

BLADDER DISEASES



SURGICAL ANATOMY OF THE BLADDER

- It is lined by transitional epithelium covering the connective tissue lamina propria, which contains a rich plexus of vessels and lymphatics.
- When the detrusor muscle hypertrophies, the inner layer, covered by urothelium, stands out, resulting in the appearance of trabeculation.
- Over the trigone is a thin layer of smooth muscle to which the epithelium is closely adherent and which extends as a sheath around the lower ureters and into the proximal urethra.
- Around the male bladder neck is the smooth muscle internal sphincter innervated by adrenergic fibres, which prevents retrograde ejaculation.
- The distal urethral sphincter is a horseshoe-shaped mass of striated muscle that lies anterior and distal to the prostate, or in the proximal two-thirds of the female urethra. It is distinct from the pelvic floor and is supplied by S2–S4 fibres via the pudendal nerve and by somatic fibres passing through the inferior hypogastric plexus.



Fascial and ligamentous supports of the bladder

- * At the posterolateral bladder neck
- * The puboprostatic ligaments
- * The urachus and obliterated hypogastric arteries,
together
with the folds of peritoneum overlying them, are called
the median and lateral umbilical ligaments



BLOOD SUPPLY:

- * superior and inferior vesical arteries are derived from the anterior trunk of the internal iliac artery.
- * branches from the obturator and inferior gluteal arteries from the uterine and vaginal arteries in females. The veins form a plexus on the lateral and inferior surfaces of the bladder. In the male the prostatic plexus is continuous with the vesical plexus, which drains into the internal iliac vein. In the female similar large veins are continuous with the vaginal plexus.

Lymphatics

- * These accompany the veins and drain to nodes along the internal iliac vessels and then to the obturator and external iliac chains.
- * Some lymphatics pass to nodes that are situated posteriorly to the internal iliac artery (hypogastric nodes).



INNERVATION :

The parasympathetic input

This is derived from the anterior primary divisions of the second, third and fourth sacral segments (mainly S2 and S3). Fibres pass through the pelvic splanchnic nerves to the inferior hypogastric plexus, from where they are distributed to the bladder. The pelvic plexus can be damaged during deep pelvic operations.

The sympathetic input

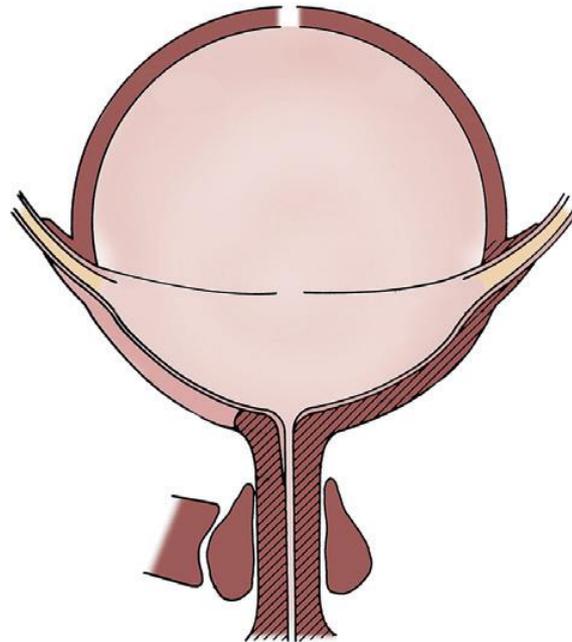
This arises in the 11th thoracic to the second lumbar segments; fibres pass via the presacral hypogastric nerve (rather than via the sympathetic chains) to the inferior hypogastric plexus.

Somatic innervation

A somatic innervation passes to the external sphincter via the pudendal nerves and also via fibres that pass through the inferior hypogastric plexus.

Functional aspects

The nervous control of the bladder: Micturition is partly a reflex and partly a voluntary act.



CONGENITAL DEFECTS OF THE BLADDER

Bladder exstrophy (Ectopia vesicae) :

Protrusion of urinary bladder through a defect in the abdominal wall.

**Bladder exstrophy occurs in 1:50 000 births
male–female ratio 4 :1**



Presentation is variable and including abnormalities in:

- **bony pelvis:** There is separation of the pubic bones, shortening of pubic rami
- **pelvic floor:** flattened of puborectal sling
- **genitalia :** In the male, the penis is broad and short, and bilateral inguinal herniae may be present. In the female the clitoris is bifid. narrowed vaginal orifice
- **In epispadias alone,** the pubes are united and external genitalia are almost normal,



management:

***Staged repair of extrophy:**

- 1 - closure of bladder and abdominal wall with or without pelvic osteotomy-
- 2 - repair of epispadias--2-3ys of age
- 3 - bladder neck repair 4-5ys of age

Some cases we need: bladder augmentation.

