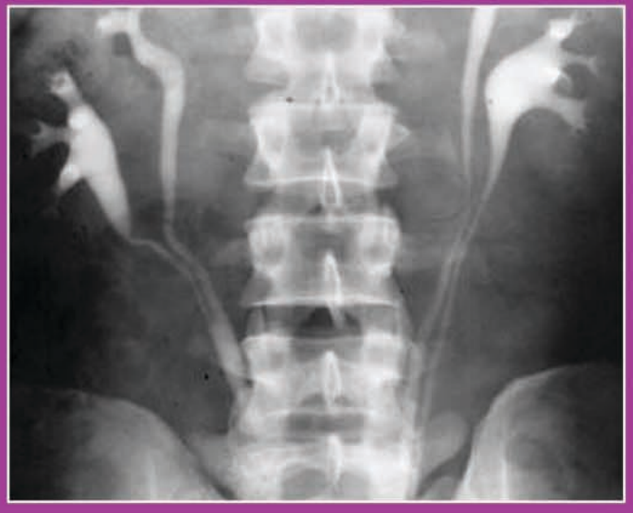
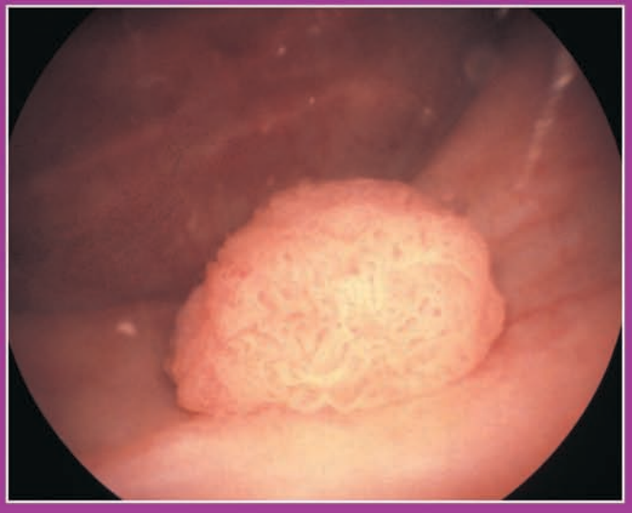
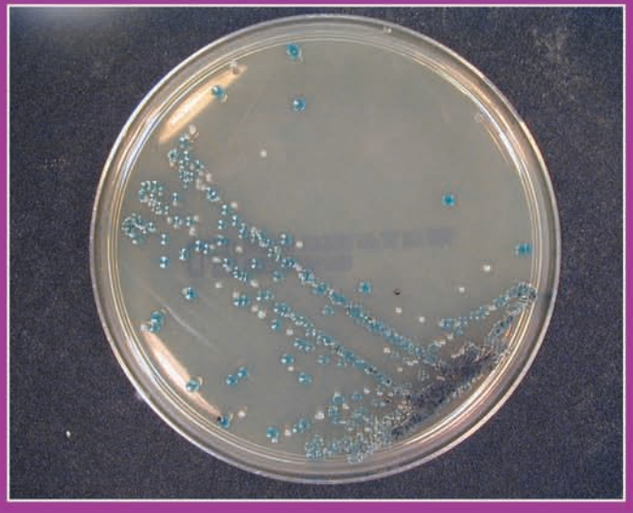
An Atlas of Investigation and Diagnosis

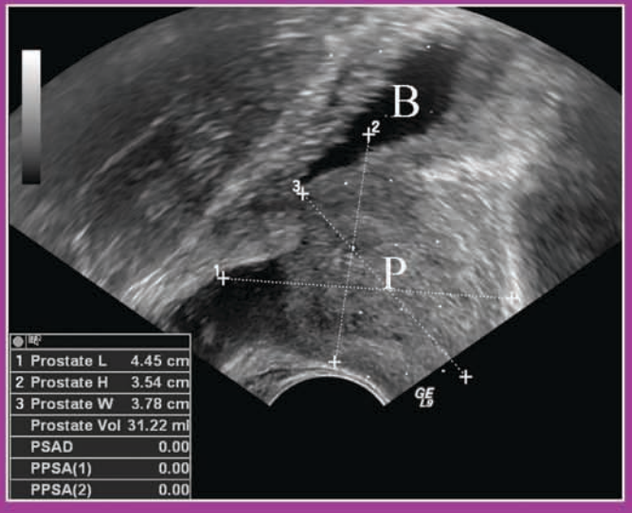
UROLOGY

John L Probert









CLINICAL PUBLISHING

An Atlas of Investigation and Diagnosis

UROLOGY

Edited by

John L. Probert, BMedSci, DM, FRCS(Urol)

Bristol Urological Institute
Southmead Hospital
Bristol, UK

CLINICAL PUBLISHING

OXFORD

Clinical Publishing
an imprint of Atlas Medical Publishing Ltd
Oxford Centre for Innovation
Mill Street, Oxford OX2 0JX, UK

Tel: +44 1865 811116
Fax: +44 1865 251550
Email: info@clinicalpublishing.co.uk
Web: www.clinicalpublishing.co.uk

Distributed in USA and Canada by:
Clinical Publishing
30 Amberwood Parkway
Ashland OH 44805, USA

Tel: 800-247-6553 (toll free within U.S. and Canada)
Fax: 419-281-6883
Email: order@bookmasters.com

Distributed in UK and Rest of World by:
Marston Book Services Ltd
PO Box 269
Abingdon
Oxon OX14 4YN, UK

Tel: +44 1235 465500
Fax: +44 1235 465555
Email: trade.orders@marston.co.uk

First published 2009

A catalogue record of this book is available from the British Library

ISBN-13 978 1 904392 65 1
ISBN e-book 978 1 84692 575 1

Project manager: Gavin Smith, GPS Publishing Solutions, Herts, UK
Typeset by Phoenix Photosetting, Chatham, Kent, UK
Printed by T G Hostench SA, Barcelona, Spain

Contents

Contributors

Samih Al-Hayek, MD, LMSSA, LRCP(Lond), LRCS(Eng), MRCS
Specialist Registrar in Urology
Department of Urology
Weston General Hospital
Weston-Super-Mare
UK

Nimalan Arumainayagam, BMedSci, BMBS, MRCS
Clinical Research Registrar in Urology
Bristol Urological Institute
Southmead Hospital
Bristol
UK

Angela M. Cottrell, MBBS, BSc, MRCS
Clinical Research Fellow
Bristol Urological Institute
Bristol
UK

Matthew Hotston, MBChB, MRCS(Eng)
Specialist Registrar in Urology
The Royal Marsden Hospital
London
UK

Kieran Jefferson, MA, FRCS(Urol)
Consultant Urological Surgeon
University Hospital of Coventry and Warwickshire
Coventry
UK

Natasha Jefferson, MA, MRCP, FRCR
Consultant Radiologist
Horton Hospital
Banbury
UK

Merce Jorda, MD, PhD
Professor of Clinical Pathology
Medical Director, Clinical Laboratory Services
UMHC/SCCC and UM Hospital
Department of Pathology
Leonard M. Miller School of Medicine
University of Miami Hospital and Clinics
Miami, Florida
USA

Jay Khastgir, MBChB, MS, FRCSEd, FRCS(Glas), FRCS(Urol)
Consultant Urological Surgeon
Department of Urology
Morriston Hospital
Swansea
UK

Anthony Koupparis, BSc, MBChB, FRCS(Urol), MD
Specialist Registrar in Urology
Department of Urology
Cheltenham General Hospital
Cheltenham
UK

Murugesan Manoharan, MD, FRCS, FRACS
Associate Professor of Urology
Department of Urology
Leonard M. Miller School of Medicine
Miami, Florida
USA

Mark S. Soloway, MD
Professor and Chairman
Department of Urology
Leonard M. Miller School of Medicine
Miami, Florida
USA

Steve K. Williams, MD
Uro-Oncology Fellow
Department of Urology
University of Miami
Miami, Florida
USA

Preface

Urology is one of the fastest developing of specialties, but the main aim here is to provide a source reference for many of the conditions and means of investigating them that are encountered and used within the context of everyday urological practice.

One of the consultants I worked for during the early stages of my training was always keen to point out that urological problems are regularly encountered in many other specialties as a consequence of a wide variety of disease processes, not least of which is the realm of the community care and general practitioner, and it is with this thought in mind that this book has been put together.

This volume is aimed at as wide a readership interested in the discipline of urology as possible, from the medical student encountering the specialty for the first time to the expert keen for some up-to-date images of common urological conditions. The aim has been to provide a readable, user-friendly text looking at the major areas dealt with by urology as a specialty, accompanied by illustrations.

The book begins with a look at renal function – its measurement and the assessment of its impairment, before moving on to look at the investigation and diagnosis of urinary tract infection. The management of lower urinary tract symptoms or LUTS as this spectrum of presenting complaints is known, is dealt with in a separate chapter, followed by a look at the investigation of stone disease. The next section of the book looks at the presentation and investigation of common urological malignancies in chapters covering prostate, bladder and renal cancer. Testicular cancer is dealt with in the following chapter, which also takes a look at common benign scrotal conditions. Finally, the book is rounded off by a summary of the investigations and assessment techniques used in patients with erectile dysfunction.

John L. Probert
June 2008

Special acknowledgement

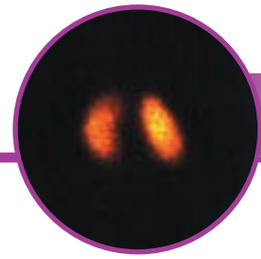
The publisher is very grateful to Mr Vivek Kumar for his kind assistance in supplying several of the images that appear in Chapter 4 of this book.

Vivekaandan Kumar, MBBS, MS(Gen. Surg), MD(Res), FRCS
Specialist Registrar
Department of Urology
Gloucestershire Royal Hospital
Gloucester
UK

Abbreviations

[^{99m}]TcMDP	[^{99m}]technetium-labelled methylene diphosphonate
5-ALA	5-aminolaevulinic acid
A2M	α_2-macroglobulin
ACT	α_1-antichymotrypsin
AFP	α-fetoprotein
AJCC	American Joint Committee on Cancer
ARE	androgen-responsive element
AUA	American Urological Association
BHD	Birt–Hogg–Dube syndrome
BOO	bladder outlet obstruction
BOOI	Bladder Outlet Obstruction Index
BPE	benign prostatic enlargement
BPH	benign prostatic hyperplasia
BPO	benign prostatic obstruction
BTA	bladder tumour antigen
BVE	bladder voiding efficiency
cGMP	cyclic guanosine monophosphate
CIS	carcinoma *in situ*
CT	computed tomography
DMSA	dimercaptosuccinic acid
DRE	digital rectal examination
DTPA	diethylenetriaminepentaacetic acid
EAU	European Association of Urology
ED	erectile dysfunction
EDTA	ethylenediaminetetraacetic acid
EDV	end diastolic flow velocity volume
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMB	eosin-methylene blue
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HAL	hexyl aminolaevulinate
H&E	haematoxylin and eosin
HIF-α	hypoxia-inducible factor-α
hK2	human kallikrein 2
hK3	human kallikrein 3
HSP	Henoch-Schönlein purpura
HU	Hounsfield unit
ICC	international correlation coefficient
ICS	International Continence Society
IgA	immunoglobulin A
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
IR(ME)R	ionizing radiation regulations
ISUP	International Society of Urological Pathologists
IVC	inferior vena cava
IVU	intravenous urography
KFP	formation product
KSP	saturation product
KUB	kidneys, ureters and bladder (radiograph)
LUTS	lower urinary tract symptom
MAG3	mercaptoacetyltrigycine
MDRD	Modification of Diet in Renal Disease
MRHA	mannose-resistant haemoagglutination
MRI	magnetic resonance imaging
MSU	midstream urine
MUCP	maximum urethral closure pressure
MUP	maximum urethral pressure
NGU	non-gonococcal urethritis
NIH	National Institutes of Health
NMP-22	nuclear matrix protein 22
NPV	negative predictive value
NSAID	non-steroidal anti-inflammatory drug
OAB	overactive bladder syndrome
OIH	orthoiodohippuran
PDE5	type 5 phosphodiesterase
PDGF-β	platelet-derived growth factor-β
PET-CT	positron emission tomography with CT
PIN	prostatic intraepithelial neoplasia
PMN	Polymorphonuclear neutrophils
PPV	positive predictive value
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
PSV	peak systolic velocity
PUNLMP	papillary urothelial neoplasm of low malignant potential
Q_{max}	maximum flow rate
Q_{ave}	average flow rate
RBC	red blood cell
RCC	renal cell carcinoma
REM	rapid eye movement
RFA	radiofrequency ablation
RI	resistance index
SCr	serum creatinine
SLE	systemic lupus erythematosus
SPA	suprapubic aspirate
STD	sexually transmitted disease
STIR	short tau inversion recovery
TcMDP	technetium-labelled methylene diphosphonate
TGF-α	transforming growth factor-α
TGF-β	transforming growth factor-β
TNM	Tumour, Nodes, Metastasis
TRUSS	transrectal ultrasound scanning
TURBT	transurethral resection of a bladder tumour
TURP	transurethral resection of the prostate
UC	urinary cytopathology
UICC	International Union Against Cancer
UPP	urethral pressure profilometry
UTI	urinary tract infection
VEGF	vascular endothelial growth factor
VHL	von Hippel-Lindau
VUDS	videodynamics
VUR	vesicoureteric reflux
VV	voided volume
WBC	white blood cell
WHO	World Health Organization

Chapter 1



Renal Function

Angela Cottrell

The kidney has a number of functions, including:

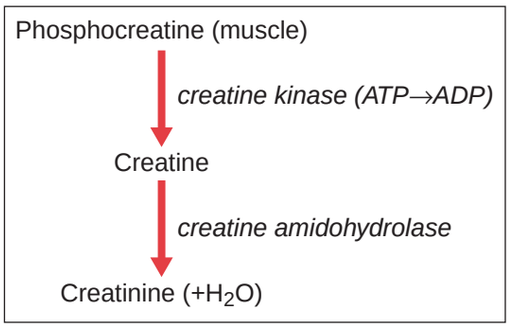
- Maintenance of homeostasis.
- Production of erythropoietin.
- Maintenance of blood pressure.
- Hydroxylation of vitamin D.

It is the investigation of the first of these with which this chapter is concerned.

Creatinine as an indicator of renal function

One of the major roles of the kidney is the excretion of soluble waste. This is achieved by the process of glomerular filtration. Creatinine is commonly used as an indicator of the glomerular filtration rate (GFR). Creatinine is a non-toxic breakdown product of creatine, a short-term energy store found in muscle (in the form of phosphocreatine) (**1.1**).

Laboratory analysis of serum creatinine entails chromographic analysis of the products of the Jaffe reaction. Creatinine is mixed with alkaline picramate and an orange coloured compound is formed (**1.2**). The product is then analysed by a colorimeter.



1.1 Metabolism of phosphocreatine to creatinine.

Table 1.1 shows possible causes for a raised creatinine.

The 'goulash effect' is a transient rise in serum creatinine after ingestion of large quantities of boiled meat.

1.2 Creatinine after alkaline picramate reaction.

Table 1.1 Causes of a raised creatinine
Renal impairment
Ingestion of stewed meat ('goulash effect')
Acute muscle necrosis
Muscular dystrophy
Starvation
Methyltestosterone therapy
Neo-bladder

Glomerular filtration rate

Measurement of serum creatinine has its limitations. The relationship between serum creatinine and GFR is not linear, and serum creatinine level may not rise significantly until GFR is as low as 30% of normal.

GFR is an important measurement that provides clinicians with information about overall renal function. GFR can be estimated in a number of ways.

Clearance concept

GFR can be estimated by measuring clearances of a substance in which filtration by the glomerulus equals excretion in the urine. Clearance is the volume of plasma that is completely cleared of a substance by the kidneys per unit time (**1.3**).

$$\frac{U \text{ (concentration of substance in urine)} \times V \text{ (urine flow rate)}}{\text{Plasma (concentration of substance)}}$$

1.3 Calculation of clearance in ml/min.

Calculation of creatinine clearance (1.4)

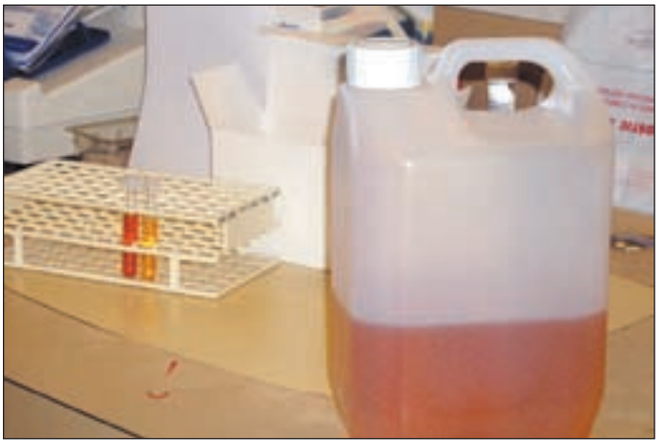
Creatinine is an endogenous substance that is present at a relatively constant level. Measurements and calculation according to the formula in figure **1.3** require 24-hour collection of urine (**1.5**). Therefore, patients need to be compliant for results to be accurate.

$$\frac{\text{Urine volume (ml/24 hours)} \times \text{Urine creatinine concentration (mmol/l)}}{\text{Plasma creatinine}}$$

1.4 Calculation of creatinine clearance (ml/min).

Formulae to estimate GFR

Isolated measurements of serum creatinine are not accurate indicators of early renal disease. By incorporating variables such as age and weight, an estimated GFR can be derived.



1.5 24-hour urine collection.

Two commonly used formulae are those attributed to Cockcroft and Gault (**1.6**), and the Modification of Diet in Renal Disease (MDRD) formula (**1.7**).

The Cockcroft and Gault formula includes age, weight and sex to estimate creatinine clearance:

$$\text{eGFR} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{SCr} \times 72 \times [0.85 \text{ if female}] \text{ and adjusted for body surface area of } 1.73\ m^2}$$

eGFR = estimated glomerular filtration rate
SCr = serum creatinine

1.6 Cockcroft and Gault formula.

The four-variable MDRD formula is used in the UK Chronic Kidney Disease guidelines to calculate estimated GFR (eGFR).

$$(\text{eGFR}_{\text{MDRD}}) = 186 \times [\text{SCr}]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if black}]$$

eGFR = estimated glomerular filtration rate
SCr = serum creatinine

1.7 Modification of Diet in Renal Disease (MDRD) formula.

This estimate allows clinicians to classify the degree of renal impairment and hence determine further management (*see Table 1.2*).

Creatinine clearance measurement has its limitations. A small amount of creatinine is secreted by the renal tubules, and therefore GFR is likely to be overestimated if it is measured by this technique.

Table 1.2 Classification of chronic kidney disease

Stage	Description
1 Normal GFR	>90 ml/min/1.73 m^2 with other evidence of chronic kidney disease
2 Mild impairment	60–89 ml/min/1.73 m^2 with other evidence of chronic kidney disease
3 Moderate impairment	30–59 ml/min/1.73 m^2
4 Severe impairment	15–29 ml/min/1.73 m^2
5 Established renal failure	15 ml/min/1.73 m^2 or on dialysis

The full table may be found at: http://www.renal.org/CKDguide/full/Conciseguid141205.pdf

Constant infusion technique

The gold standard method of measuring GFR is with inulin infusion. Inulin is a polymer of fructose that is derived from the tubers of dahlias. It is freely filtered by the glomerulus and neither secreted nor reabsorbed at the tubules. Accurate urine samples are taken following the infusion of inulin to maintain a constant concentration. This technique, although accurate, is limited to the research laboratory.

Radioisotope measurement of GFR

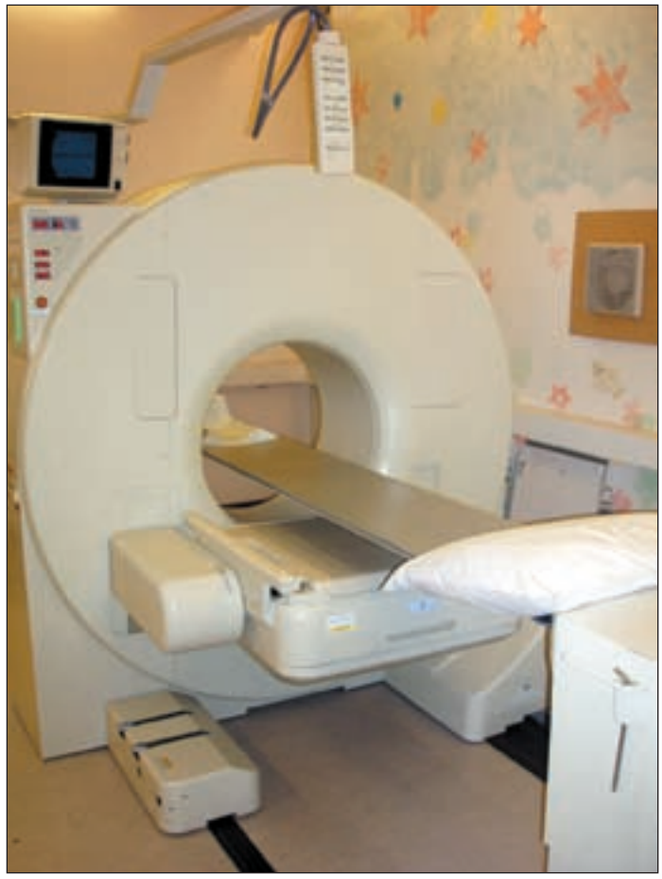
Ethylenediaminetetraacetic acid (EDTA) is added to many commercial beers to stabilize foaming and when chelated with copper it produces a blue colour used in shampoo. Chromium-labelled EDTA may also be used in the laboratory as a method of measuring GFR as it is cleared by glomerular filtration. Following injection of the substance, blood samples are taken and a rate of decay of the sample is plotted to enable calculation of GFR.

Radioisotope scans

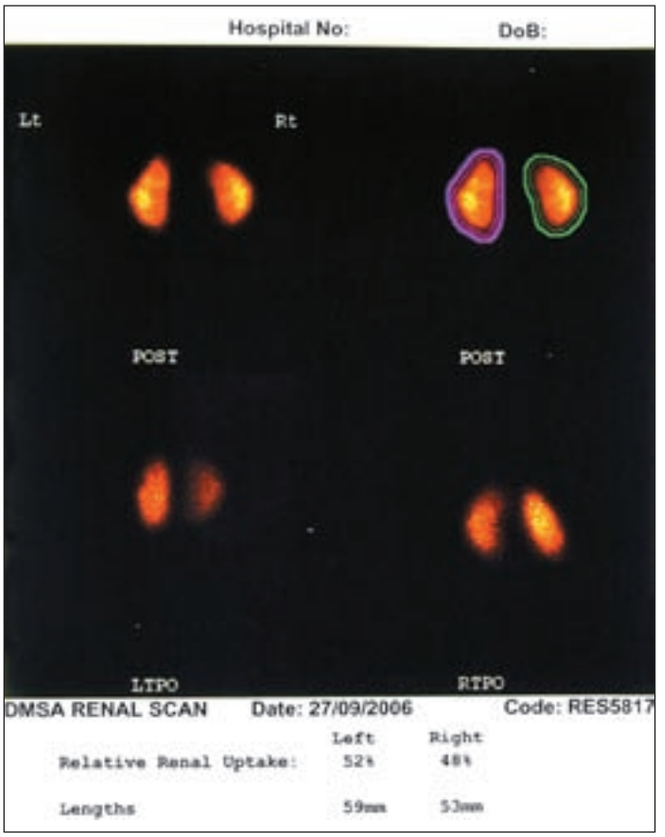
Injection of radioisotopes that are handled by the kidney can provide useful information in the diagnosis and management of renal disease. Radioisotope imaging may be described as static or dynamic, depending on whether or not the radioisotope is freely filtered through the kidney and excreted, or taken up and bound to live renal tubules.

Static imaging

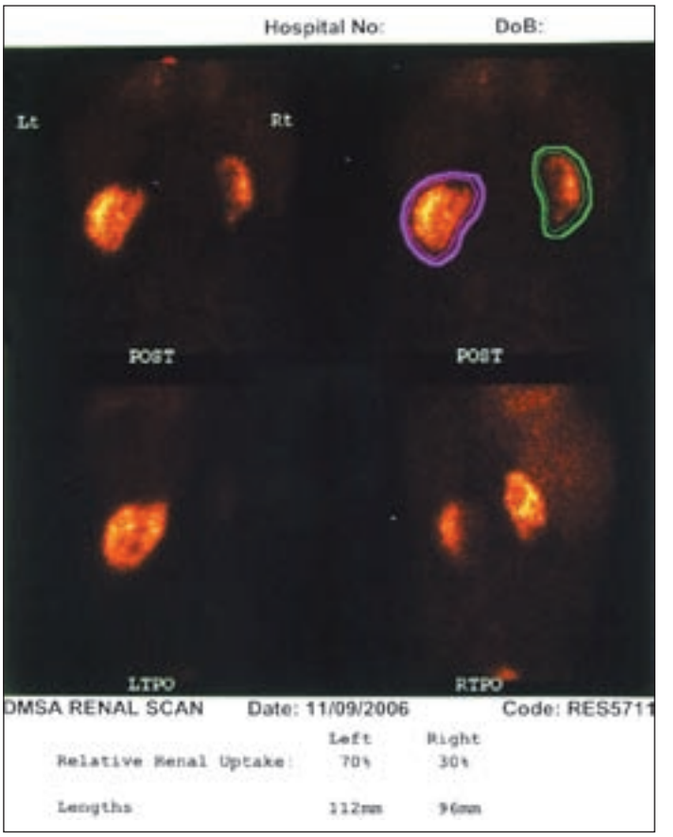
The commonest biological molecule used in static renography is technetium-labelled DMSA (dimercaptosuccinic acid). This is filtered by the glomerulus and binds to the renal tubules, where it can be detected using a gamma camera 2–3 hours after injection (**1.8**). DMSA scans are useful in providing anatomical information, assessing the degree of any renal scarring that may be present, and in determining split renal function (**1.9**, **1.10**).



1.8 Gamma camera.



1.9 Normal DMSA.

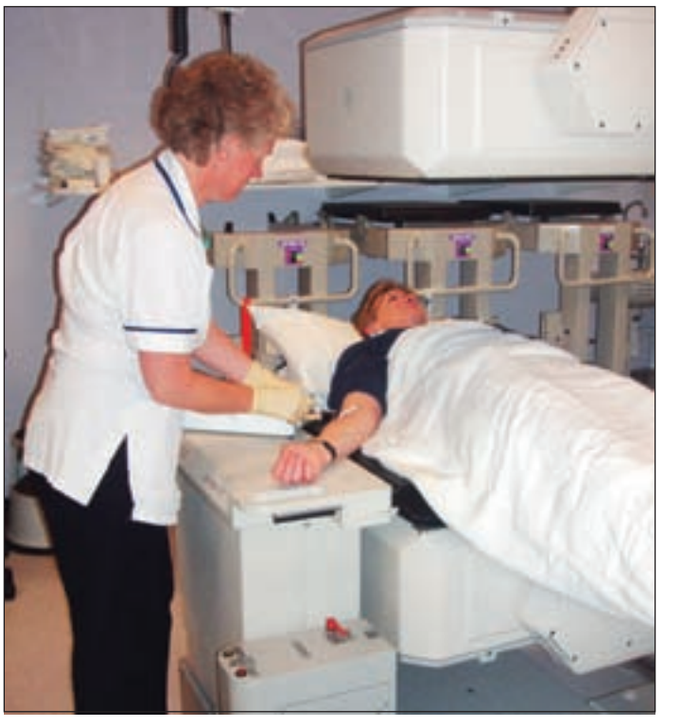


1.10 Split DMSA.

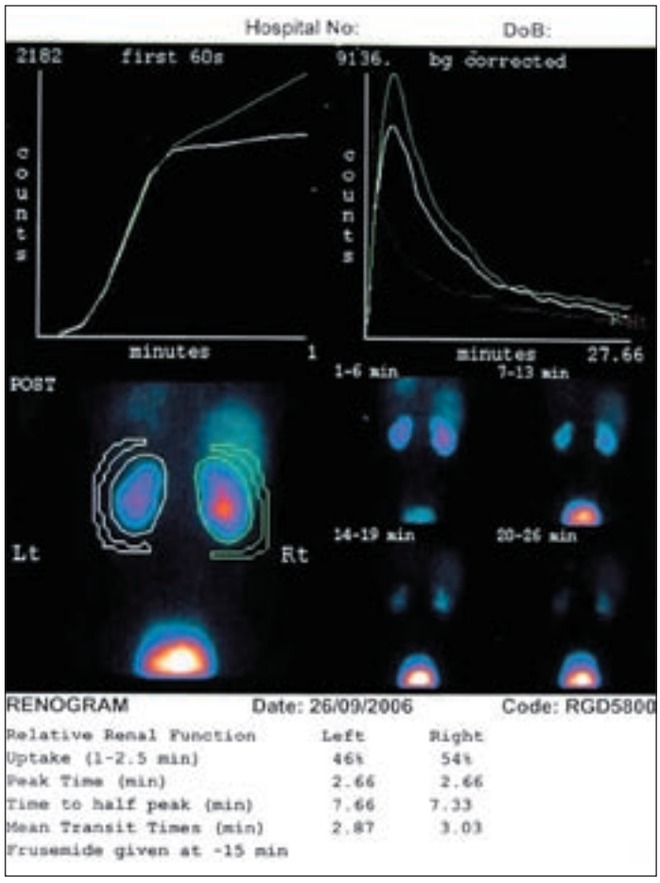
Dynamic imaging (renography)

Dynamic renography is used primarily in the assessment of pelviureteric junction obstruction. As the injected radioisotopes are freely filtered by the glomerulus and excreted by the kidney, information can also be provided about glomerular filtration. Following isotope injection, gamma camera images are taken and the results are plotted over time. The commonest isotopes used are technetium-labelled diethylenetriaminepentaacetic acid (DTPA) and mercaptoacetyltriglycine (MAG3). Orthoiodohippuran (OIH) may also be used but it is more expensive (**1.11**).

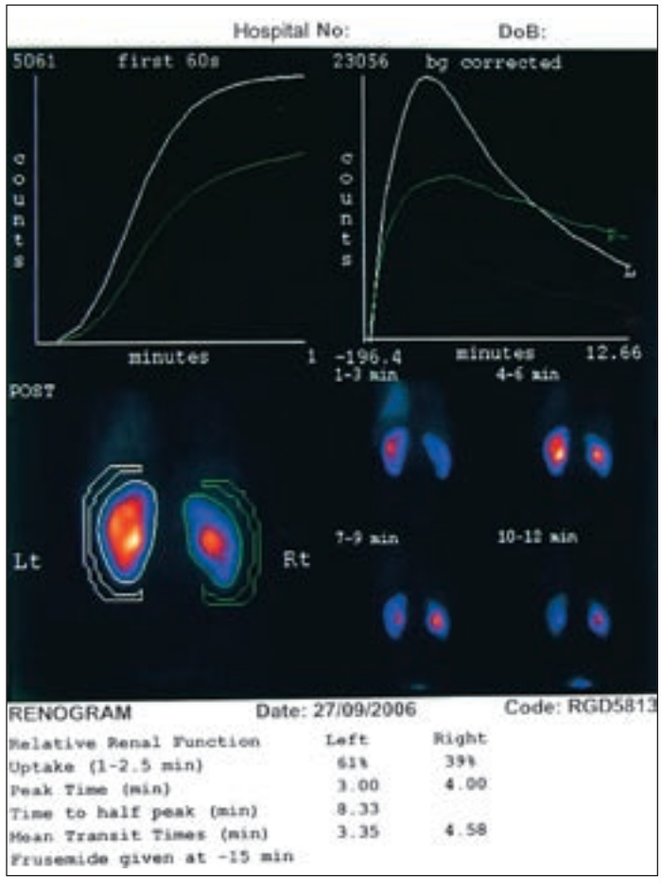
Before renography, the patient should be well hydrated and, to minimize any effects from a full bladder, the bladder either catheterized or emptied beforehand. This is particularly important in cases such as neuropathic bladder or vesicoureteric reflux. Dehydration and bladder effect may lead to equivocal results. In current practice, furosemide is given 15 minutes prior to isotope injection (typically 0.5 mg/kg of furosemide). The flow of urine across the pelviureteric



1.11 Set-up of renogram.



1.12 Normal DTPA renogram.



1.13 DTPA renogram showing obstruction.

junction is maximal at 15 minutes after injection of furosemide. The number of otherwise equivocal scans that might be obtained can be reduced by performing the renogram at the time of maximal diuresis (F-15 renogram).

In analysing renograms three distinct phases are described. The first phase is 'uptake'. This corresponds to the speed of injection of the radioisotope and the blood supply to the kidney. An abnormal uptake phase may be due to impaired renal function. The second phase is that of renal 'handling', determined by the transfer of isotope across the tubule cell. The third phase is that of 'washout' or drainage, and this is determined by the rate of excretion of tracer in the urine. An abnormal uptake phase may be due to impaired renal function (**1.12**).

Analysis of the washout phase of the renogram will indicate the degree and nature of obstruction. In certain cases an equivocal result may be obtained, where a brisk 'washout effect' is not observed but the pattern of the curve is not diagnostic of obstruction either. Diuresis renography can help interpret such cases. Traditionally, furosemide is given 20 minutes after the injection of isotope, hence increasing the flow of urine at the renal pelvis (F+20 renogram). This diuresis can help determine whether the original trace pattern has been caused by obstruction, in which case the curve will continue to be flattened (type 2 obstruction), or by stasis, in which case the curve will fall (type 3a obstruction). A partial response to furosemide may be due to renal impairment of partial obstruction (type 3b obstruction). Type 4 obstruction is indicated by the 'double peak' phase, or Homsy's sign. In this case the system may follow a normal pattern of washout until about 15 minutes after injection. At this time the curve will fall, hence indicating obstruction at maximal flow across the pelviureteric junction. This indicates decompensation, where the pelviureteric junction cannot tolerate the increased urine load at maximal diuresis (**1.13**).

The Whitaker test

Despite the use of diuretics, either in the form of F+20 or F-15 renography, some test results will still be inconclusive as to the presence of obstruction. The Whitaker test is another, more invasive, method of investigating equivocal cases of suspected obstruction. It may also be used in patients with poor renal function when a dynamic renogram is not appropriate. A fine bore nephrostomy is inserted into the renal pelvis and a catheter inserted into the bladder. Both the nephrostomy and bladder catheter are connected to pressure transducers. Contrast medium is injected into the renal pelvis at a rate similar to that of maximal diuresis. The bladder pressure is recorded with a gradual increase in pressure of the renal pelvis. An increase in pressure indicates ureteric obstruction.

Captopril test

The Captopril test is used to investigate cases of renovascular hypertension caused by possible renal artery stenosis. Patients with renal artery stenosis have high serum levels of angiotensin II. Captopril reduces angiotensin II formation and therefore relaxes efferent arterioles. The GFR subsequently falls.

Before the test angiotensin-converting inhibitors should be stopped. The test is performed following a baseline dynamic renogram. Captopril is given and a repeat renogram taken 30 minutes later. The test is positive if there is a drop in GFR or delayed transit times.

Acute renal failure

Acute renal failure is sudden onset of renal impairment that takes place over a short duration of time, such as days or weeks. It is characterized by an increase in the serum creatinine, which is reversible.

Classification

Acute renal failure may be classified by its aetiology as pre-renal, renal or post-renal:

Pre-renal renal failure

The commonest cause of pre-renal renal failure is hypotension. The kidneys are able to maintain a constant GFR over a wide range of perfusion pressures, a mechanism known as autoregulation. The commonest cause of hypotension is shock, whether secondary to hypovolaemia, sepsis or cardiogenic. Vascular causes such as renal artery stenosis or renal vein thrombosis may also be considered. If the cause of hypotension is prolonged or severe, the decrease in blood flow and hence GFR will lead to acute tubular necrosis.

Renal causes

Renal causes of acute renal failure may be due to systemic disease or secondary to specific insults (*Table 1.3*).

Table 1.3 Renal causes of acute renal failure

Systemic disease
SLE
HSP
Sarcoid

Surgical / trauma
Pancreatitis
Aortic aneurysm repair
Burns
Rhabdomyolysis

Glomerular causes
Vasculitis (e.g. Wegener's granulomatosis)
Infective (e.g. endocarditis)
Primary glomerulonephritis (e.g. IgA nephropathy)

Interstitial causes
Drug related (e.g. aminoglycosides, NSAIDS, diuretics, anti-epileptics)
Systemic disease (e.g. SLE)

HSP = Henoch–Schönlein purpura; IgA = immunoglobulin A; NSAID = non-steroidal anti-inflammatory drug; SLE = systemic lupus erythematosus

Post-renal renal failure

Post-renal renal failure is otherwise known as obstructive uropathy. It may occur as a result of malignant obstruction, either by local spread of prostatic or bladder malignancy, or by secondary infiltration of the retroperitoneum causing malignant retroperitoneal fibrosis. Tumours that commonly

metastasize to the retroperitoneum include adenocarcinoma of the breast and colorectal tumours. Stone disease only rarely causes obstructive uropathy, either by causing ureteric obstruction to patients with a solitary renal unit, or in the case of large bilateral staghorn calculi obstructing both kidneys. More distal causes include benign prostatic hyperplasia or urethral stricture causing chronic high pressure retention of urine leading to bilateral hydroureters and hydronephrosis.

Chronic renal failure

Chronic renal failure is a progressive deterioration in renal function over a long time-scale, which may be over a period of many years. Ultimately the chronic renal failure may progress to end-stage renal failure, where death is inevitable if renal replacement therapy is not implemented. There are a number of clinical manifestations. The patient can be asymptomatic until the GFR is below 20. Features such as nocturia and metabolic acidosis may be present. More specific features can be related to metabolic, excretory and endocrine sequelae.

Anaemia is common and the causes are multifactorial. A failing kidney is unable to produce sufficient erythropoietin, resulting in anaemia. Bone marrow function is depressed, resulting in decreased erythropoeisis and the life span of erythrocytes may diminish. Intake and absorption of iron is reduced because of the chronic disease state. Neuropathy may ensue, resulting in sensory, motor and autonomic neuropathies. Endocrine function is abnormal due to hyperparathyroidism. Hyperparathyroidism can also contribute to renal osteodystrophy, a metabolic bone disease, which produces a range of pathologies including osteomalacia, osteoporosis and osteosclerosis. An important cause of death in patients with chronic renal failure is from ischaemic heart disease. Hypertension is present in the majority of patients secondary to sodium retention, and atherosclerosis is accelerated. In late stages, a metabolic acidosis may ensue, leading to uraemia and convulsions (*Table 1.4*).

Ultimately, a patient with end-stage renal failure will require renal replacement therapy, whether in the form of dialysis or renal transplant.

Dialysis

Dialysis entails the exchange of solutes from the blood to a dialysis solution through a semipermeable membrane. This may be in the form of peritoneal dialysis or haemodialysis.

Table 1.4 Common causes of chronic renal failure

Congenital	Polycystic kidney disease Alports' syndrome
Acquired	Vascular Renal artery stenosis Hypertension Diabetes Glomerular disease (e.g. IgA nephropathy) Interstitial disease (e.g. sarcoid) Systemic inflammatory disease (e.g. SLE)
Idiopathic	

IgA = immunoglobulin A; SLE = systemic lupus erythematosus

Peritoneal dialysis uses the peritoneum as a semipermeable membrane and thus enables solute exchange between peritoneal capillaries and the dialysis solution. A Tenchkoff catheter is inserted into the peritoneum through which a dialysis solution is instilled. Chemical equilibrium is achieved after time and the fluid is removed from the abdomen. Continuous ambulatory peritoneal dialysis describes the commonest regimen by which 2 litres of solution are exchanged four times a day.

Haemodialysis

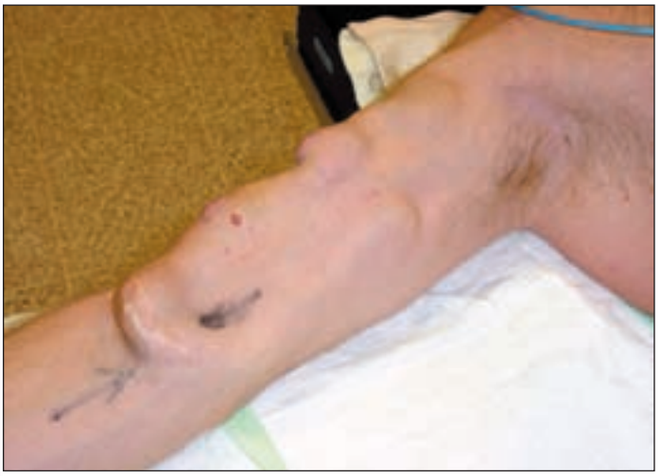
In haemodialysis, blood is taken from the body and passed through a dialysis machine that contains a semipermeable membrane. Blood is then returned to the body. The patient usually dialyses three to four times a week. In order to perform haemodialysis, appropriate vascular access is required. In the short term wide bore central venous catheters can be used but in the long term a more permanent solution is needed. An arteriovenous fistula or prosthetic graft may provide a more permanent needling site (**1.14**).

