Calculi right kidney 3 times. Hydronephrosis. Haematuria. Left ureteric reflux. Filling defect in bladder. Lump supra-pubic scar.	13	Transitional and squamous cells

8	H. G.	M	55	G.S.W.	L2	Flaccid	Complete	Chronic cystitis. Supra-pubic drainage 20 yrs. Calculi both kidneys. Calculi in bladder 9 times. Haematuria.	20	Squamous cells
9	A. W.	M	68	G.S.W.	L3	Flaccid	Incomplete	Chronic cystitis. Supra-pubic drainage 8 mths. Indwelling urethral drainage 5 yrs. Calculi kidneys and bladder. Bilateral hydronephrosis and reflux. Diverticula in bladder.	42	Papillary carcinoma
10	A. L.	M	58	Fracture L1	S2	Flaccid	Complete	Chronic cystitis. Supra-pubic drainage 9 yrs. Bladder calculi twice. Orchitis, left. Right ureteric reflux.	21	Squamous cells
11	S. H.	M	58	Fracture L1	S2	Flaccid	Complete	Chronic cystitis. Indwelling urethral drainage 2 yrs. Calculi right kidney and bladder. Right hydronephrosis and hydroureter. Haematuria Undescended testicle removed 31 years before bladder cancer.	23	Transitional cells

Some of the patients (Cases 7, 8, 9, 10, 11) complained of pain in the bladder. Case 1 is of special interest as the first clinical symptom was the appearance of a metastatic cyst over the left clavicle with a histological picture of a squamous cell carcinoma (fig. 2). The patient was injured while serving in Germany in 1945, when a truck swerved and he was thrown out. He sustained a subluxation of C7 vertebra with an incomplete transverse spinal cord syndrome below C7 and a

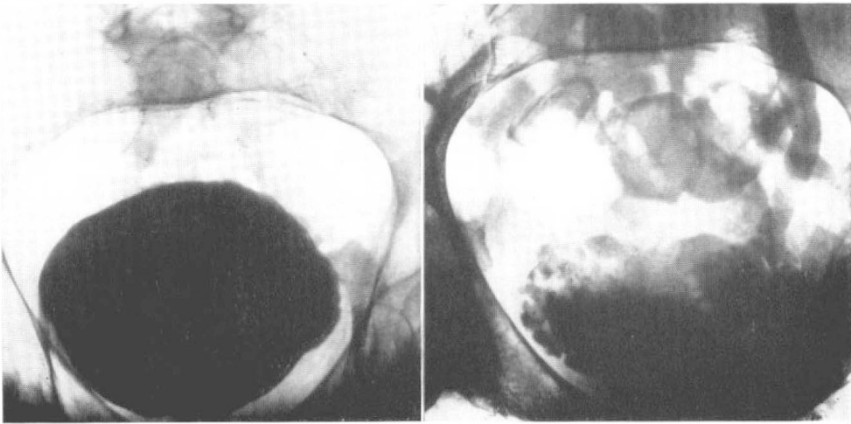


FIG. 1

Cystogram on the left shows a bladder of 12 ounces capacity (Case 7). No diverticula or reflux. On the right, cystogram of the same man showing filling defect, reflux, and hydro-ureter with fistula into large bowel.

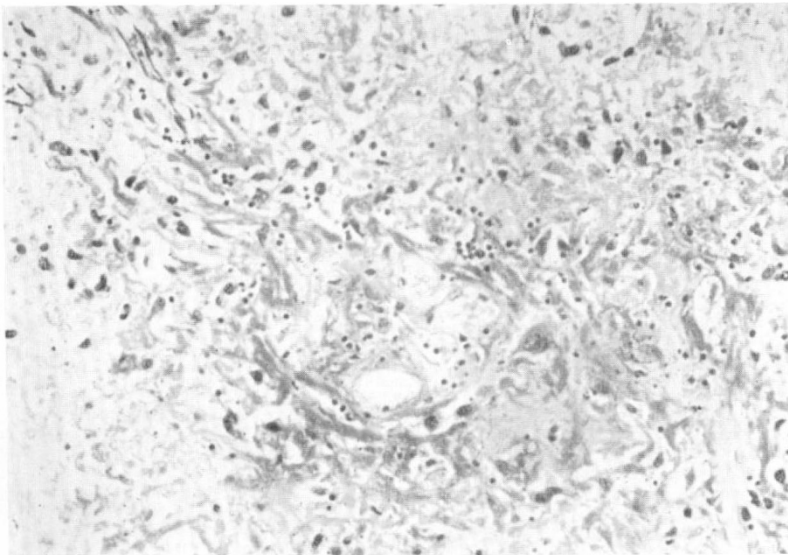


FIG. 2

Shows section of tumour in region of left clavicle (Case 1). Squamous cell carcinoma, hyperchromasia.