*** Less satisfactorily**, urinary diversion can be carried out by means of ureterosigmoid anastomosis, an ileal or colonic conduit, or continent urinary diversion with cystectomy



Interstitial cystitis: (Hunner's ulcer)

PRESENTATION:

- * confined to women mostly.
- * The first symptom is increased frequency; pain, relieved by micturition and aggravated by jarring and overdistension of the bladder.
- * In most patients pyuria and urinary infection are absent. Haematuria also occurs.

AETIOLOGY:

The aetiology remains obscure .in good numbers of cases associated with psychological upset.

PATHOLOGY:

It consists of a chronic **pancystitis**, often with marked **infiltration** with lymphocytes , macrophages and mast cells. **Fibrosis** of the vesical musculature . Ulceration of the mucosa occurs in the fundus of the bladder. In severe cases the bladder capacity is reduced to 30–60 ml. The characteristic **linear bleeding ulcer** is caused by splitting of the mucosa when the bladder is distended under anaesthesia. The inflammation may involve the trigone, the urethra and, in severe cases, the peritoneum.

DIAGNOSIS:

It is important to check urinary cytology and to biopsy the mucosa to exclude underlying neoplastic disease.

On cystoscopy the characteristic ulcer is found in the fundus, but it may be absent. This area bleeds readily as the bladder is decompressed.

TREATMENT:

It is difficult and unsatisfactory. Hydrostatic dilatation under anaesthesia may give relief for some months. Instillation of dimethylsulphoxide results in improvement in some patients. Other drugs that have been tried include intravesical heparin, oral ranitidine and steroid therapy. Patients with severe symptoms may well require cystectomy and orthotopic bladder substitution. In patients with severe inflammation involving the trigone and urethra, this operation may not result in complete relief and some type of urinary diversion may be needed.



Acute abacterial cystitis (acute haemorrhagic cystitis):

- * The patient presents with severe UTI.
- * Pus is present in the urine but no organism can be cultured.
- * It is commonly sexually acquired but tuberculous infection and CIS must be ruled out.
- * The underlying causative organism may be *Mycoplasma* or herpes simplex virus.
- * Cyclophosphamide can also cause this problem.



SCHISTOSOMIASIS OF THE BLADDER

- * The disease is endemic in middle east and Iraq .
- * Slow-running fresh water provide the habitat for the freshwater snail (*Bulinus truncatus*) that is the intermediate host. The disease is acquired through exposure of the skin to infected water. The free-swimming, bifid-tailed embryos (**cercariae**) of the trematode *Schistosoma haematobium* penetrate the **skin**. Shedding their tails, they enter blood vessels and are swept to all parts of the body but they flourish in the **liver** where they live on erythrocytes and develop into **male and female worms**. Sexual maturity having been attained, the nematodes leave the liver and enter the **portal vein**. The male worm bends into the shape of a gutter (the gynaecophoric canal) into which a female worm nestles, and the pair makes its way towards **the inferior mesenteric vein**. *Schistosoma haematobium* has an affinity for the vesical venous plexus, which it reaches through the portosystemic anastomotic channels. Having reached the **bladder** the female worm eventually enters a submucous venule which is so small that she completely blocks it. She now proceeds to lay about 20 **ova** in a chain; each ovum is provided with a terminal spine that penetrates the vessel wall. A heavily infected subject passes hundreds of ova a day. If ova reach **fresh water**, the low osmotic pressure causes rupture and the ciliated **miracidium** emerges. To survive, it must reach and penetrate the intermediate **snail** host within 36 hours. Within the snail's liver, the miracidium enlarges and gives rise to myriads of daughter cysts, which are set free on the death of the snail. A single miracidium begets thousands of **cercariae** to complete the life cycle.



Clinical features

- * **After penetration of the skin, urticaria lasting about 5 days can occur (swimmer's itch).**
- * **Following an incubation period of 4–12 weeks, a high evening temperature, sweating and asthma, together with leucocytosis and eosinophilia, occur.**
- * **Usually, an asymptomatic period of several months supervenes before the ova are released, causing the typical early sign and symptom of intermittent, painless, terminal haematuria.**
- * **Men are affected three times more frequently than women.**



Diagnosis:

BESIDE HISTORY PHYSICAL EXAMINATION

1 - Examination of the urine

*The last few millilitres of an early-morning urine specimen are collected and centrifuged. Examination on several consecutive days may be required, but a negative result does not exclude bilharziasis, especially in patients no longer resident in bilharzial districts.