Steal syndrome is a complication of an arteriovenous fistula. Blood is 'stolen' from the palmar arch and this can ultimately lead to necrosis of the digits (**1.15**).

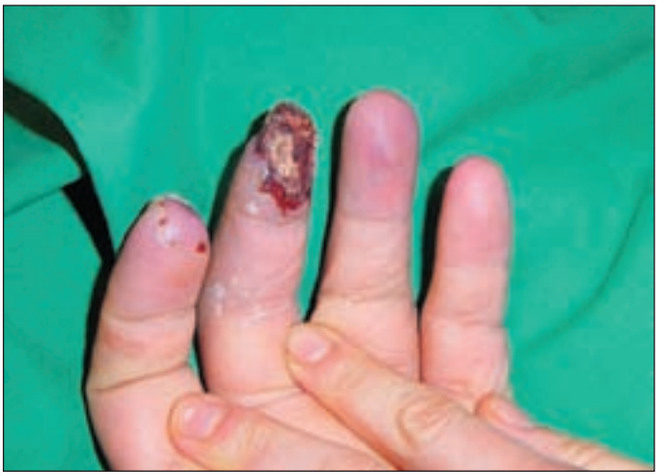
Renal transplantation

The ideal management of end-stage renal failure is renal transplantation. This enables patients to lead a near normal

life. The costs associated with transplantation are considerably less that lifelong dialysis. Transplants may originate from cadaveric or living (related or unrelated) donors (*Table 1.5*). Patients must undergo lifelong immunosuppression.



1.14 Arteriovenous fistula for renal access demonstrating aneurysm formation.



1.15 Steal syndrome.

Table 1.5 Renal transplantation: 5-year survival of graft and patients

	Cadaveric transplant	Living donor transplant
Graft survival	66.7%	80.2%
Patient survival	81.1%	90.2%

Source: US Scientific Registry of Transplant recipients

Further reading

Blandy J (1997). *Lecture Notes on Urology*. Blackwell Science, Oxford.

Cockcroft DW, Gault MH (1976). Prediction of creatinine clearance from serum creatinine. *Nephron* **16**: 31–41.

Davison AMA, Cameron JS, Grunfeld J-P, Ponticelli C, Van Ypersele C, Ritz E, Winearls C (eds) (2005). *Oxford Textbook of Clinical Nephrology*. Oxford University Press.

Laupacis A, Keown P, Pus N, Krueger H, Ferguson B, Wong C, Muirhead N (1996). A study of the quality of life and cost-utility of renal transplantation. *Kidney Int* **50**: 235–242.

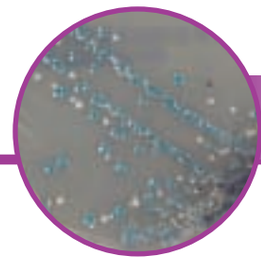
Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* **130**: 461–470.

O'Reilly PH (1986). Diuresis renography 8 years later: an update. *J Urol* **136**(5): 993–999.

O'Reilly PH, Testa HJ, Lawson RS, Farrar DJ, Edwards EC (1978). Diuresis renography in equivocal urinary tract obstruction. *Br J Urol* **50**(2): 76–80.

Walsh PC, Retik AB, Darracott Vaughan E, Wein AJ (2002). *Campbell's Urology*, 8th edition. WB Saunders, Philadelphia.

Warrell D, Cox TM, Firth JD, Benz EJ (2004). *Oxford Textbook of Medicine*. Oxford University Press.



Chapter 2

Urinary Tract Infection

Samih Al-Hayek

Definitions

Urinary tract infection (UTI) is currently defined as the inflammatory response of the urothelium to bacterial invasion usually associated with bacteriuria and pyuria.

Bacteriuria is the presence of bacteria in the urine. This can be symptomatic or asymptomatic.

Pyuria is the presence of white blood cells (WBC) in the urine, which indicates inflammation of the urothelium. This could be due to bacterial infection or other pathology such as tumour, stones, foreign body or tuberculosis.

In 1960 Edward Kass proposed defining UTI based on the finding of at least 10^5 bacteria colonies/ml of urine regardless of symptoms. He found that a single culture of 10^5 cfu/ml or more had a 20% chance of representing contamination. Since then, it has been shown that about 20–40% of women with symptoms of UTI have bacterial counts of less than 10^5 (Stamey *et al.*, 1965). In men, counts as low as 10^3 cfu/ml of a pure or predominant organism have been shown to be significant in voided urine (Lipsky *et al.*, 1987). Where there is evidence of contamination, a carefully collected repeat specimen should be examined.

In children, confirmation of UTI is dependent on the quality of the collected specimen. Negative cultures or growth of $<10^4$ cfu/ml from bag urine may be diagnostically useful. However, counts of 10^5 cfu/ml should be confirmed by culture of a more reliable specimen. This could be either a single urethral catheter specimen or, preferably, a suprapubic aspirate (SPA). Bacteriuria usually exceeds 10^5 cfu/ml in SPAs from children with acute UTI (Ginsburg and McCracken, 1982).

For patients with indwelling catheters, urine cultures may not reflect bladder bacteriuria because sampled organisms may have arisen from biofilms on the inner surface of the catheter.

In conclusion, when making a diagnosis of UTI, the patient's clinical condition and symptoms should be taken into account. A count of $>10^5$ cfu/ml is likely to be associated with UTI regardless of symptoms. However, lower counts of 10^2 cfu/ml may be potentially significant in symptomatic patients, regardless of sex. A pure isolate of between 10^4–10^5 cfu/ml needs to be evaluated on clinical information or confirmed by repeat culture.

Classification

The main classification of UTI is (1) complicated and (2) uncomplicated. Uncomplicated UTI occurs in healthy patients with a structurally and functionally normal urinary tract. UTIs can also be classified anatomically into lower (cystitis, urethritis, prostatitis, epididymitis or orchitis) or upper tract infection (pyelonephritis).

Complicated UTI occurs in patients with underlying anatomical or functional abnormality (*Table 2.1*). Complicated UTIs can take longer to eradicate and tend to recur.

Clinical manifestations

Acute uncomplicated cystitis usually occurs in young women. It is an infection of the bladder that has an abrupt onset and produces severe symptoms that are usually accompanied by pyuria and bacteriuria. Symptoms include frequency, dysuria, urgency, nocturia, haematuria and occasionally incontinence. Uncomplicated cystitis can occur in some men.

Acute urethral syndrome occurs in women with acute lower urinary tract symptoms with either a low bacterial

Table 2.1 Conditions predisposing to complicated UTI (Johnson and Stamm, 1987)

Structural/anatomical:
Urethral stricture
Ureteric stricture
Bladder diverticulum
Fistulae
Urinary diversion

Functional:
Neurogenic bladder (incomplete emptying due to dyssynergia)
Bladder outflow obstruction (e.g. prostatic enlargement)
Vesicoureteric reflux

Foreign bodies:
Indwelling catheter
Ureteric stents (**2.1**)
Nephrostomy tube
Urolithiasis

Other:
Pregnancy
Diabetes mellitus
Immunosuppression
Hospital-acquired infection
Chronic renal disease
Adult polycystic disease
Renal transplantation
Malignancy

count or without demonstrable bacteriuria or vulvovaginal infection.

Acute pyelonephritis (pyelitis) is an inflammatory process of the kidneys and adjacent structures. Symptoms include loin or abdominal pain and fever. Symptoms of cystitis may also be present. Severity ranges from mild disease to full blown Gram-negative sepsis with a few patients developing complications such as intrarenal and perinephric abscess. Such cases often require aggressive diagnostic and therapeutic measures.

Chronic pyelonephritis (chronic interstitial nephritis, or reflux nephropathy) is the second commonest cause of end-stage renal failure. It is thought to be a result of renal damage caused by UTI in infants and children with vesicoureteric reflux (VUR), or in adults with obstructive uropathy. However, it is still unclear whether recurrent infection causes progressive kidney damage.

Perinephric abscess is an uncommon complication of UTI, affecting patients with one or more anatomical or physiological abnormalities. The abscess may be confined to the perinephric space or may extend into adjacent structures. Pyuria, with or without positive culture, is seen on examination of urine. Patients may present with swinging fever, back or loin pain, and very occasionally with loin fistula. Causative organisms are usually Gram-negative bacilli but can also be staphylococci or *Candida* species. Mixed infections have also been reported.

Pyonephrosis results from bacterial infection of an obstructed ureter such as with a ureteric stone. Patients usually present with symptoms of pyelonephritis but will also usually have signs of obstruction on imaging. Diagnosis is made from blood culture or pus drained from the kidney. It is a urological emergency and draining the kidney is the first line of treatment.

Renal abscesses are localized in the renal cortex and may occur as a result of *Staphylococcus aureus* bacteraemia but they can also happen as a complication of acute pyelonephritis caused by Gram-negative bacilli. Pyuria may be present, but urine culture is usually negative.

Urethritis is common in both male and female patients. It is often associated with UTI and occasionally with bacterial prostatitis.

Male urethritis is commonly caused by sexually transmitted diseases (STD) and is associated with urethral discharge. The main organisms responsible are: *Neisseria gonorrhoeae* (gonococcal urethritis), *Chlamydia trachomatis* and *Ureaplasma urealyticum* (non-gonococcal urethritis or NGU).

Female patients may present with acute urethral syndrome or urethrocystitis caused by enterobacteria, *Staphylococcus saprophyticus* and less commonly by *C. trachomatis* and *N. gonorrhoeae*.

Prostatitis is an inflammation of the prostate gland. Routes of infection of the prostate include ascending urethral infection, reflux of infected urine into the prostatic ducts that empty into the posterior urethra, invasion of rectal bacteria by direct extension or by lymphatic spread or by haematogenous spread.

Acute bacterial prostatitis presents as an acute, febrile illness with marked constitutional and genitourinary symptoms. Chronic bacterial prostatitis is less dramatic and

features relapsing, recurrent UTIs, caused by the organisms persisting in the prostatic secretions despite antimicrobial therapy. Chronic bacterial prostatitis is less common than non-bacterial prostatitis. Bacterial prostatitis is associated with UTI. Organisms responsible are similar to those that cause UTI.

Pathogenesis

UTI is a result of a disturbed balance between the host defence and the infective organisms (**2.2**). If the host defence is strong, an increased bacterial virulence is needed to cause infection; however, if the patient's defence is weakened, bacteria with minimal virulence will be able to cause infection. Virulence is the degree of pathogenicity of the organism concerned.

2.1 A ureteric stent removed from a patient.

Host factors

Most UTIs are ascending. Women are at greater risk than men because they have a shorter urethra and this sits in close proximity to the introitus. The preputial sac of uncircumcised men may harbour urinary pathogens especially *Proteus* causing ascending infection.

An important protective factor is dilution from fresh uninfected ureteric urine and then voiding, which must be complete. Stasis of urine increases the risk of UTI.

Factors that predispose an individual to UTI are summarized in *Table 2.2*.

Bacterial Virulence	Host Defence
Adhesion: type 1 pili (cystitis) and MRHA fimbrae (pyelonephritis)	Urine (low osmolality and pH, urine salt, urea and organic acids, Lactoferrin)
Resistance to serum bactericidal activity	Urine flow and micturition
High quantity of K-antigen	Vaginal flora: lactobacilli
Siderophore aerobactin expression	Urinary tract mucosa (bactericidal activity, cytokines)
Cytotoxic necrotizing factor type I proteolytic toxin	Urinary inhibitors of bacterial adherence
Capsule and lipopolysaccharide	Tamm-Horsfall protein
Haemolysine (06:H31) for pyelonephritis	Bladder mucopolysaccharide
	Low-molecular-weight oligosaccharides
	Secretory immunoglobulin A (IgA)
	Inflammatory response
	Polymorphonuclear neutrophils (PMNs)
	Cytokines (IL6 and 8)
	Humoral immunity
	Cell-mediated immunity
	Epithelial cell receptivity: HLAs and blood group antigens
	Miscellaneous
	Vaginal secretions
	Prostatic fluid

2.2 Host and virulence factors in UTI. HLA = human leukocyte antigen; IL = interleukin; MRHA = mannose-resistant haemagglutinin.

Many pregnant women have asymptomatic bacteriuria (about 5%). If not treated, 30% may develop into acute pyelonephritis.

Diabetic women have a higher incidence of asymptomatic bacteriuria than non-diabetic women. There is no difference in the prevalence of bacteriuria between diabetic and non-diabetic men. Bladder dysfunction as a result of diabetic neuropathy may play a part as a predisposing factor in the high prevalence of UTI. UTIs tend to be more severe in diabetics.

Bacteriuria occurs in 10–20% of catheterized patients but UTI occurs in only 2–6%. Bacteraemia develops in 1–4% of catheterized patients with UTI. This has a mortality of 13–30%. Infecting organisms may originate from the patient's perineal flora or the hands of healthcare staff during catheterization. It might be introduced via the periurethral route along the external catheter surface, or the intraluminal route as a consequence of faulty catheter care. In patients catheterized long term (>30 days), prevalence of bacteriuria is virtually 100%, infecting strains change frequently and polymicrobial bacteriuria may be present. Treatment of asymptomatic bacteriuria has not been shown to be of any benefit in reducing complications in these catheterized patients and is likely to encourage the emergence of resistant strains (Warren *et al.*, 1982).

Table 2.2 Risk factors for UTI

1 Congenital:
Duplex kidney
Horseshoe kidney
Dysplastic kidney
Pelviureteric junction obstruction
Vesicoureteric reflux
Obstructive megaureter
Ectopic ureters
Urethral valves

2 Structural:
Cystocoele
Urethral diverticulum
Bladder diverticulum
Urinary diversion
Renal transplant
Instrumentation
Foreign bodies (urethral catheterization)
Urinary tract stones
Female sex
Tumours
Uncircumcised men

3 Functional:
Bladder outflow obstruction
Detrusor underactivity
Detrusor dyssynergia

4 General conditions:
Age
Menopause
Pregnancy
Diabetes mellitus
Immunosuppression including steroid use
Malnutrition
Radiotherapy
HIV

5 Other:
Sexual intercourse
Spermicidal contraceptive gels
Diaphragm
Atrophic vaginitis
Other pelvic tumours
Mental impairment

6 Risk factors for UTI in post-menopausal women*:
Vaginal dryness
Urge incontinence
Pelvic prolapse
Incomplete bladder emptying
Previous childbirth
Diabetes

*Jackson *et al.*, 2004.

Bacterial virulence

Not all bacteria are able to adhere to the urothelium and cause infections. For *Escherichia coli*, only specific strains can cause UTI and these are known as O, K and H serogroups.

For an organism to cause infection, it has to adhere to the urothelial cell membrane. The most important mechanism of bacterial adherence is a filamentous protein appendage called the pilus or fimbria. These are classified according to the nature of the urothelial cell receptors to which they attach, termed as globosides and are composed of glycosphingolipids. Some fimbriae are dependent on the presence of mannose within the receptor molecules to cause invasion. Two types of pili are identified for *E. coli*:

- *Type 1:* binds to guinea pigs' blood and urothelium and is mannose sensitive. It is more involved in cystitis cases (Martinez *et al.*, 2000).
- *Mannose-resistant pili (P):* bind to globosides of glycolipids found on P-blood group antigens and on renal tubular cells. They mediate haemoagglutination of human red cells that is not altered by mannose and hence this is called mannose-resistant haemoagglutination (MRHA) and they are found in most pyelonephritis cases of *E. coli* (Roberts *et al.*, 1997).

Bacteria can undergo phase variation from fimbriated to non-fimbriated forms. The specific adhesin determines the degree and the site of invasion. The commonest is fimH adhesion at the tip of the type 1 fimbrae. This needs to attach to mannose receptors on the bladder wall situated on so-called uroplakin plaque. These cells undergo apoptosis and are shed into the urine with their adherent bacteria.

Adhesion is followed by proliferation, invasion and initiation of the inflammatory process. This results in the breakdown of the protective glycoprotein layer covering the urothelium, promoting colonization of the exposed deeper layers of mucosa.

A few factors mediate the persistence and dissemination of infection. They allow invasion and induce inflammation. These include toxins such as haemolysin, cytotoxin necrosing factors, the siderophore aerobactin, bacterial capsules and lipopolysaccharide.

The presence of a capsular acidic polysaccharide antigen (K antigen) in some *E. coli* strains in a high quantity enhances its ability to cause pyelonephritis (Whitfield and Roberts, 1999). It seems that this antigen protects the bacteria from phagocytosis with neutrophils.

Routes of infection

- *Ascending:* most infections of the urinary tract invade from the urethra to the bladder, up the ureter to the renal pelvis. VUR does not need to be present for this to take place.
- *Haematogenous:* infections can occasionally reach the kidney through the blood especially *Staph. aureus*, *Candida* and *Mycobacterium tuberculosis* infections.
- *Lymphatic:* from the adjacent organs through the rectal, colonic and periuterine lymphatics. This route is of doubtful significance.
- *Direct extension:* from adjacent organs. For example with vesicointestinal fistulae.

Bacterial spectrum (Table 2.3)

Most UTIs are caused by a single bacterial species. In general, bowel organisms can cause UTI. The majority of organisms are Gram-negative bacilli. The sick, elderly or immunosuppressed patients are susceptible to infections by a wider selection of organisms compared with fit patients.

E. coli is by far the most common cause of UTI causing about 85% of community-acquired and 50% of nosocomial UTIs with most strains being O serogroups.

Other Gram-negative organisms that cause UTI include *Proteus* and *Klebsiella*. Gram-positive organisms could also cause UTI such as *Enterococcus faecalis* and *Staphylococcus saprophyticus*. The latter usually occurs in young women, mainly in the summer months and almost certainly related to sexual activity accounting for about 10% of symptomatic UTIs in young women (Hovelius and Mardh, 1984). *Staph. saprophyticus* adheres to uroepithelial cells significantly better than *Staph. aureus* or other coagulase-negative staphylococci. Other coagulase-negative staphylococci are often considered as urinary contaminants as they are part of the normal perineal flora. However, they may cause complicated infections in patients of both sexes with structural or functional abnormalities of the urinary tract, prostatic calculi or predisposing underlying disease.

Streptococci rarely cause uncomplicated UTI, although Lancefield Group B haemolytic streptococci may cause infection in pregnancy.

Proteus mirabilis is associated with urinary tract abnormalities, particularly calculi. In hospital patients it may cause chronic infections.

The range of organisms causing UTI in children is slightly different from adults, with *Klebsiella* and *Enterobacter* being the more common causes of UTI.

Salmonella typhi and *S. paratyphi* are frequently isolated from urine in the early stages of typhoid and paratyphoid fever. Testing the urine should be performed in suspected cases of *Salmonella* infection. Urine samples taken from the patient's contacts should also be cultured in specific medium to exclude infection.

Hospital-acquired and complicated UTIs are frequently caused by *E. coli* and *E. faecalis* and those organisms mentioned above, in addition to uncommon organisms such as *Enterococcus* species (usually associated with instrumentation and catheterization), and *Pseudomonas aeruginosa* (associated with structural abnormality or long-term catheterization). *Staph. aureus* rarely causes infection and is associated with renal abnormality or as a secondary infection to bacteraemia, surgery or catheterization. It is frequently seen as a contaminant due to perineal carriage.

Mycobacterium tuberculosis and other *Mycobacterium* species may also infect the urinary tract. Less common causes include *Haemophilus influenzae*, *C. trachomatis*, *Mycoplasma hominis*, *U. urealyticum* and *Corynebacterium urealyticum*.

There is still debate over the role of fastidious organisms such as anaerobes, *Lactobacillus* species, *Gardnerella vaginalis* and fastidious streptococci.

Many viruses may be cultured from urine but apart from adenoviruses and BK virus, which have been implicated in haemorrhagic cystitis, herpes simplex and cytomegalovirus, their role remains uncertain.

Fungal infections are rare. Bladder colonization with *Candida* species is associated with indwelling catheters. *Candida albicans* is the most frequently isolated species.

Table 2.3 Common causative organisms of UTI

- *Escherichia coli*
- *Klebsiella* species
- *Proteus* species
- *Enterobacter* species
- *Staphylococcus saprophyticus*
- *Pseudomonas aeruginosa*

Biofilms

A biofilm is a group of microbes immobilized at a solid surface in a single or multiple layers and embedded in or surrounded by an organic polymer matrix, which is primarily of microbial origin (Reid, 1998).

They have been observed on ureteric stents and urinary catheters and form on the urothelium of the kidney to prepare for renal invasion. A biofilm will have matrix and bacteria in variable proportions (75–90% is made of matrix), depending on the organism. A mature biofilm is conventionally described as comprising three layers:

- *Linking film:* comprising the conditioning film (macromolecules from the body fluid) and the initial layer of bacteria that adhere to it using its fimbriae or a sticky polysaccharide capsule.
- *Base film:* consisting of slowly growing compact organisms.
- *Surface film:* this is made up from loosely attached bacteria and can give rise to planktonic organisms (present as individual organisms rather than communities).

The surface of the film can prevent the diffusion of detergents or antibiotics into the inner layers of the film, which makes it difficult to eradicate the bacteria. The films can exist in symptomatic or asymptomatic patients.

Investigations

Urine testing

Urine collection

Most of the female urethra and the distal part of male urethra are likely to be contaminated, whereas the bladder and upper tract should have no organisms. When collecting urine samples, precautions should be taken to avoid contamination by bacteria from the distal urethra.

- *Midstream urine (MSU):* collecting the urine sample after discarding the first few millilitres is the most commonly used way of collecting urine samples. Periurethral cleaning is recommended before collection but this is not of definite benefit.
- *Clean-catch urine:* is a reasonable alternative to MSU. Thorough periurethral cleaning is recommended. The whole specimen is collected into a sterile container and then an aliquot sent for examination.
- *Urethral catheterization:* the validation of the MSU specimen can be questioned if numerous squamous epithelial cells (indicative of preputial, vaginal or urethral contaminants) are present. In these cases, a midstream catheter-collected sample might be indicated. There is always the risk of catheter-induced bladder bacteriuria and UTI.
- *Suprapubic aspiration:* this method gives the highest degree of reliability. It is mainly used in infants. However, it is unpleasant for patients.
- *In children*, a bag placed over the genitalia can be used to collect urine but has the risk of contamination from the vagina and perirectal area. Negative culture is reliable but significant growth might need to be confirmed with suprapubic aspiration. Pad urine is an alternative collection method to bag urine for infants and young children. After washing the nappy area thoroughly, a pad is placed inside the nappy. As soon as the pad is wet with urine (but no faecal soiling), the tip of a syringe is pushed into the pad to draw urine into the syringe. If difficult, the wet fibres may be inserted into the syringe barrel and the urine squeezed directly into the container using the syringe plunger.
- *Other methods:* from ileal conduit, nephrostomy, urostomy, cystoscopy urine, ureteric urine or washout.

Three entire, first voided early morning urines are required for culture for *M. tuberculosis*.

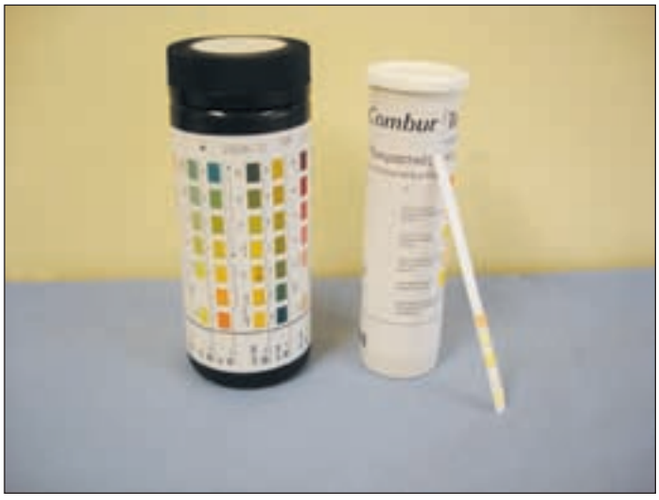
Diagnosis of *Schistosoma haematobium* may be undertaken on urine taken at a specific time coinciding with maximum egg secretion, or on the terminal portion of voided urine. The container should not have boric acid preservative in it. Haematuria is the most common presentation of *S. haematobium* infection.

Urine dipstick

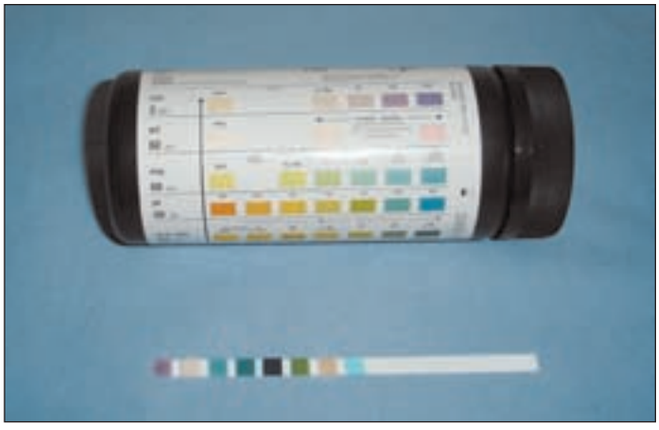
Urine dipstick is an easy, quick and cheap test. The test is informative but less sensitive than microscopic examination of urine. It is most useful for the screening of asymptomatic patients such as pregnant women. If all tests on the strip are negative, quantitative culture is probably unnecessary. However, this is controversial in fastidious organisms.

The stick can test for pH, blood, protein, glucose, white cells, ketones and nitrite (**2.3–2.5**, *Table 2.4*). When using the dipstick, urine should be fresh, should not have been centrifuged and should be at room temperature. A gentle mix throughout is recommended. A brief dip in the urine (about 1 second) is enough. Wait for about 1 minute before reading the results. Colour change that appears only at the edges of the dipstick strip or takes a long time (>2 min) to show has no diagnostic significance.

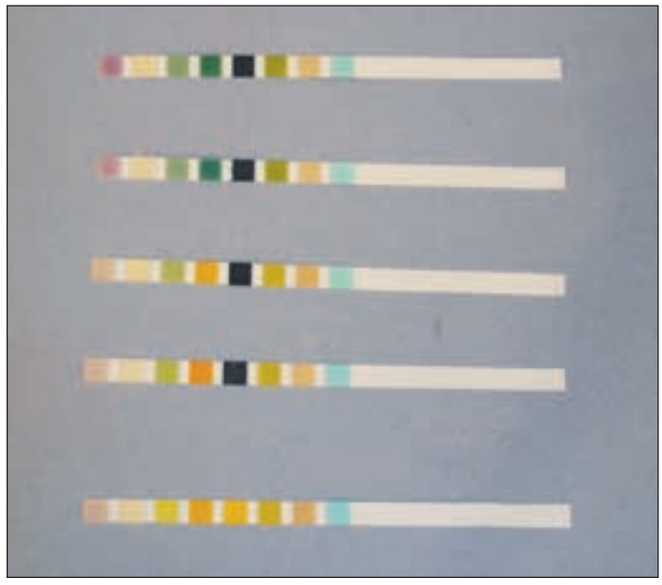
Reading colour changes in dipstick strips using colorimetric measurement is preferred, as results are more reliable, reproducible and free from observer error, particularly if



2.3 Two types of urine dipstick kit: basic tests (right) and extended range (left).



2.4 Urine dipstick showing a change in colour (positive) for leucocytes, nitrite, protein and blood, indicating UTI.



2.5 A range of urine dipstick results. The bottom one is the original stick (not dipped in urine); the two sticks above this show positive blood and protein; the top two sticks are positive for blood, protein and leucocytes.

an automated reading system is used. Boric acid and some antimicrobial agents such as nitrofurantoin and gentamicin will adversely affect the leucocyte esterase test.

Dipsticks may be more sensitive in detecting blood than microscopy as a result of the detection of haemoglobin released by haemolysis.

- *pH:* normal values vary between 4.5 and 8 (usually lying between 5 and 6). The test pad detects the hydronium ions. It contains the indicators methyl red, phenolphthalein and bromthymol blue.
- *Blood:* normal urine contains less than three red blood cells (RBCs) per high-powered field. Haemoglobin and myoglobin have a peroxidase-like activity and cause oxidation of a chromogen indicator. This changes colour when oxidized. So a positive dipstick indicates the presence of haemoglobin. The sensitivity of the test is more than 90% but specificity is lower. A false positive could be due to dehydration or because of menstrual blood, which can extend from 3 days before to 3 days after menstruation. Strenuous exercise might give a false positive. Ascorbic acid has no effect on the results. The presence of intact erythrocytes will be indicated by packed dots (usually green on the yellow test area), whereas haemoglobin, haemolysed erythrocytes and myoglobin will show as a uniform change of colour.
- *Protein:* normal protein concentration is <20 mg/dl. A tetrabromophenol blue dye on the dipstick changes into green in the presence of protein >20 mg/dl. This could indicate renal disease, multiple myeloma or can happen after strenuous exercise. False negative results may be obtained after infusion of blood substitute (polyvinylpyrrolidone) or collecting samples from a vessel that contains residues of disinfectants based on quaternary ammonium compounds or chlorhexidine.
- *Glucose:* the detection of glucose is based on the glucose oxidase/peroxidase reaction. The test is not dependent on pH, specific gravity of urine or presence of ketone

bodies. Ascorbic acid may have an effect but only in small concentrations of glucose.

- *Leucocytes:* a chromogen salt on the dipstick changes colour due to the leucocyte esterase produced by neutrophils. A false positive can occur in contamination while a false negative can occur in glycosuria, urobilinogen or consumption of a large amount of ascorbic acid. The leucocyte esterase dipstick has a reported sensitivity of 75–96% in detecting pyuria associated with infection.
- *Ketone bodies:* some strips have an indicator for ketone bodies.
- *Nitrite test:* nitrites are not normally present in urine and their detection indicates bacteriuria. Gram-negative bacteria convert nitrates to nitrites, which react with the reagents on the dipstick forming red dye. The sensitivity is not great (35–85%) but the test has very good specificity (>90%). Some Gram-negative bacilli (e.g. pseudomonas) and faecal streptococci (e.g. enterococcus) do not reduce the nitrate, so they will give false negative results.

In a study by Little *et al.* (2006) only nitrite, leucocyte esterase (more than just a trace), and blood (haemolysed trace or greater) independently predicted diagnosis (adjusted odds ratios: 6.36, 4.52, 2.23 respectively). A dipstick decision, based on having nitrite, or both leucocytes and blood, was moderately sensitive (77%) and specific (70%); positive predictive value (PPV) was 81% and negative predictive value (NPV) was 65%. Predictive values were improved by varying the cut-off point: NPV was 73% for all three dipstick results being negative, and PPV was 92% for having nitrite and either blood or leucocyte esterase.

Microscopy

The urine should be tested microscopically for RBCs, white blood cells (WBCs), casts, crystals and bacteria. The sample can be surveyed using a simple microscope or with enhanced facilities such as a mirror slide with grid and an inverted phase contrast microscope. Microscopy is mainly used in symptomatic patients to assist in the interpretation of culture results. It is not needed in screening asymptomatic patients. In the past, microscopy of uncentrifuged, unstained urine has been used as a method of screening for bacteriuria without the need for culture, but it is unreliable for $<10^4$–cfu/ml. The sensitivity increases if the specimen is centrifuged and/or stained.

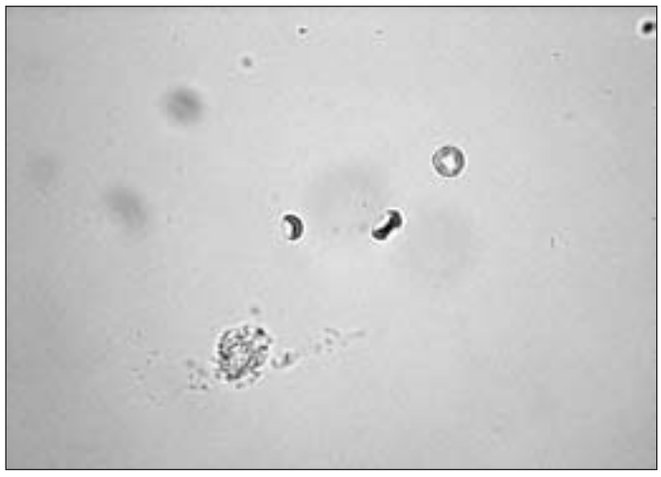
Red blood cells

If the RBCs come from the glomerulus then they will be distorted, whereas those derived from the tubules or lower urinary tract will be a normal shape (**2.6**).

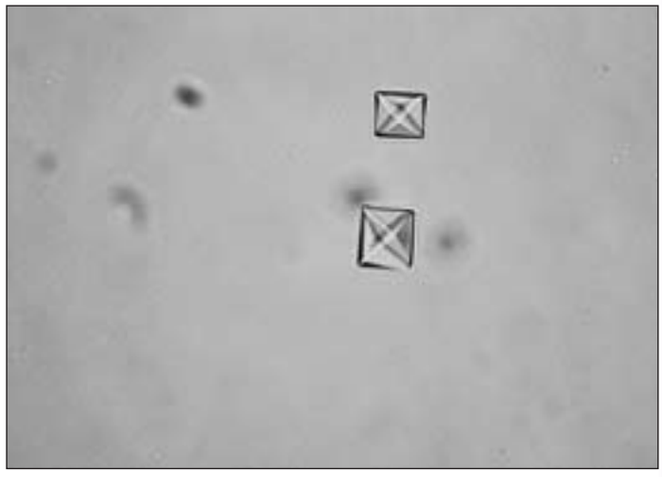
Table 2.4 Urine dipstick testing

Test	Principle	Indicates	False positive	False negative	Sensitivity	Specificity
Blood	Peroxidase-like activity of haemoglobin	Haemoglobin >3 RBC/HPF	Menstruation, dehydration, strenuous exercise		>90%	
Protein	Tetrabromophenol blue dye	Protein >20 gm/dl	Blood substitute, residues of disinfectants		90%	
WBC	Esterase from neutrophils	Pyuria	Contamination	Concentrated urine, glycosuria, urobilinogen, high ascorbic acid intake	75–96%	
Nitrite	Nitrate is converted to nitrite	Bacteriuria	Contamination	Smaller concentration of bacteria, pseudomonas and enterococcus	30–85%	>90%
pH	Hydronium ions	Normal is 4.5–8			>95%	

HPF = high-powered field



2.6 Light microscopy of red blood cells.



2.7 Calcium oxalate crystals.

Casts

Casts are cylindrical protein mouldings formed in the renal tubules and often indicate renal pathology but are less useful in differentiating between types of renal disorders.

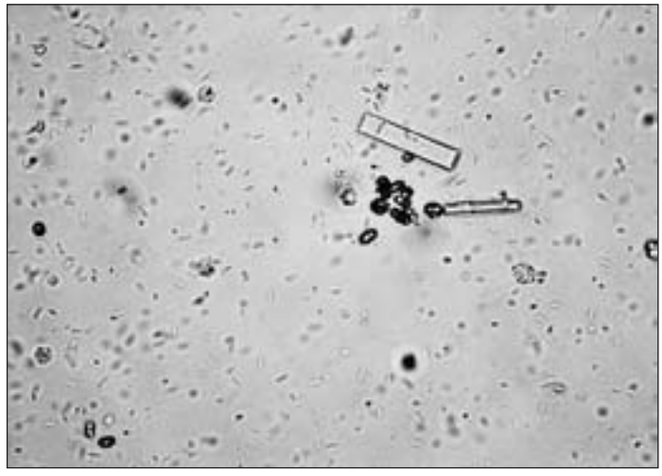
Large numbers of hyaline casts are associated with renal disease but may be found in patients with fever or following strenuous exercise. Cellular and densely granular casts indicate pyelonephritis or glomerulonephritis. RBC casts usually indicate glomerular bleeding and are excreted in large numbers in the acute phase of post-streptococcal nephritis or rapidly progressive nephritis. Less commonly seen epithelial cell and fatty casts accompany acute tubular necrosis and nephrotic syndrome.

Crystals

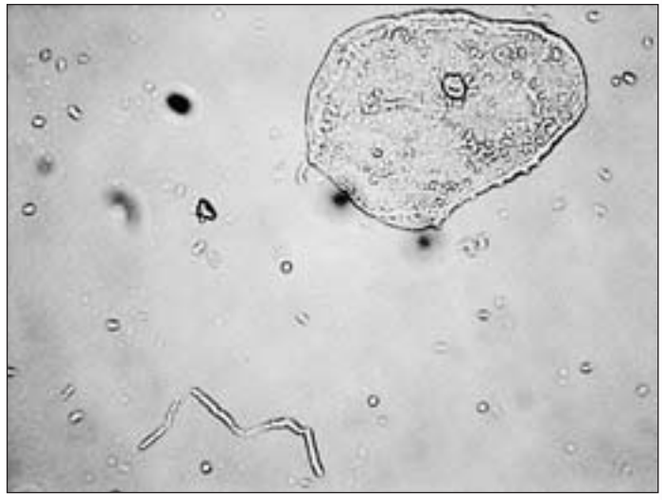
Specific crystals (**2.7**, **2.8**) may precipitate in acidic urine (such as cysteine, uric acid, calcium oxalate), whereas others may precipitate in alkaline urine (calcium phosphate and triple phosphate). Crystals may be asymptomatic or may be associated with the formation of urinary tract calculi. They may help in diagnosing the underlying problem.

Bacteria

A negative urinalysis for bacteria never excludes the presence of bacteria in numbers of 30 000/ml and less. There is a chance of a false positive result where bacteria are seen in the microscopic sediment but the urine culture shows no growth. This mainly happens in females as voided urine may contain many thousands of lactobacilli and corynebacteria. These bacteria are readily seen under the microscope, and although they are Gram-positive, they often appear

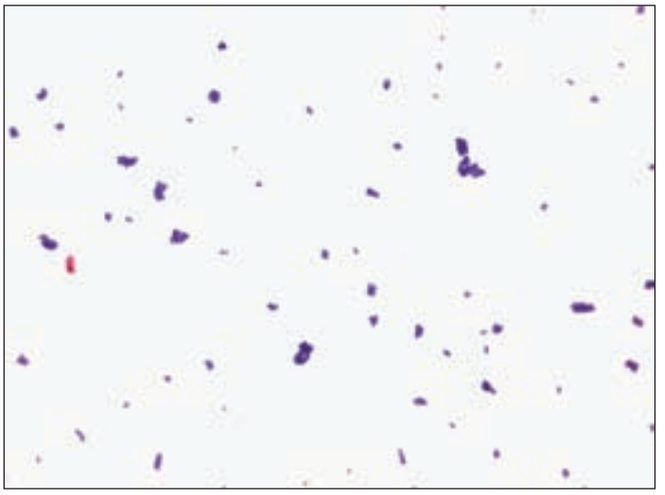


2.8 Light microscopy demonstrating crystals, red and white blood cells and bacteria.

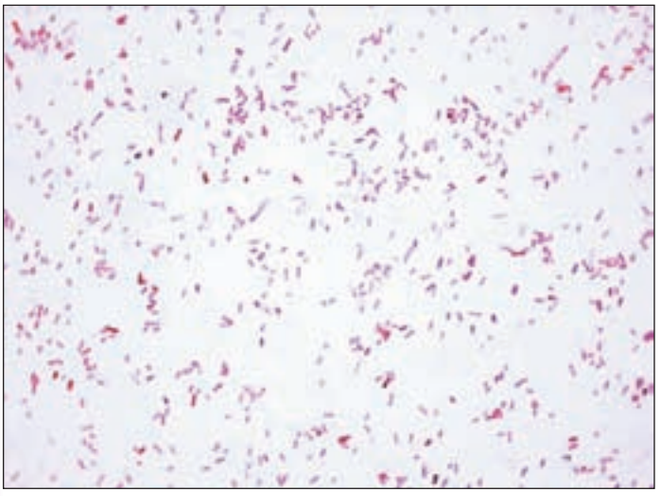


2.9 Light microscopy of red blood cells and bacteria (bottom left).

Gram-negative (Gram-variable) if stained. Strict anaerobes, usually Gram-negative bacilli, also make up a significant mass of the normal vaginal flora. A heavy presence of epithelial cells without organisms may indicate contramination (**2.9**). Gram stain may be useful on urgent specimens with pyuria to identify the infecting organism (**2.10**, **2.11**).



2.10 Gram-positive cocci on light microscopy.



2.11 Gram-negative bacilli on light microscopy.

White blood cells

The absence of pyuria should make the diagnosis of UTI doubtful until urine culture data are available. However, as mentioned before, pyuria can be found in a few conditions other than UTI. Significant pyuria is defined as the occurrence of 10^7 or more WBC/l (10^4 WBC/ml) although higher numbers of WBC are often found in healthy asymptomatic women. A level of $>10^8$ WBC/l ($>10^5$ WBC/ml) has been suggested as being more appropriate in discriminating infection. Pyuria is present in 96% of symptomatic patients with bacteriuria of $>10^8$ cfu/l (10^5 cfu/ml), but only in <1% of asymptomatic, abacteriuric patients. It should be determined accurately in uncentrifuged urine.