Horner syndrome on the left. He had suprapubic drainage for two months and his urine remained always infected in spite of treatment. After rehabilitation, although, his fingers were weak, he managed to complete a course in radio repairs. After transfer to the Duchess of Gloucester House he worked at Gillette's factory. In 1957 he fractured accidentally the left femoral neck, which healed well. In September 1965 the patient was admitted to Stoke Mandeville Hospital after he got a cystic tumour over the left clavicle which, on exploration, contained squamous carcinoma cells. The tumour was considered by the chest physician as originating from a mediastinal primary tumour. Cytological examination of urine (Papanicolaou) on 10 September 1965 and 23 September 1965 showed presence of malignant transitional cells (fig. 3). Cystoscopy and biopsy were performed on 24 September by Dr. J. J. Walsh and confirmed the diagnosis of cancer in the bladder (fig. 4.) Patient died on 3 October 1965 and on post-mortem an extensive carcinoma of the bladder was found infiltrating pelvic organs, the ileopsoas muscles, the thoracic lymphatic duct and communicating with the tumour behind the left clavicle.

In three more cases, metastatic tumours were found in pelvis and abdomen (Cases 3, 6, and 8).

*Suprapubic Tract Involvement.* In Case 7 a lump appeared in the suprapubic scar at the time the cancer was discovered and in Case 6 hardening of the scar and a pussy discharge mixed with blood appeared. In Case 4 a biopsy taken from the suprapubic fistula showed presence of cancer. In Case 7 the suprapubic scar burst discharging pus with blood, and in Case 8 at operation, the cancer was seen to extend along the suprapubic tract.

*Histology of Biopsy or Post-Mortem.* In nine cases (Cases 1, 2, 3, 4, 5, 7, 8, 10, 11), biopsy showed the presence of cancer. In two cases (Cases 4 and 11), the cells were of transitional type, in three cases (Cases 1, 3, 7), mixed transitional and squamous type and in four cases (Cases 2, 5, 8, 10) there was a squamous cell carcinoma. In two cases (Cases 6 and 9), the presence of cancer was found at autopsy—in Case 6 it was of transitional type, and in Case 9 it was a papillary carcinoma.

*Treatment.* Cases 1 and 3 were admitted in very advanced stages of bladder cancer involving not only the neighbouring tissues of the pelvis but with multiple metastases in the abdominal and (in Case 1) thoracic cavities. In fact, as pointed out, in Case 1 the metastatic cyst in the left clavicle precipitated the search for the primary tumour in the bladder. The general condition of these patients precluded any attempt of surgical or X-ray treatment. In all the other patients where the diagnosis was made *intra vitam*—in Cases 6 and 9 the cancer was discovered at autopsy—surgical procedures were the methods of choice, followed in three cases by deep X-ray treatment (Cases 4, 8, 10). Surgery consisted of cystectomy followed in the majority of patients by bilateral or unilateral cutaneous ureterostomy. In Case 7 where the cancer was found to involve rectum and sigmoid a colostomy was performed in addition to the urinary diversion by abdominal ureterostomy. In Case 8 cystectomy and urinary diversion through ileal bladder was performed.

*Survival.* Of the 11 patients described, only one patient—Case 4—is still alive. On this case, cystectomy and deep X-ray therapy were performed in January 1962 following bilateral abdominal ureterostomy; the patient has been in good condition for 4 years and 5 months. In seven cases, survival lasted between 7 days and 3 months after diagnosis; only patient No. 8 survived for 13 months. In Cases 6 and 9, cancer was discovered at autopsy.