2 - Immunological Ex.

*Antibody detection by enzyme-linked immunoabsorbent assay (ELISA) using *Schistosoma mansoni* adult microsomal antigen (MAMA) can be performed. The test is positive 1 month after infection and is specific for *Schistosoma mansoni* and *Schistosoma haematobium*.

3 - Cystoscopy

Depending on the length of time for which the disease has remained untreated, cystoscopy will reveal one or more of the following: 1 *Bilharzial pseudotubercles* are the earliest specific appearance of the disease.



2 *Bilharzial nodules* are caused by the fusion of tubercles.



3 '*Sandy patches*' are the result of calcified dead ova with degeneration of the overlying epithelium .



4 *Ulceration* is the result of sloughing of the mucous membrane containing dead ova .



- 5 ***Fibrosis*** is mainly the result of secondary infection.
- 6 ***Granulomas***. Bilharzial masses are caused by the aggregation of nodules.
- 7 ***Papillomas*** are more pedunculated .
- 8 ***Carcinoma*** is a common end result in grossly infected bilharziasis of the bladder that has been neglected for years.



Treatment

1 - ACUTE CASES

Safe and effective drugs are available for the treatment of schistosomiasis, including praziquantel taken in three doses of 20 mg kg⁻¹ (total 60 mg kg⁻¹) 4 hours apart.

2 - complications:

requiring specific treatment, include the following:

- urinary calculi;
- stricture of the ureters;
- prostatoseminal vesiculitis;
- fibrosis of the bladder and bladder neck = **SMALL CONTRACTED BLADDER OR DILATED LARGE BLADDER**
- bilharzial urethral strictures;
- squamous bladder cancer.



BLADDER TRAUMA

Bladder rupture

- * **intraperitoneal** (20%) :usually happened with distended bladder.It is associated with sudden severe pain in the hypogastrium, often accompanied by syncope. The shock subsides and the abdomen distends and there is no desire to micturate. Peritonitis does not follow immediately if the urine is sterile; varying degrees of rigidity are present on examination
- * **extraperitoneal** (80%)-- blunt trauma or surgical damage.some cases associated with fracture pelvis. Gross haematuria can be absent. It may be difficult to distinguish extraperitoneal rupture from rupture of the membranous urethra.

Investigation

- * Computerised tomography (CT) is ideal.
- * Plain erect radiographs may show a ground-glass appearance (fluid).
- * Intravenous urography (IVU) may confirm a leak.
- * Retrograde cystography will confirm the diagnosis .

Management of bladder trauma

- * Extravesical injury – catheter drainage for 10 days
- * Intraperitoneal injury – laparotomy, repair and bladder drainage



Injury to the bladder during operation

in :

- (1) inguinal or femoral herniotomy;**
- (2) hysterectomy;**
- (3) excision of the rectum.**
- (4) by transurethral resection .**

- * If the injury is recognised, the bladder must be repaired and catheter drainage maintained for 7 days.**
- * If it is not recognised, the treatment is similar to that of rupture of the bladder.**
- * When accidental extraperitoneal perforation of the bladder occurs during endoscopic resection, drainage of the bladder with a urethral catheter and the administration of antibiotics usually suffice. If a mass of extravasated fluid is present it is best to place a small drain through a stab incision.**
- * A laparotomy will usually be required if an intraperitoneal perforation is caused by transurethral resection .**



DIVERTICULAE OF THE BLADDER

Congenital diverticulae :

These are situated in the midline anterosuperiorly and represent the unobliterated vesical end of the urachus.

Pulsion diverticula (Acquired)

The usual cause is bladder outflow obstruction.

PATHOLOGY:

- * The mouth of the diverticulum is situated above and to the outer side of one ureteric orifice.
- * The size varies from 2 to 5 cm, but they may be larger.
- * Diverticula are lined by bladder mucosa and the wall is composed of fibrous tissue only .
- * A large diverticulum enlarges in a downward direction and sometimes may obstruct a ureter – probably because of peridiverticular inflammation.