Urine culture

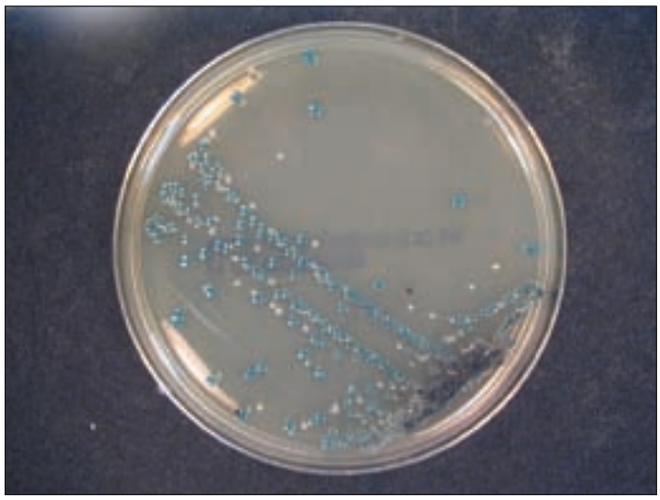
The urine should be cultured immediately after being collected in a sterile container. If that is not possible, the sample should either be refrigerated at 4°C or boric acid preservative should be added to the urine. Even then, the urine needs to be tested within 24 hours to reduce the risk of multiplication of organisms. A specific amount of urine is spread on a culture plate and the number of colonies per millimetre of urine are counted as colony forming units (cfu/ml).

Two techniques for urine culture are available. Direct surface plating of a known amount of urine on split-agar disposable plates (**2.12**–**2.14**) is the traditional quantitative culture technique used by most microbiology laboratories. One half of the plate is blood agar, which grows both Gram-positive and Gram-negative bacteria, and the other is desoxycholate or eosin–methylene blue (EMB), which grows Gram-negative bacteria (some of them, such as *E. coli,* in a very characteristic manner). Simple curved-tip eye-droppers are sufficient to deliver about 0.1 ml of urine onto each half of the plate. After overnight incubation, the number of colonies is estimated, often identified (after some experience), and multiplied by 10 to report the number of cfu/ml of urine. Different bacteria may produce distinctive colonies that help when making the diagnosis (*Table 2.5*, **2.12**–**2.14**)).

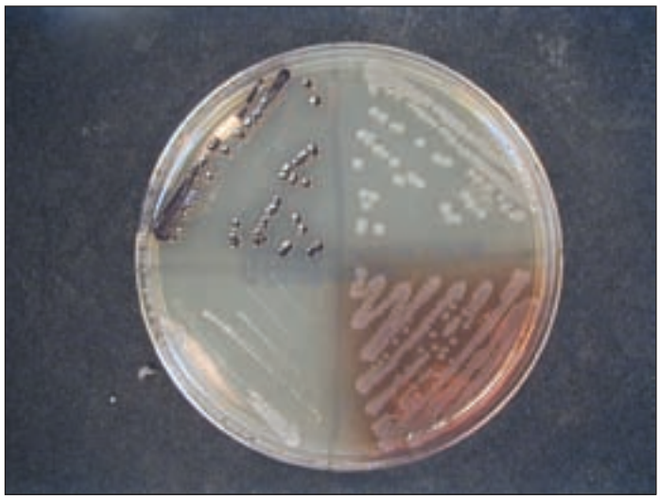
A simpler but somewhat less accurate technique is the use of dip-slides. These inexpensive plastic slides are attached to screw-top caps; they have soy agar (a general nutrient agar to grow all bacteria) on one side and EMB or MacConkey's agar for Gram-negative bacteria on the opposite side. A slide is dipped into urine, the excess is allowed to drain off, and the slide is replaced in its plastic bottle and incubated. The volume of urine that attaches to the slide is between 1/100 and 1/200 ml. Hence, the colony count is 100–200 times the number of colonies that become visible with incubation. In actual practice, the growth is compared with a visual standard and reported as such. The species of bacteria is more difficult to

Table 2.5 Characteristics of bacterial colonies

Organism	Colony colour	Ferments lactose
Escherichia coli	Metallic green	Yes
Coliform	Black/colourless	
Enterococcus	Black	Yes
Klebsiella pneumoniae	Black	Yes
Serratia marcescens	Red pigment	No
Proteus	Brown	No
Pseudomonas aeruginosa	Blue green pigment and fruity odour	No
Salmonella	Colourless	
Staphylococcus aureus	Cream/white	
Group B streptococci	Cream	
Yeast	White	



2.12 Harlequin CLED (chromogenic) medium showing a mixed growth of organisms. The black colonies are *Enterococci*, the white colonies are *Staphylococci* and the green colonies are *Escherichia coli*.



2.13 Organisms isolated from different MSU samples. Clockwise from top right: coliforms (colourless), *Proteus* (brown with halo), yeasts (white) and *Klebsiella* (black).

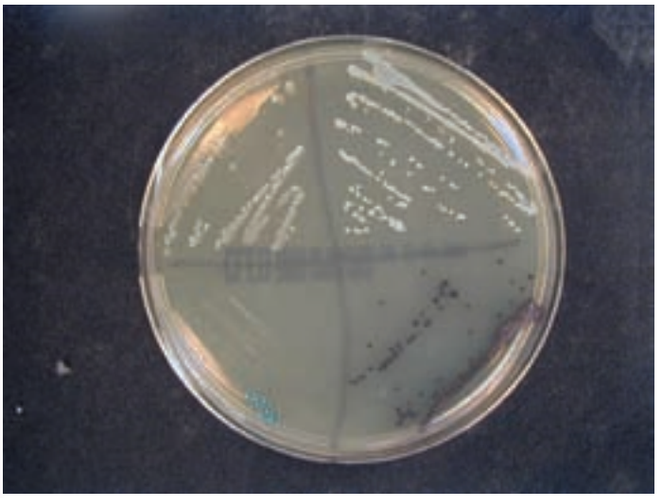
recognize when this technique is used, but the technique is completely adequate.

One advantage to the dip-slide is the ease with which the urine can be immediately cultured without the necessity of refrigeration. Patients can culture their own urine at home, keep the slide at room temperature, and bring it to the office within 48 hours.

Localization of the infection

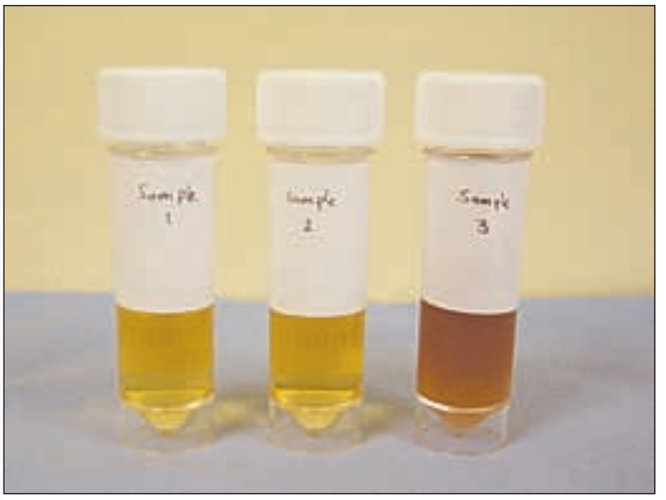
Few tests were used to identify the site of infection. Practically, these tests are rarely used with the advance of imaging and the ability to treat infections readily with antibiotics.

A sample of urine collected from a ureteric catheter after bladder washout could differentiate cystitis from renal infection.



2.14 Organisms isolated from different MSU samples. Clockwise from top right: *Staphylococci* (white/cream), *Enterococci* (black), *Escherichia coli* (green) and *Pseudomonas aeruginosa* (colourless, with no clear edges).

In men, staged urine sampling, described by Meares and Stamey (1968), can be used. A positive sample taken at the start of the void represents urethral infection. A positive midstream sample reflects cystitis. The prostate is then massaged (expressed prostatic secretions) and the patient produces a urine sample, which indicate prostatic infection if positive (**2.15**).



2.15 Collected urine samples based on the Meares–Stamey method. Sample 1: initial void (for urethritis). Sample 2: midstream (for cystitis). Sample 3: after prostatic massage (for prostatitis).

Other immunological tests were used including agglutination tests, enzyme-liked immunosorbent assay (ELISA) and radioimmunoassays for immunoglobulins.

Other investigations

Simple one-off lower UTI does not usually need further investigation. However, in some cases more investigations are needed. These are:

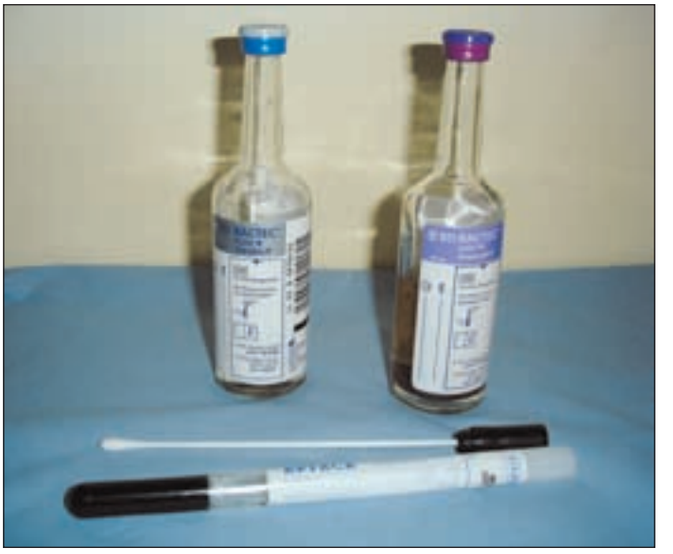
- Upper UTI with possible pyelonephritis or perinephric abscess.
- Recurrent UTIs.
- Pregnant women.
- UTI with possible obstructed urinary tract.
- Symptoms or signs indicating complicated UTI such as renal colic, renal failure or diabetes.
- UTI with unusual or resistant organism suggesting complicated UTI.
- No response to treatment.

Blood culture and urethral swab

If the patient develops a high fever or signs of septicaemia, a blood culture should be done. A urethral swab is needed if there is suspicion of urethritis or in the presence or urethral discharge (**2.16**).

Urodynamics

A simple flow test will assist in estimating flow pattern (obstructive or not) and post-void residual indicating stasis.



2.16 Blood culture bottles and urethral swab.

Standard pressure–flow studies can distinguish between obstructive causes of stasis and detrusor underactivity.

Plain X-ray

A plain X-ray film of the kidneys, ureters and bladder (KUB) might show radio-opaque calculi or absent psoas shadow suggesting abscess.

Ultrasound scan

Easy, quick, non-invasive and has no risk of radiation. It is useful to check for hydronephrosis, pyonephrosis and perirenal abscess.

Intravenous urography

This is useful in confirming the presence and the location of urinary tract obstruction but has limitations and many units now use computed tomography instead.

Voiding cystourethrogram

This is to check for VUR or urethral diverticulum.

Computed tomography

This is more sensitive than intravenous urography or ultrasonography in the diagnosis of acute focal bacterial nephritis and renal and perirenal abscesses.

Radionuclide studies

Hippuran I-131 and technetium Tc-99m glucoheptonate scans are used to detect focal parenchymal damage, renal function impairment and decreased renal perfusion in acute renal infections. Two radionuclides that have been used to detect renal or perirenal infections are gallium 67 and indium 111.

Screening for UTI

There is no justification for asymptomatic bacteriiuria screening in the general population as the effect of prolonged asymptomatic bacteriuria is not clear. However, in some cases, screening for asymptomatic bacteriuria is recommended:

- Young infants with family history of congenital uropathy to prevent renal damage.
- During pregnancy as covert bacteriuria has serious consequences.
- Diabetic patients.

Treatment

Principles

The aim when treating UTI is to eradicate the infection. This depends on the level of antimicrobials in the urine and not in the serum. If the correct antimicrobial agent is used, then the urine should show no bacterial growth within 24 hours of starting the treatment. Treating UTI in as short a period as possible and with the smallest effective dose of antibiotic(s) is ideal in reducing the risk of resistance.

Bacterial resistance

Antibiotic resistance is a major healthcare problem. It usually emerges as a result of inappropriate use of antibiotics. Organisms may be resistant to a single or to multiple antibiotics. This makes it difficult to eradicate the infection.

The resistance could be natural, due to mutants or transferable.

- *Natural resistance:* the organism is not susceptible to the antimicrobial used. For example, *Proteus* is always resistant to nitrofurantoin.
- *Mutants:* a resistant organism exists in a small quantity to start with but increases in numbers and will show during culture while treating the main bacteria. The way to reduce this resistance is to hydrate the patient well and to dilute the urine in order to decrease the concentration of bacteria. It is also better to use antibiotics that have their maximum concentration in the urine.
- *Transferable resistance:* this is presented with extrachromosomal plasmid-mediated factor (r-factor). It is the most common cause of resistance and can cause multiple resistances. It mainly occurs in the faecal flora before infecting the urinary tract.

When treating UTI and choosing the right antibiotics, a few factors should be considered. Some of these are related to the actual causative bacteria and some are related to the patient (*Table 2.6*).

- *Screening for antimicrobial substances*. This is a subject of debate but may be useful in patients with significant pyuria and culture showing insignificant or no growth.
- *Antibiotic susceptibility testing*. Results should be interpreted carefully and should only be reported if the inoculum size is correct, one organism predominates, and there is no evidence of an antimicrobial agent in

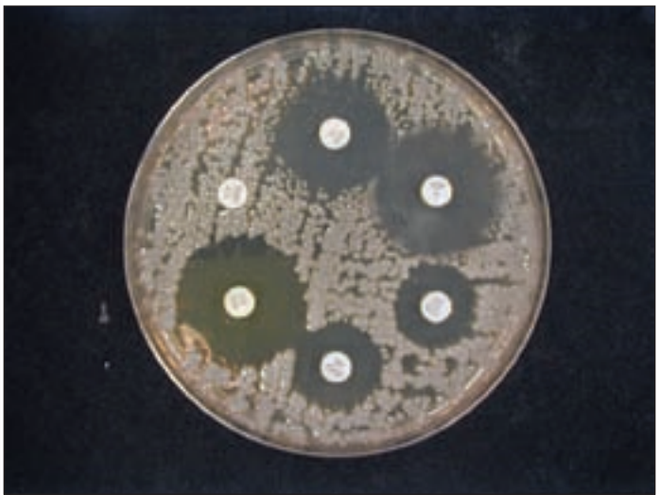
the specimen. Breakpoint sensitivities using multipoint inoculation are not recommended for mixed cultures (**2.17**, **2.18**).

Acknowledgments

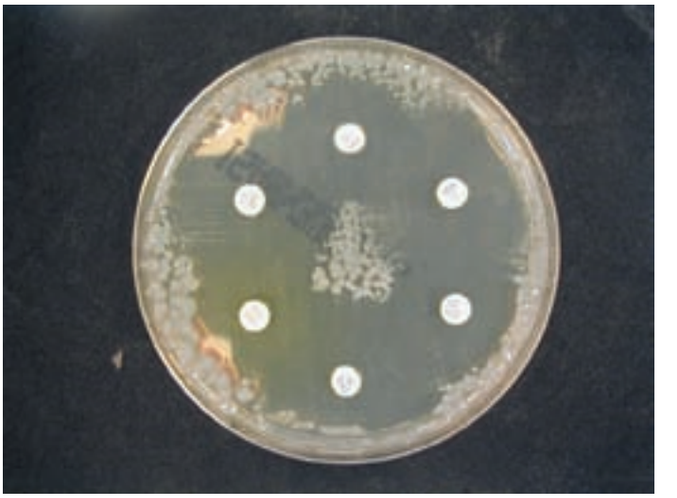
The author is extremely grateful to the staff at the department of pathology and microbiology at Weston General Hospital for their help in obtaining most of the slides, in particular to Elisa Holman, Andrew Garry, Jon Mitchell and to Dr David Paterson.

Table 2.6 Factors influencing antibiotic choice

Bacteria factors	Patient factors
Single or multiple organisms	Age
Normal flora or pathogens	Previous infection sensitivity
Antibiotic susceptibility	Underlying diseases
	Renal or hepatic impairment
	Allergy
	Inpatient or community
	Site of infection
	Concomitant medications
	Pregnancy



2.17 Disk diffusion sensitivity testing for routine coliforms. The antibiotics used here are Nitrofurantoin, Trimethoprim, Gentamicin, Ciprofloxacin, Cephalexin and Cefpodoxime. The zones are measured against a template: in this case, the coliforms are resistant to Trimethoprim (TMP).



2.18 Disk diffusion sensitivity testing: the coliform is fully sensitive to the six routine antibiotics seen in **2.17**.

References

Ginsburg CM, McCracken GH, Jr (1982). Urinary tract infections in young infants. *Pediatrics* **69**(4): 409–412.

Hovelius B, Mardh PA (1984). Staphylococcus saprophyticus as a common cause of urinary tract infections. *Rev Infect Dis* **6**(3): 328–337.

Johnson JR, Stamm WE (1987). Diagnosis and treatment of acute urinary tract infections. *Infect Dis Clin North Am* **1**(4): 773–791.

Jackson SL, Boyko EJ, Scholes D, Abraham L, Gupta K, Fihn SD (2004). Predictors of urinary tract infection after menopause: a prospective study. *Am J Med* **117**(12): 903–911.

Lipsky BA, Ireton RC, Fihn SD, Hackett R, Berger RE (1987). Diagnosis of bacteriuria in men: specimen collection and culture interpretation. *J Infect Dis* **155**(5): 847–854.

Little P, Turner S, Rumsby K, Warner G, Moore M, Lowes JA Smith H, Hawke C, Mullee M (2006). Developing clinical rules to predict urinary tract infection in primary care settings: sensitivity and specificity of near patient tests (dipsticks) and clinical scores. *Br J Gen Pract* **56**(529): 606–612.

Martinez JJ, Mulvey MA, Schilling JD, Pinkner JS, Hultgren SJ (2000). Type 1 pilus-mediated bacterial invasion of bladder epithelial cells. *EMBO J* **19**(12): 2803–2812.

Meares EM, Stamey TA (1968). Bacteriologic localization patterns in bacterial prostatitis and urethritis. *Invest Urol* **5**(5): 492–518.

Reid G (1998). Bacterial colonization of prosthetic devices and measures to prevent infection. *New Horiz* **6**(2 Suppl): S58–S63.

Roberts JA, Kaack MB, Baskin G, Marklund BI, Normark S (1997). Epitopes of the P-fimbrial adhesin of E. coli cause different urinary tract infections. *J Urol* **158**(4): 1610–1613.

Stamey TA, Govan DE, Palmer JM (1965). The localization and treatment of urinary tract infections: the role of bactericidal urine levels as opposed to serum levels. *Medicine* (*Baltimore*): **44**: 1–36.

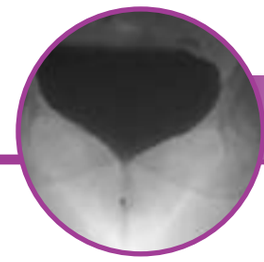
Warren JW, Tenney JH, Hoopes JM, Muncie HL, Anthony WC (1982). A prospective microbiologic study of bacteriuria in patients with chronic indwelling urethral catheters. *J Infect Dis* **146**(6): 719–723.

Whitfield C, Roberts IS (1999). Structure, assembly and regulation of expression of capsules in Escherichia coli. *Mol Microbiol* **31**(5): 1307–1319.

Further reading

Nguyen HT. Bacterial infections of the genitourinary tract. In: Tanagho EA, McAninch JW (eds) (2004). *Smith's General Urology*, 6th edition. McGraw-Hill Companies Inc., New York.

Schaeffer AJ. Infections of the urinary tract. In: Walsh PC, Retik AB, Darracott Vaughan E, Wein AJ (2002). *Campbell's Urology*, 8th edition. WB Saunders, Philadelphia.



Evaluation of Lower Urinary Tract Symptoms

Jay Khastgir

Introduction

Lower urinary tract symptoms or 'LUTS', is a descriptive term for a symptom complex which is often characterized by bothersome voiding. The investigation of LUTS is an excellent example of the art of deductive diagnosis as it requires a combination of good history taking, physical examination including digital rectal or pelvic examination, and appropriate use of an array of laboratory, outpatient and complex investigations. The term 'LUTS' itself requires some clarification. Contrary to the term 'prostatism' which is inaccurate but has nevertheless remained in common usage, the term LUTS is more appropriate considering that various forms of urethrovesical dysfunctions often not related to the prostate may contribute to LUTS, as may other causes outside the urinary tract, obvious examples being excessive diuresis, cardiovascular pathology and diabetes.

When one considers the underlying pathology, LUTS tend to be rather non-specific. In relation to symptomatic benign prostatic enlargement (BPE), no specific symptom can reliably suggest benign prostatic hyperplasia, and furthermore there is no correlation between the degree of prostatic enlargement and the severity of symptoms. In addition, the relationship between symptoms and objective data from urodynamic studies is also weak.

In evaluating a person with LUTS, the clinician should endeavour to formulate a urodynamic diagnosis from the start to achieve an understanding of the individual's symptoms from an ætiological point of view, on the intuitive presumption that reversal of these causative processes should intuitively lead to more effective management. This is built up progressively from the available clinical information available, and altered accordingly as further information is received. Subsequent confirmation or refutation of this understanding by further investigations also serves to enhance the clinician's understanding of the disease process.

It should be noted however, that the pathway of achieving a urodynamic diagnosis is not always completed, and often does not need to be, as complex investigations are reserved for more complex situations where the diagnosis is not apparent from initial tests. In clinical practice, the majority of cases actually require a minimum number of tests to achieve a working diagnosis. The diagnostic pathway chosen also depends largely on the presentation and results of preceding tests. For example, the investigation of an elderly man initially presenting with straightforward voiding symptoms suggestive of symptomatic benign prostatic enlargement (BPE) is quite different from a woman re-presenting after failed incontinence surgery with voiding dysfunction. However, a broad diagnostic pathway is summarized in *Table 3.1*.

In general clinical usage, the term LUTS has become almost synonymous with symptomatic prostatic enlargement without incontinence. Although this chapter encompasses the diagnostic approach of both these conditions in a general sense, the investigation of complicating factors that may underlie LUTS such as haematuria, urinary tract infections and specialist clinical and urodynamic tests for incontinence are outside its remit.

History and physical examination

The urinary bladder and its outlet function as a continent reservoir which is able to intermittently expel urine under voluntary control in socially acceptable circumstances. Consequently, its functions may be described as occurring in two phases:

Table 3.1 Investigations for LUTS and incontinence

Clinical and outpatient investigations
- History including symptom score
- Physical examination which includes
  - Digital rectal examination (DRE) for men
  - Pelvic examination for women
  - Focused neurological examination
- Frequency–volume chart / voiding diary
- Urine dipstick analysis
- Urine microscopy and culture
- Post-void residual volume (bladder scan)
- Pad test
- Q-tip test

Urodynamic studies
- Uroflometry
- Cystometry / pressure–flow studies
- Videourodynamics
  - Urethral pressure profile

Table 3.2 Classification of lower urinary tract symptoms

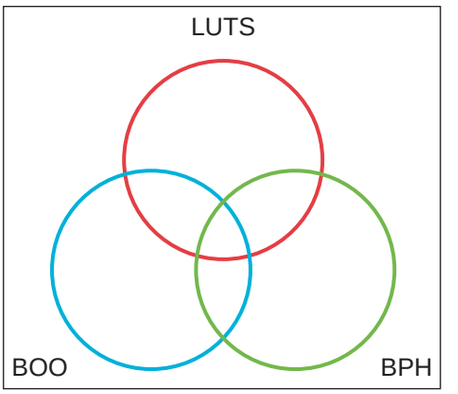
Voiding symptoms
- Poor urinary stream
- Abdominal straining
- Hesitancy
- Intermittency
- Incomplete bladder emptying
- Terminal and post-micturition dribble
- Dysuria

Storage symptoms
- Frequency
- Nocturia
- Urgency
- Incontinence
- Bladder pain

- Storage phase.
- Voiding phase with voluntary expulsion of urine at socially appropriate times.

LUTS have been classified into storage and voiding symptoms corresponding to the two phases of lower urinary tract function (*Table 3.2*). Storage symptoms are usually more bothersome as they are associated with decreased control over an individual's life, particularly as voiding occurs for relatively small periods of time each day and storage is the predominant normal function by far. The limited expression of bladder dysfunction as either storage or voiding symptoms confers non-specificity to pathological processes.

Historically, bladder outlet obstruction (BOO), 'prostatism' and benign prostatic hyperplasia (BPH) have been considered almost synonymous, with 'prostatism' implying a prostatic origin for these symptoms. As alluded to earlier, lower urinary tract symptoms are not specific to the prostate and nor are they gender-specific, as they are also prevalent amongst women; furthermore, the causes of LUTS may originate from causes outside the urinary tract, as in polyuria which may present as urinary frequency or nocturia. Although BPH accounts for a large proportion of LUTS in the older male, other conditions such as bladder dysfunction, neurological disorders, and renal or extra-renal conditions often give rise to LUTS. This relationship is best illustrated by Tag Hald's rings (**3.1**). BPH is a histological diagnosis which is the most common urological affliction of older men, affecting 40–70% of men aged 60–70 years. Over 80% of all men with functioning testicles will develop BPH within their lifetime, and nearly 30% will undergo surgery for this condition. Approximately 15–30% of these men will complain of lower urinary tract symptoms. LUTS occur in



3.1 Tag Hald's rings. Note the original version described LUTS by its previous term 'prostatism'. BOO = bladder outlet obstruction; BPH = benign prostatic hyperplasia; LUTS = lower urinary tract symptoms.

about 25% of men >40 years, with an age-related increase in prevalence.

A detailed history for LUTS should include:

- Details of each symptom including duration, description, severity, association with other symptoms and daily activities, and response to any lifestyle changes.
- Related symptoms which require specific investigation such as haematuria, strangury, incontinence and loin pain should be specifically enquired about.
- Details of comorbidities and their treatment, and any surgical history.
- Specific details of conditions that may give rise to neurogenic bladder dysfunction (e.g. trauma/spinal injury, vertebral degenerative conditions, diabetes, parkinsonism, stroke) and other conditions such as urinary tract infection which may cause similar symptoms.
- Current medications including non-proprietary medicines. Medications with anticholinergic properties and diuretics have obvious effects on the bladder. It is useful to find out what has been prescribed for LUTS in the past and whether they have been helpful.
- Average 24-hour fluid intake with details of the type of fluids consumed, particularly caffeinated, carbonated or alcoholic drinks.

Symptom scores

Several symptom scores have been developed as measurement tools to allow the quantification of LUTS. *Table 3.3* lists some of the better-known symptom score questionnaires that are in use. The most widely accepted system internationally is the International Prostate Symptom Score (IPSS).

Most questionnaires are self-completed by patients, but some need to be completed by clinicians, which may therefore be susceptible to bias. The criteria for scientific soundness usually applied to the development of such measures include feasibility, validity, reliability and responsiveness. Feasibility denotes acceptability to users, usually evidenced by high response rates, and includes the cost and technical aspects of implementation of the measuring tool. Validity relates to the extent to which a measurement method measures what it is intended to, and is in turn described by various forms of validity: face, content, criterion, construct, discriminant and convergent. Reliability of a measuring instrument refers to its stability, or the degree to which it will yield the same result on different occasions. Test–retest reliability refers to this stability when the measurement instrument is used in the same situation over a short period of time, usually 2–14 days. Obviously assuming that the domains measured have not actually changed in that period, any change in the readings obtained by the scoring tool is assumed to be an error. Test–retest reliability is best measured by a derivative of the analysis of variance method known as the intraclass correlation coefficient (ICC) in the case of continuous scales. Internal consistency indicates the extent to which the independent domains or items within a questionnaire all measure the same problem. This is particularly important when a questionnaire contains a large number of items. It also follows that the scores for the individual items should correlate with each other. Internal consistency is most frequently measured by the Cronbach's coefficient alpha, whereas the Kuder-Richardson formula 20 is more suitable if the responses have a dichotomous response format (e.g. yes/no). Responsiveness of a measurement system refers to the sensitivity of a measure in picking up changes of clinical significance. This property is difficult to measure, but is most frequently estimated by calculating the effect size. The effect size is arrived at by calculating the difference between the mean scores at assessments divided by the standard deviation of the baseline scores, or alternatively the standard deviation of the change scores, and expressed in standardized units which allow comparison.

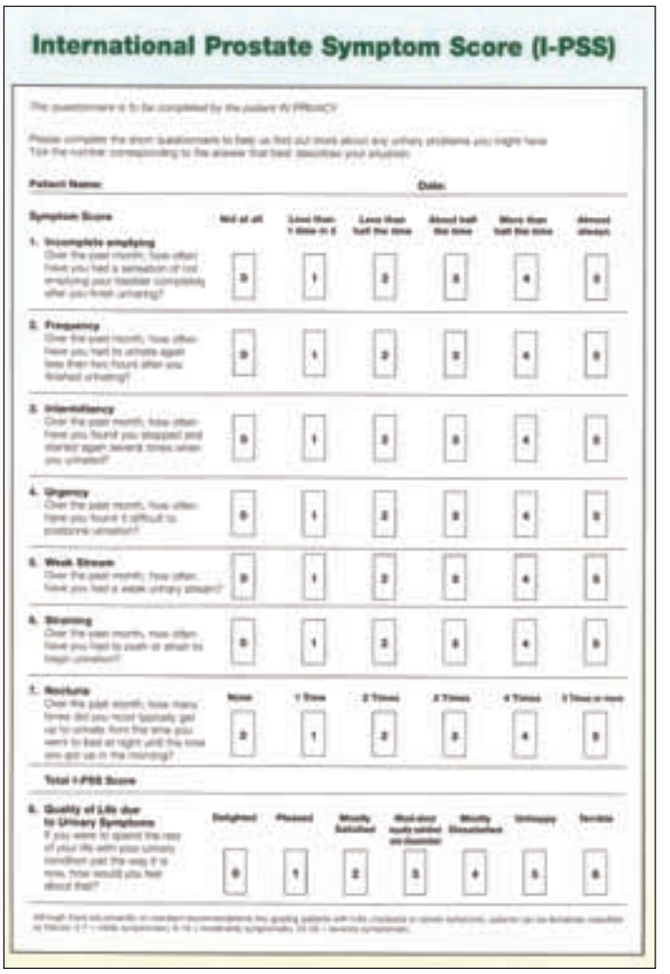
The IPSS questionnaire, which has been adopted by the World Health Organization, is derived from and almost identical to the American Urological Association (AUA)

Table 3.3 Symptom score questionnaires for LUTS / BPH

- AUA-7 Symptom Index (patient rated)
- International Prostate Symptom Score (patient rated)
- Madsen-Iversen (clinician rated)
- Boyarski system (clinician rated)
- Maine Medical Assessment Programme (patient rated)
- Danish Prostate Symptom Score (patient rated)
- International Continence Society Score (patient rated)
- QOL9 (patient rated)
- Prostate Outcomes Questionnaire (patient rated)
- Generic Measures (e.g. SF-36)

Symptom Score, with the addition of a quality-of-life domain (**3.2**). The IPSS has excellent test–retest reliability, is internally consistent, and has been translated into several languages for successful use in different populations without loss of efficacy. There are seven domains, each of which can be scored from 0 to 5, giving a maximum score of 35. The IPSS scoring instrument is recommended for use as a baseline assessment of symptom severity and patients should ideally complete it prior to their appointment with the clinician to allow review during the outpatient consultation in conjunction with history taking. The IPSS system may be used to categorize an individual's symptoms as mild, moderate or severe for scores between 0 and 7, 8 and 19, and 20 and 35 respectively.

Symptom scoring systems help the clinician to objectively measure symptoms in individual patients, as well as to obtain a global picture of the degree of bother and the deterioration in quality of life. Examination of the score sheet during the outpatient consultation also helps to direct questions appropriately. Interestingly, high pre-operative symptom scores have been shown to correlate well with good post-operative outcomes. Furthermore, deterioration of symptom scores over a period of time helps identify men at risk of disease progression.


International Prostate Symptom Score (I-PSS)

3.2 The International Prostate Symptom Score (IPSS).

Frequency–volume chart / voiding diaries

Charts which document the volumes and frequency of micturition are an essential part of the evaluation of lower urinary tract symptoms. Often ignored by clinicians as part of the initial evaluation, these actually provide a wealth of useful information. Examinations of charts provide diagnostic clues, help plan urodynamic tests and allow provision of appropriate lifestyle advice. In practice, the patient is sent out a frequency–volume chart with instructions on how to complete it prior to the outpatient appointment. The individual is asked to record the time and volume (in millilitres) of every void for 3–7 days by keeping a measuring jug in the toilet. The chart documents day- and night-time voids separately, along with any episodes of incontinence.

Three types of charts are in usage:

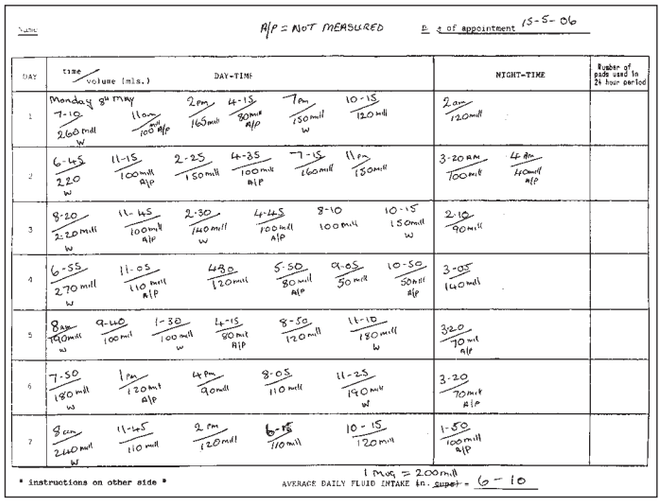
1. *Frequency–volume chart:* records the time and volume of each void over a 24-hour period, as described above (**3.3**, **3.4**).
2. *Bladder diary:* considerably more detailed and comprehensive but requires better compliance and attention to detail by patients. In addition to the recording of the voiding times and volumes, it also documents incontinence

Name _____ Date of appointment _____

DAY	Time Volume (mls.) Day-Time	Night -Time	Number of pads used in 24 hour period
1			
2			
3			
4			
5			
6			
7			

* instructions on other side * AVERAGE DAILY FLUID INTAKE (in cups) = _____

3.3 Frequency–volume chart.



A/P = NOT MEASURED P. = of appointment 15-5-06

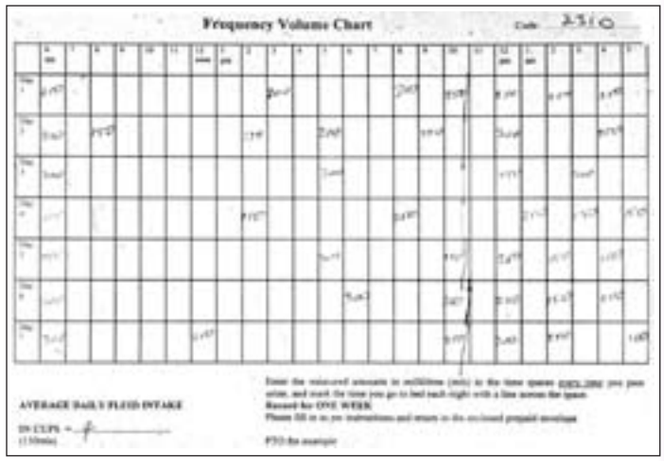
DAY	time / volume (mls.) DAY-TIME	NIGHT-TIME	Number of pads used in 24 hour period
1	Monday 8th May 7-10 / 2.60 mill W; 11am / 100 A/P; 2pm / 165 ml; 4-15 / 80 ml A/P; 7pm / 150 ml W; 10-15 / 120 ml	2am / 120 ml	
2	6-45 / 220 W; 11-15 / 100 ml A/P; 2-25 / 150 ml; 4-35 / 100 ml A/P; 7-15 / 160 ml; 11pm / 150 ml	3-20 am / 100 ml; 4 am / 40 ml A/P	
3	8-20 / 2.20 ml W; 11-45 / 100 ml A/P; 2-30 / 140 ml W; 4-45 / 100 ml A/P; 8-10 / 100 ml; 10-15 / 150 ml W	2-10 / 90 ml	
4	6-55 / 2.70 ml W; 11.05 / 110 ml A/P; 4.30 / 120 ml; 5.50 / 80 ml A/P; 9-05 / 50 ml; 10-50 / 50 ml A/P	3-05 / 140 ml	
5	8am / 190 ml W; 9-40 / 100 ml; 1-30 / 100 ml W; 4-15 / 80 ml A/P; 8-50 / 120 ml; 11-10 / 180 ml W	3.20 / 70 ml A/P	
6	7-50 / 180 ml W; 1pm / 120 ml A/P; 4pm / 90 ml; 8-05 / 110 ml; 11-25 / 190 ml W	3.20 / 70 ml A/P	
7	8 am / 240 ml W; 11-45 / 110 ml; 2 pm / 120 ml; 6-15 / 110 ml; 10-15 / 120 ml	1-50 / 100 ml A/P	

* instructions on other side *

1 mug = 200 ml

AVERAGE DAILY FLUID INTAKE in ~~cups~~ = 6 - 10

3.4 Frequency–volume chart completed by a patient with LUTS.



Frequency Volume Chart

AVERAGE DAILY FLUID INTAKE

3.5 Nocturnal polyuria detected by examination of the frequency–volume chart completed in a man referred for 'nocturia'.

episodes and severity, 24-hour pad usage, presence and quantification of urgency, and details of fluid intake.

3. *Micturition time chart:* represents a simpler version of the preceding two, and comprises a record of the times of voids only.

The recording of the presence and degree of urgency, the use of pads, size and number of pads used over a 24-hour period and degree of pad soakage, provides information on the severity of the problem and its impact on the individual's quality of life. Charts provide information on frequency, nocturia, average and maximum voided volumes, and help identify relationships between fluid intake and bothersome symptoms. An example is the association between fluid intake in the evenings and severity of nocturia. It is worth remembering that certain types of food such as fruit and vegetables contain significant amounts of water.

Frequency–volume charts may provide important diagnostic clues. They distinguish between nocturia and nocturnal polyuria, and frequency from global polyuria (defined in adults as the production of >2.8 litres of urine in 24 hours). Nocturnal polyuria is identified when the nocturnal voided volume exceeds approximately 30% of the total 24-hour urine output and may reflect the presence of extra-urinary tract pathology such as congestive cardiac failure, and abnormalities of antidiuretic or atrial natriuretic hormone secretion (**3.5**). In global polyuria, as may occur in diabetes insipidus or mellitus, or excessive fluid intake, the voided volumes tend to remain normal but occur with increased frequency and a high 24-hour output. In contrast, in the overactive bladder, urgency and increased frequency are generally accompanied by reduced voided volumes.

Urinanalysis

Urinanalysis is a fundamental test that must be performed in all patients who present with urinary symptoms. Dipstick analysis of urine is simple to perform and can be done by nurses immediately on presentation at the outpatient clinic or in the ward (**3.6**). Dipsticks contain multiple reagent strips that are able to detect the presence of blood, glucose, protein, leukocyte esterase and nitrite in the urine, apart from others (*see* Chapter 2).

Formal microscopy of a centrifuged specimen provides confirmation of dipstick findings as well as quantification of haematuria and pyuria. Cultures are indicated when dipstick analysis suggests the presence of infection, or when strong clinical suspicion exists (**3.7**).

The primary use of urine dipstick analysis is to rule out significant pathology that may require specific investigations.

- Haematuria may indicate the presence of important pathology such as urothelial carcinoma, carcinoma *in situ*, urinary tract infections, urethral stricture or urinary stone disease. The diagnostic pathway for the investigation of haematuria is discussed elsewhere, and includes imaging of the urinary tract, cystoscopy, and often urine cytology. Dipstick tests detect the peroxidase-like activity of haemoglobin; orthotolidine is oxidized by cumene

3.6 Urine dipstick analysis kit with urine sample in a sterile receptacle.

3.7 Plated culture medium demonstrating positive cultures.

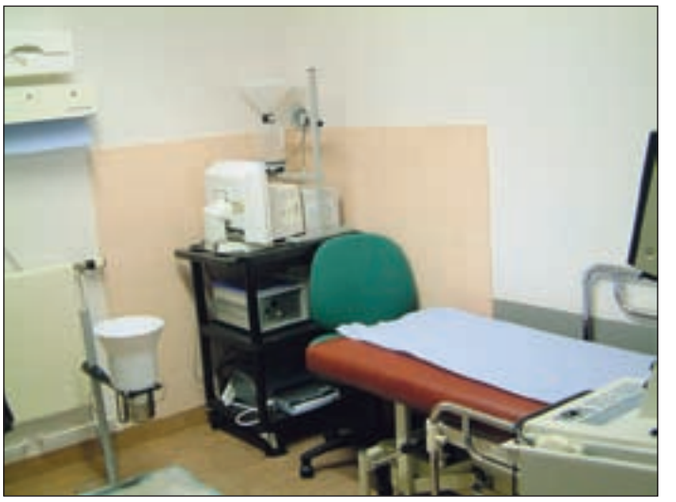
hydroperoxide catalysed by haemoglobin to produce a blue product.