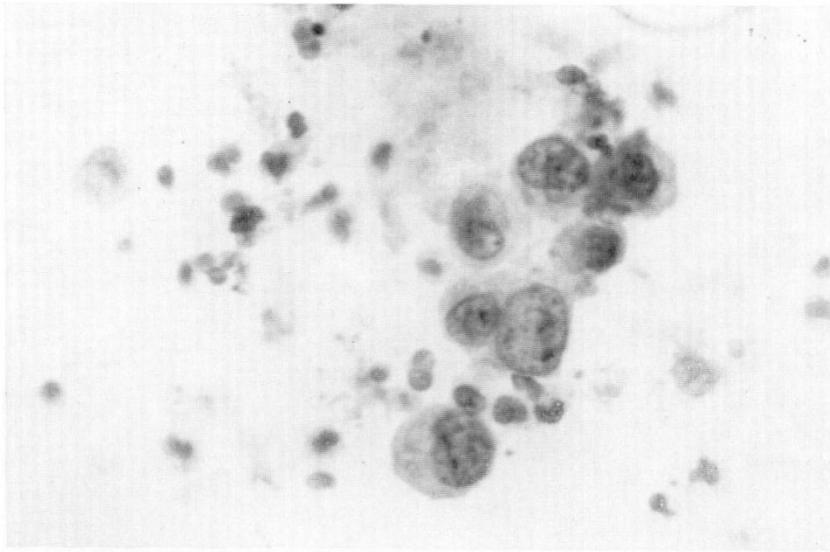


FIG. 3  
Smear of urinary sediment (Papanicolaou) (Case 1). A number of large cells present with grossly abnormal appearance, highly suggestive of malignancy.

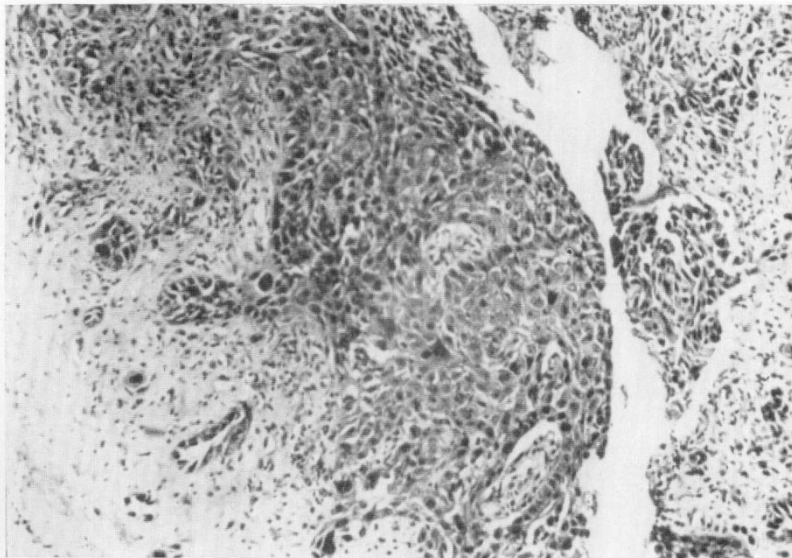


FIG. 4.  
Section shows invasion of the bladder wall by a poorly differentiated carcinoma (Case 1).



## DISCUSSION

It is of interest to compare the incidence of bladder cancer with that of cancer in other organs amongst our 3800 paraplegics and tetraplegics. Altogether 27 cases were observed: urinary tract 12 (11 bladder and 1 ureter), alimentary tract 7, lungs 5, long standing pressure sore 2, ovary 1. This reveals a high percentage of cancer of the urinary tract in our material. It is difficult, if not misleading, to make a comparison between the incidence of bladder cancer and death rate in our material of 3800 cases with that of the population in this country as a whole. According to Wallace (1964), there are about 6000 cases of bladder tumours in this country every year, and about 3000 deaths from bladder tumours. In our series of 11 patients with bladder cancer we had during the period 1957-1965, 10 deaths in nine years. This figure is too insignificant to attempt a statistical evaluation of the death rate in comparison with that given in Table 8 of the Registrar General's Statistical Review of England and Wales (1966) which is 97 per million per year for men and 72 per million per year for women. It is worthwhile mentioning that 3 out of 11 paraplegics with bladder cancer were under 40 years of age at the time of death. As a rule bladder cancer develops in later age-groups. A further point of interest is the fact that in the majority of cases bladder cancer developed in paraplegia with flaccid cord and cauda equina lesions with hypotonic bladders.