Complications

- 1 - Recurrent urinary infection***
- 2 - Bladder stone***
- 3 - Hydronephrosis and hydroureter***
- 4 - Neoplasm : <5%***



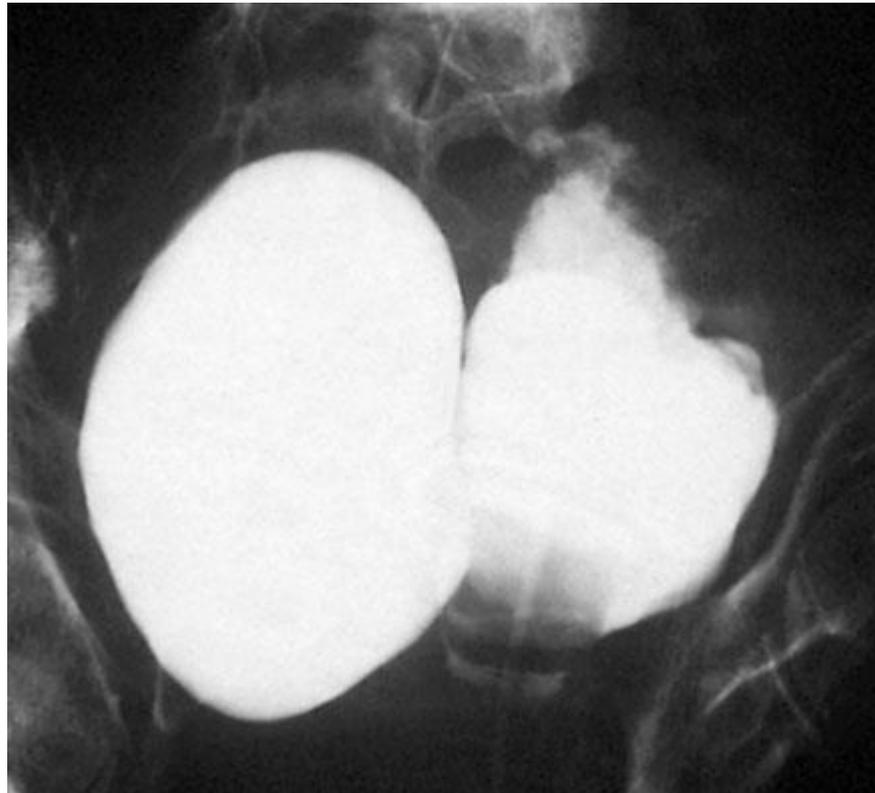
Clinical features

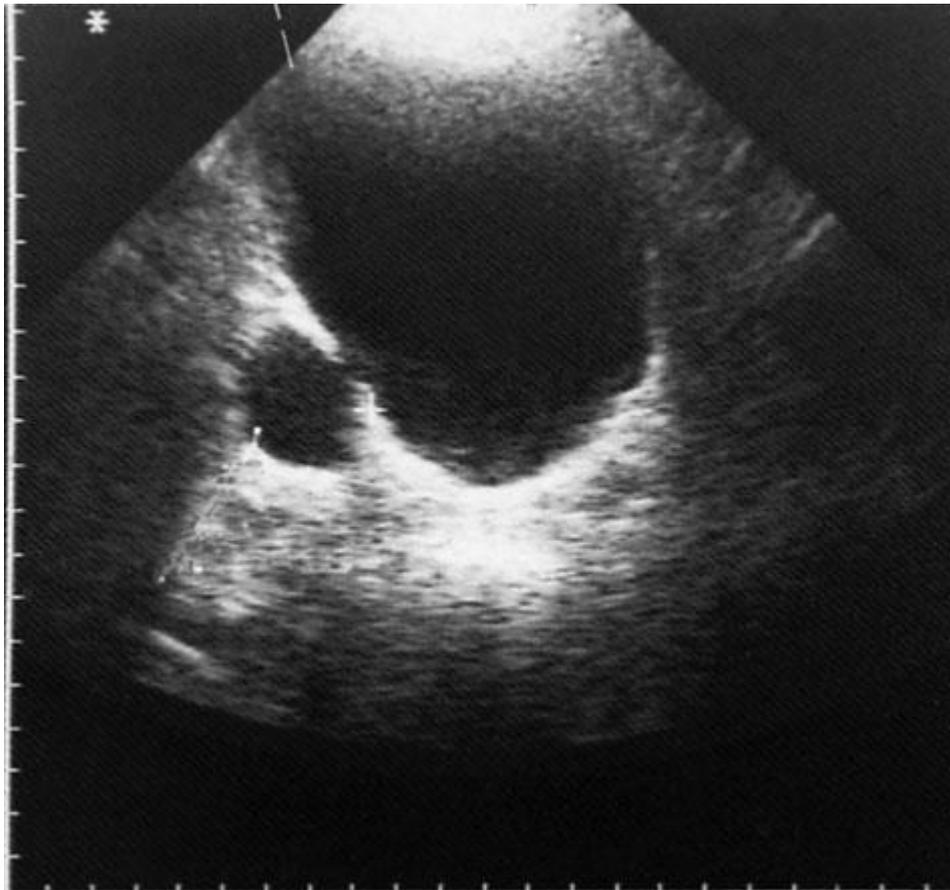
- * **An uninfected diverticulum of the bladder usually causes no symptoms.**
- * **The patient is nearly always male (95%) and over 50 years of age. Symptoms are those of associated urinary tract obstruction, recurrent infection and pyelonephritis.**
- * **Haematuria (due to infection, stone or tumour) is a symptom in about 30%.**
- * **In a few patients micturition occurs twice in rapid succession (the second act may follow a change of posture).**