- Glycosuria may indicate the presence of diabetes mellitus. Diabetics may develop LUTS via several mechanisms: peripheral autonomic neuropathy may impair bladder function, osmotic diuresis from the glycosuria may result in polyuria, and glycosuria and impaired bladder emptying may predispose the individual to infection.
- Leukocyte esterase and nitrite in the dipstick test detect pyuria and bacteriuria respectively. Although both are important independent indicators of urinary tract infection their sensitivity and specificity is increased when used together. In many cases simple visual examination of turbid offensive urine provides the answer, but this should not replace formal testing.

Uroflowmetry

Uroflowmetry is a simple and non-invasive urodynamic test that measures voided urine volume per unit time, employing technology that has been available for several decades. It is the simplest functional study of bladder and urethral function apart from frequency–volume charts, but provides a wealth of meaningful information. The recorded urinary flow rate is the product of detrusor contractility and urethral resistance, and may consequently be modified by abdominal straining and other artefacts. As a consequence, uroflowmetry provides information on voiding function as a whole but cannot differentiate between the effects of its component parts. Nevertheless, careful examination of characteristic traces and the numeric information from flow tests provide important information. It is also quite useful in providing a permanent trace that can be referred to in the future, especially when the test is repeated after a specific intervention such as after transurethral resection of the prostate (TURP) or optical urethrotomy.

Flow studies are performed using uroflowmeters, ideally in a dedicated flow clinic (**3.8**). The clinic should have in it the uroflowmeter and its transducer and integral recording device, an ultrasound scanner and an examination couch for performance of the post-void residual scans, a sluice for disposal of waste, and a desk for paperwork. In practice, an instruction sheet is mailed out to patients along with their clinic appointments to explain the procedure (**3.9**), and they are asked to bring a completed frequency–volume chart to



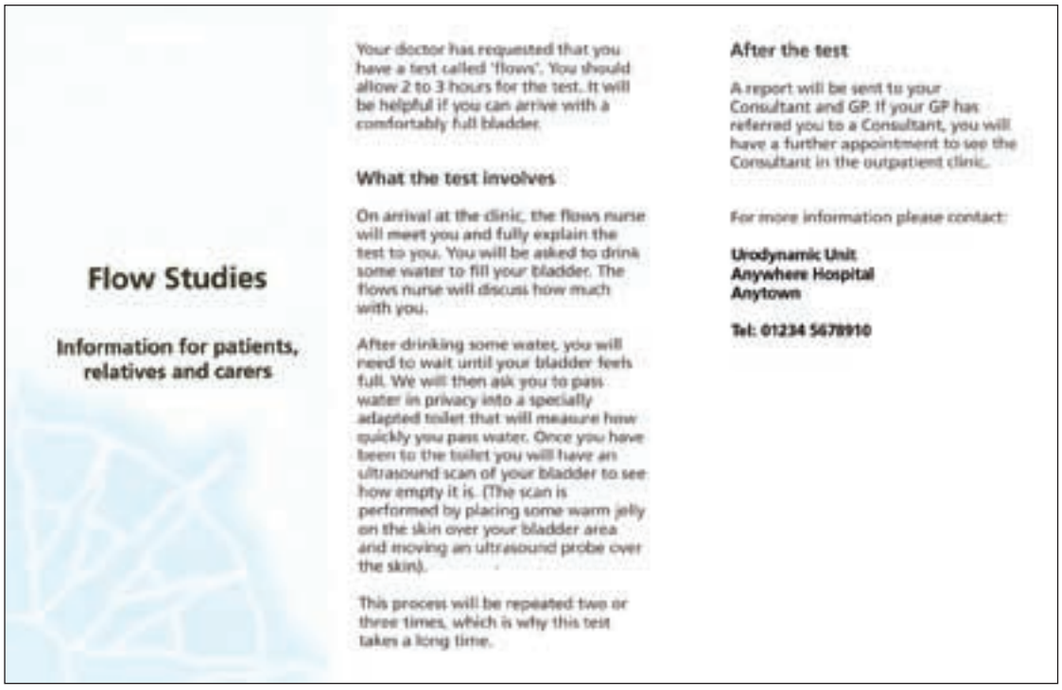
3.8 Typical layout of a flow clinic.

the flow clinic if not already completed. Instructions include the requirement for a full bladder that is neither under-filled nor over-distended, as both these situations lead to erroneous interpretations. The flow clinic should allow adequate privacy and time for the patient to void as naturally as possible in the artificial environment of the clinic. Three flow tests are obtained for optimal accuracy, and the residual volume is measured following each flow.

The flowmeter comprises a receptacle or container to collect urine, a measuring system, and an integral recording system that generates the flow trace and the measurements; the receiving funnel is configured to the requirements of male and female patients (**3.10**, **3.11**). Most modern commercially available products are reasonably accurate, and have an error rate of less than 5%. There are several physical principles that may be used to measure flow rates, but commercially available flowmeters are of three main types:

1. *Rotating disc flowmeter:* This uses a funnel to direct the urinary stream onto a spinning disc, which is maintained at a constant speed by a servomotor. The flow rate is directly proportional to the weight of the urine falling on the disc per unit time, which is read by the instrument in terms of the differing power that is required by the motor to keep the disc speed constant. Although mechanically complicated, this system is the least likely to give rise to artefacts.

3.10 Uroflowmeter set up for use by male patients.



Flow Studies

Information for patients, relatives and carers

Your doctor has requested that you have a test called 'flows'. You should allow 2 to 3 hours for the test. It will be helpful if you can arrive with a comfortably full bladder.

What the test involves

On arrival at the clinic, the flows nurse will meet you and fully explain the test to you. You will be asked to drink some water to fill your bladder. The flows nurse will discuss how much with you.

After drinking some water, you will need to wait until your bladder feels full. We will then ask you to pass water in privacy into a specially adapted toilet that will measure how quickly you pass water. Once you have been to the toilet you will have an ultrasound scan of your bladder to see how empty it is. (The scan is performed by placing some warm jelly on the skin over your bladder area and moving an ultrasound probe over the skin).

This process will be repeated two or three times, which is why this test takes a long time.

After the test

A report will be sent to your Consultant and GP. If your GP has referred you to a Consultant, you will have a further appointment to see the Consultant in the outpatient clinic.

For more information please contact:

Urodynamic Unit
Anywhere Hospital
Anytown

Tel: 01234 5678910

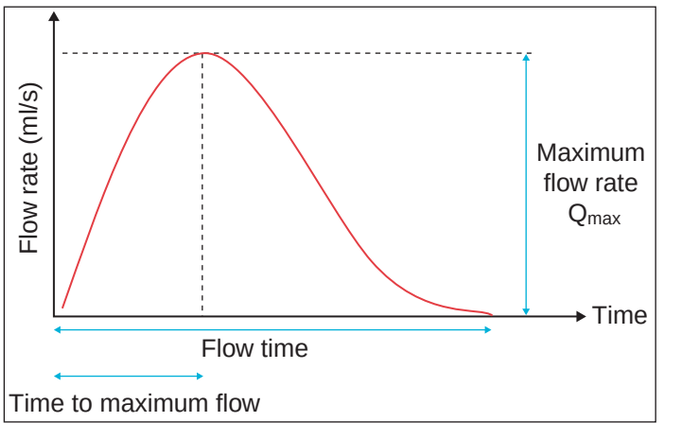
3.9 Information leaflet for the flow clinic.

3.11 Uroflowmeter set up for females with a micturition chair in place.

2. *Weight transducer flowmeter:* This apparatus weighs the urine and the volume voided and calculates the flow rate by differentiation with respect to unit time. The weight of urine is within 3% of the weight of water, which allows it to be equated to volume and computed into flow rate.
3. *Capacitance flowmeter:* This has a dipstick integral to the system that measures the changing height of the urine column in the collecting vessel. The capacitance of the dipstick is proportional to the height of the urine column; the change in capacitance differentiated over time provides the flow rate. The main drawback of this system is its tendency to go out of calibration.

Portable home flowmeters have also been developed to allow multiple readings in the natural and more relaxed environment of the patient's own home. The apparatus is loaned out to the patient by the hospital for a sufficient period of time to allow for several flow readings to be obtained, and the data are recorded in a microprocessor which is subsequently analysed by a computer in the department. The clinical role of home uroflowmetry has not been established as yet.

The International Continence Society (ICS) has published its definitions to aid the description of flow traces (**3.12**). As per the ICS terminology, flow rate is defined as the volume of fluid expelled via the urethra per unit time, expressed in millilitres per second (ml/s). The maximum flow rate (Q_{max}), the measure most urologists look at first for the interpretation of the flow rate, is the maximum measured value of the flow rate. The time to maximum flow is the time from the start of flow to maximum flow, which reflects the slope of the initial part of the flow trace; this has been suggested as an important determinant of the presence or absence of bladder outlet obstruction. The average flow rate (Q_{ave}) represents the voided volume divided by flow time, the flow time being the time over which measurable flow occurs. The flow curve is largely described by the shape of the flow curve, maximum flow rate (Q_{max}), the flow time and time to Q_{max}. The voided volume (VV) is the total quantity of urine voided at the time of the test, and is crucial to the interpretation of the results. A low voided volume renders the test difficult to interpret, whereas a large over-filled bladder gives rise to unrepresentative poor flows as the detrusor becomes less efficient when over-stretched; as a consequence, normality of flow rates for a given age range is determined by the average range of voided volume. The optimal voided volume for reliable interpretation of results is considered to be between 200 and 400 ml, at which the detrusor performs optimally. Apart from the numerical data described by these



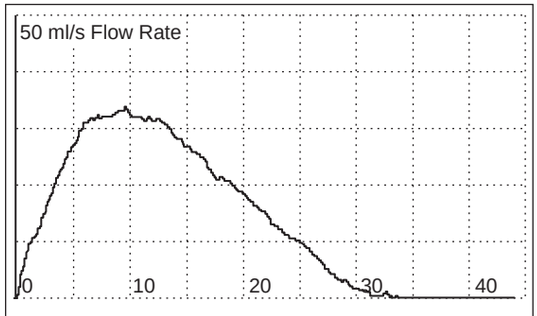
3.12 International Continence Society (ICS) terminology for interpretation of flow traces.

definitions, the actual shape of the flow trace curve is important in the determination of a urodynamic diagnosis, as explained below. Note that the age and sex of the patient is important and must be established at the outset when asked to examine an unknown flow trace, such as in an examination situation.

A normal flow trace has a characteristic 'bell' shape (**3.13**). The Q_{max} occurs within the first 30% of the trace and within 3–10 seconds of the start of the void. Although normal flows may vary considerably in appearance in the same patient depending on the voided volume, the start and the end phases of each flow are very similar, with the final phase of each flow demonstrating a rapid diminution from high flow and a sharp cut-off at the end.

The interpretation of flow rates is aided by the use of nomograms, which have been constructed by examination of numerous flow reports and traces. Specific nomograms exist for children and adults of different ages, and for males and females. For example, the Siroky nomogram (**3.14**) is employed for the interpretation of traces in men under 55 years, the Bristol nomogram (**3.15**) for men above 55 years, and the Liverpool nomogram for interpretation of traces in women. The predictive value of the test is enhanced by plotting the flow rates onto the nomogram (**3.16**); often the individual traces are attached to the reverse of the reporting sheet for easy reference (**3.17**)

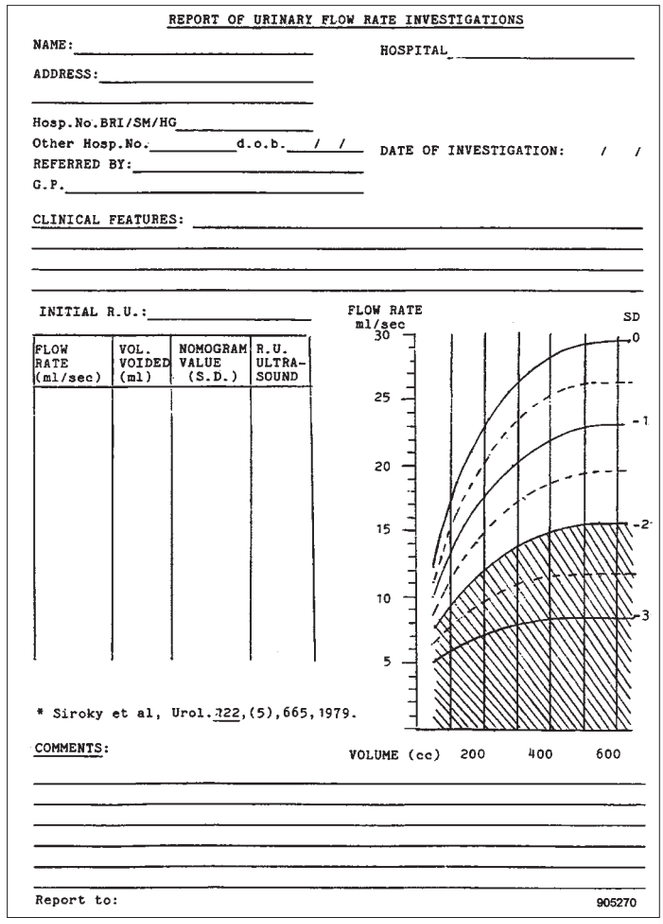
It should be clear that differentiation between normal and abnormal voiding may occasionally prove to be difficult, since the flow trace represents the product of detrusor contractility and the resistance encountered by the outlet.



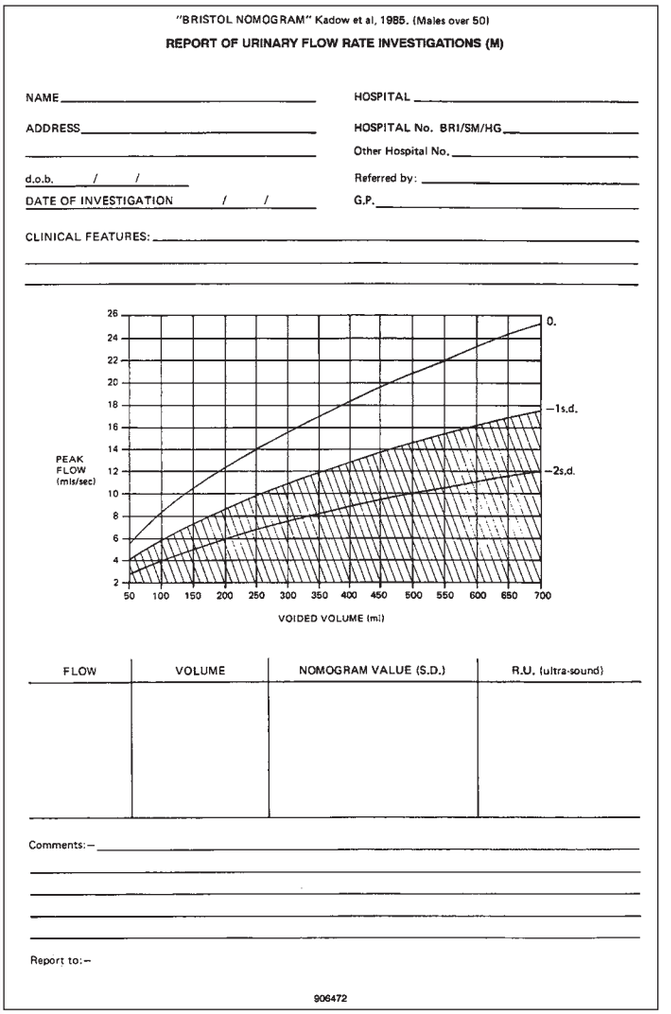
Voiding time	T100	33	s
Flow time	TQ	32	s
Time to max. flow	TQ_{max}	9	s
Max. flow rate	Q_{max}	33.8	ml/s
Average flow rate	Q_{ave}	18.6	ml/s
Voided volume	V_{comp}	602	ml

3.13 Normal flow trace.

In the case of benign prostatic enlargement, the flow characteristically demonstrates reduced diminished maximum and average flow rates with a prolonged voiding time (**3.18**). Such traces require careful evaluation as the diminished flow rate may indicate either bladder outlet obstruction or detrusor underactivity. Conversely, an apparent normal flow rate can be produced in the presence of bladder outflow obstruction by generating abnormally high voiding pressures. Studies examining the specificity of uroflowmetry have demonstrated that approximately 90% of men with a Q_{max} <10 ml/s, 65% of those with Q_{max} of 10–15 ml/s and 30% of men with Q_{max} >20 ml/s are obstructed. Bladder outlet obstruction (BOO) is usually classified as 'compressive' or 'constrictive' on the basis of the appearances of flow traces, the former signifying obstruction by conditions such as benign prostatic obstruction (BPO) and the latter in urethral stricture disease.



3.14 Flow test reporting sheet with Siroky nomogram for use in men under 55 years of age.


"BRISTOL NOMOGRAM" Kadow et al, 1985. (Males over 50)

REPORT OF URINARY FLOW RATE INVESTIGATIONS (M)

NAME _____ HOSPITAL _____

ADDRESS _____ HOSPITAL No. BRI/SM/HG _____

_____ Other Hospital No. _____

d.o.b. / / Referred by: _____

DATE OF INVESTIGATION / / G.P. _____

CLINICAL FEATURES: _____

PEAK FLOW (mls/sec)

VOIDED VOLUME (ml)

0. −1s.d. −2s.d.

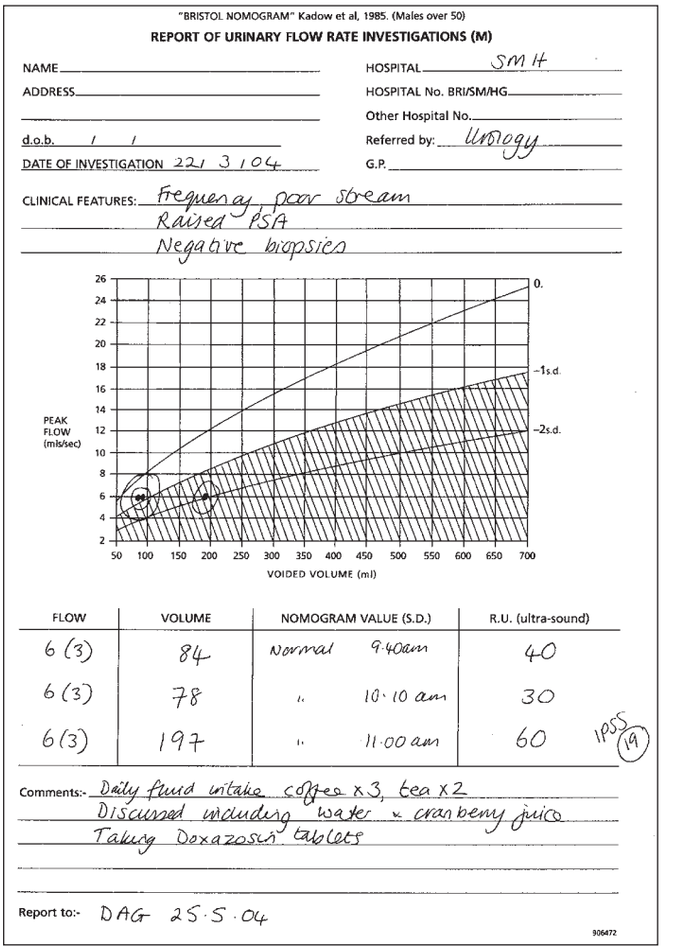
FLOW	VOLUME	NOMOGRAM VALUE (S.D.)	R.U. (ultra-sound)

Comments:– _____

Report to:– _____

906472

3.15 The Bristol nomogram for use in men at or over 55 years of age.


"BRISTOL NOMOGRAM" Kadow et al, 1985. (Males over 50)

REPORT OF URINARY FLOW RATE INVESTIGATIONS (M)

NAME _____ HOSPITAL SMH

ADDRESS _____ HOSPITAL No. BRI/SM/HG _____

_____ Other Hospital No. _____

d.o.b. / / Referred by: Urology

DATE OF INVESTIGATION 22/3/04 G.P. _____

CLINICAL FEATURES: Frequency poor stream
Raised PSA
Negative biopsies

PEAK FLOW (mls/sec)

VOIDED VOLUME (ml)

0. −1s.d. −2s.d.

FLOW	VOLUME	NOMOGRAM VALUE (S.D.)	R.U. (ultra-sound)
6 (3)	84	Normal 9.40am	40
6 (3)	78	" 10.10 am	30
6 (3)	197	" 11.00 am	60

IPSS 19

Comments:- Daily fluid intake coffee x3, tea x2
Discussed including water & cranberry juice
Taking Doxazosin tablets

Report to:- DAG 25.5.04

906472

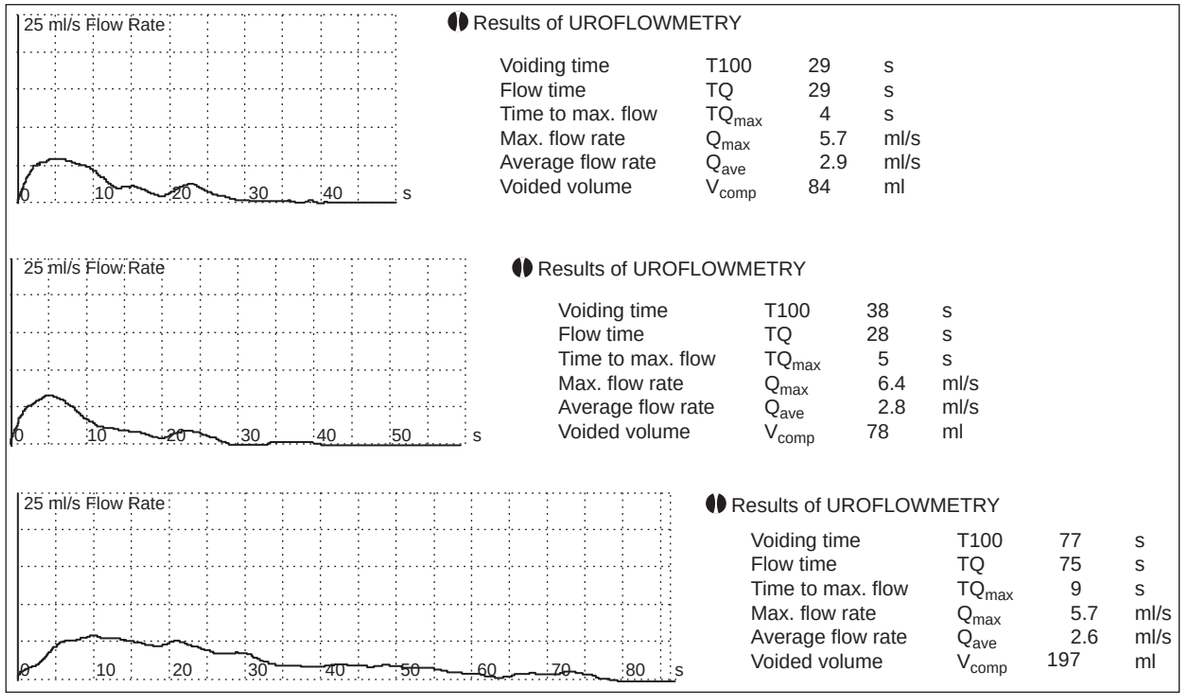
3.16 A typical completed flow report with three sets of readings. Note the helpful observations documented by the experienced flow clinic nurse.

An underactive detrusor may be suspected from the characteristics of the trace and bladder capacity (**3.19**), but often requires pressure–flow studies for confirmation. Note the diminished flow rate, often symmetrical shape of the curve, and variable time to maximum flow, which may occur in the second half of the flow. Evidence of straining or abdominal compression may be apparent from the trace as the patient attempts to forcibly empty the bladder.

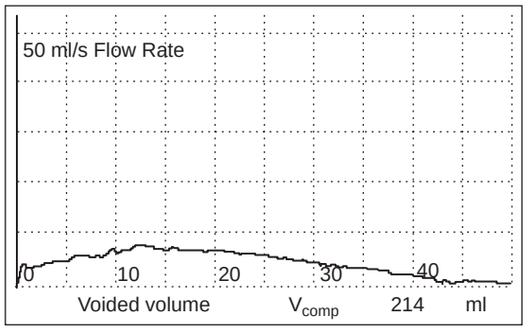
A urethral stricture illustrates a 'constrictive' pattern of bladder outflow obstruction (**3.20**), with its typical plateau shape; this may be quite severe (**3.21**). Repeating the flow test after division of the stricture helps confirm the result (**3.22**).

On the other hand, detrusor overactivity demonstrates a high maximum flow rate that is often achieved very quickly (within 1–3 seconds), and may in fact appear to be 'supranormal' with the trace often extending outside the upper margin of the paper (**3.23**). As with detrusor underactivity, this may require confirmation by pressure–flow studies; indications for this are discussed under cystometry.

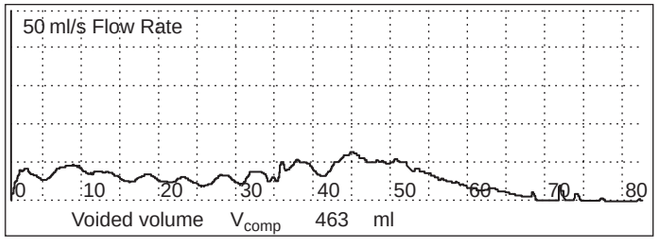
Several artefacts are interesting to be aware of in the practice of uroflowmetry as they may occasionally mislead the unwary clinician. For example, some men tend to move their urinary stream from side to side around the funnel of the flowmeter, giving rise to the characteristic trace known as 'cruising' (**3.24**). The spikes on the trace occur when the stream is advanced from the side of the funnel to the centre as the urine draining down onto the transducer catches



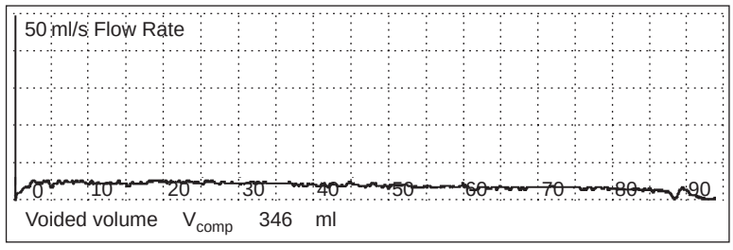
3.17 Individual flow traces attached to the flow clinic report for easy reference.



3.18 'Dynamic' bladder outflow obstruction from benign prostatic hyperplasia.

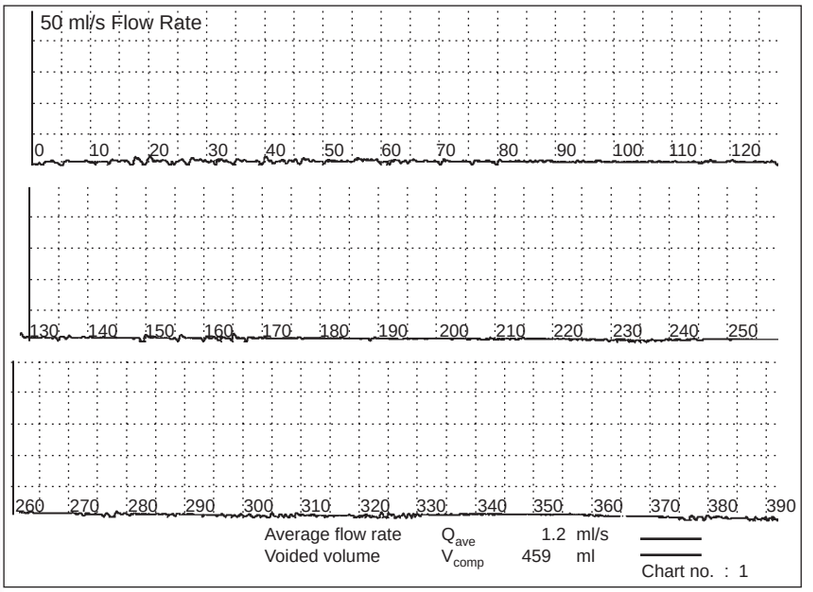


3.19 The underactive detrusor.

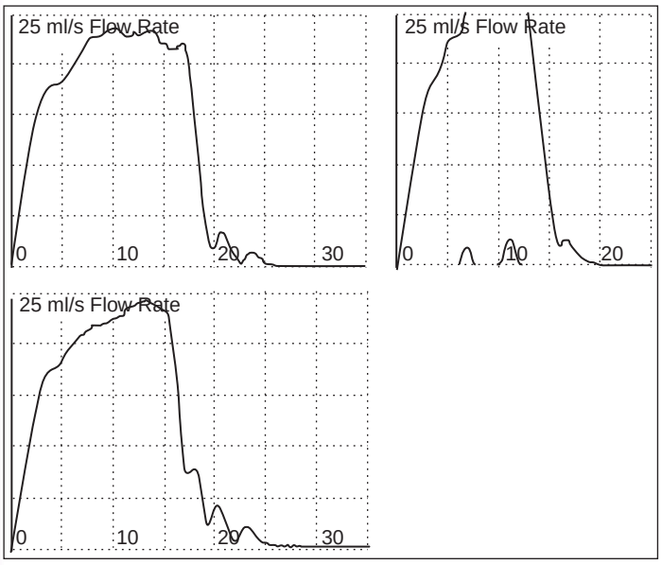


3.20 'Constrictive' bladder outflow obstruction from urethral stricture disease.

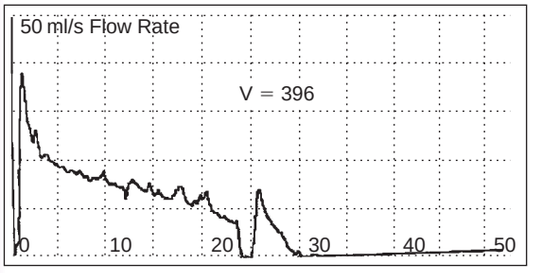
up with that voided just previously. 'Straining' is another characteristic pattern observed when the individual uses abdominal muscles to enhance or complete the void (**3.25**); this is typically an irregular trace with reduced but continuous flow. This may be involuntary or habitual and may occur with or without a detrusor contraction. 'Squeezing' is encountered in some men who attempt to improve the flow rate artificially by squeezing the tip of the penis or foreskin, perhaps in an attempt to mask what they consider the stigma of age (**3.26**). The flow trace in such cases records a characteristic series of irregular spikes. These may be reported



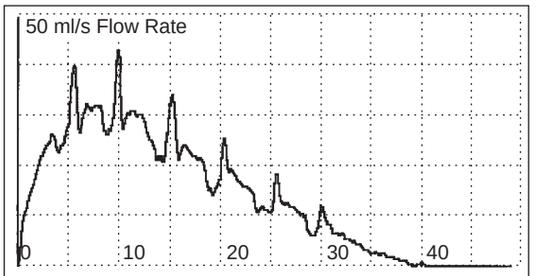
3.21 An example of a severely reduced flow rate.



3.22 Improved flow rates post optical urethrotomy.

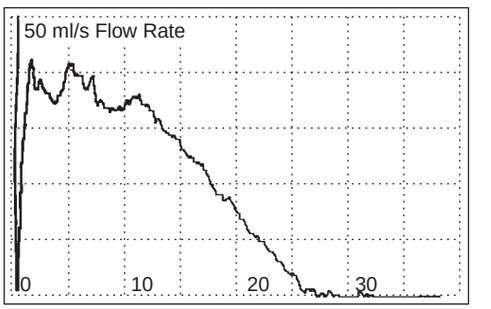


3.23 Flow trace suggestive of detrusor overactivity.

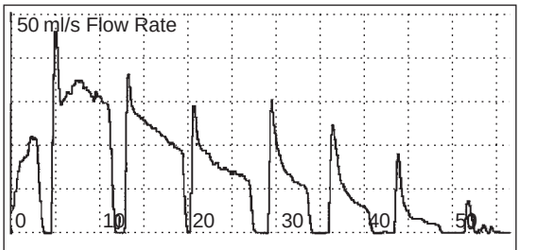


Voiding time	T100	40	s
Flow time	TQ	39	s
Time to max. flow	TQ_{max}	10	s
Max. flow rate	Q_{max}	42.7	ml/s
Average flow rate	Q_{ave}	17.1	ml/s
Voided volume	V_{comp}	669	ml

3.24 Cruising.



3.25 Straining.



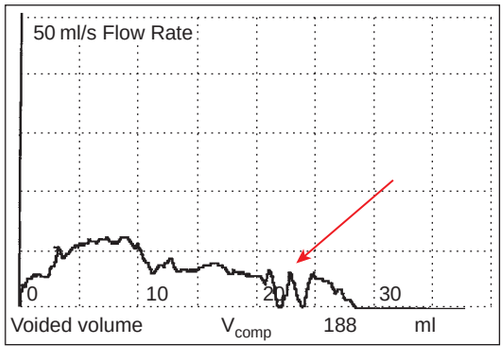
Voiding time	T100	58	s
Flow time	TQ	44	s
Time to max. flow	TQ_{max}	5	s
Max. flow rate	Q_{max}	45.9	ml/s
Average flow rate	Q_{ave}	15.6	ml/s
Voided volume	V_{comp}	688	ml

3.26 Squeezing.

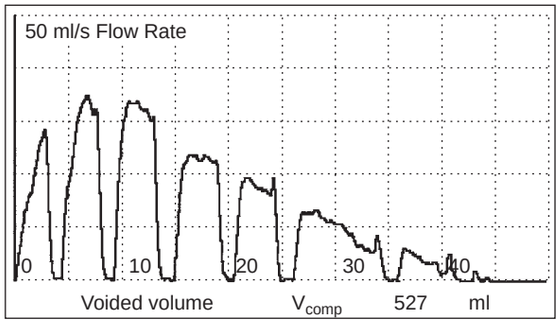
as a higher than actual maximum flow rate, a pitfall of failure to examine the traces on the part of the clinician. In such cases, asking the individual to repeat the flow test without squeezing often reveals an obstructed pattern. More complex situations such as abnormal pelvic floor contractions consequent to neurogenic bladder dysfunction and non-neurogenic dysfunctional voiding may also be apparent from characteristic traces (**3.27**, **3.28**). In the former situation, detrusor–sphincter dyssynergia is characterized by involuntary contractions of the external urethral sphincter coinciding with detrusor contractions.

Post-void residual volume

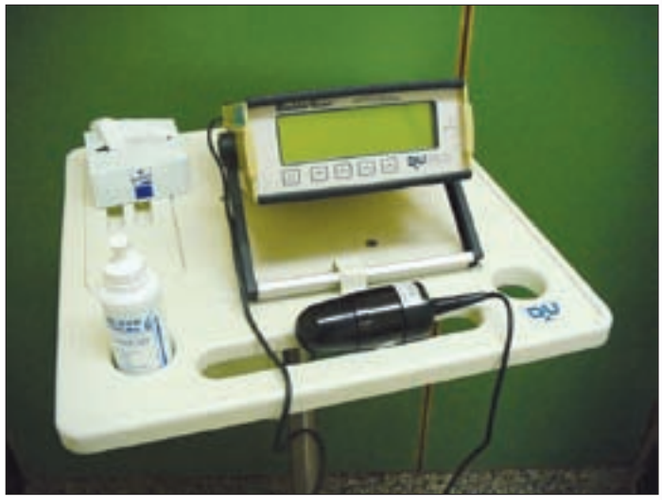
The measurement of post-void residual urine volume provides an estimate of bladder emptying and may be measured by an ultrasound scanner or by catheterization, the latter being occasionally employed during investigations in patients who self-catheterize. Various types of bladder scanners are available for use in the outpatients or community setting, or on the ward (**3.29**). Printouts of the scans kept in the patient's notes are useful for future reference to help assess the outcome of interventions (**3.30**).



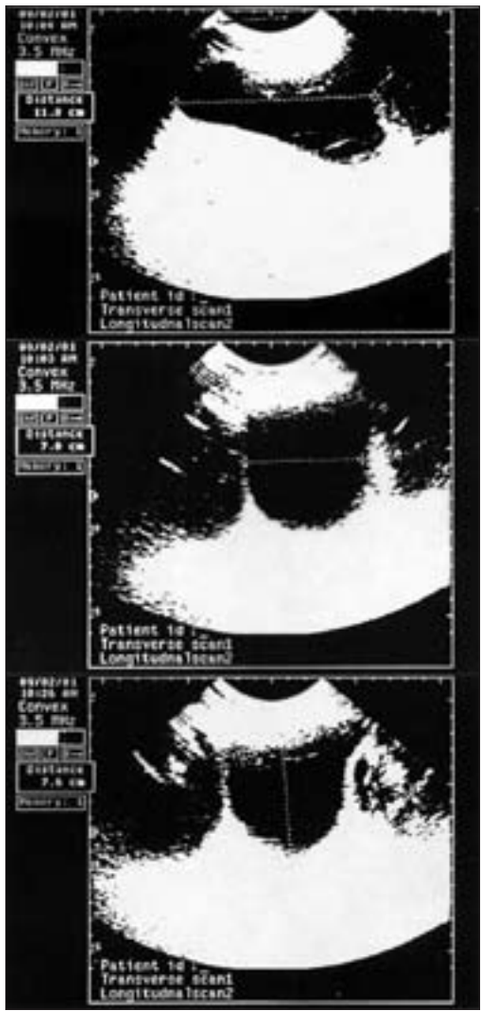
3.27 Pelvic floor contractions demonstrated by the sharp spikes (arrow) on the downward part of the flow trace.



3.28 Pelvic floor contractions.



3.29 Bladder scanner.



3.30 Printouts of typical bladder scans with computed readings of post-void residual volume.

Scanners calculate bladder volume by using the formula $D_1 \times D_2 \times D_3 \times 0.7$, with D representing the diameter of the bladder measured in three planes (coronal or side-to-side, apical-to-base, and antero-posterior. This is occasionally a source of error as the formula assumes a spherical shape for the bladder, which it of course does not have in real life, and can lead to variations in readings.

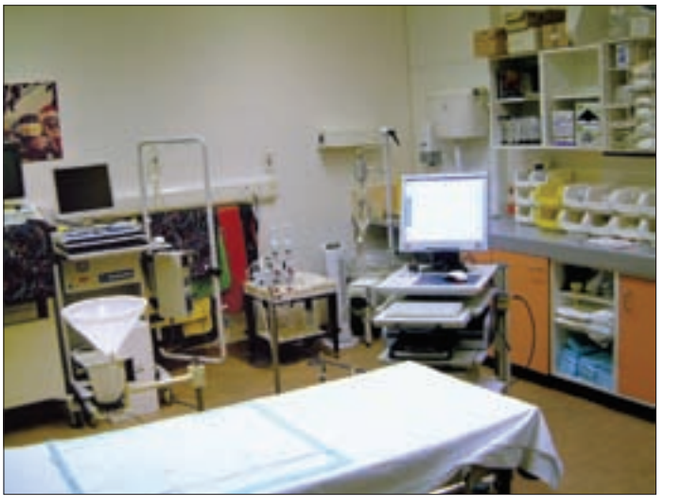
The significance of post-void residual volumes continues to be debated, and no single cut-off value of 'acceptable' residual volume has been scientifically validated. Large post-void residual volumes may not be considered significant in the absence of symptoms and complicating factors such as renal dysfunction, but do provide clues on likely bladder function when very large. The Bladder Voiding Efficiency (BVE) is an index of voiding function that quantifies the proportion of the bladder capacity that is voided, which is sometimes used as a useful measure of the effectiveness of bladder emptying.

Cystometry

Cystometry is the study of the pressure–flow relationships of the storage and voiding phases of micturition, and consequently aims to provide objective information on the function of the urinary bladder and its outlet. This is achieved by providing urodynamic explanations for symptoms, which can only occur if the symptoms are reproduced in the urodynamic laboratory. However, it is important to be aware that urodynamics provide observations and not the diagnosis and that, as with any other technique, it has its limitations. Consequently, the formulation of clear clinical questions to ask of the urodynamic investigation is of paramount importance. The patient's understanding and communication during the test greatly improves the quality of the results.

Some of the common indications for pressure–flow studies are listed below, but these often vary depending on the facilities available (**3.31**); the role of pre-operative urodynamics in women with incontinence is currently a subject of debate.

- Equivocal flow studies.
- Young patients with LUTS.
- Neurogenic bladder dysfunction.
- Suspected underactive bladder function.
- Overactive bladder syndrome (OAB) after unsuccessful conservative management.
- Planned surgery for correction of incontinence.