In discussing the possible causes of bladder cancer in paraplegic and tetraplegic patients occupational exposure of anyone of these patients to aniline derivatives as well as an hereditary relationship can be excluded. As far as smoking is concerned, 6 out of 11 patients were smokers to varying degrees. Clemmensen (1962) regards smoking to be statistically correlated to bladder cancer in non-paraplegic patients. Kerr *et al.* (1965) have shown that during smoking there is an average of 50 per cent. increase in the excretion of Tryptophan metabolites in the anthranilic acid series which produce cancer when placed in the bladder of mice. Having regard to the fact that the vast majority of our paraplegics and tetraplegics are smokers it is unlikely that smoking can be accused as a cause in our cases.

The only common factor in all our patients was long-standing chronic urinary infection and cystitis which preceded the cancer of the bladder, lasting between 13 and 42 years. In eight cases, suprapubic cystostomy was performed before admission to this Centre and kept for a period of 2 months to 20 years. In one case (Case 7) a lump appeared in the suprapubic scar at the time the cancer was discovered. In Case 6, hardening of the scar and pussy discharge mixed with blood appeared when the patient already had the bladder cancer. In Case 8, at operation the cancer was seen extending along the suprapubic tract. Laskowski and Brantley-Scott (1965) performed vesicostomies as described by Lapides (1960) on 45 patients. Histologic examination of the bladder flaps in 13 patients selected at random showed presence of squamous metaplasia in all cases and cystitis glandularis in two cases, caused probably by chronic irritation and environmental exposure, which usually results in metaplasia of the bladder epithelium to a mucus secreting glandular type of cystitis. From these glands adenocarcinoma may develop. In this connection a paper of McIntosh and Worley (1955) who observed two cases of adenocarcinoma among 25 cases of exstrophy of the bladder is of interest. They also reviewed 38 cases described in the literature previously. The prevailing opinion at present is that the exposure of the exstrophied bladder to the environment and

constant infection stimulates the mucosa to alter its cell type in areas, as thought, to produce protective mucus. But all cases of exstrophied bladder that were subjected to biopsy revealed cystitis cystica and glandularis, from which malignancy may develop.

Wyder, Onderdonk and Mantel (1963) suggest a possible association between cystitis and bladder cancer. Although the incidence of chronic urinary infection with cystitis is frequent among patients with paraplegia, only in these 11 cases was bladder cancer diagnosed. It is probable, therefore, that some other unknown factors are necessary to start cancerogenous malformation in long-standing cystitis. One of these factors may be constant friction of an indwelling catheter acting as a foreign body or faulty intermittent catheterisation leading to damage of the bladder mucosa and thus facilitating abnormal cell formation. Until our knowledge on carcinogenic factors is widened we can only confine ourselves to combating chronic urinary infection with all available means, and in particular to prevent urinary infection from the onset of paraplegia by using intermittent catheterisation with the non-touch technique as described by L. Guttmann (1953, 1963). It will be seen whether the prevention of bladder infection from the start and the early successful elimination of bladder infection in paraplegic patients will result in a decrease of cancer formation of the bladder and urinary tract.

It is, of course, of the utmost importance to do everything to make an early diagnosis possible. Apart from a watchful eye on clinical symptoms, regular cytological investigations can be helpful. Grabstald (1962) found tumour cells two years before the tumour could be detected clinically. Papanicolau's method of staining (1945) can give a good smear where abnormal cells with nuclear hyperchromasia and bizarre cells could be found. Regular cytological investigations were started at the National Spinal Injuries Centre in June 1965. Since then 374 urines were investigated and among them there was one true positive—Case 1 (fig. 2). Cystoscopy followed (Dr. J. J. Walsh), and biopsy confirmed cancer of the bladder (fig. 3). Atypical cells were also found in smears of seven other patients. These cases are watched and smears are taken at regular intervals and these tests are combined with other investigations. In this connection it may be noted that in the series of examinations of smears from people employed in the Rubber Industry, performed at the Health Research Unit, Birmingham, between 1958 and 1964 among 50,000 smears 31 were found to be true positive and one false negative (personal communication from Dr. H. G. Parkes, the Medical Director of the Health Research Unit). These results seem to correspond with ours. One can only hope that the development of cytological investigation and early diagnosis of bladder cancer will be followed by improvement of therapeutic results.