Diagnosis

- * Diverticula are usually discovered incidentally on cystoscopy or ultrasound
- * Cystogram





Indications for operation:

The presence of a diverticulum – even quite a large one – is not an indication for diverticulectomy unless symptoms or cancer are present

Operation is necessary only for the treatment of complications.



RETENTION OF URINE :

Definition:

Types:

Acute retention: PAINFULL

The most frequent causes of acute retention

Male

- Bladder outlet obstruction (the commonest cause)
- Urethral stricture
- Acute urethritis or prostatitis
- Phimosis

Female

- Retroverted gravid uterus
- Bladder neck obstruction (rare)

Both

- Blood clot
- Urethral calculus
- Rupture of the urethra
- Neurogenic (injury or disease of the spinal cord)
- Smooth muscle cell dysfunction associated with ageing
- Faecal impaction
- Anal pain (haemorrhoidectomy)
- Intensive postoperative analgesic treatment
- Some drugs including antihistamines, anti-hypertensives, anti-cholinergics and tricyclic antidepressants.
- Spinal anaesthesia .



Clinical features:

- No urine is passed for several hours.
- Pain is present.
- The bladder is visible, palpable, tender and dull to percussion.



- Potential neurological causes should be excluded by checking reflexes in the lower limbs and perianal sensation.



Treatment

- * Urethral catheterization
- * Suprapubic puncture
- * Investigation & treatment of the cause.



Chronic retention; PAINLESS

- * there is no pain.
- * These patients are at risk of upper tract dilatation because of high intravesical tension
- * Men with impaired renal function may develop postobstructive diuresis following catheterisation.

Such men need careful monitoring, with replacement of inappropriate urinary losses by intravenous saline; they are also at risk of haematuria as the distended urinary tract empties. Often it is several days before full renal recovery occurs.

Retention with overflow

The patient is incontinent with small amounts of urine passing involuntarily from the distended bladder. It usually follows a neglected retention.



The acute neuropathic bladder

Immediately after spinal cord injury, 'spinal shock' occurs, which may last for days or months. The detrusor is not able to contract, the bladder distends and overflow incontinence occurs. Neglected bladder distension will lead to damage to the detrusor, infection and ultimately renal failure.

Management is as follows:

- The bladder should be emptied during spinal shock by catheterisation
- Encourage high fluid intake
- Commence intermittent catheterisation
- When the patient is stable undertake full urodynamic



The typical patterns of bladder function seen after spinal cord injury.

Lesions above T10

Usually leads to an 'upper motor neurone' bladder with reflexes intact but isolated from higher control mechanisms. Such patients are at risk of autonomic dysreflexia. Because of detrusor–sphincter dyssynergia, bladder contractions are high pressure and ineffective in producing bladder emptying; the bladder neck is normally open. If left untreated, upper tract dilatation and renal failure may result. Bladder capacity is usually decreased with the development of trabeculation and a typical 'fir-tree' appearance. Patients are incontinent during high-pressure phasic contractions because the sphincter resistance suddenly diminishes. Some patients with low-pressure bladders that empty may be managed by means of condom drainage. Others will require clean intermittent self-catheterisation (CISC). Patients with poor emptying, low bladder capacity and upper tract dilatation require treatment with endoscopic sphincterotomy and condom drainage.

Lesions involving the sympathetic outflow (T11, T12, L1, L2)

These patients are usually similar to the group with lesions above T10.



Damage to the sacral centre S2, S3, S4 and cauda equine lesions

Usually leads to a 'lower motor neurone' bladder, also found in spina bifida (myelodysplasia); the detrusor is acontractile. Abdominal straining can produce reasonable emptying but the mainstay is CISC. Some patients may have sensation of filling through the hypogastric nerves if T11 and T12 are intact. The bladder capacity may be good, but some patients have high resting pressures and high increases during bladder filling, which means that there is a risk to the upper urinary tract. The bladder neck is usually open and the distal sphincter mechanisms may be paralysed but of fixed resistance. Vesicoureteric reflux is common and upper tract damage is frequent in neglected cases. Patients who can achieve satisfactory bladder emptying by means of CISC usually have reasonable continence.