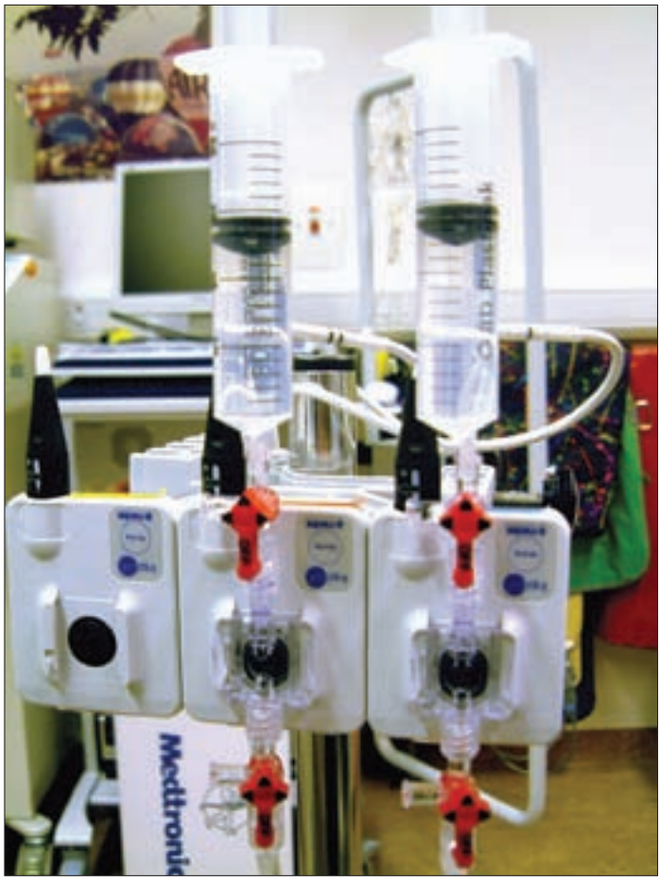


3.31 Set-up for urodynamics.

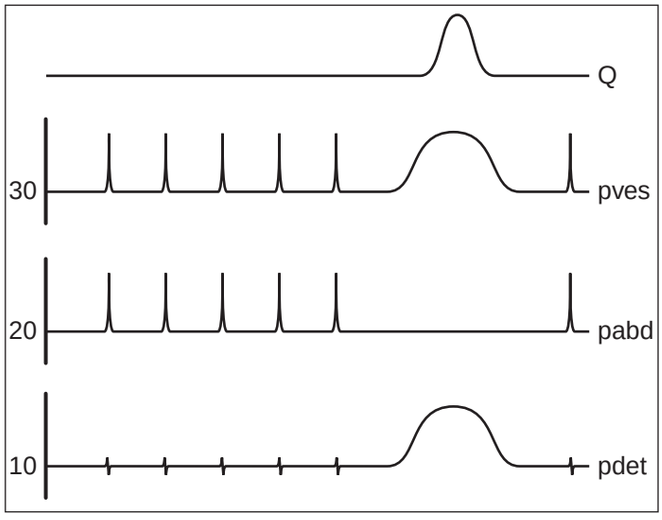
- Diabetics with LUTS.
- When things don't quite 'add up' – particularly when intervention is being contemplated.

Cystometry may be performed with two types of media: gas and liquid. Gas cystometry is not popular as it is a relatively non-physiological material that may evoke detrusor overactivity and does not allow for measurement of leak-point pressures. Standard pressure–flow studies involve insertion of fluid-filled lines into the bladder and rectum, which simultaneously record intravesical and intra-abdominal pressures in real time. A filling line is introduced into the bladder alongside the intravesical pressure line to fill the bladder. This is achieved at a predetermined rate by an infusion pump; under most circumstances this is between 10 and 100 ml/min. The vesical line is inserted by either piggybacking it on the filling line, or by using a dual-lumen catheter, which allows filling and recording of bladder pressure through a single catheter. Pressure changes transmitted back through the fluid-filled system are converted into electrical information by transducers (**3.32**). This information is analysed by a computer which subtracts the abdominal pressure from the bladder pressure to provide the detrusor pressure. This is meaningfully displayed by the computer as a series of traces that are generated in real time as the bladder is progressively filled (**3.33**).

Understanding the relationship $P_{det} = P_{ves} - P_{abd}$ is the key to reading urodynamics traces; a rise in intravesical pressure observed on its own could reflect either a detrusor contraction or represent an abdominal pressure event such



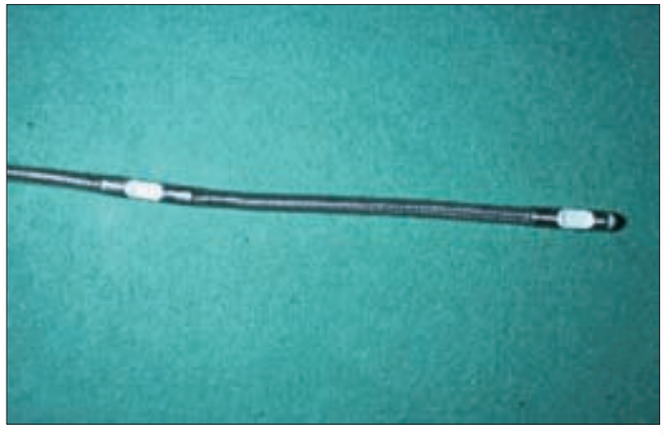
3.32 Transducers as they are set up for pressure–flow studies.



3.33 Diagramatic representation of cystometric tracings. Note the regular voluntary coughs elicited to ensure the quality of the subtraction throughout the tracing.

as a cough, whereas if accompanied by a normal abdominal pressure tracing this would signify a rise in detrusor pressure. Efficient subtraction is a key part of good urodynamic technique, and is checked by asking the patient to cough at regular intervals.

Transducers are an important component of the urodynamic apparatus, and require close attention as the lines are set up during each test. There are two varieties of transducer: strain gauge and solid. The former are connected to the bladder and the rectum via water-filled lines, and pressure changes transmitted to the transducer result in deformation of a thin metal diaphragm within the transducer. This changes the electrical resistance of a metal alloy strain gauge attached to it and thereby converts the pressure change into an electrical signal. The readings are affected by the vertical position and zeroing of the transducers, and consequently they should be placed at the level of the superior edge of the pubic symphysis and zeroed to atmospheric pressure as standardized by the International Continence Society. Syringes attached to each transducer allow flushing of the lines to clear blockages and check the integrity of the lines. In contrast, solid-state transducers are mounted on the tip of the catheter (**3.34**). These may have multiple transducers mounted on a single catheter to allow simultaneous recording of urethral or bladder neck pressure, and have the advantage of eliminating artefacts that occur from a fluid-filled column. However, these are expensive, fragile and difficult to position accurately, and the pressure readings are influenced by the position of the catheter tip within the bladder. Alternative routes for line placement may sometimes be called for in some specific situations such as in children, severe urethral stricture disease, and absence of a rectum after colorectal surgery.



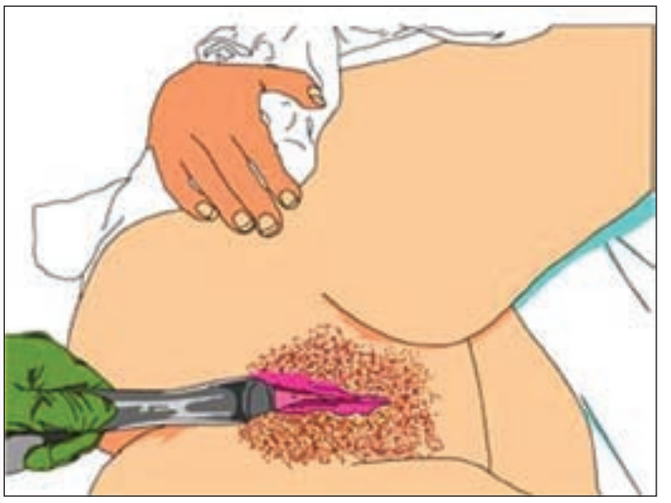
3.34 Catheter-mounted solid-state transducers.

The appointment for urodynamics provides an opportunity for a detailed evaluation of the individual's symptoms and signs, and for various streams of information to be put together. A two-way discussion with the person being investigated leads to a better understanding of the clinical problem for the individual as well as the clinician, and leads to more meaningful information from the urodynamic tests. Following a detailed history which should include details of bowel and sexual function, and all past and present medical and surgical interventions, the individual is asked to perform a flow test, known in urodynamic circles as a 'free flow'. Other tests for incontinence such as the pad test are also carried out at this point (**3.35**). This is followed by clinical examination; this should be methodical and orderly (*Table 3.4*) with documentation of all findings. An important aim of the examination is to rule out pelvic malignancy or

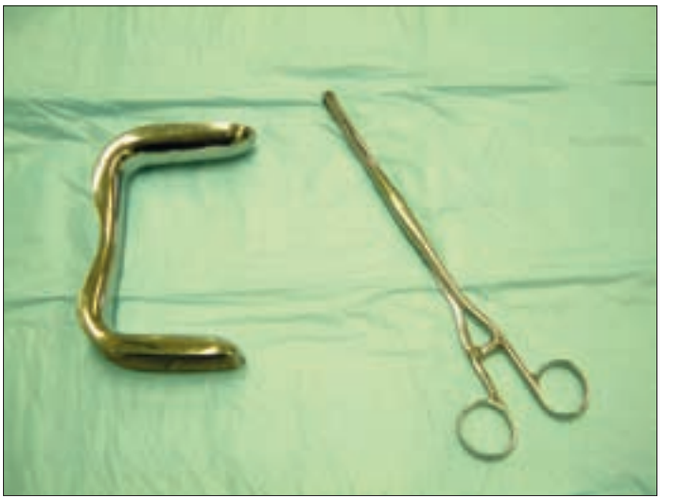
3.35 Pad test: weighing pads worn over a specified period of time.

Table 3.4 Clinical examination at urodynamics should include the following

- Rectal examination in men:
  - Prostate size, consistency, and other features
  - Anal sphincter tone (passive and on voluntary squeeze)
  - Perianal sensation
  - Rectal contents (e.g. constipation)
  - Rectal mucosal abnormalities
- Pelvic examination in women:
  - Vulval pathology and oestrogen status
  - Observation of stress incontinence on multiple coughs
  - Pelvic organ prolapse in each of the specific compartments, often examined in the lateral position (**3.36**) and aided by a speculum, forceps, and a good source of light (**3.37**)
  - Any pelvic mass lesion, including examination of the uterine cervix
  - Rectal examination
- Focused neurological examination in all cases



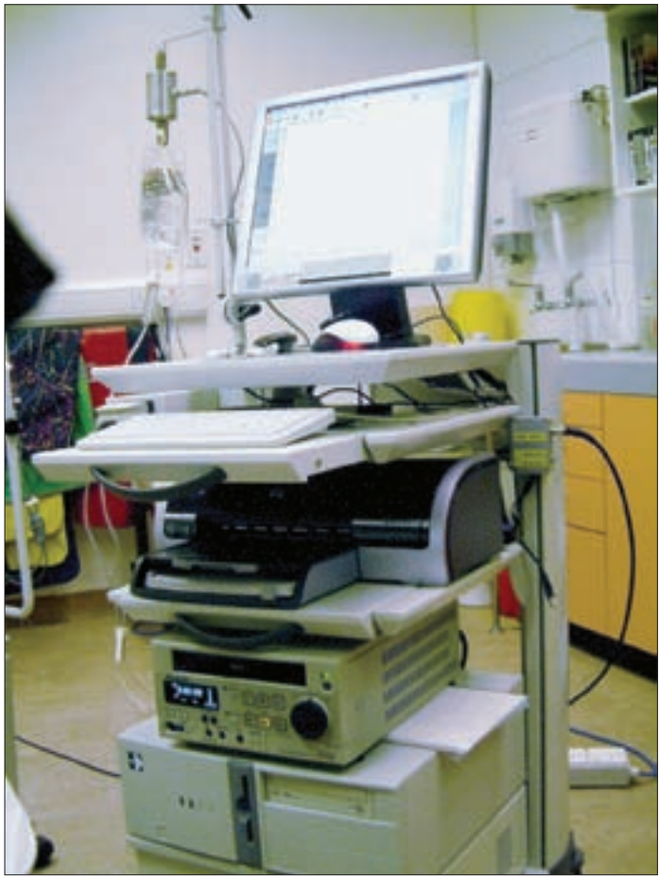
3.36 Vaginal examination in the left lateral position with Sims speculum in place.



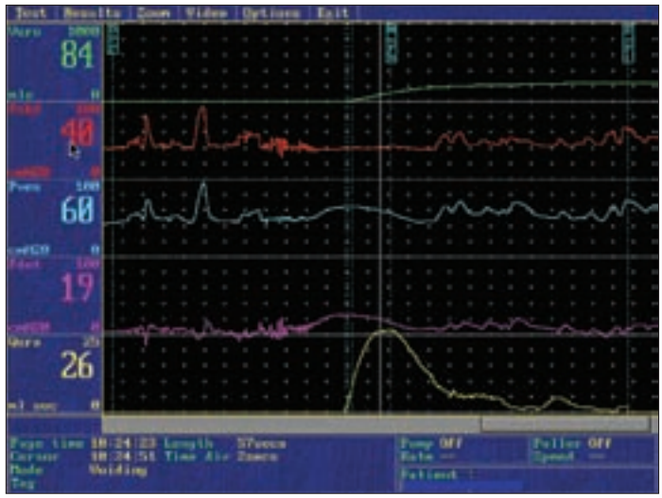
3.37 Tools for pelvic examination.

any other significant pathology that may present with lower urinary tract or pelvic symptoms.

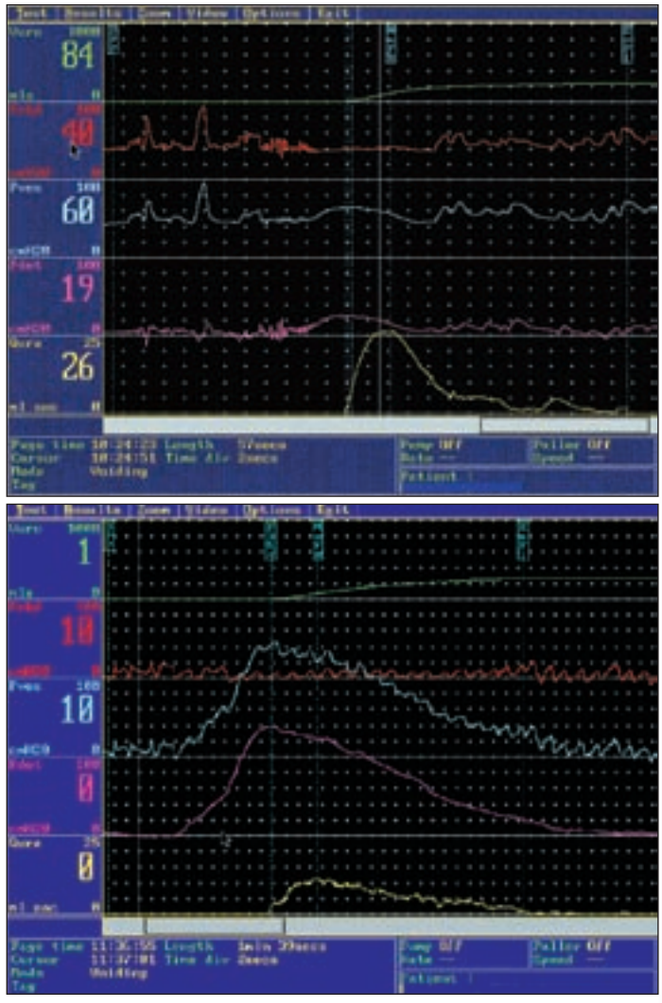
Computers for modern urodynamic systems are accompanied by good-quality monitors, printers, and video recording equipment (**3.38**). The colour-coded traces allow easy recognition of individual lines (**3.39**). The grids on the tracing represent the scale, which must be established prior to making a recording. A good urodynamicist makes observations in real time with constant corroboration of symptoms experienced by the individual under scrutiny, and creates urodynamic impressions based on this. The technique of urodynamics may be 'tweaked' in several different ways depending on the requirements of the specific question being asked. The relationship between pressure and flow of the reservoir and its outlet is probably best illustrated in bladder outlet obstruction. **3.40** illustrates a normal flow phase study and, in contrast, an obstructed void, demonstrating characteristic high pressure and low flow. In contrast, detrusor overactivity is mainly a fill-phase phenomenon with characteristic phasic or end-fill overactive waves observed in the detrusor pressure trace (**3.41**),



3.38 The urodynamic computer stack.



3.39 CMG traces.



3.40 Normal and obstructed traces on voiding phase cystometrograms.

although voiding may occur intermittently off the top of a large intravesical pressure rise. In such situations, the bladder volume falls below the threshold required to cause overactivity with consequent decrease in detrusor pressure until continued bladder filling leads to a further rise and urinary leakage. Overactive pressure waves such as these may or may not be voluntarily controlled by the individual when asked to do so, and may or may not be accompanied by symptoms. Neurogenic detrusor overactivity, previously known as detrusor hyperreflexia, is often more pronounced compared to the idiopathic variety, and may in some situations be accompanied by an active dyssynergic contraction of the external sphincter and pelvic floor, a condition known as detrusor–sphincter dyssynergia (**3.42**).

The interpretation of pressure–flow studies may be enhanced by the use of indices to assess voiding function. Three important indices are in common usage:

- Bladder Outlet Obstruction Index (BOOI).
- Bladder Contractility Index (BCI).
- Bladder Voiding Efficiency (BVE).

The Bladder Outlet Obstruction Index (BOOI), previously known as the Abrams–Griffiths number, is particularly helpful in men with symptoms suggestive of outflow obstruction. It has been shown that 89% of men with maximum flow rates of <10 ml/s and 71% with maximum flow rates between 10–15 ml/s are obstructed on pressure–flow studies, which obviously suggests that almost one-third of individuals with flow rates between 10–15 ml/s are unobstructed. It is therefore important to establish bladder outflow obstruction as accurately as possible in equivocal cases, particularly if surgical management is being considered. The calculation of BOOI and its interpretation may be summarized as:

$$BOOI = pdetQ_{max} - 2Q_{max}$$

BOOI	>40	Obstructed
BOOI	20–40	Partially obstructed or equivocal
BOOI	<20	Unobstructed

The BOOI derived from this formula may be plotted on to the ICS nomogram to confirm the diagnosis and quantification of the degree of obstruction in a visually helpful manner (**3.43**).

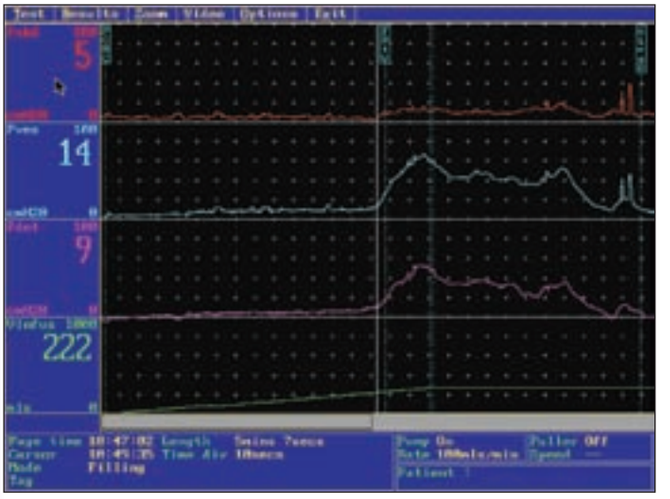
The Bladder Contractility Index (BCI) is useful in understanding detrusor function in equivocal cases. The BCI may similarly be plotted on a nomogram (**3.44**).

$$BCI = pdetQ_{max} + 5Q_{max}$$

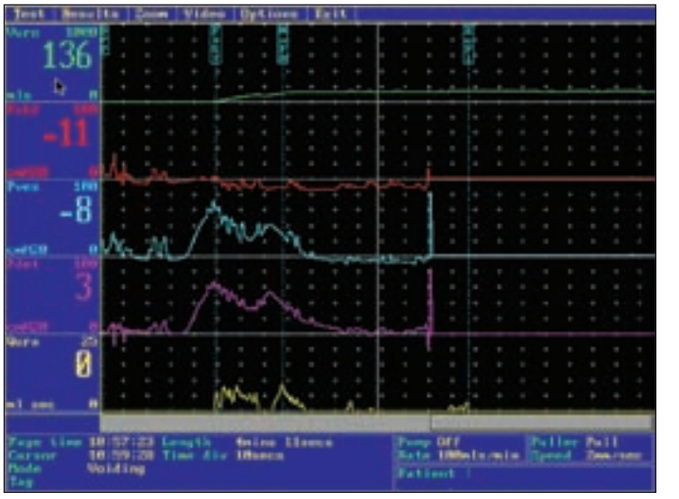
BCI	>150	Strong Contractility
BCI	100–150	Normal Contractility
BCI	<100	Weak Contractility

Bladder Voiding Efficiency (BVE) is a measure of bladder emptying and is calculated by:

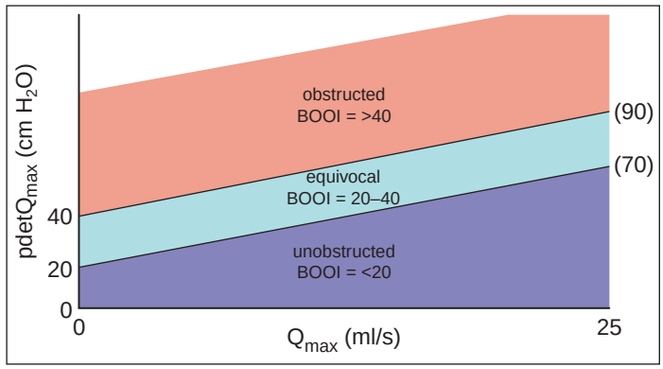
$$BVE = \frac{\text{voided volume}}{\text{total bladder capacity}} \times 100\%$$



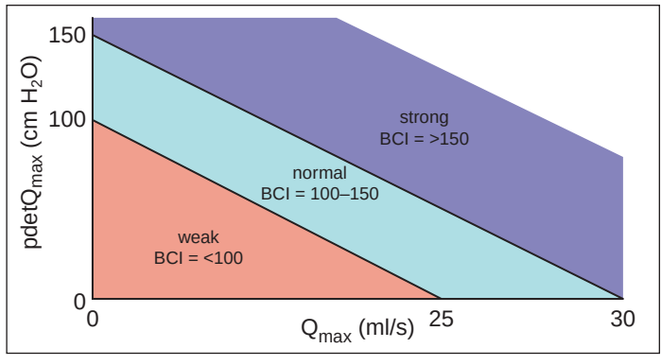
3.41 Detrusor overactivity.



3.42 Detrusor–external sphincter dyssynergia in a man with a spinal cord injury.



3.43 BOOI plotted on the ICS nomogram.



3.44 BCI nomogram.

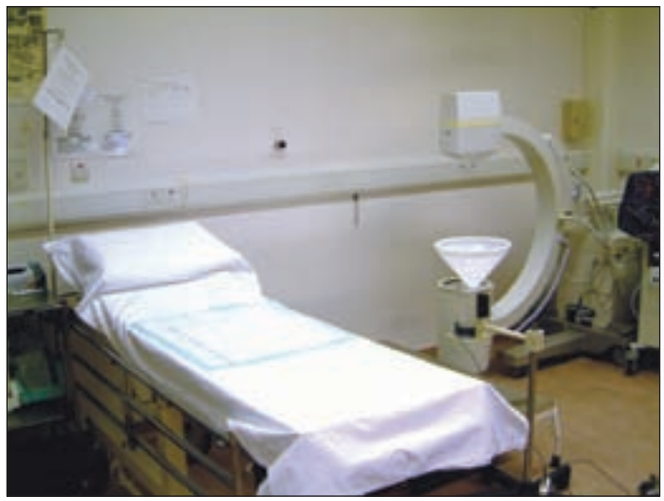
Videourodynamics

Videourodynamics (VUDS), or videocystometry, combines fluoroscopic imaging with pressure–flow studies. The obvious advantage of this is to add anatomical information to functional data, which is indicated when simultaneous study of structure and function is required. Morphological correlation of pressure readings also reduces the chances of misinterpretation of the pressure readings alone, and furthermore a retrospective frame-by-frame re-examination of the study allows for correlation with subtle cystometric findings. This is especially useful in the setting of a multidisciplinary team meeting.

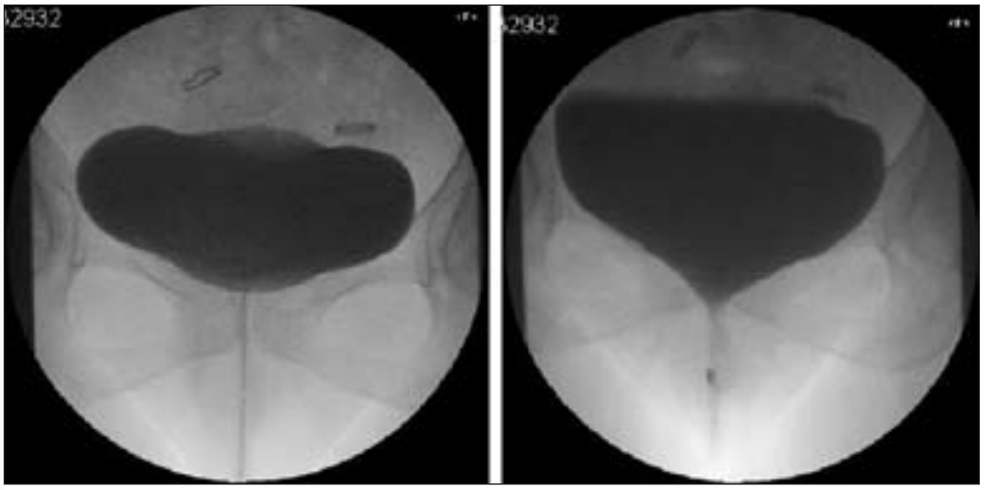
Indications for VUDS include situations where the diagnosis cannot be made with more simple investigations such as standard cystometry and physical examination, and when structural information is required, such as to detect the presence or grade of vesicoureteric reflux or the level of infravesical obstruction. Some of these are listed below:

- Neurogenic bladder dysfunction (spinal cord injury, cerebrovascular accidents, Parkinson's disease, multiple sclerosis, myelomeningocoele, etc.).
- Suspected poor compliance.
- Failed incontinence surgery.
- Hypermobility or pelvic organ prolapse associated with incontinence.
- Bladder outflow obstruction in females.
- Incontinence following radical prostatectomy, radical hysterectomy and abdominoperineal resection.
- Malfunctioning artificial urinary sphincter.
- Paediatric dysfunctional voiding.
- Pre-transplant evaluation.

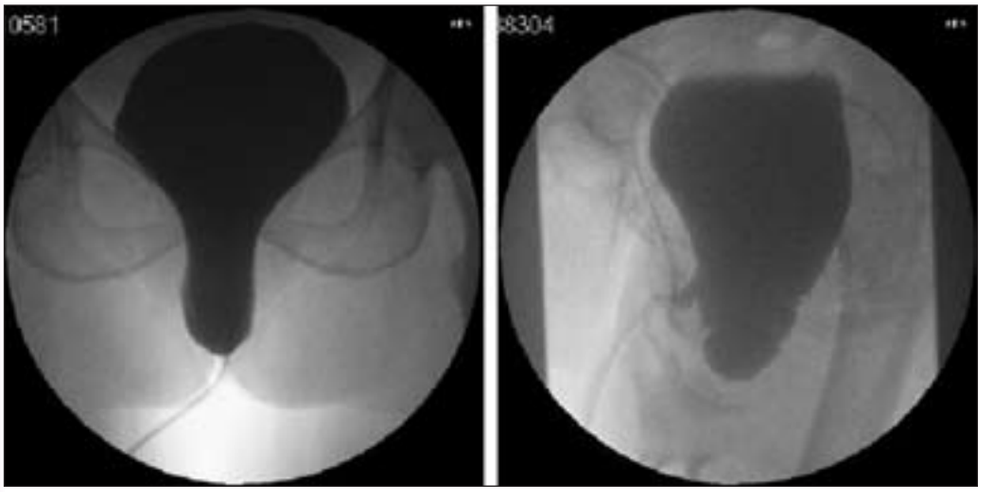
The videourodynamic equipment that is required is illustrated in **3.45**. A tilting table and an image intensifier (C-arm) are basic requirements. Although fluoroscopy time is minimal (usually <1 minute), with radiation exposure less than that for an intravenous pyelogram, the technique has to comply with ionizing radiation regulations IR(ME)R. Pressure–flow studies are performed as for standard cystometry with instillation of contrast medium into the bladder, and with imaging performed intermittently as dictated by the requirements of the study. The variety of observations that can be made on VUDS would fill an entire atlas; consequently some conditions have been touched upon here merely to illustrate the range of conditions that may be diagnosed by VUDS. Imaging of women with stress incontinence provides information on the position and behaviour of the pelvic floor and urethra during stress and voiding (**3.46**). Cystocoeles are also easily diagnosed on video studies (**3.47**); it may be possible to demonstrate a change in symptomatic and urodynamic status after repositioning of



3.45 C-arm for videourodynamics.

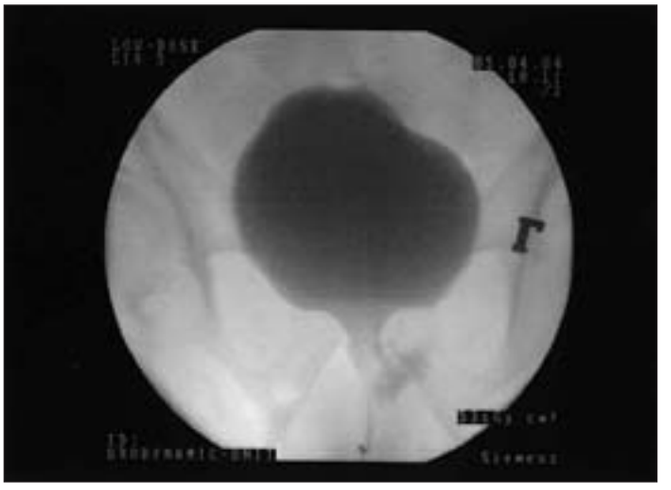


3.46 Type 1 stress incontinence: notice the well-supported bladder neck at rest on the left, and urinary leak on coughing.



3.47 Cystocoele (AP and lateral views).

the prolapsed organ. Videourodynamic studies are used in males to diagnose intrinsic sphincter deficiency, prolapse of the external sphincter complex following radical pelvic surgery, and poor bladder compliance. Post-prostatectomy incontinence is characterized by an open bladder neck (**3.48**). A distinctive 'fir tree appearance' suggests neurogenic bladder dysfunction (**3.49**) which may or may not be associated with vesicoureteric reflux (**3.50**). Artificial urinary sphincter malfunctions may also be diagnosed by video studies (**3.51**).



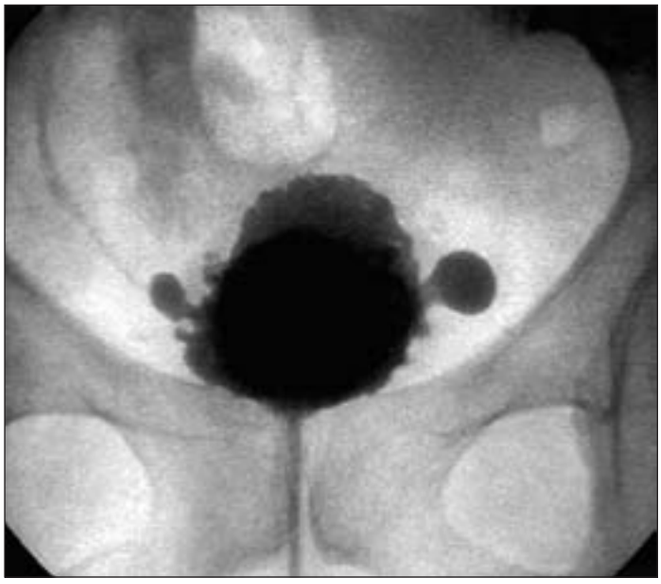
3.48 Post-prostatectomy incontinence.

Ambulatory urodynamics

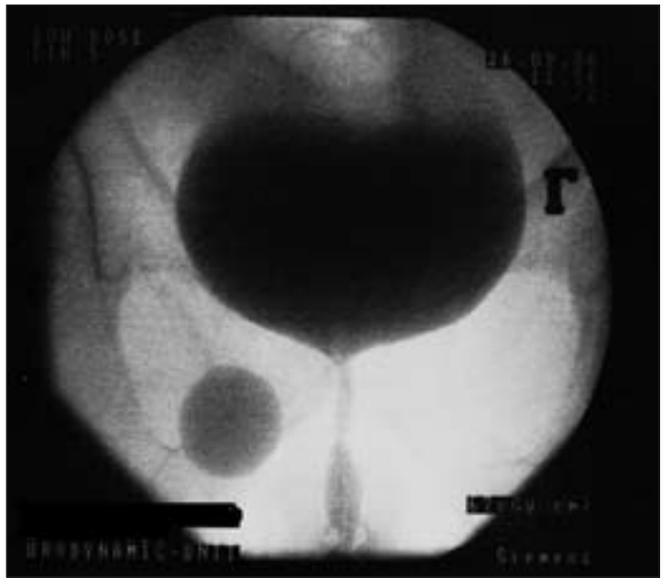
Ambulatory urodynamics employs a portable urodynamic technique with natural-fill to record the behaviour of the lower urinary tract during normal physical activity. The obvious advantage of this technique is the near-physiologic

process of cystometry using a natural filling medium at a natural filling rate in a natural environment. The patient is able to be more active than would be possible within the confines of the urodynamics laboratory and perhaps to perform a large amount of normal daily activities whilst being monitored. Furthermore, ambulatory urodynamics is able to reproduce patients' symptoms and detect detrusor overactivity in a significant proportion of the 20% of cases in which standard cystometry fails to do so. However, as always, there are limitations. Those critical of the technique argue that the increased proportion of detrusor overactivity detected by ambulatory urodynamics may be attributable to the increased provocation from increased activity, the prolonged duration of the test, or catheter irritation during ambulation. Furthermore, approximately 30% of normal individuals have detrusor overactivity on ambulatory urodynamics, although this is by itself considered to be of dubious clinical significance unless accompanied by symptoms suggestive of an overactive bladder.

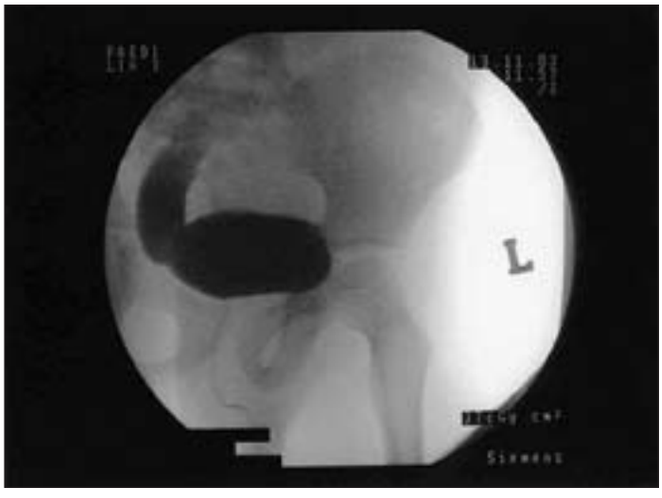
The ambulatory urodynamics equipment (**3.52**) comprises a microcomputer that is able to store the recording; this is carried by the patient via a strap that allows it to be



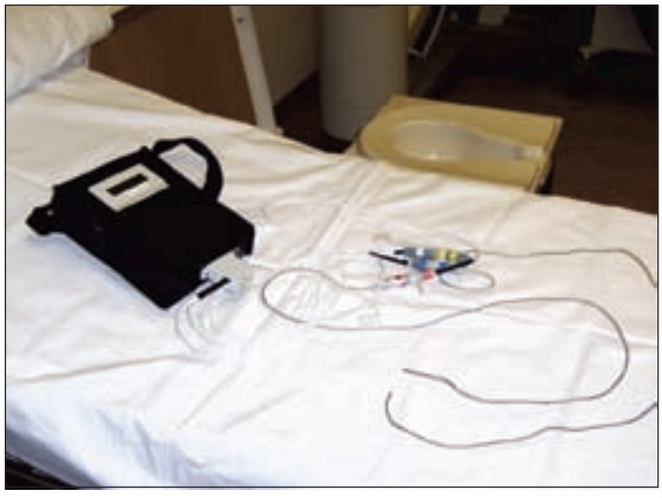
3.49 Neurogenic bladder.



3.51 Intact reservoir noted near a leaking artificial sphincter.



3.50 Vesicoureteric reflux.



3.52 Ambulatory monitoring set-up.

slung over the shoulder. An event marker allows the patient to record events such as urinary leakage or urgency. Pressure lines are inserted as for standard cystometry, and securely taped to avoid displacement. Regular coughs are encouraged to allow quality control by confirming satisfactory line position. An incontinence pad with temperature-sensitive diodes used to detect leakage is worn by the individual (**3.53**). This provides a continuous reading of the perineal temperature and detects any rise of temperature consequent to urinary leakage. The individual is requested to maintain a steady fluid intake, and to undertake usual physical activity such as climbing a flight of stairs and any specific activity that would tend to result in leakage in normal circumstances. Three phases are recorded: a resting phase with the patient sitting, an ambulatory phase when the patient is asked to walk around the hospital, and an exercise phase which should include any physical manoeuvres that would normally cause incontinence for that patient. The patient is provided with an ambulatory urodynamics diary, which should be used to record all events such as urinary leakage and physical activities, including coughs. Both storage and voiding phases should be recorded as in routine cystometry, and the patient unit consequently should allow connection to a flowmeter.

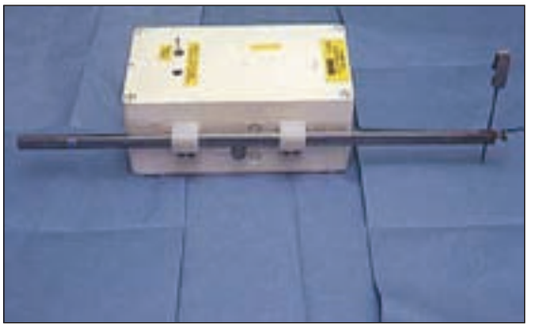
Ambulatory urodynamics remains a second-line urodynamic investigation in cases where standard pressure–flow studies fail to explain a given set of symptoms or a specific phenomenon. It is also useful in 'bashful voiders', investigation of urodynamic disorders in children and research.

3.53 Incontinence pad with temperature-sensitive diodes.

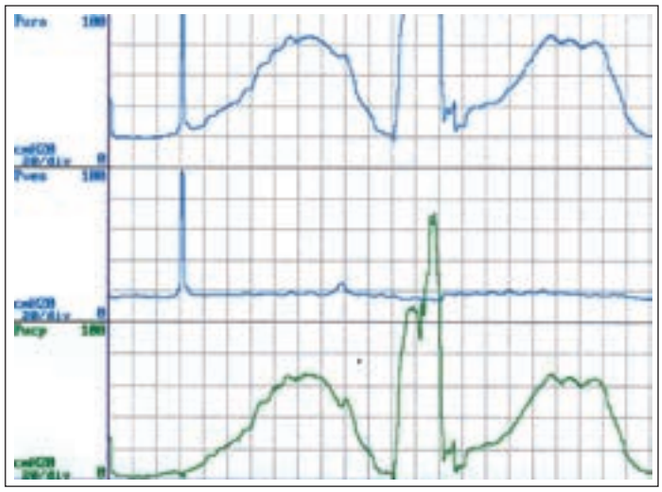
Urethral pressure profilometry

Urethral function studies include a range of procedures including static, dynamic and voiding urethral pressure profilometry (UPP), urethral electrical conductance, the fluid bridge test and measurement of leak-point pressure. These tests are primarily used to classify urinary incontinence, such as the differentiation of urethral hypermobility from intrinsic sphincter dysfunction. Urethral function tests are not without controversy and are often debated in scientific meetings, and are consequently not part of the routine armamentarium of a urodynamic service. Perhaps their greatest value today is in their application in research.

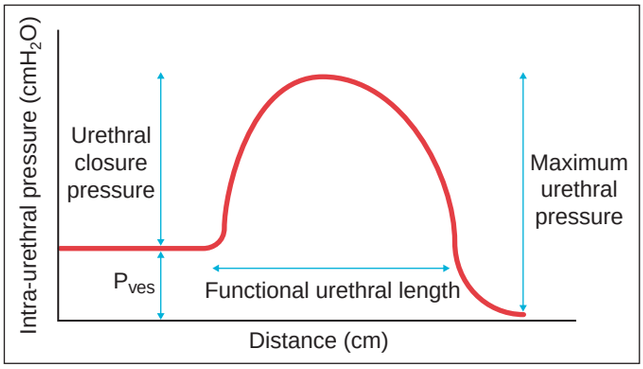
The technique of UPP utilizes a motorized withdrawal system known as the Brown and Wickham technique (**3.54**), by which a catheter is withdrawn through the urethra at a predetermined rate (1 mm/second). A fluid perfusion technique enables the occlusive pressure of the urethral sidewalls to be simultaneously measured as the catheter travels down the urethra; an alternative is to use a solid-state catheter. This produces a characteristic tracing (**3.55**) which is described by employing the descriptive terminology provided by the International Continence Society (**3.56**). The urethral pressure profile (UPP) is the intraluminal pressure along the length of the urethra with the bladder at rest. Maximum urethral pressure (MUP) is the maximum pressure measured, whereas maximum urethral closure pressure (MUCP) is the difference between the maximum urethral pressure and the intravesical pressure. Functional profile length indicates the length of the urethra along which the urethral pressure exceeds intravesical pressure.