#### ACKNOWLEDGEMENTS

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#### SUMMARY

Eleven cases of bladder cancer were observed at the National Spinal Injuries Centre out of 3800 paraplegic and tetraplegic patients treated since 1944.

There were nine men and two women: the average age of the patients was 51 years.

Seven patients were flaccid and four spastic.

Diagnosis was made 13-42 years after the onset of paraplegia.

Haematuria was the first symptom in seven cases.

Cystography showed filling defect in two cases.

With regard to the aetiology of bladder cancer various carcinogenic factors are discussed. Occupational exposure as well as smoking and hereditary causes could be excluded.

The only common factor in all these patients was long-standing, chronic bladder infection. Moreover all patients had either long-standing suprapubic or urethral drainage by indwelling catheter.

In order to facilitate early diagnosis of bladder cancer, cytological examination of urine for cancer cells are carried out systematically at the National Spinal Injuries Centre. Since 1965 out of 374 cases examined, only one was found to be positive, and biopsy and later necropsy confirmed cancer of the bladder.

### RÉSUMÉ

Onze cas de cancer de la vessie ont été observés au Centre National Anglais pour les Traumatisés de la Moëlle Epinière, ceci sur un total de 3.800 paraplégiques et tétraplégiques traités depuis 1944.

Ils comprennent 9 hommes et 2 femmes; la moyenne d'âge était de 51 ans.

7 malades présentèrent des lésions flasques et 4 spastiques.

Le diagnostic a été fait entre 13 et 42 ans après le début de la paraplégie.

L'hématurie a été le premier symptôme dans 7 cas.

La cystographie a montré un défaut de remplissage dans 2 cas.

En ce qui concerne l'étiologie du cancer de la vessie, différents facteurs cancérogènes ont été discutés. Pouvaient être exclues: les occupations professionnelles, l'hérédité et l'emploi du tabac.

Il apparaît que le facteur commun chez tous ces malades a été, pendant très longtemps, une infection chronique de la vessie. De plus, tous les malades avaient eu, soit un drainage suprapubien, ou urétral par sonde à demeure.

De façon à faciliter le diagnostic rapide, des examens cytologiques d'urine, dans le but de retrouver des cellules cancéreuses, sont pratiqués systématiquement au Centre. Depuis 1965, sur les 374 cas examinés, un a été trouvé positif, ce qui a été confirmé par la biopsie et l'examen post mortem.

### ZUSAMMENFASSUNG

Il Fälle von Blasenkarzinom wurden seit 1944 im National Spinal Centre unter 3,800 Paraplegikern und Tetraplegikern beobachtet.

9 waren Männer und 2 Frauen; das Durchschnittsalter der Patienten was 51 Jahre.

7 Patienten hatten eine schlaffe Lähmung und 4 waren spastisch.

Die Diagnose wurde 13-42 Jahre nach dem Beginn der Paraplegie gestellt.

In 7 Fällen war Haematurie das erste Symptom. Cystographie ergab Füllungsdefekte nur in 2 Fällen.

In der Besprechung der Aetiologie des Blasenkarzinoms werden verschiedene karzinogene Faktoren diskutiert. Bestimmte Berufstätigkeit, Rauchen sowie hereditäre Ursachen konnten ausgeschlossen werden.

Der einzige gemeinsame Faktor war eine lang andauernde chronische Infektion der Blase. Ausserdem hatten alle Patienten eine jahrelange suprapubische oder urethrale Drainage mittels Dauerkatheter.

Um die Frühdiagnose des Blasenkarzinoms zu ermöglichen, werden in Stoke Mandeville zytologische Untersuchungen des Urins auf Kanzerzellen systematisch ausgeführt. Seit 1965 sind 374 Fälle untersucht worden. Nur in einen Fall war das Ergebnis positiv und Biopsie sowie später Nekropsie bestätigten die Kanzerdiagnose.

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*Addendum:* There are only very few observations published on bladder cancer in paraplegics. (Kawaichi, Pyzik, Lowry, 1961)