Bladder dysfunction after excision of the rectum or radical hysterectomy

Between 10% and 15% of patients undergoing radical rectal excision for cancer sustain damage to the inferior hypogastric plexus, leading to impotence in the male and neurogenic bladder dysfunction. This type of bladder dysfunction is similar to the cauda equine lesion. Postoperative retention in other patients may also be caused by simple bladder outlet obstruction. The best plan is to catheterize the patient to allow postoperative recovery and then carry out urodynamic investigation to determine the appropriate treatment.



INCONTINENCE OF URINE

* occurs in 5% of men and 20% of women. Up to 40% of women over the age of 60 years and 50% of institutionalised elderly patients experience regular episodes of urinary incontinence.

* Continence is dependent on:

- 1 - normal brain function allowing a perception of when it is socially acceptable to void,
- 2 - normal bladder sensation,
- 3 - normal voluntary detrusor contraction producing good bladder emptying,
- 4 - a normally competent sphincter mechanism, which relaxes appropriately during a voluntary detrusor contraction allowing good bladder emptying,
- 5 - and good bladder capacity with normally low pressures during filling.

This is clearly a fine balance and several factors can cause incontinence.

TYPES & CAUSES:

- 1 - TOTAL; Post-prostatectomy, Fistula
- 2 - STRESS; increase of intra-abdominal pressure with defective sphincter.
- 3 - URGE
- 4 - RETENTION WITH OVER FLOW

Diagnosis of urinary incontinence

The following investigations are required:

- A careful history and physical examination and completion of frequency voiding charts
- Urodynamic testing in most patients and in all patients in whom surgical intervention is proposed
- Urine culture to exclude infection and measurement of serum creatinine
In selected cases IVU is carried out if a ureteric fistula is suspected, although ultrasound examination will often provide adequate details



Urodynamic testing

The principle is to artificially simulate bladder filling and emptying while obtaining pressure measurements

- * The normal bladder will accept approximately 400–550 ml when filled at room temperature at a rate of $< 50 \text{ ml min}^{-1}$.**
- * The pressure increase in the bladder should be less than 15 cmH₂O.**
- * Phasic pressure increases should not be seen.**
- * The normal voiding pressure should not exceed 60 cmH₂O in men and about 40 cmH₂O in women, with a flow rate of between 20 and 25 ml s⁻¹.**



TREATMENT :

can be summarised as follows:

- 1 - Devices for collection: external penile condom, or an indwelling urethral or suprapubic catheter.**
- 2 - Drugs: to decrease the strength of the bladder neck (e.g. adrenergic blockers); with mixed action on the bladder neck and central nervous system (e.g. tricyclic drugs); to inhibit bladder activity (e.g. anti-cholinergic drugs).**
- 3 - Intermittent self-catheterisation: to improve emptying.**
- 4 - Increasing outlet: pelvic floor physiotherapy; resistance colposuspension or TVT tapes or slings; periurethral injections of 'bulking agents' such as cross-linked collagen or other particles; use of the artificial urinary sphincter.**
- 5 - Denervation of bladder: S3 sacral nerve blockade, neurectomy or surgical transection of the bladder to inhibit bladder activity and improve functional capacity.**
- 6 - Sacral nerve stimulation devices can improve incontinence. They involve percutaneous insertion of electrodes through the sacral foramina under radiological control and implantation of an electronic stimulator.**
- 7 - Augmentation of bladder: 'clam' enterocystoplasty, bladder capacity substitution with detubularised bowel segment.**
- 8 - Urinary diversion: ileal conduit, continent urinary diversion.**



NEOPLASMS OF THE BLADDER

- Primary :

- * 95% of primary bladder tumours originate in transitional epithelium;*
- * the remainder arise from connective tissue (angioma, myoma, fibroma and sarcoma) or are*
- * extra-adrenal pheochromocytomas.*

- Secondary:

tumours of the bladder are common and most frequently arise from the sigmoid and rectum, the prostate, the uterus or the ovaries, although bronchial neoplasms may also spread to the bladder



Benign papillary tumours :

Inverted papilloma is a condition in which the proliferative cells penetrate under normal mucosa so that the lesion is covered with smooth urothelium. It is benign.