3.54 UPP: mechanical system to allow catheter withdrawal at a predetermined rate.



3.55 Normal urethral pressure profile in a female.



3.56 ICS terminology for urethral pressure profilometry.

Summary

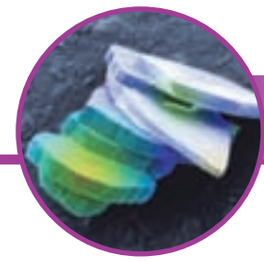
Lower urinary tracts are fascinating in that they provide an opportunity for true deductive clinical diagnosis. Many of the tests described in this chapter will not be required for the majority of straightforward cases that urologists encounter in the outpatient clinic. Conversely, some cases may require complex investigations that are outside the remit of this book, such as complex neurophysiological tests. The clinical skill and judgement of the clinician is paramount in determining the optimal combination of tests to achieve a diagnosis and to ask the pertinent question of the investigation being requested. Although in many cases the cause of the symptoms may be found to lie outside the urinary tract, in most cases a reasonably precise diagnosis is possible and should be aimed for in order to be able to offer appropriate and effective treatment advice.

Further reading

Abrams P (ed.) (2006). *Urodynamics*, 3rd edition. Springer-Verlag Limited, London.

Boone TB (ed.) (2006). *Urodynamics I. The Urological Clinics of North America*. WB Saunders, Philadelphia.

Schäfer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spangberg A, Sterling AM, Zinner NR, van Kerrebroeck P. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure–flow studies. *Neurourol Urodyn* **21**: 261–274.



Stone Disease of the Urinary Tract

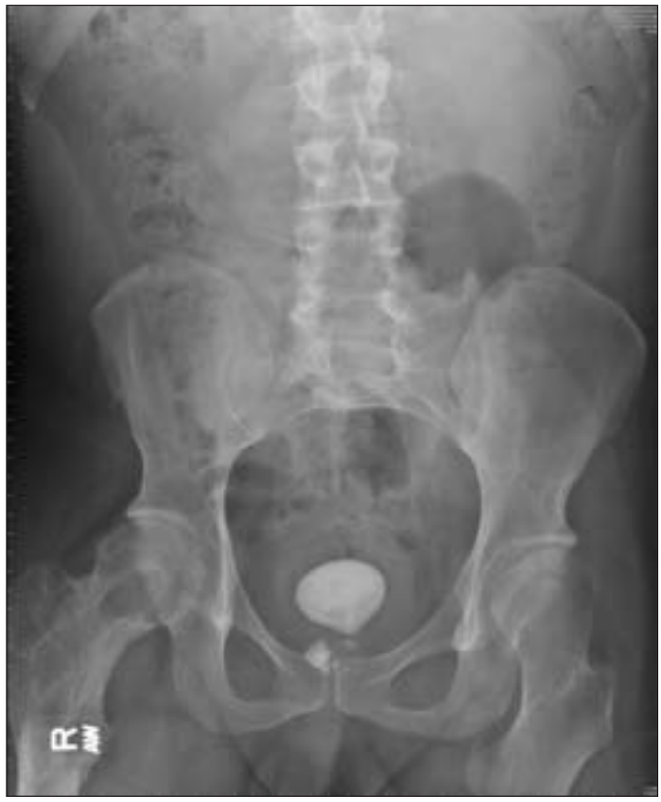
Nimalan Arumainayagam

Introduction

The first documented urinary tract stones were found among the 7000-year-old remains of the pelvic bones of a teenage boy in El-Amara. Before the Industrial Revolution in Britain, bladder stones were more common than upper urinary tract calculi. Later, around the turn of the nineteenth century, upper tract stone disease began to become more prevalent. In developing countries bladder calculi are still endemic. **4.1** shows the radiographic images of such bladder stones.

Stone disease in developed countries is more common in males, and in up to 80% of cases there is no obvious precipitating cause.

The presenting symptoms of upper urinary tract stones are loin pain, which may radiate to the groin in a colicky nature, and haematuria (microscopic or macroscopic). If urinary sepsis is present, there may also be symptoms and signs of infection. Stones in the bladder, and sometimes in the lower ureter, may cause lower urinary tract symptoms (frequency urgency and nocturia from their irritative effects, poor stream and hesitancy. Bladder calculi may also cause sudden changes in urinary stream due to the stone acting as a 'ball-valve' over the bladder outlet, and the symptom of 'strangury' where the bladder can contract strongly and painfully in an attempt to evacuate a calculus.

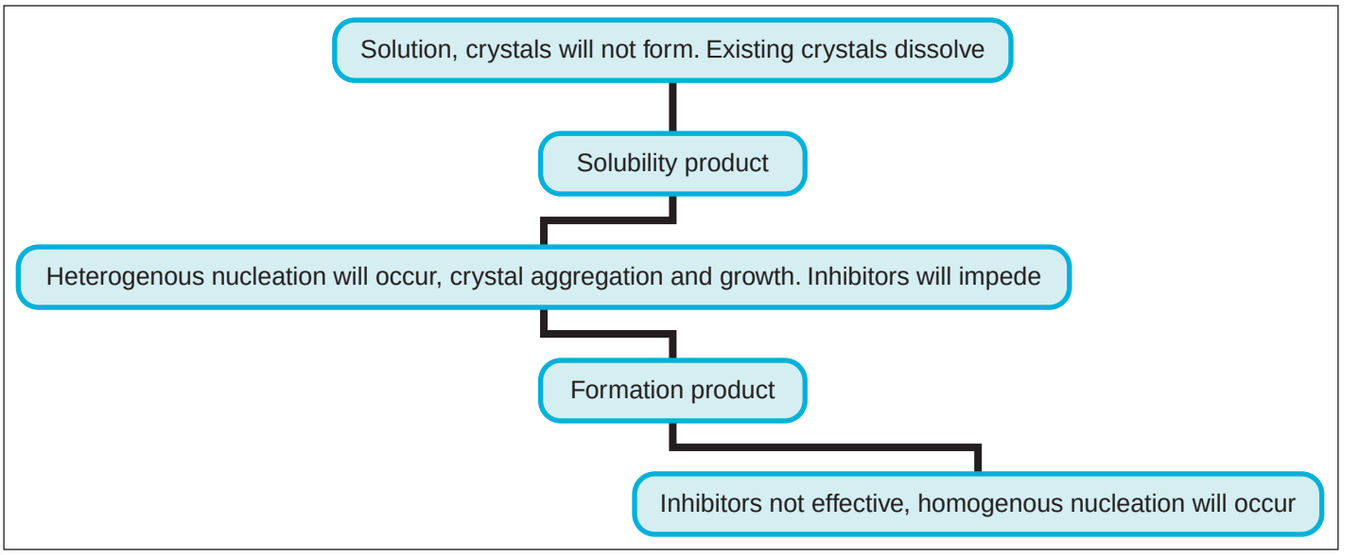


4.1 Plain X-ray showing a large bladder stone.

Stone formation

Stone formation occurs when elements normally dissolved in the urine form crystals that then aggregate (**4.2**). Stone formation may be either homogeneous (where the nucleus of the stone around which crystals aggregate is the same material as that of the crystal) or heterogeneous (where it is different).

Critical to the formation of any crystal is the saturation state of the solution. The saturation state of a solution depends on the pH and ionic strength of the given solution, as well as the presence of any soluble complexes.



4.2 Crystallization theory of stone formation.

When the solution is not saturated with a specific solute, then no crystals will form or grow, and any crystals already present will dissolve.

With increasing concentrations of solute, the solution will become fully saturated with that solute (saturation product KSP). If the concentration of the solute is increased even more, then the formation product (KFP) is reached.

Between the saturation product and the formation product, crystals of the solute cannot form spontaneously, but can aggregate on previously formed crystals (homogeneous crystallization), or aggregate on different formed crystals or foreign bodies (heterogeneous crystallization).

Once the concentration of the solute is greater than the formation product (KFP), the solution becomes unstable and spontaneous crystal formation occurs. Such crystallization can be inhibited by other constituents (e.g. magnesium and citrate are proven inhibitors of stone formation in urine).

Stasis contributes to stone formation and thus stones tend to form at sites of obstruction to urinary flow.

Risk factors for stone formation

There are specific risk factors that if present in an individual can lead to an increased incidence in the formation of certain types of stones (*Table 4.1*). There are a number of general factors that have been identified as rendering an individual more likely to make any of a number of types of stones which are summarized in *Table 4.2*.

Table 4.1 Risk factors for stone formation

Presence of promoters of stone formation
Absence (or reduced levels) of inhibitors of stone formation
Infection
Urinary stasis
Concentrated urine (poor fluid intake)
Diet too high or too low in calcium
Sedentary occupations
Anatomical abnormalities of the urinary tract

Table 4.2 Common types of stone

Calcium oxalate and phosphate	38%
Calcium oxalate	26%
Calcium phosphate	7%
Magnesium ammonium phosphate (Struvite)	21%
Uric acid	5%
Cystine	3%

Specific inhibitors of stone formation include magnesium, citrate, nephrocalcin, Tamm–Horsfall glycoprotein and uropontin.

Calcium stones

Calcium is the most common constituent of urinary tract calculi. Such stones are radio-opaque. Common states leading to calcium oxalate stone formation are listed in *Table 4.3*.

Sixty per cent of people with calcium stones will have an absorptive hypercalciuria, i.e. an altered intestinal response to vitamin D, leading to increased absorption of calcium. Ten per cent of patients with calcium stones will have renal hypercalciuria, i.e. the kidneys are unable to conserve calcium, and such patients develop hypercalcaemia (*Table 4.4*) and subsequent increased parathyroid secretion.

Hyperparathyroidism accounts for 6% of people with such urinary tract stone disease.

Type 1 renal tubular acidosis (autosomal dominant inheritance) usually leads to the formation of pure calcium phosphate stones. In this disease, patients are unable to acidify their urine below a pH of 6.0, and have decreased excretion of bicarbonate, potassium and citrate in the urine.

Table 4.3 Metabolic risk factors for calcium oxalate stone formation

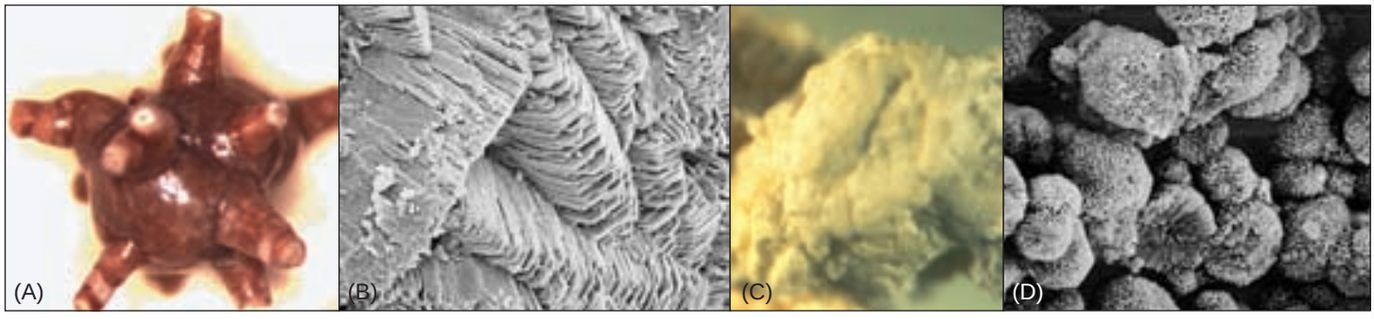
Hypercalciuria
Hypercalcaemia
Hyperoxaluria
Hyperuricosuria
Hypocitraturia
Hypomagnesuria
Hypophosphaturia

Hyperoxaluria may be either congenital or acquired. Primary hyperoxaluria (excessive production and hence urinary excretion of oxalic acid) is rare, and results in severe recurrent calcium oxalate stone formation leading to nephrocalcinosis. The most common type of acquired hyperoxaluria is enteric and occurs in malabsorption-type syndromes where the colonic epithelium is exposed to bile salts, resulting in increased permeability of the colon to oxalate. Dietary factors are important in all types of hyperoxaluria. Dietary calcium binds oxalate and prevents it from being absorbed from the gut. Large quantities of dietary calcium supplements are sometimes needed in the treatment of enteric hyperoxaluria.

- *Calcium oxalate*. Also called whewellite or 'mulberry' stones, these stones are characteristically dark brown/black in colour, with a dense, smooth appearance (**4.3A**). **4.3B** shows the crystals under electron microscopy. Calcium oxalate monohydrate crystals are dumbbell-shaped when viewed under light microscopy.
- *Calcium phosphate*. Calcium hydroxyphosphate stones commonly comprise a significant proportion of carbonate to form apatite stones. These apatite stones are normally white in colour (**4.3C**) and are relatively poorly crystallized (**4.3D**) compared to hydrated acid calcium phosphate stones.

Table 4.4 Common causes of hypercalcaemia

Hyperparathyroidism (primary and tertiary)
Malignancy
Sarcoidosis
Hyperthyroidism
Cushing's disease



4.3 Calcium stones: (A) calcium oxalate stone (monohydrate); (B) electron micrograph of (A). (C) a calcium hydroxyphosphate stone; (D) electron micrograph of (C); calcium phosphate apatite crystals, which are irregular in shape under the electron microscope.

Magnesium ammonium phosphate stones

These are also called triple phosphate or struvite stones, named after Heinrich von Struve who first described them.

They are usually formed in the presence of chronic urinary infection. Urea-splitting organisms within the urine (e.g. *Proteus* species) cause the urine to become more alkaline with its pH rising above 7.0, which causes precipitation and stone formation (*Table 4.5*).

Table 4.5 Common infectious organisms capable of struvite stone formation

Proteus mirabilis
Klebsiella
Pseudomonas
Bordetella
Haemophilus influenzae

This classically causes the formation of staghorn calculi within the renal pelvis and calyces. The classic staghorn calculus is composed of magnesium ammonium phosphate. They are usually yellow/white in colour and smooth in texture (**4.4A**). Note its appearance under electron microscopy (**4.4B**)

Struvite stone crystals are said to have a 'coffin-lid' appearance under light microscopy.

Uric acid stones

Humans are unable to convert uric acid to allantoin, and therefore uric acid levels in humans are much higher than in many other mammals. Pure uric acid stones are radiolucent and therefore are not seen on plain KUB (kidneys, ureters and bladder) radiographs.

Uric acid is the end product of purine metabolism (*Table 4.6*). It is very insoluble in water and thus, as urine becomes more acidic, more uric acid becomes insoluble and this leads to stone formation (**4.5**).

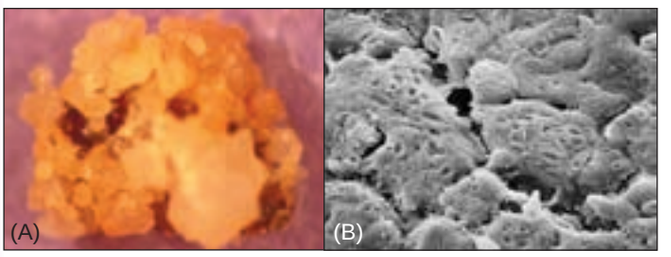
Uric acid stone formation can be idiopathic, and hence occurs in people with normal serum and urine uric acid levels, and may be secondary to hyperuricaemia.

Cystine stones

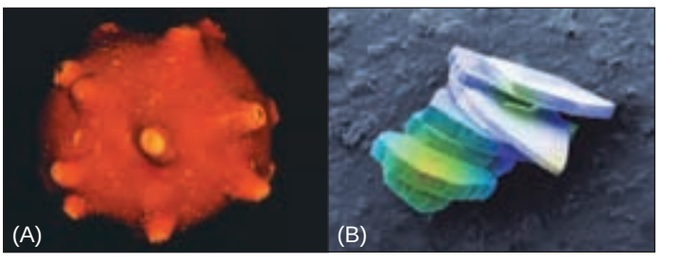
Cystinuria occurs due to an inherited defect in the transport of amino acids cystine, lysine, arginine and ornithine. Cystine is insoluble, and hence excessive concentrations within urine lead to cystine stone formation.

Table 4.6 Causes of high serum uric acid

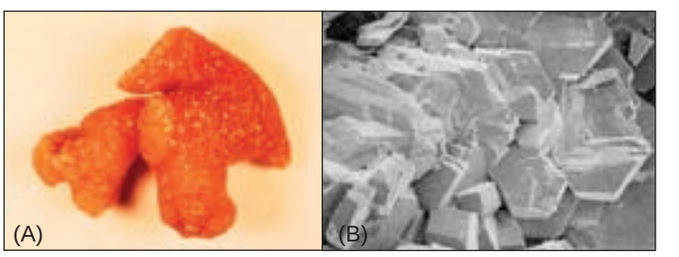
Gout
Myeloproliferative disorders
Chemotherapy
Thiazide diuretic and salicylate treatment



4.4 Magnesium ammonium phosphate stones shown macroscopically (A) and under the electron microscope (B).



4.5 Uric acid stones shown macroscopically (A) and under the electron microscope (B).



4.6 Cystine stones shown macroscopically (A) and under the electron microscope (B).

Note the yellow appearance of this stone, which in this case is smooth (**4.6A**). Under the electron microscope cystine crystals are hexagonal or benzene ring shaped (**4.6B**).

Evaluation of the stone former

Most patients who form stones require what may be termed a simple evaluation to determine any common factors that may predispose them to forming further calculi. For recurrent stone formers, or those who may be termed 'high risk', i.e. those with known underlying metabolic conditions or a strong family history of stone disease, more extensive evaluation may be required. The first step in both evaluations is to take a history, carefully assessing fluid and dietary intake. It is important to have a full record of any other medical problems the patient may have (in particular, conditions such as gout, hyperparathyroidism, myeloproliferative disorders or recurrent urinary tract infections). Knowledge of the medication a patient is currently taking is also important. Steroids, antacids, loop diuretics, colchicine and probenecid are all common drugs that can influence an individual's ability to form stones. Family history, any known congenital abnormalities, level of general activity, and previous surgery are all important.

Investigations for simplified evaluation

- Stone analysis.
- Renal function.
- Serum calcium and uric acid.
- Urine microscopy and culture.
- KUB X-ray.

Investigations suggested for more extensive evaluation

- Serum phosphate.
- Serum magnesium.
- Urinary pH.
- 24-hour urine collection (*Table 4.7*).

Table 4.7 24-hour urine collection for extensive evaluation of the known stone-former

Acidified specimen	Plain specimen
Calcium	pH
Magnesium	Protein
Oxalate	Uric acid
Citrate	Cysteine
Creatinine	Volume
Volume	

Laboratory tests and techniques

Urinalysis

A simple first-line investigation in someone who presents with a history suggestive of urinary tract calculus is to perform a urine dipstick test as shown in **2.3**–**2.5**. The pH of the urine can be ascertained.

Any urine sample positive on dipstick for blood, can be further analysed by urine microscopy. It should be noted, however, that microscopic haematuria is not always present in cases of urinary lithiasis. Press and Smith reported in 1995 that 15% of a series of 140 patients had no haematuria.

The presence of pus cells will give an indicator as to the presence of any infection in the urine, which can be confirmed by further microbiological culture of the urine sample.

In recurrent stone formers a 24-hour urine collection can be performed to assess calcium, uric acid, oxalate and citrate levels within the urine.

Blood tests

- Urea, creatinine and electrolytes to assess renal function.
- Serum calcium, phosphate, uric acid, bicarbonate.
- If serum calcium is high, then the parathyroid hormone level may need to be checked.

Stone analysis

- Chemical analysis of urinary calculi is no longer used due to its inaccuracy.
- Greater accuracy is achieved using optical crystallography and X-ray crystallography.
- Infra-red spectroscopic analysis of stones has the advantage of being able to perform semiquantitative analysis on a small volume of calculus.
- Infra-red reflectance analysis takes less than a minute to perform, needs only very small amounts of stone substance and can perform semiquantitative analysis.

Imaging

Plain radiographs

This is usually the first-line radiological investigation of patients with suspected urinary tract stones (**4.7**). As outlined previously, not all urinary tract calculi are radio-opaque (notably pure uric acid stones are radiolucent and cystine stones are ground glass in appearance).

4.8 shows the typical appearance of a staghorn calculus, where the stone forms within the pelvicalyceal anatomy and thus replicates its shape. The large (>5 mm) left ureteric stones shown in **4.9** were unlikely to pass spontaneously and a ureteric stent was placed to aid drainage from the kidneys.

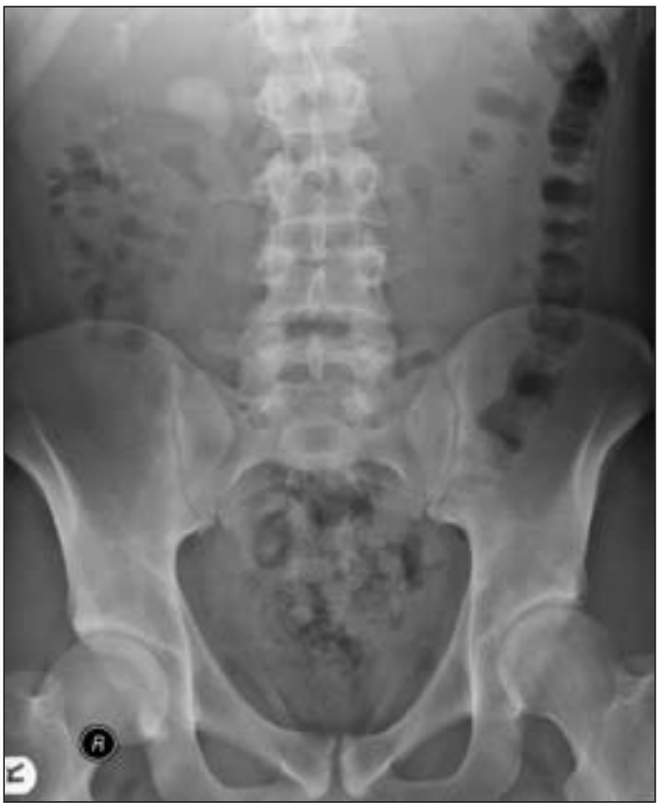
Primary bladder stones are rare in Western countries, but are still prevalent in Asian and Middle-eastern countries. Secondary calculi (**4.10**) may occur due to incomplete bladder emptying and subsequent urinary stasis. Of note, phleboliths may be mistaken for small bladder stones. Phleboliths are calcifications in pelvic veins, and are seen lateral to the bladder outline and outside the position of the ureters on KUB films.

Calcium can be deposited in the parenchyma of the kidney outside of the collecting system. This is called nephrocalcinosis, which can be microscopic or macroscopic. The cause of nephrocalcinosis is a high serum calcium concentration, the causes of which have already been outlined.

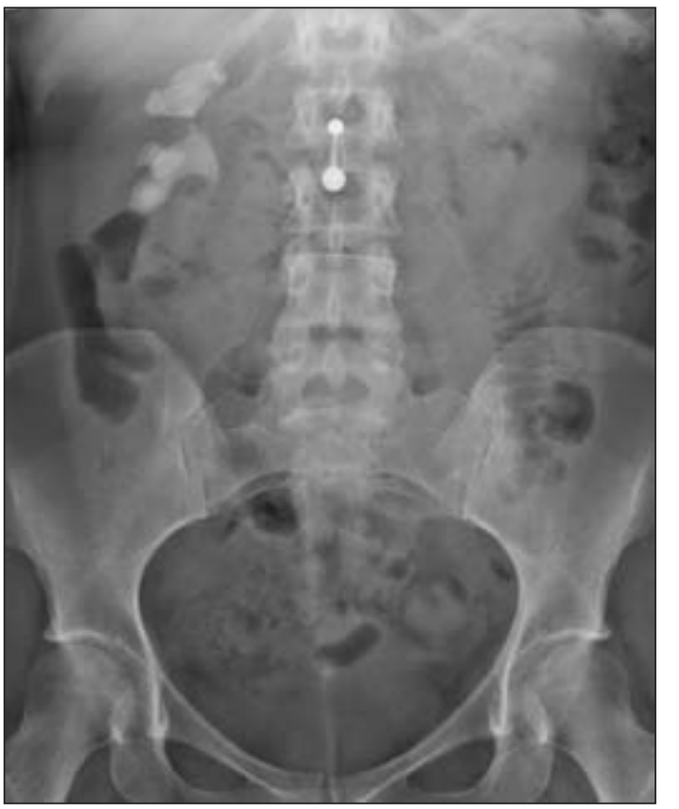
The radiograph in **4.11** shows the classic appearance of 'steine strasse' or 'stone-street' – the entire length of the ureter has a calcified appearance after treatment of a pelvicalyceal stone, with extracorporeal shock wave lithotripsy.

Intravenous urography

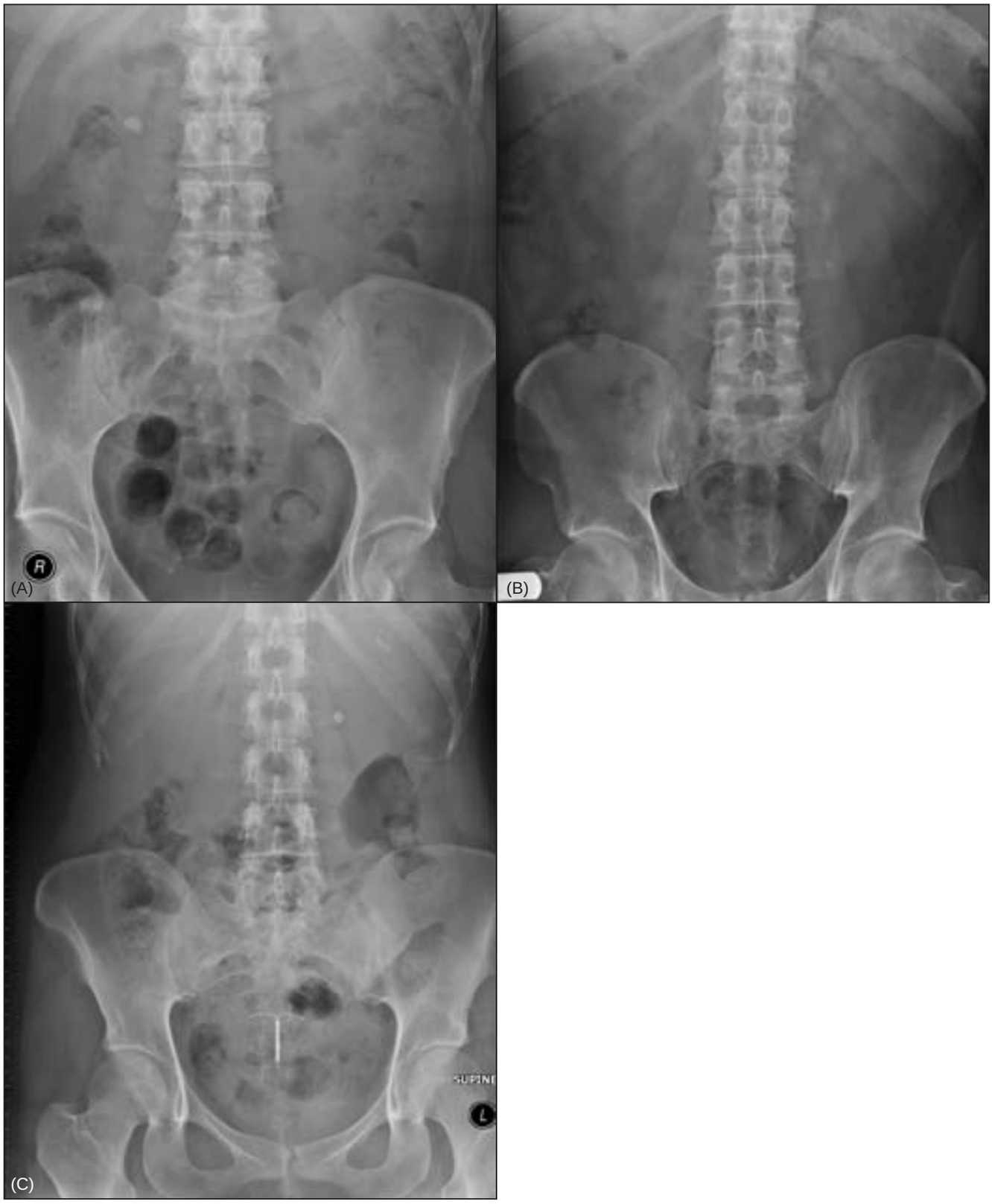
The patient is injected with an intravenous water-soluble contrast, which is then excreted by the kidneys. After an initial control film (i.e. before injection of contrast), a series of plain KUB X-rays are taken to image the excretion of contrast from each kidney. Contrast can be



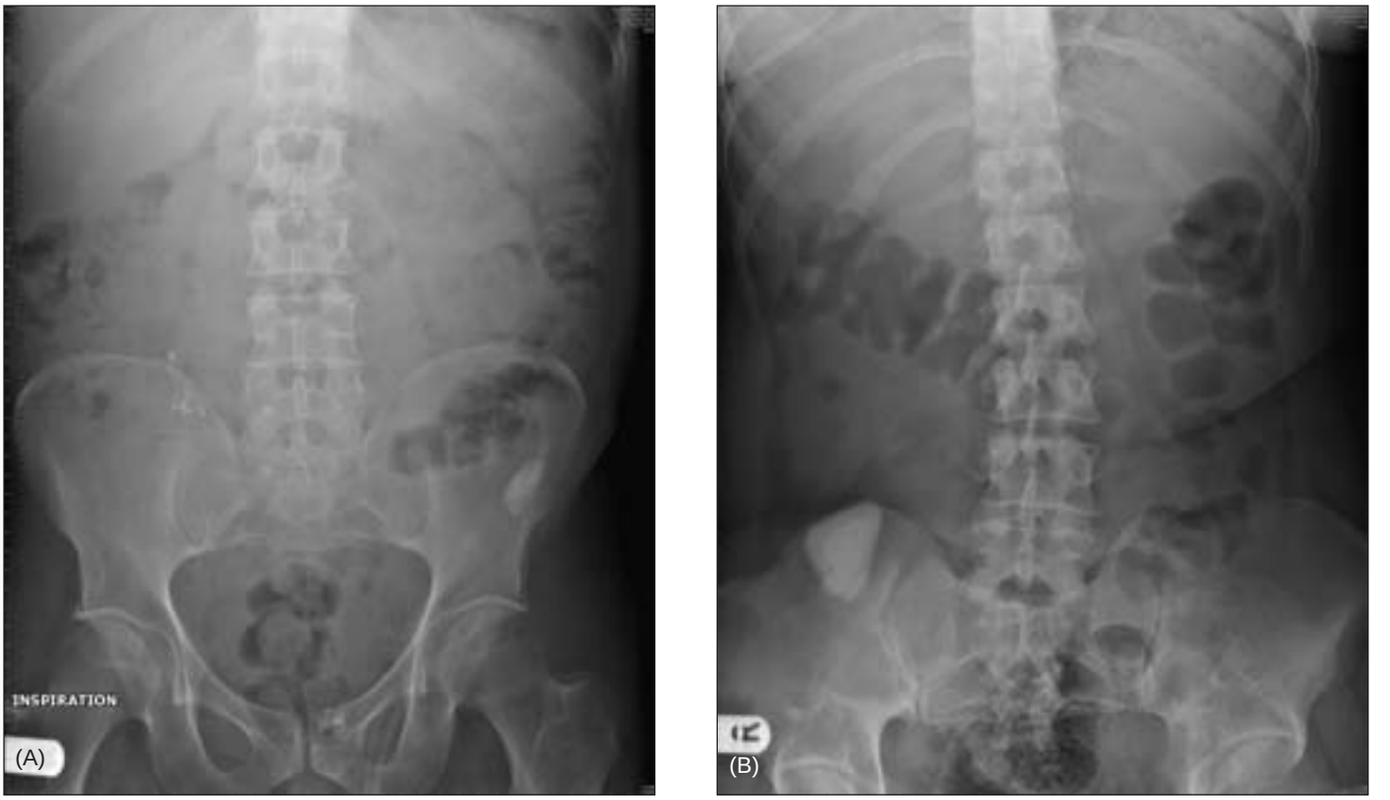
4.7 Plain KUB X-ray of renal calculus.



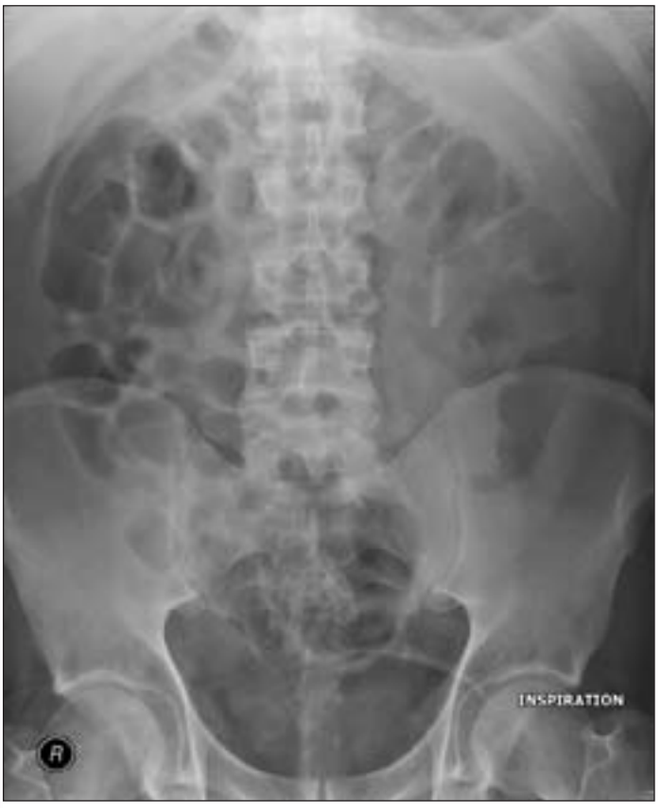
4.8 Plain KUB X-ray of staghorn calculus.



4.9 Plain KUB X-ray of large ureteric calculus: (A) right PUJ stone; (B) left upper ureteric stone; (C) left upper ureteric stone.



4.10 Plain KUB X-ray of bladder calculus: (A) small bladder calculus; (B) bladder calculus in a neo-bladder.

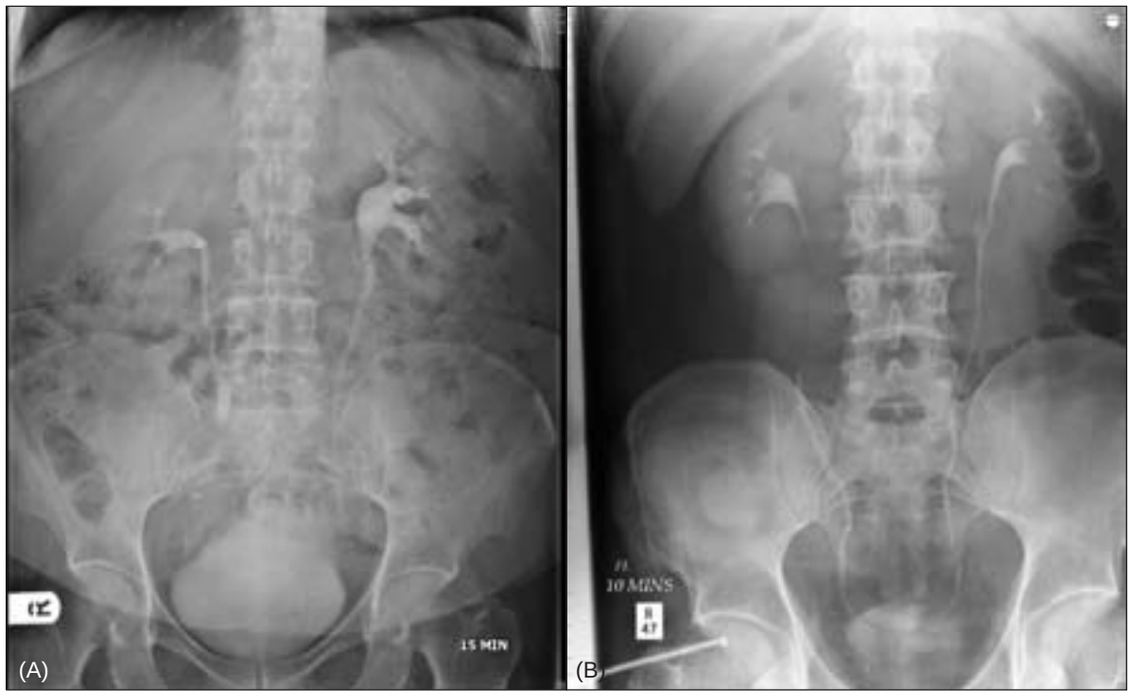


4.11 Plain KUB X-ray of steine strasse stone.

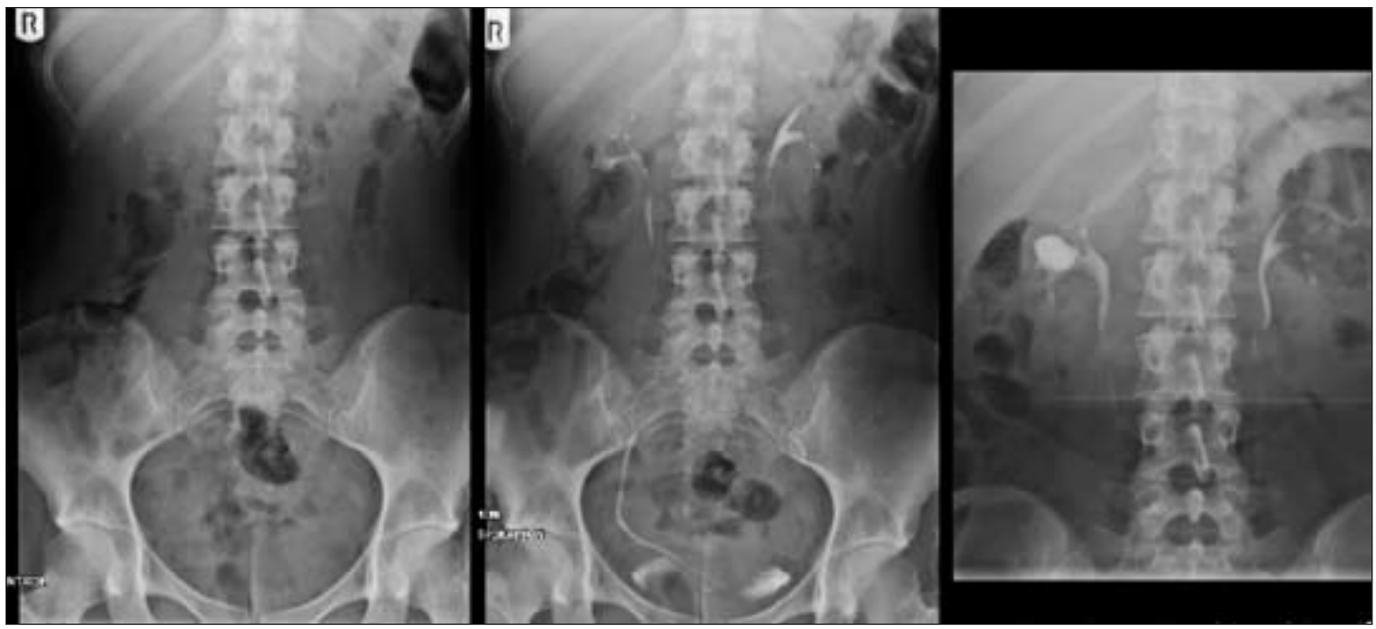
seen draining freely into the bladder. Once the bladder is filled with contrast, the patient is asked to void, and a post-micturition film is taken – this allows for better visualization of the lower ureters. **4.12** shows a normal intravenous urography (IVU) series.

The IVU in **4.13** shows a right kidney stone and **4.14** shows a right VUJ stone causing delayed excretion of contrast from the right kidney.

Notice the delayed excretion of contrast from the right kidney compared with the left side. Subsequently there is a



4.12 Normal IVU series with no obstruction and no abnormality.



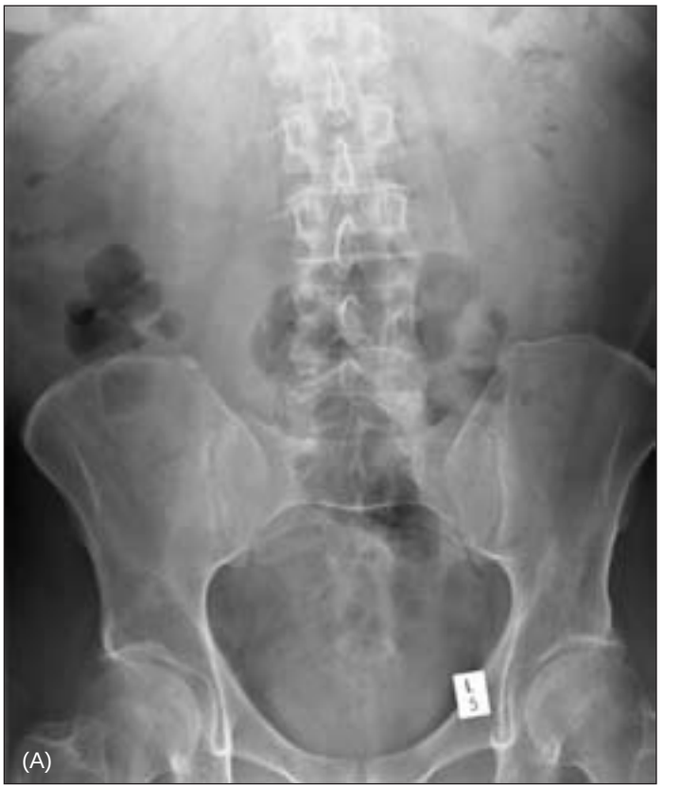
4.13 IVUs of renal calculus.

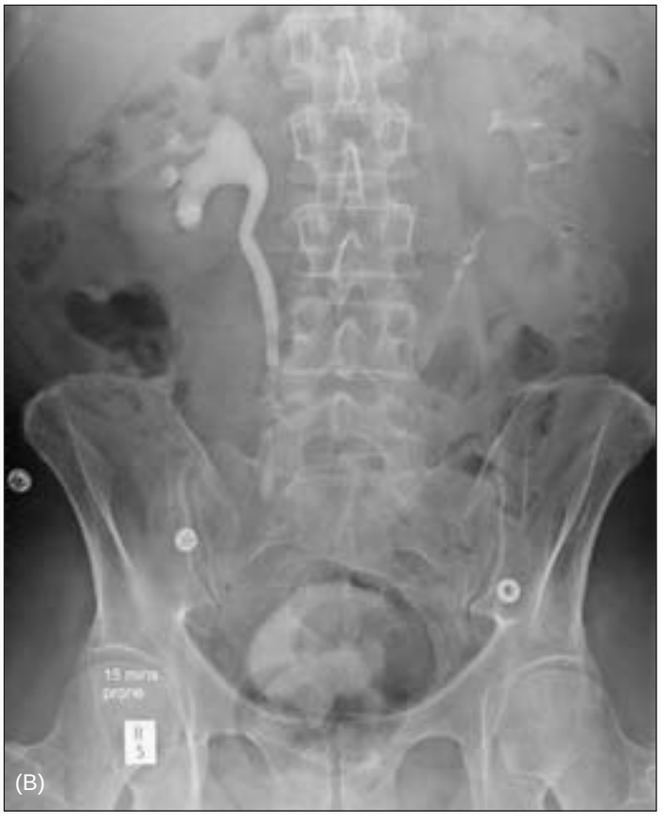
'standing column' of contrast in the right collecting system and ureter, which leads down to the position of the obstructing calculus. Also note the dilatation of the ureter on the right side.

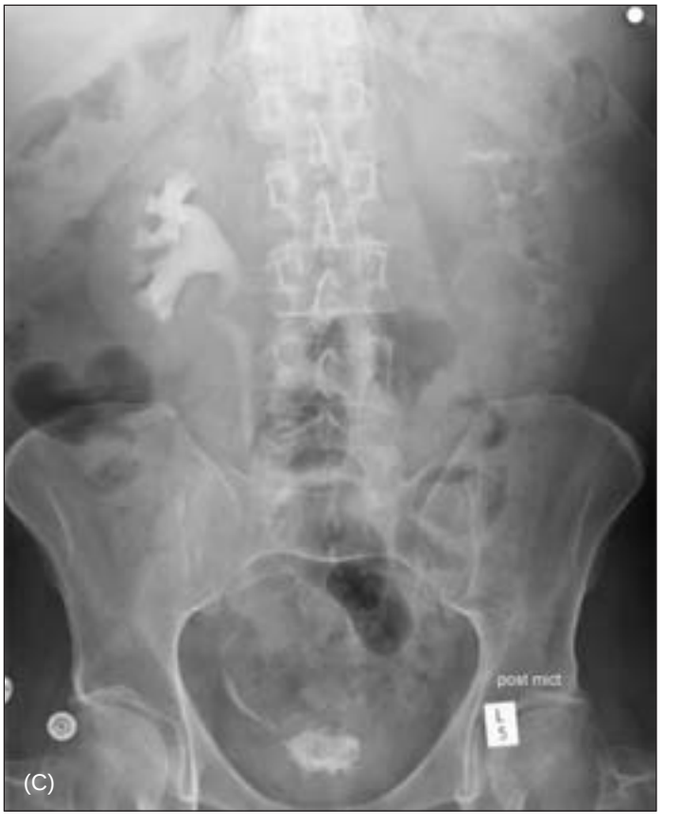
An IVU may also reveal an anatomical abnormality, which will predispose the patient to developing stones (e.g. duplex system; **4.15**).

Retrograde pyelogram

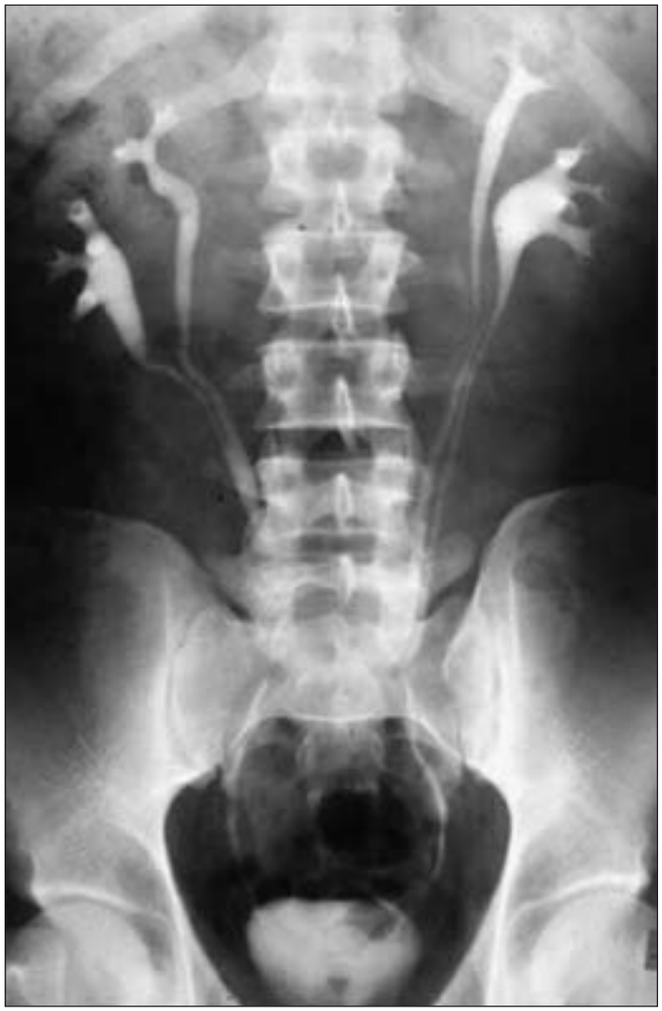
In certain cases, it may be necessary to image one or both ureters by injecting contrast into the distal end of the ureter (i.e. after cannulation of the ureteric opening in the bladder under direct cystoscopic visualization) (**4.16** and **4.17**).







4.14 IVU series of vesicoureteric calculus.



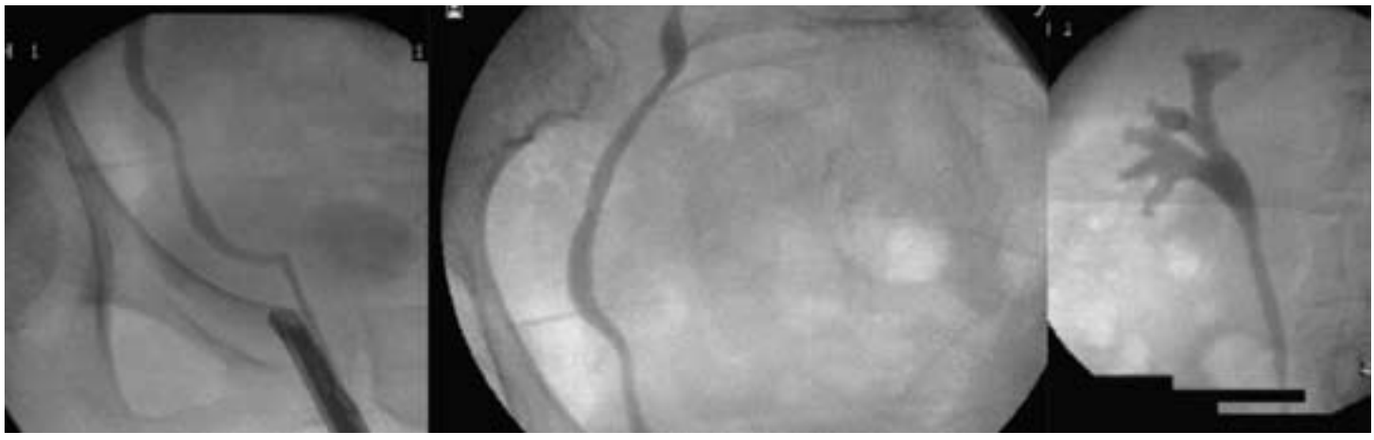
4.15 IVU showing duplex system.

Nephrostogram

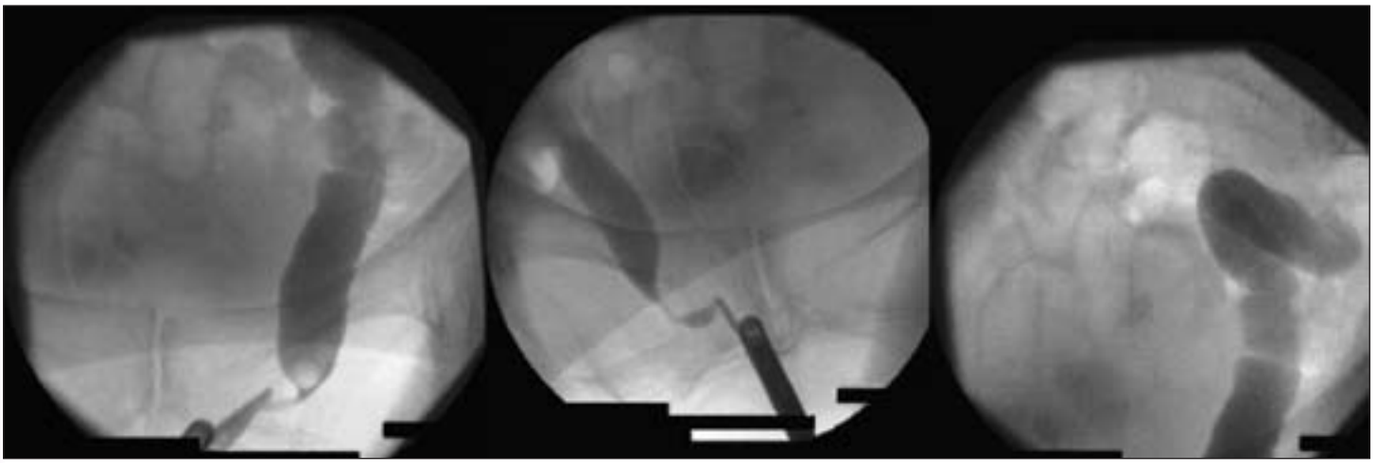
If a stone is causing obstruction, another method of relieving this (other than retrograde stent placement), is to place a percutaneous nephrostomy tube (**4.18**) to allow drainage of urine. Subsequently, contrast can be injected via the nephrostomy tube to image the ureter and any obstruction.

Ultrasound images

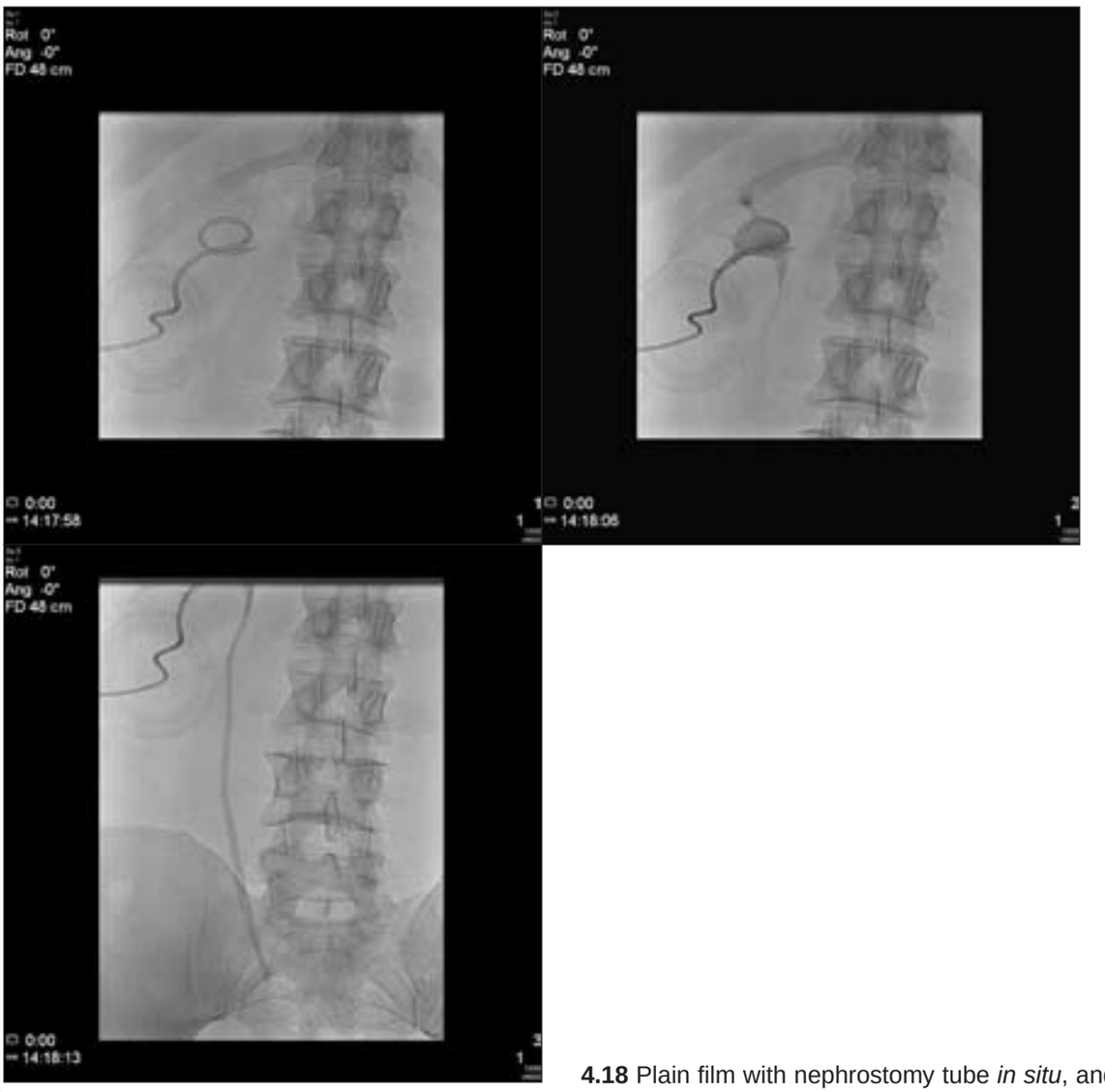
Ultrasound is a non-invasive method capable of demonstrating both urinary calculi and subsequent hydronephrosis (**4.19**). However, ultrasound may be falsely normal with small calculi and no hydronephrosis. Thus, it has been shown that up to one-quarter of patients with normal ultrasound scans have proven stones on IVU.



4.16 Normal retrograde pyelogram.



4.17 Retrograde pyelogram showing dilated ureter.



4.18 Plain film with nephrostomy tube *in situ*, and nephrostogram.

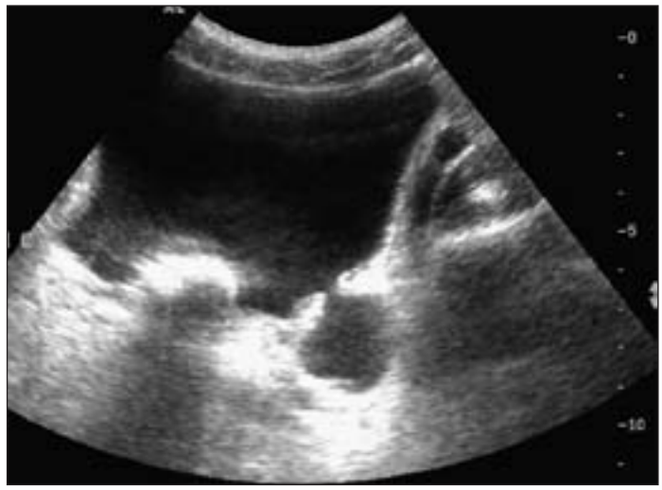
Note the significant hydronephrosis produced by an obstructing calculus (**4.19)** and also the hyperacoustic shadow projected by a bladder calculus (**4.20**).

CT-KUB images

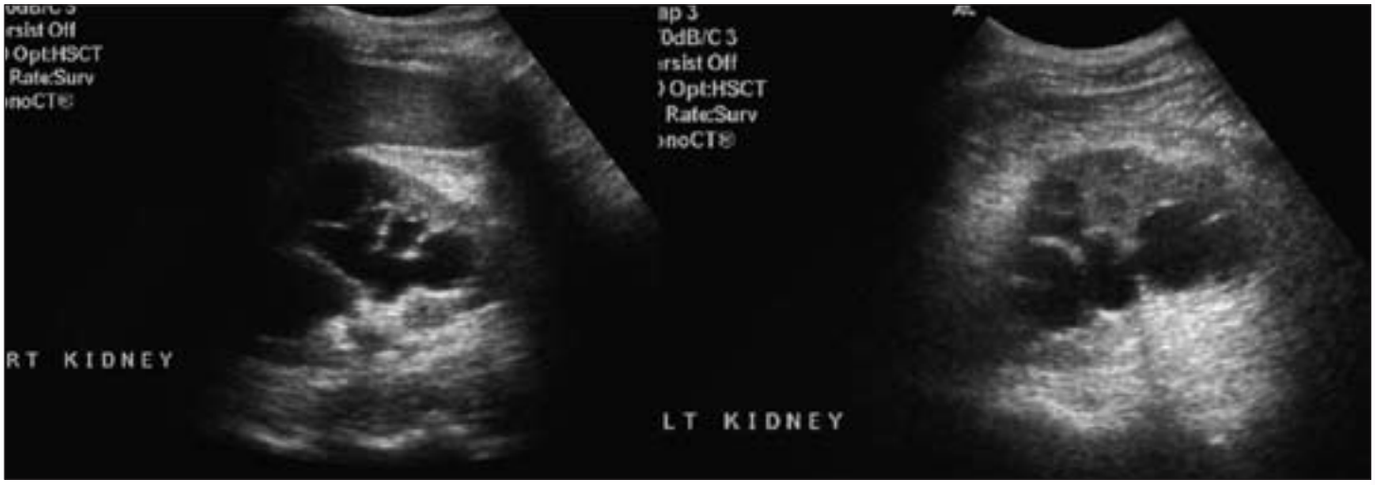
Computed tomography (CT) scanning has the advantage of being quicker than IVU (especially in cases of significant obstruction where numerous repeat films may be needed at delayed intervals), and hence more time and labour efficient. The radiation dose to which the patient is exposed is not greatly different, and CT also provides information regarding other structures, which may be causing the patient's symptoms (e.g. abdominal aortic aneurysm giving symptoms similar to renal colic).

A CT-KUB involves no contrast, and hence the stone can be seen easily as a radio-opaque density in the line of the urinary tract.

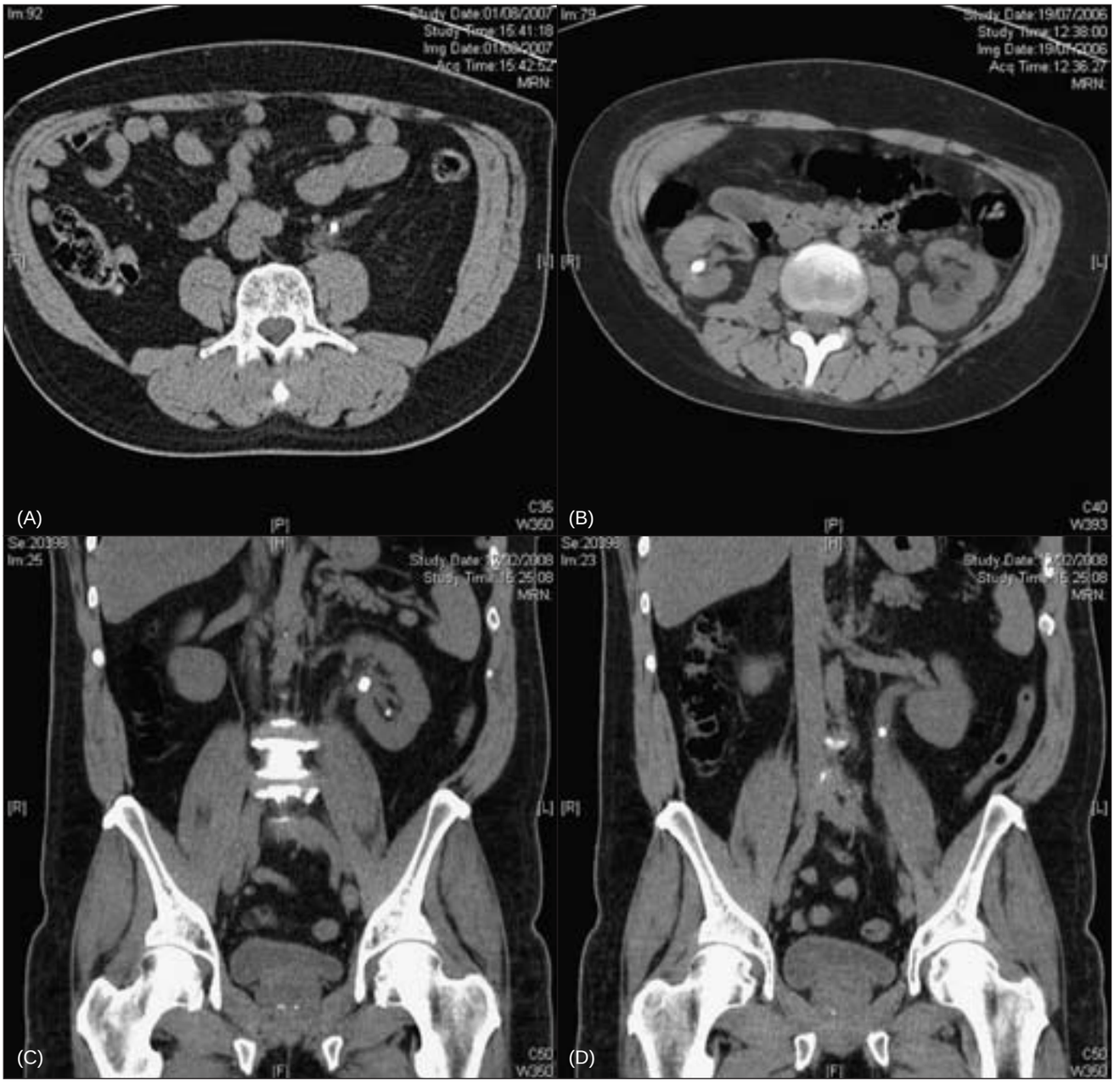
Note the position of the stones at different levels in the upper urinary tract in **4.21**. There is also significant perinephric stranding (**4.21D**), which indicates a degree of obstruction.



4.20 Ultrasound image of large bladder calculus.



4.19 Ultrasound image of hydronephrosis.



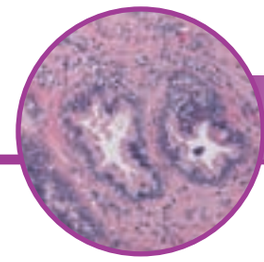
4.21 CT-KUB films showing a left upper ureteric stone: (A) left upper ureteric stone; (B) right kidney stone; (C) left renal pelvis stone; (D) left upper ureteric stone.

Further Reading

Press SM and Smith AD (1995). Incidence of negative haematuria in patients with acute urinary lithiasis presenting to the emergency room with flank pain. *Urology* **45**(5): 753–757.

Acknowledgements

Figures **4.3–4.6** reproduced with permission: Andrew Leonard / APL Microscopic, New York, NY, USA (**4.5B**); Louis C Herring and Co., Orlando, FL, USA (**4.3A, 4.3C, 4.4A, 4.5A, 4.6A**). Electron micrographs courtesy of Robin E Holdren, Western Michigan University, Kalamazoo, MI, USA (**4.3B, 4.3D, 4.4B, 4.6B**).



Chapter 5

Prostate Cancer

Kieran Jefferson and Natasha Jefferson

Introduction

Prostate cancer is the most common non-dermatological malignancy among British men. Almost 25 000 men were diagnosed with prostate cancer in the UK in 1999 and nearly 10 000 died from the disease in 2001. Prostate cancer is therefore responsible for about 6% of all male cancer deaths. The incidence increases with age; indeed men approaching 80 years have a more than 100-fold increased risk of prostate cancer compared with those approaching 50 years.

Men with suspected or confirmed prostate cancer are offered a wide variety of biochemical, histological and radiological investigations to diagnose, stage and grade the disease. Accurate staging and grading enables the urologist to optimize treatment for the individual patient. This chapter describes the investigations undertaken during the patient journey associated with prostate cancer.

Laboratory investigations

Prostate-specific antigen

In most developed countries, the most common mode of presentation of prostate cancer is that of an asymptomatic man with a raised serum prostate-specific antigen (PSA), detected at opportunistic testing. There has been considerable debate about the potential merits of a PSA-based screening programme, but there is little evidence at present to suggest that screening meets the World Health Organization (WHO) criteria for screening. Two large, multicentre trials of prostate cancer screening, based on serum PSA assay and digital rectal examination, and involving more than 100 000 men, are in progress; results are not expected until 2008. Asymptomatic men may also present as a result of diligent use of the digital rectal examination in the primary or secondary care setting; this is the primary means of diagnosing the large number of cancers in men whose serum PSA lies within the age-specific 'normal' range.

Symptomatic men may present with symptoms from either the primary prostate cancer or from metastases. Local symptoms include those of bladder outlet and ureteric obstruction, haemospermia, impotence and reduced ejaculatory volumes. Investigation of lower urinary tract symptoms and erectile dysfunction is discussed elsewhere in this book and will not be discussed further here; it is important, however, that prostate malignancy is not forgotten as a potential cause.

PSA is a 28.5 kDa glycoprotein containing 237 amino acids; the mature protein is cleaved from a 261 amino acid precursor molecule. It is a serine protease belonging to the kallikrein protease family and is also classified as human kallikrein 3 (hK3). Transcription of the *PSA* gene is under the control of an androgen-responsive element (ARE) within its promoter; expression therefore increases when prostate cells are treated with androgens or become more sensitive to androgens. High-level expression of PSA is exclusive to the prostate epithelium; lower levels of expression are seen in the placenta, some breast carcinomas and the male peri-anal glands.

Healthy prostate glands sequester PSA in an inactive state within the glandular lumina, where it may be activated on cleavage by human kallikrein 2 (hK2). PSA is thought to be responsible for liquefying semen; it is present in the semen at high concentration (0.5–2 g/l – about 1 000 000-fold the normal serum concentration), with the ability to digest seminogelins, the proteins which stabilize the seminal clot. PSA in the seminal fluid is predominantly 'free PSA', although a small proportion is in an inactive complex with protein C inhibitor.

Both normal and malignant prostate tissue secretes a large amount of PSA, although the rate of production of 'normal' (i.e. assay-detectable) PSA can decline as a result of cellular de-differentiation in advanced malignancy. Development of a focus of prostate cancer leads to increased production of PSA by individual cells as well as disruption of the normal glandular architecture with consequent increased leakage of PSA into the circulation. Serum PSA can therefore be used as a prostate cancer tumour marker. It is neither a particularly sensitive, nor specific, tumour marker because benign diseases of the prostate (for example, bacterial prostatitis or benign hyperplasia) may also result in elevated serum PSA.

Within the circulation, PSA is almost completely complexed to protease inhibitors. The predominant complex-forming protein is α_1-antichymotrypsin (ACT), with smaller amounts being bound to α_1-protease inhibitor and α_2-macroglobulin (A2M). Between 5% and 40% of serum PSA is free and it is believed that this represents an enzymatically inactive form, either pro-PSA or nicked PSA. Complex formation with ACT dramatically increases the half-life of PSA (from a couple of hours for the free form to 2 or 3 days for the PSA–ACT complex). Conversely the PSA–A2M complex is metabolized within minutes; this complex probably represents the major route of metabolism for serum PSA. PSA does not appear to have any enzymatic function within the circulation.

Serum immunoassay for PSA has become a standard diagnostic test for prostate cancer. Because of the confounding effect of PSA produced from benign prostatic tissue, a 'cut-off' level of serum PSA has to be used, accepting that this will result in a number of false-positive and false-negative results. There has been considerable debate about the appropriate cut-off. Initially a cut-off of 4 ng/ml was commonly used as the trigger for further investigation; this has been superseded by age-specific cut-offs due to a significant false-negative rate using the higher level. Some studies have suggested that as many as 25% of men with prostate cancer have a serum PSA measuring less than 4 ng/ml. Reducing this cut-off to 2.5 ng/ml improves the sensitivity of testing, but with an inevitable reduction in specificity and a consequent increase in the number of negative prostatic biopsies. Many groups have attempted to improve the performance of PSA by the use of modifications such as prostatic PSA density, transition zone PSA density, PSA velocity and ratio of free:total PSA.

Serum PSA velocity is perhaps the current favourite method of improving the diagnostic performance of PSA. Data from the USA, where a large proportion of men undergo yearly measurement of PSA, suggests that the rate of change of PSA is a more accurate predictor of a positive prostate biopsy than absolute level of PSA. This seems particularly evident in the detection of high-grade adenocarcinomas – prostate cancers that are most threatening to the patient.

PSA is also central to staging and prognostication in men diagnosed with prostate cancer. Using validated tables and nomograms, the combination of PSA, Gleason grade and clinical stage enables reliable estimation of the likelihood of capsular penetration, involvement of pelvic lymph nodes and bone metastases. These probabilities are used, with an assessment of comorbidity and life expectancy, to select the appropriate management option for each patient. Many clinicians will use these variables to determine the need for staging using imaging techniques such as isotope bone scanning or pelvic magnetic resonance imaging (MRI).

Once treatment or active surveillance has commenced, PSA is a central element of patient monitoring and determines most of the changes in management. Several studies have shown that changes in serum PSA pre-date clinical events by months or years. Men who have an undetectable (after surgery) or stable (after radiotherapy) serum PSA are frequently cured. Small increases in PSA levels can give a very early indication of failure of radical treatment, allowing the opportunity for salvage treatment before the development of macroscopic disease or symptoms.

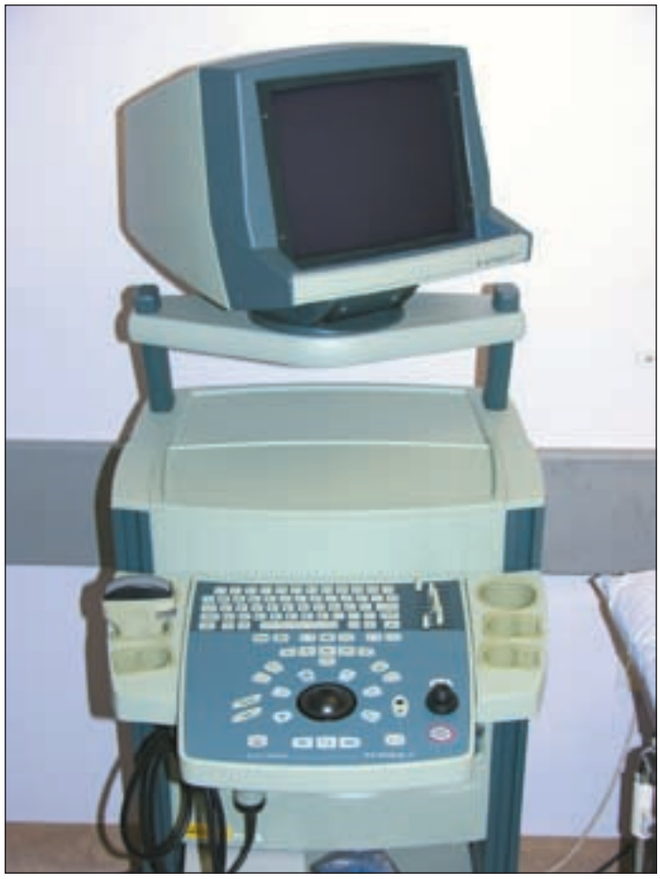
Histopathology of prostate cancer

The 'gold standard' for diagnosis of prostate cancer is histological assessment of biopsied tissue. This is most commonly in the form of needle-core biopsies obtained using a transrectal ultrasound scanning (TRUSS) guide according to a standard biopsy protocol; frequently, however, prostate cancer is an incidental diagnosis in chippings from a transurethral resection of the prostate (TURP), in a specimen from a radical cystoprostatectomy or in percutaneous, laparoscopic or open biopsies from distant lymph nodes or organs.

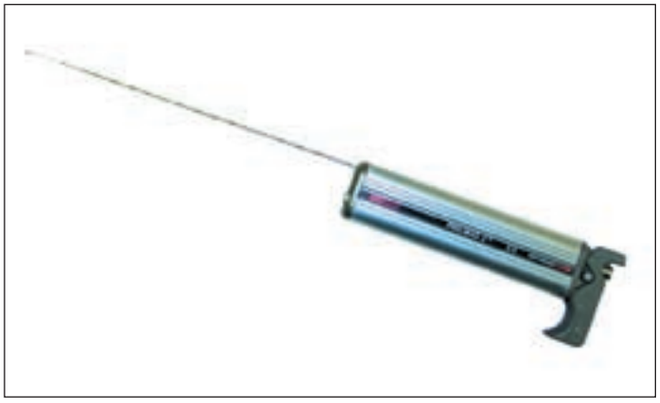
In a standard TRUSS-guided prostate biopsy, at least 10 areas are routinely sampled, along with any areas which are found to be hypo-echoic, or otherwise abnormal on TRUSS. A typical ultrasound machine used for TRUSS-guided biopsy is shown in **5.1**; a typical 'rapid-fire' biopsy gun is seen in **5.2**. As well as its use in the initial diagnosis of prostate cancer, histological analysis of TRUSS-guided biopsy specimens can be used to monitor grade progression in men being managed by active surveillance and to confirm local recurrence of prostate cancer after radical radiotherapy.

In prostate cancer, as in other epithelial cancers, a stepwise progression from normal tissue, via benign neoplasms, has been proposed. The typical histological appearance of normal prostate at medium magnification is shown in **5.3**; the glands are regular in size and distribution and a basal cell layer is evident within them. The appearance of the ejaculatory ducts can sometimes cause diagnostic confusion (**5.4**). A low magnification view of an area of prostate cancer next to an area of normal prostate is seen in **5.5**.

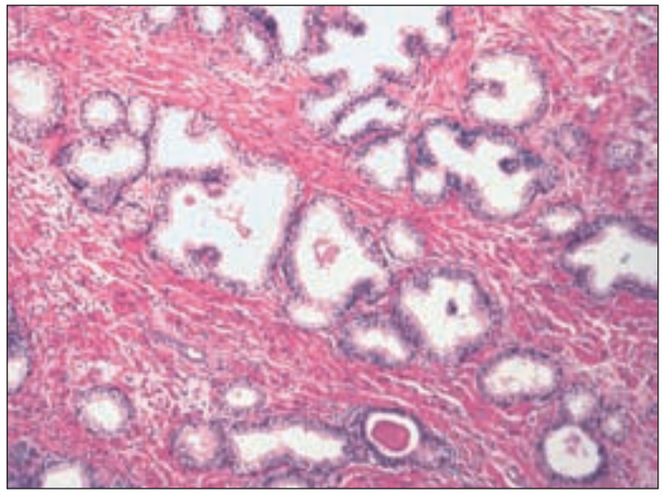
Prostatic intraepithelial neoplasia (PIN) is often diagnosed in prostate biopsy tissue; the term describes tissue that has focal neoplastic changes in the lining of the prostatic ducts and acini, which do not invade the basement membrane and cannot therefore be diagnosed as a carcinoma. Perhaps because of the maintenance of glandular integrity, isolated PIN is not thought to cause increased serum PSA. Medium and high magnification views of PIN are seen in **5.6** and **5.7**, respectively; many cells lining the glands are enlarged, with increased nuclear/cytoplasmic ratio and prominent nucleoli.



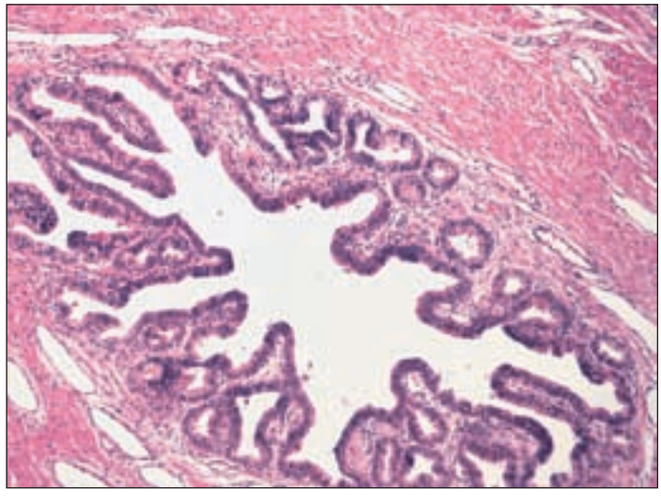
5.1 A transrectal ultrasound machine.



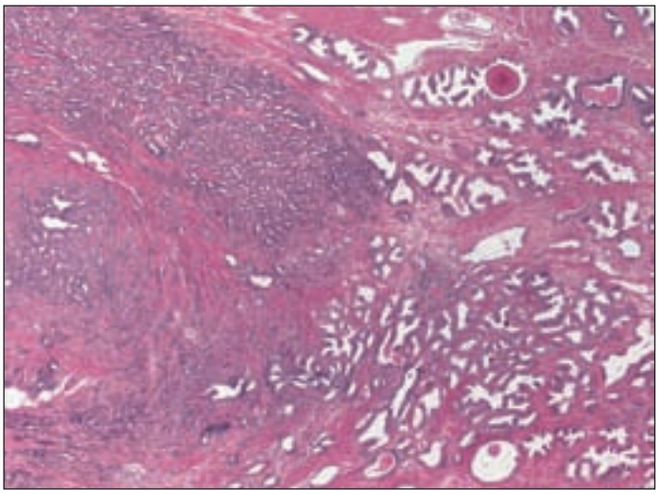
5.2 A rapid-fire biopsy gun.



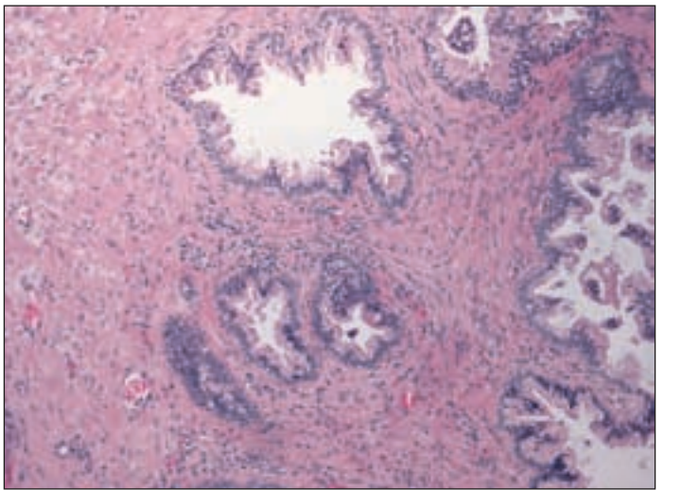
5.3 Normal prostate. Haematoxylin and eosin (H&E) stained specimen viewed at medium magnification (×100).



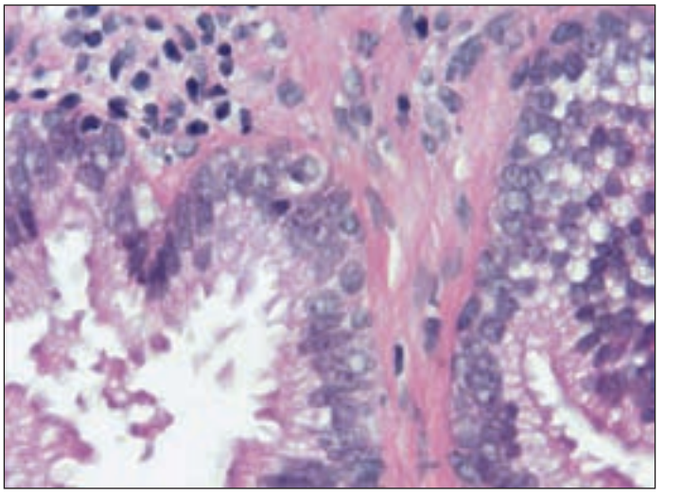
5.4 Ejaculatory duct within normal prostate (H&E stain, ×100).



5.5 Low magnification (H&E stain, ×25) view of focus of prostate adenocarcinoma (left side) abutting normal prostate (right side).