Treatment : TURt



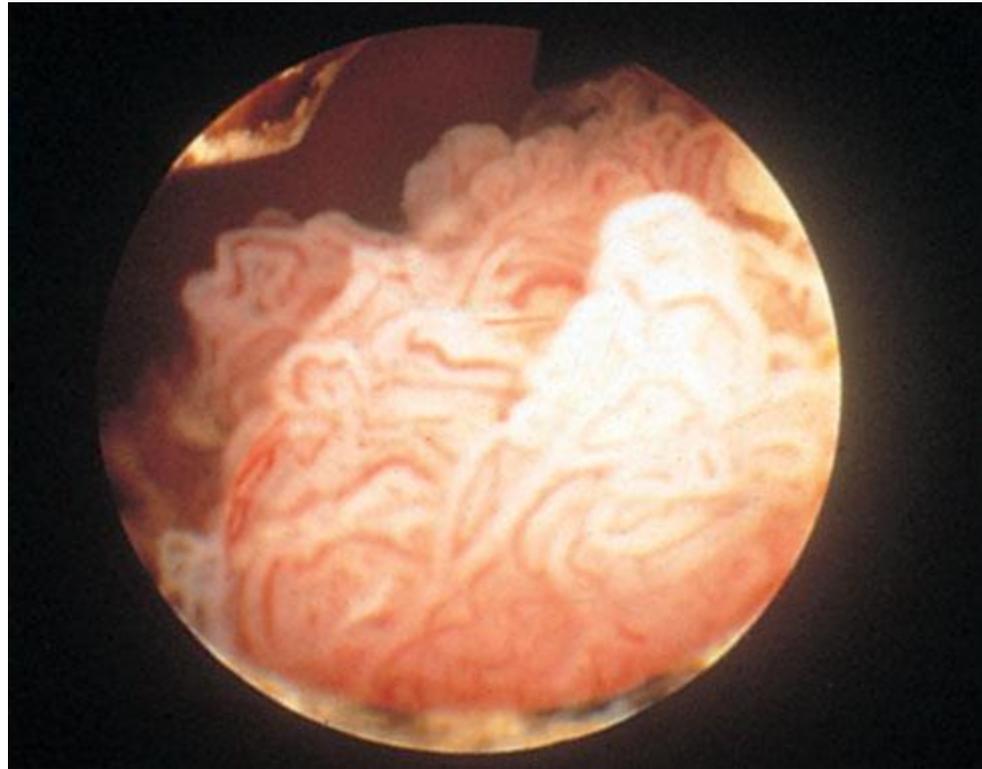
CARCINOMA OF THE BLADDER

Histological types :

- 1 - urothelial, TCC- 90%**
- 2 - squamous CC -5% Un common, except in areas where bilharzia is endemic area,**
- 3 - adenocarcinoma which arises either from the urachal remnant or from areas of glandular metaplasia, and some times associated with Ectopia Vesica, accounts for 1–2% of cases.**
- 4 - mixed, as a result of metaplasia in a transitional cell carcinoma (TCC).**



Urothelial cell carcinoma



Aetiology

- * **Cigarette smoking** is the main aetiological factor (40% of cancers).
- * Occupational exposure to urothelial carcinogens remains common. The first suspicion of a chemical cause for bladder cancer was raised by Rehn in 1895 when he recorded a series of tumours in workers in aniline dye factories.

Subsequent investigation demonstrated that the following compounds may be carcinogenic:

- 2-naphthylamine;
- 4-aminobiphenyl;
- benzidine;
- chlornaphazine;
- 4-chloro-*o*-toluidine;
- *o*-toluidine;
- 4,4'-methylene bis(2-choloroaniline);
- methylene dianiline;
- benzidine-derived azo dyes.

Occupations associated with an increased risk of bladder cancer are:

- textile workers;
- dye workers;
- tyre rubber and cable workers;
- petrol workers;
- leather workers;
- shoe manufacturers and cleaners;
- painters;
- hairdressers;
- lorry drivers;
- drill press operators;
- chemical workers;
- rodent exterminators and sewage workers.



Bladder cancer became a prescribed industrial disease .

Urothelial cell carcinoma of the bladder

- The fourth most common non-dermatological malignancy in men (male–female ratio 3:1)
- Strongly associated with smoking and chemical exposure in western societies
- Reducing in incidence in countries where smoking is decreasing



Tumour staging and grading

TNM :

Depth of invasion- (T)

node-(N)

metastasis (M)

classification and grade are important factors in planning treatment and determining prognosis in bladder cancer.

Classification:

- **Non-muscle-invasive('superficial' bladder cancer):papillary shape growth**
pTa :no invasion of lamina propria pT1 :tumours may reveal invasion of the lamina propria (pT1) but not of the muscle account for 70% of all new cases; these are known as 'superficial' bladder cancer. These tumours may be single or multiple – single papillary pTa tumours account for a significant proportion of bladder cancers and carry an excellent prognosis.
- **Muscle-invasive disease accounts for 25% of new cases.T2,and more** Such tumours carry a much worse prognosis as they are subject to local invasion and distant metastasis.Tumor was tend to be solid mass growth.
- **Flat, non-invasive CIS (primary CIS) accounts for 5% of new cases.**
Unless diagnosed and treated promptly it carries a poor prognosis .



CLINICAL FEATURES

- * Painless gross haematuria is the most common symptom and is indicative of a bladder carcinoma until proven otherwise. The bleeding may give rise to clot formation and clot retention.
- ** Constant pain in the pelvis usually heralds extravesical spread.
- *** There is often frequency and discomfort associated with urination.
- **** Pain in the loin or pyelonephritis may indicate ureteric obstruction and hydronephrosis.
- ***** A late manifestation is nerve involvement causing pain that is referred to the suprapubic region, groins, perineum, anus and into the thighs.



INVESTIGATION

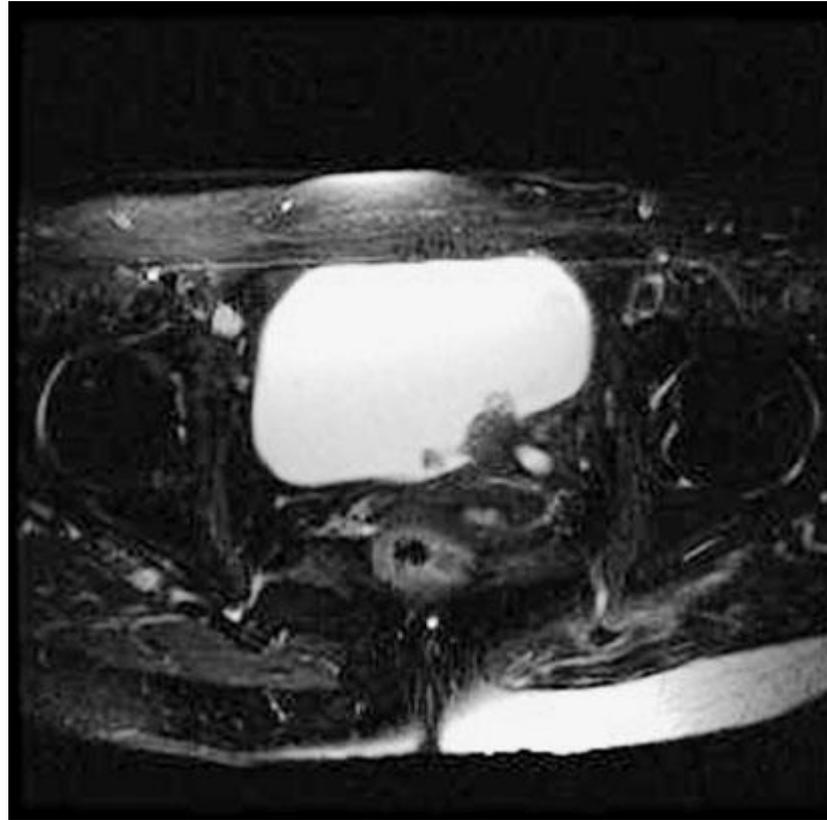
Urine cytology

Blood

IVU or ultrasound scanning



Cross-sectional imaging(CT &MRI)



Cystourethroscopy+ Bimanual examination



TREATMENT :

- * the patients with a single low- or medium-grade pTa tumour can safely be treated by resection alone plus a single instillation of mitomycin, followed up with regular cystoscopies.
- * The treatment of patients with multiple low- or medium-grade pTa tumours can be by either resection alone or resection followed by a 6-week course of intravesical chemotherapy with mitomycin, doxorubicin or epirubicin. , followed up with regular cystoscopies
- * The treatment of pT1 disease is by endoscopy followed by immunotherapy with intravesical BCG or chemotherapy for 6 weeks.

Many urologists would offer immediate cystectomy to a patient with a high-grade pT1 tumour, particularly if it were multiple or accompanied by CIS, because of the 30–50% risk of progression to muscle invasion.

Follow-up cystoscopies are essential; every 3 months for 2 years or more.

The factors that result in an increased recurrence and progression rate are:

- high grade;
- pT1 disease;
- concomitant CIS;
- multiple primary tumours;
- recurrent disease at the first check cystoscopy 3 months after diagnosis.

Invasive tumours:

Radical cystectomy + urinary diversion

Radiotherapy- partial response : alone or with surgery .

Systemic chemotherapy- neoadjuvant pre and post operative or as palliative treatment