5.6 Medium magnification (H&E stain, ×100) view of high-grade PIN.



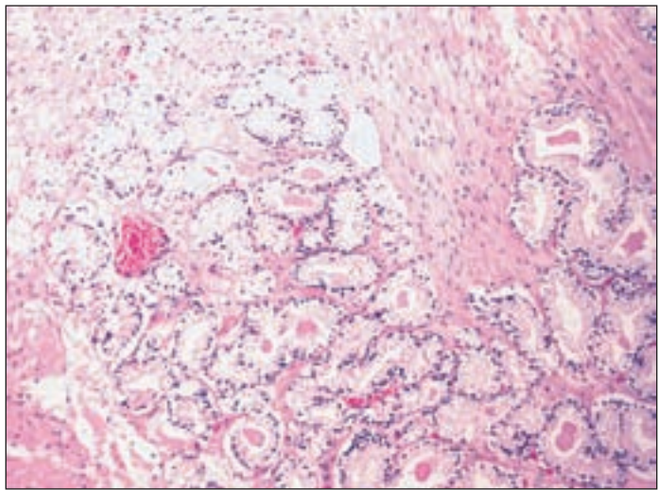
5.7 High power (H&E stain, ×630) view of high-grade PIN.

The dark blue staining reflects the large amount of nuclear chromatin. PIN is a significant risk factor for subsequent development of prostate cancer and is often diagnosed synchronously with carcinoma.

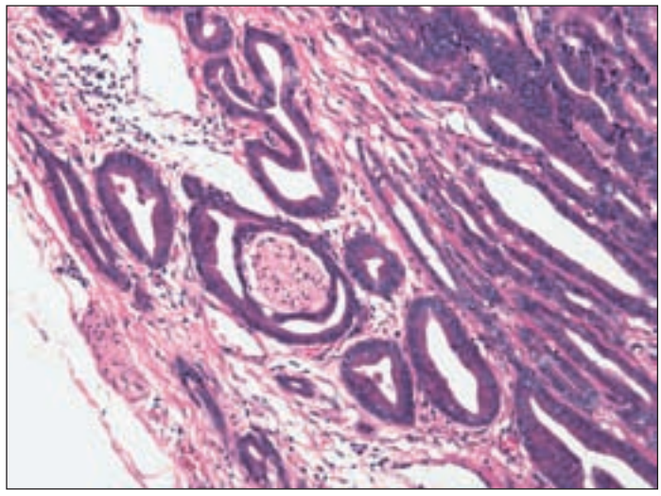
Adenocarcinomas predominantly occur in the peripheral zone of the prostate, as defined by McNeal, with the transition zone being the second commonest site. Tumours are commonly multifocal, with local extension occurring predominantly via perineural or seminal vesicle invasion. Metastasis occurs to regional lymph nodes and via the circulatory system to the bones, lungs and other viscera. The histological features of adenocarcinoma vary widely, according to the grade of tumour (see below). Typically, the basal cell layer within the ducts and acini is lost and glands become less regular in size, shape and distribution. It is also common to see invasion along nerve sheaths (perineural invasion). In high-grade disease, the glandular structures may disappear completely, being replaced by sheets of cells. As well as the changes in gland architecture, the cytological changes of neoplastic change are seen including nuclear enlargement, prominent nucleoli and hyperchromasia.

Grading of prostate adenocarcinomas gives important prognostic information and is a key element in management decisions. The grading system defined by Gleason is now the accepted WHO standard; this system classifies the glandular architecture seen at low magnification, rather than cytological appearances. A 'Gleason score' is the sum of the value ascribed to the predominant and second-most predominant patterns seen, each of which may score 1–5. Thus the lowest Gleason score is 2, denoting a particularly low-grade (and rare) tumour, whereas a Gleason score of 10 describes a very high-grade lesion where the sample contains only Gleason pattern 5 tumour. To complicate matters further, many pathologists now cite a tertiary histological pattern when this is of high Gleason grade. In contemporary practice, Gleason 1 and 2 tumours are rarely diagnosed, partly because of the histological limitations imposed by the use of fine cores of prostate tissue. By far the most common Gleason scores diagnosed are 6 and 7.

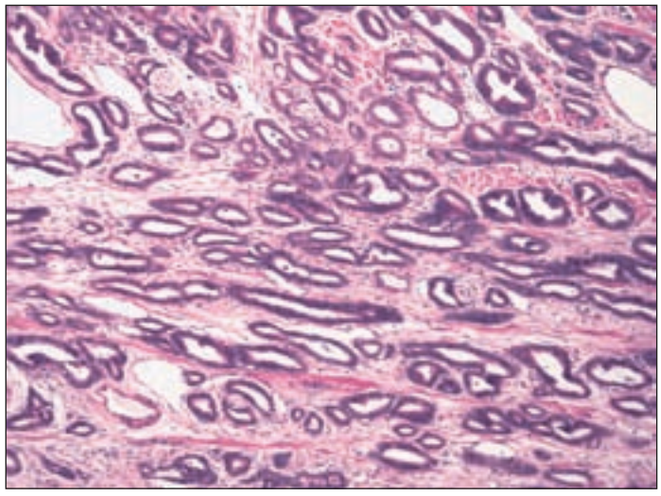
A Gleason grade 2 adenocarcinoma at medium magnification is seen in **5.8**. Glandular structures are obvious but



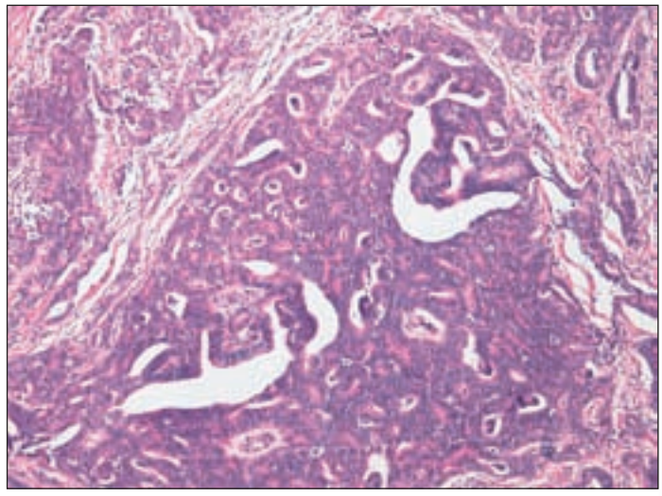
5.8 Gleason pattern 2 prostate adenocarcinoma at medium magnification (H&E stain, ×100).



5.10 Higher power view (H&E stain, ×250) of Gleason pattern 3 prostate adenocarcinoma demonstrating perineural invasion.



5.9 Gleason pattern 3 prostate adenocarcinoma at low magnification (H&E stain, ×100). An area of perineural invasion is evident.



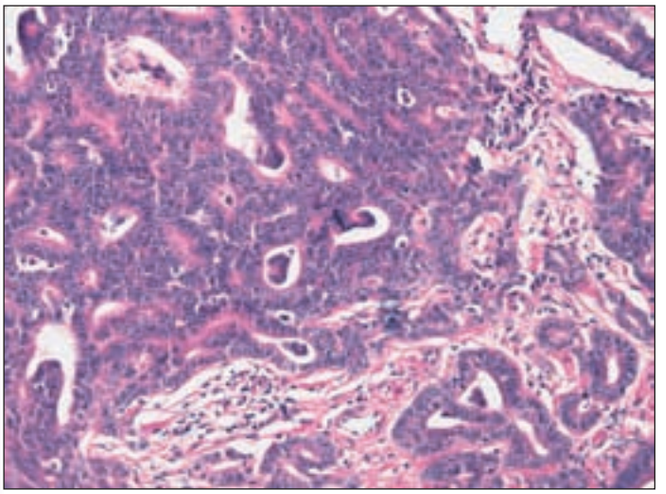
5.11 Gleason pattern 4 adenocarcinoma of the prostate (H&E stain, ×100).

there is a loss of uniformity of size and shape compared with normal prostate. However, compared with Gleason grade 3 adenocarcinoma (**5.9**, **5.10**), the glands are larger and more regular. Gleason pattern 4 (**5.11**, **5.12**) demonstrates gland fusion and loss of segments of the epithelial lining in some glands. In Gleason pattern 5, loss of glandular lumina is complete or almost complete, with solid sheets of cells evident (**5.13**).

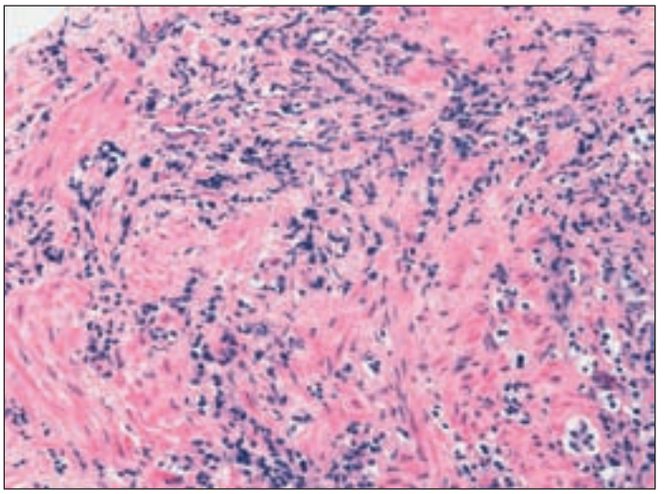
In addition to histological analysis using the standard H&E staining, labelled monoclonal antibodies can be used to identify (for example) PSA or prostate-specific membrane antigen (PSMA) within a tissue sample. This is of particular use in the analysis of samples of adenocarcinoma from metastases where the primary tumour remains unidentified.

Staging

Staging of prostate cancers offers a guide to prognosis and enables selection of the most appropriate therapy. The International Union Against Cancer (UICC) Tumour, Nodes, Metastasis (TNM) classification (1997) is shown in *Table 5.1*. The routine staging investigations for suspected organ-confined prostate cancer are: serum PSA (as discussed



5.12 High magnification view (H&E stain, ×250) of Gleason pattern 4 prostate adenocarcinoma.



5.13 Gleason pattern 5 adenocarcinoma of the prostate at high magnification (H&E stain, ×250).

Table 5.1 The UICC TNM system for prostate cancer staging (UICC 2002)

Primary tumour	Tx		Primary tumour cannot be assessed
	T0		No evidence of primary tumour
	T1	a	Incidental histological finding in <5% resected tissue
		b	Incidental histological finding in >5% resected tissue
		c	Tumour identified on needle biopsy after elevated serum PSA
	T2	a	Tumour confined to half of one lobe of prostate
		b	Tumour involving more than half of one lobe
		c	Tumour involves both lobes of the prostate
	T3	a	Extra-capsular extension of tumour
		b	Seminal vesicle invasion
	T4		Tumour fixed or invading other pelvic structures
Lymph nodes	Nx		Regional lymph nodes cannot be assessed
	N0		No regional lymph node involvement
	N1		Regional lymph node involvement
Metastasis	Mx		Distant metastasis cannot be assessed
	M0		No distant metastasis
	M1	a	Non-regional lymph node involvement
		b	Bone metastases
		c	Extra-skeletal metastases

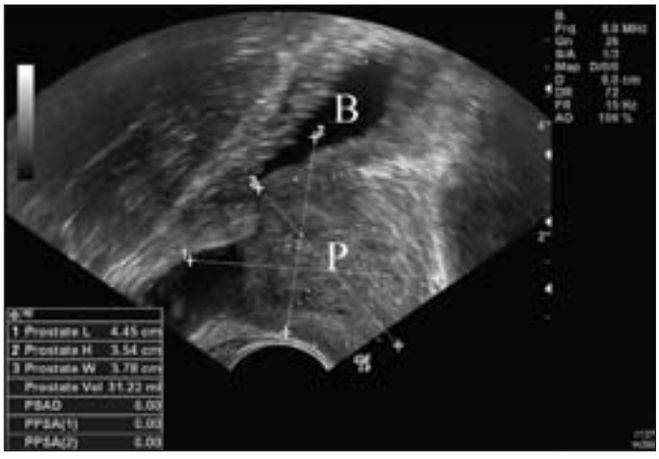
above), isotope bone scanning (dependent on PSA) and, in some units, MRI of the prostate or vertebrae. In some units, open or laparoscopic pelvic lymph node sampling is regularly undertaken to accurately stage patients before radical local treatments. Many other units rely on the use of predictive tables or nomograms in combination with selective MRI of the pelvis.

Imaging modalities used in prostate cancer

Transrectal ultrasound scanning

TRUSS is the most commonly used imaging modality in patients with prostate cancer. Virtually all men with suspected prostatic malignancy will undergo TRUSS-guided prostate biopsy to obtain histological tissue. Many prostate cancers are visible on TRUSS as hypo-echoic areas; more than 60% however are iso-echoic and, for this reason, the predominant role of TRUSS is to guide needle placement to allow representative sampling of the whole prostate. A typical TRUSS image of the prostate is seen in **5.14**. In addition, the seminal vesicles are easily visible on TRUSS and can be separately sampled if this appears to be advantageous for more accurate staging. Most modern ultrasound processors contain an algorithm to allow easy measurement of prostate volume. Knowledge of prostate volume is important if considering brachytherapy or radical prostatectomy.

TRUSS can also be used to guide a number of radical treatment modalities for prostate cancer. Brachytherapy, cryotherapy and high-intensity focused ultrasound are all dependent on TRUSS guidance for effective targeting. Following local radical treatment, TRUSS-guided biopsy may help in the diagnosis of residual prostate cancer tissue, first suggested by measurement of serum PSA.

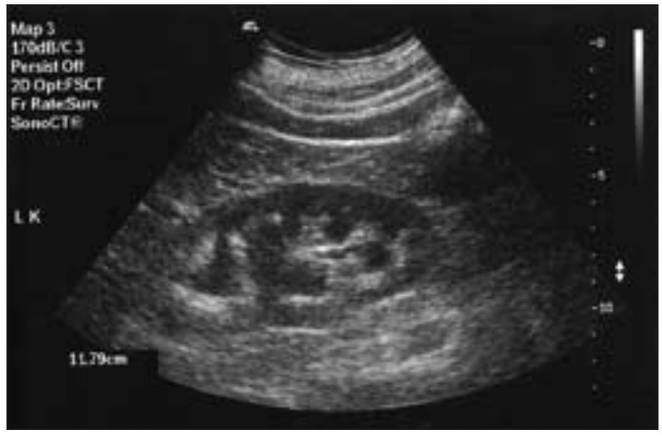


5.14 Sagittal transrectal image of prostate (P) and bladder (B).

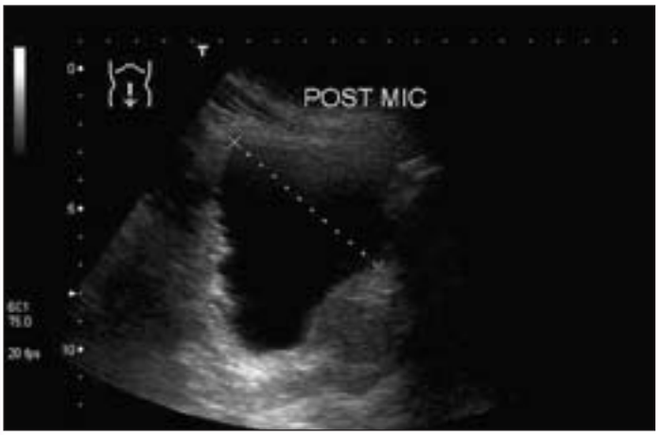
Transabdominal ultrasound scanning

Obstruction of both ureters, or significant bladder outlet obstruction in the presence of high pressure chronic retention, can result in obstructive uropathy. Patients may develop acute or chronic renal impairment, ranging from mild perturbation of serum creatinine and electrolytes to immediately life-threatening acidosis, hyperkalaemia or fluid overload. Transabdominal ultrasound of the urinary tract is essential in the early investigation of such men and will reveal bilateral hydronephroses (**5.15**), usually in the presence of a distended bladder and enlarged prostate (**5.16**). Placement of a percutaneous nephrostomy tube under ultrasound or fluoroscopic guidance is generally required if urethral or suprapubic catheterization fails to relieve the obstruction and the prognosis is good enough for the patient to benefit from such intervention.

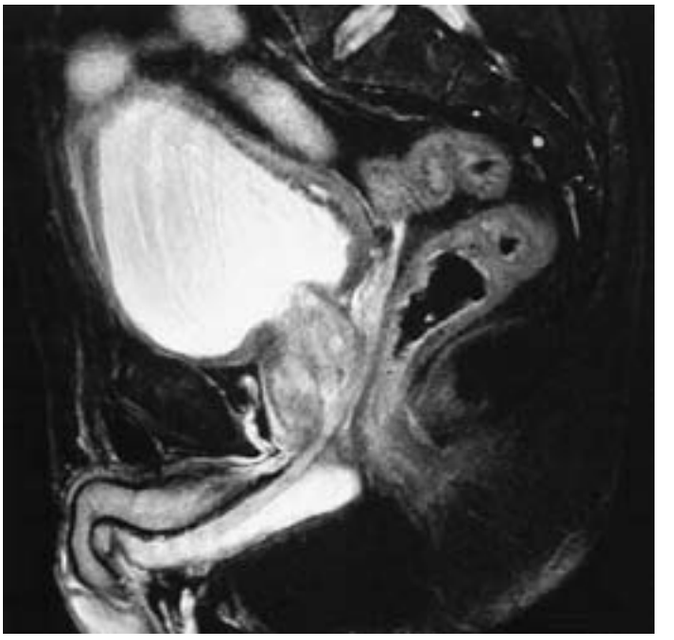
In the absence of ureteric obstruction, transabdominal ultrasound may be useful in measuring post-void residual urine volume, as for benign prostatic disease (see Chapter 3). Knowledge of bladder function has implications for the selection of radical treatments (for example, brachytherapy is usually avoided in men with objectively poor bladder function) and in more advanced disease may be used to decide on the potential value of channel TURP or hormone blockade.



5.15 Moderate hydronephrosis of the left kidney in a patient with prostate cancer. The right kidney was also hydronephrotic and the patient presented in acute renal failure.



5.16 Sagittal post-micturition ultrasound image of the bladder showing a significant residual volume and prostatic enlargement.



5.17 Sagittal, fat-saturated T2 MR image of the pelvis showing a bulky prostate malignancy indenting the base of the bladder.

Computed tomography

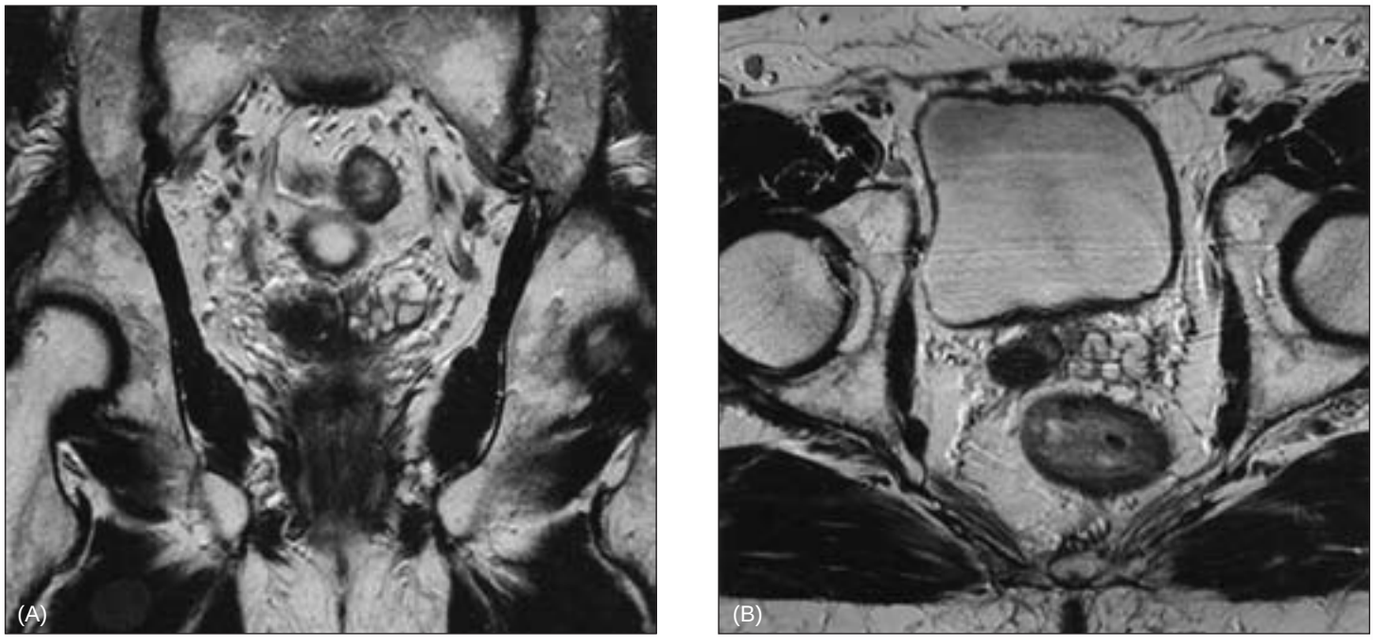
In a proportion of patients, upper tract abnormalities will be incidental findings on computed tomography (CT) of the abdomen for another indication. Conventional CT is not widely used in the staging of most prostate cancers, but it can be used to target external beam radiotherapy or as a problem-solving tool in men developing metastatic complications not directly referable to the urinary tract. The combination of positron emission tomography with CT (PET-CT) using [^{11}C]choline is an experimental technique, which appears to offer promise in the identification of both the primary tumour and any metastases in men with prostate cancer. The advantage of this technique is that it gives both functional and anatomical information which can be co-registered so enabling accurate localization of sites of high uptake and improving confidence in their significance. [^{11}C]choline is not exclusive for prostatic malignancy and increased uptake can also be seen in benign prostatic hypertrophy, in which uptake is generally less avid than with prostate cancer but greater than in the normal gland.

Magnetic resonance imaging

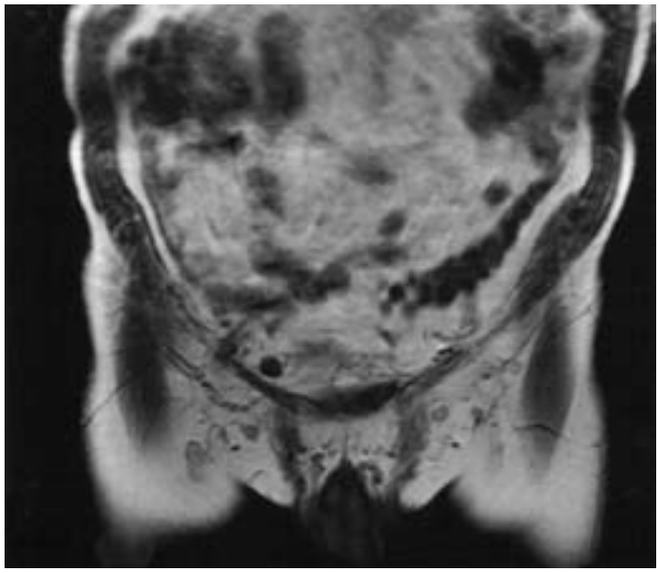
MRI staging of potentially organ-confined prostate cancer is widely practised (**5.17**), often in an attempt to exclude extension beyond the prostatic margins, seminal vesicle invasion (**5.18**) or enlarged pelvic lymph nodes (**5.19**) prior to radical prostatectomy or other radical local therapy. Bone metastases may be incidentally noted (**5.20**). Imaging protocols vary from centre to centre and between different MR scanners. A typical MRI staging protocol utilizes coronal and axial T2-weighted images of the pelvis, combined with axial T1-weighted pelvic images and either fat-saturated T2 or STIR (short tau inversion recovery) images in the sagittal or another plane. Despite its widespread use, there is little high-quality published evidence to support its effectiveness in pre-operative staging. The use of endo-rectal coils has been recently promoted as a means of improving the accuracy of MRI staging but such scanning is not yet widely available in the UK.

'Strip' MRI scanning of the vertebrae is attracting increasing interest as a means of detecting bone metastases from prostate cancer. Several groups have proposed that MRI of the axial skeleton could be a cost-effective substitute for isotope bone scanning (see below), however, this is not widely practised.

MRI scanning is routinely used in the diagnosis of cord compression in men with appropriate symptoms where findings guide treatment. In these circumstances the whole of the spine is imaged, regardless of the patient's signs/sensory level, as MRI studies have shown that the clinical level of cord compression frequently correlates poorly with the actual level. MRI studies also often demonstrate unsuspected regions of cord compression in addition to



5.18 (A) Coronal T2 MR image of pelvis showing low signal in right seminal vesicle. This is highly suggestive of seminal vesicle invasion. (B) Axial T2 MR image of pelvis. Findings as for (A).



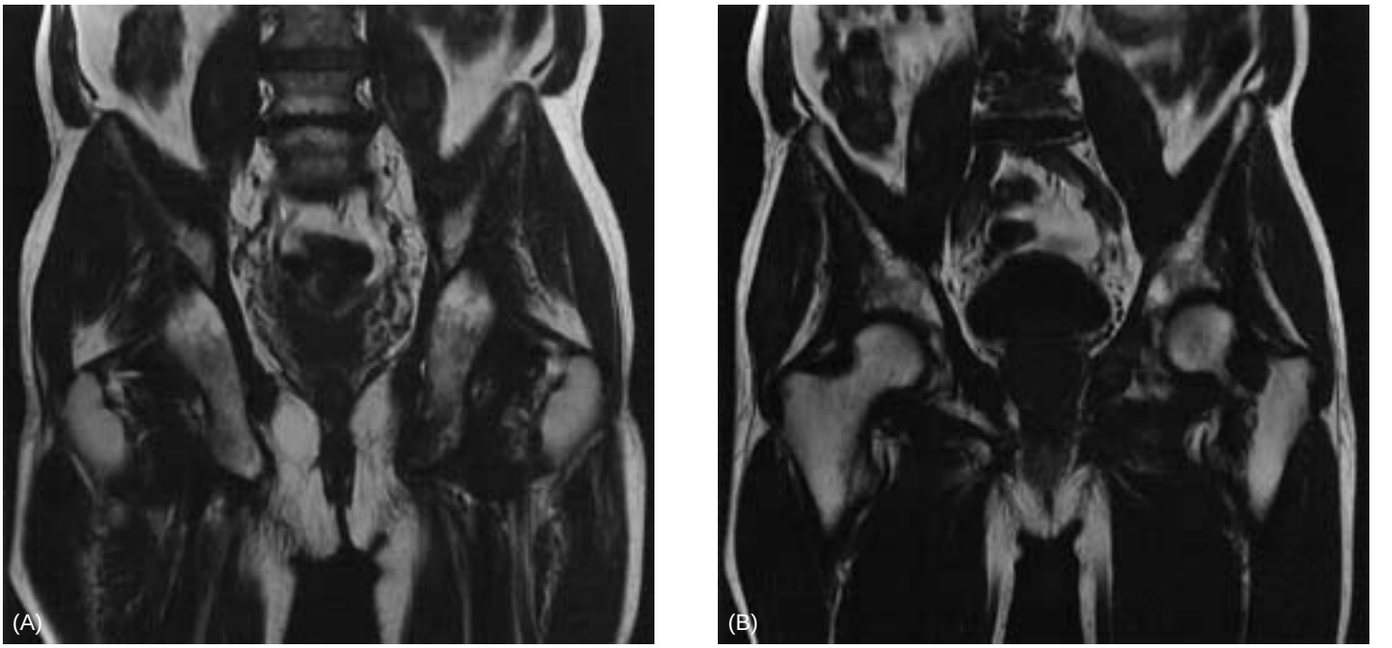
5.19 Coronal T1 MR image of pelvis showing a low signal 9 mm right iliac lymph node, suggestive of extra-prostatic spread.

the clinically suspected lesion. Whole-spine MRI will also demonstrate any anatomical variants that might affect planning of the radiotherapy field or the approach for surgical decompression. A typical scanning protocol would include sagittal T1 and T2 images of the entire vertebral column with selected axial sections through lesions detected on the sagittal scans.

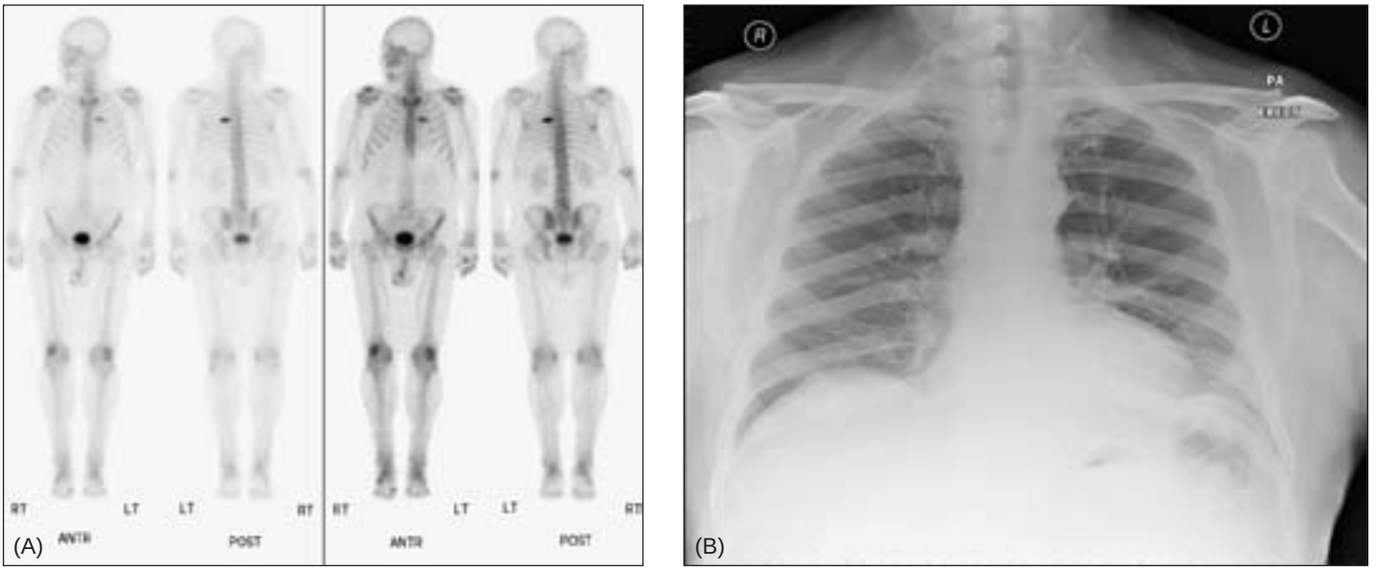
Isotope bone scanning

Metastases from prostate cancer most commonly occur in the axial skeleton and may cause pain, pathological fracture or spinal cord compression. Isotope bone scanning using [^{99m}]technetium-labelled methylene diphosphonate ([^{99m}]TcMDP) is usually the initial imaging modality to screen for bone metastases. This exploits the fact that areas of bone with high turnover, such as osteoblastic metastases, will exhibit higher than normal uptake of [^{99m}]TcMDP which can be seen on gamma camera images. Large foci of increased uptake may be seen even in the presence of normal plain films of the skeleton (**5.21**). However, in symptomatic men, the sclerotic changes seen in bone associated with (and almost unique to) prostate cancer metastases are often visible on plain X-rays of the relevant bones (**5.22**).

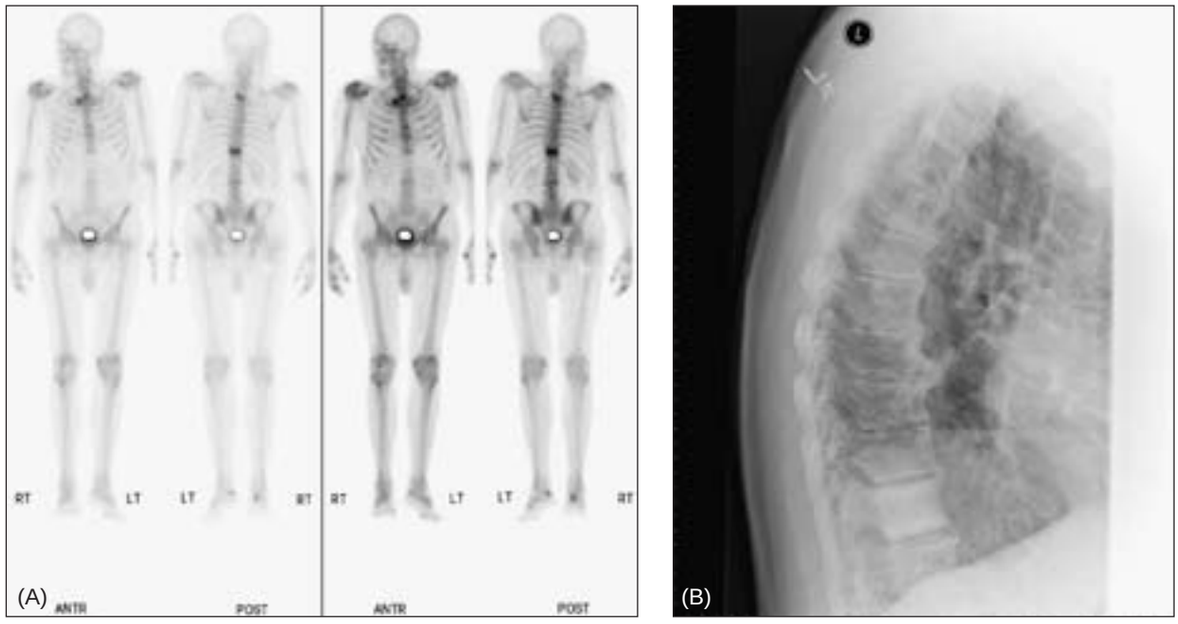
The pelvic outlet view is an additional bone scan image sometimes used in men with prostate cancer who may have bone metastases within the pelvis. This image removes the superimposition of bladder activity and pelvic bone uptake, improving confidence in diagnosing pelvic bone metastases. This additional image is not associated with an increase in



5.20 (A) Coronal fat-saturated T2 MR image of pelvis shows an area of low signal representing a metastasis in the left iliac bone. (B) Coronal fat-saturated T2 MR image from the same patient as in (A) showing low signal lesion in the left femoral neck consistent with another bone metastasis.



5.21 (A) Bone scan showing increased uptake in the left seventh posterior rib. This extends along the rib in a longitudinal direction making it highly suspicious for a solitary bone metastasis. Increased uptake in shoulders, sternoclavicular joints, knees, hands and feet is explained by degenerative change. (B) A chest X-ray taken at same time as the bone scan in (A). No abnormality is detected at the site of the rib in question. This increases the suspicion of a metastatic deposit as there is no rib fracture or other bone lesion to explain the increased rib uptake.



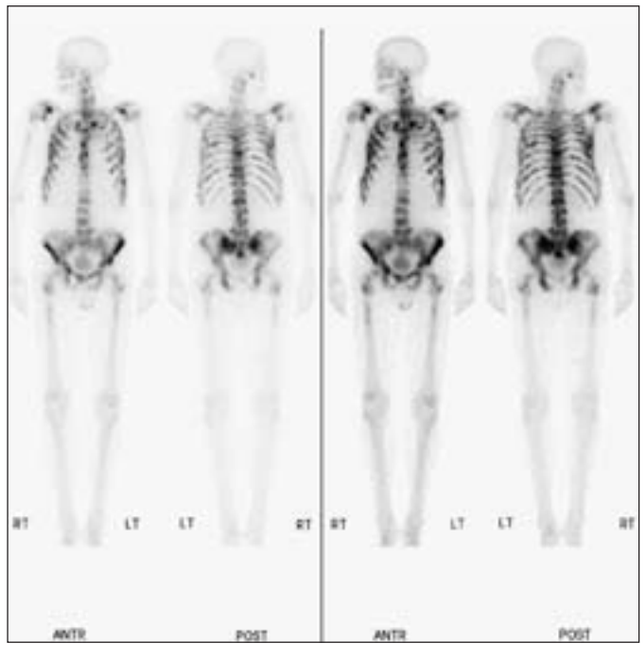
5.22 (A) Bone scan showing increased uptake in the T3 and T11 vertebral bodies, highly suggestive of bone metastases. Degenerative changes, which can be seen in the small joints of hands, knees and shoulders have more patchy, less intense increase in uptake. (B) A lateral plain film of the thoracic spine in the same patient as in (A) confirms the presence of sclerotic vertebral body metastases at T3 and T11 levels from the known prostate cancer. Degenerative changes are also seen in the form of bridging anterior osteophytes. ANTR, anterior; POST, posterior.

radiation dose as it is acquired immediately after conventional images (after repositioning the patient in relation to the gamma camera) and does not require an additional injection of radioisotope.

The main patterns of metastatic bone disease seen on isotope bone scanning are:

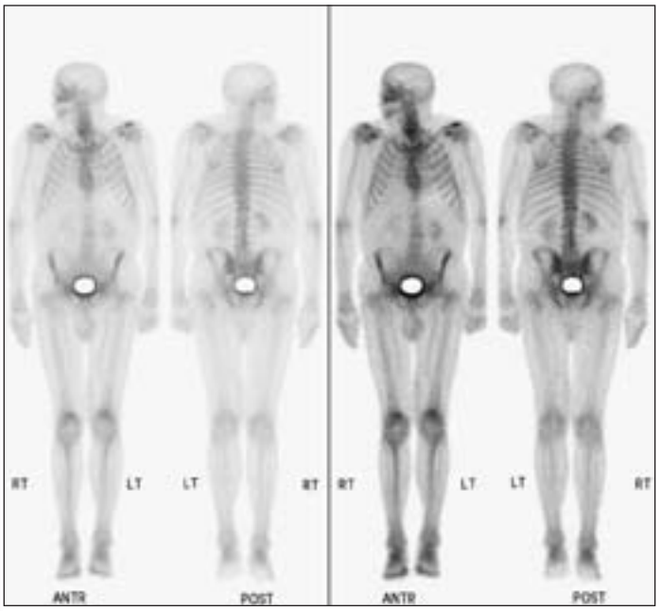
- the isolated bone metastasis (**5.21A**);
- multiple discrete foci of increased uptake (**5.22A**);
- multiple discrete foci of increased uptake with no renal uptake and relatively decreased soft tissue and distal skeletal uptake – a 'superscan' (**5.23**); and
- widespread increased uptake in axial skeleton associated with no renal uptake and relatively decreased soft tissue and distal skeletal uptake, again, a 'superscan', which can look almost normal if the renal, soft tissue and distal skeletal abnormalities are not noted.

Correlation with plain films is often helpful when discrete lesions are present on the bone scan to exclude benign bone lesions, such as degenerative changes, which may demonstrate increased uptake of [^{99m}]TcMDP (**5.24**). It is worth noting that in the case of a single bone scan abnormality, not



5.23 Bone scan showing multiple bone metastases predominantly in the axial skeleton. This is an example of the so-called 'superscan' where renal uptake is not visible and soft tissue uptake is poor due to extensive metastatic lesions which show relatively greater uptake of [^{99m}]MDP. ANTR, anterior; POST, posterior.

easily explained by benign plain film abnormalities, in a man with known malignancy such as prostate cancer, the chances of this representing a single bone metastasis are significant.



5.24 Bone scan showing the features of degenerative joint disease only (common in the prostate cancer age group). Bone uptake of [^{99m}]MDP is otherwise normal. ANTR, anterior; POST, posterior.

Summary

Effective management of men with prostate cancer requires information from a variety of investigations, as well as an assessment of the comorbidity, life expectancy and wishes of the individual patient. The urological surgeon should lead a multidisciplinary team approach to managing such men with judicious use of imaging and other resources to optimize the prognosis for each patient.

Further reading

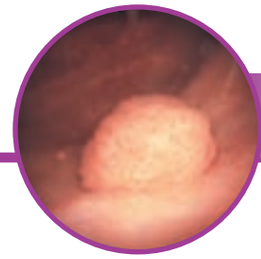
Eble JN, Epstein JI, Sesterhenn IA (eds) (2004). World Health Organization Classification of Tumours: Tumours of the Urinary System and Male Genital Organs. IARC Press, Lyon.

Adam A, Dixon AK, Grainger RG, Allison DJ (eds) (2008). *Grainger & Allison's Diagnostic Radiology. A Textbook of Medical Imaging* 5th edition. Churchill Livingstone, Edinburgh.

Kaisary AV, Murphy GP, Denis L, Griffiths K (eds) (1999). *Textbook of Prostate Cancer.* Martin Dunitz, London.

Peters AM (2003). *Nuclear Medicine in Radiological Diagnosis*. Martin Dunitz, London.

Chapter 6



Bladder Cancer

Steve Williams, Merce Jorda, Murugesan Manoharan and Mark Soloway

Introduction

Bladder cancer ranks as the fourth leading cause of cancer-related death in men and tenth leading cause in women in the United States (Parkin *et al.,* 2002). A delay in the diagnosis and treatment of bladder cancer results in a poorer outcome (Sanchez-Ortiz *et al.,* 2003). An interval of longer than 3 months from the time of diagnosis of muscle invasion to cystectomy correlates with a higher pathological stage and decreased survival (Chang *et al.,* 2003; May *et al.,* 2004). Early recognition of symptoms of bladder cancer by primary care physicians with prompt referral and evaluation and treatment by a urologist is necessary for a successful result.

Diagnosis

Early symptom recognition is the key to a better prognosis. The most common symptom of bladder cancer is painless haematuria, which occurs in 85% of patients. Nearly all patients with bladder cancer have at least microhaematuria if sufficient urine samples are tested (Messing and Vaillancourt, 1990). The degree of haematuria does not correlate with the extent of disease. Haematuria may be measured by indirect examination of the urinary sediment by the dipstick method, by direct examination of the centrifuged sediment (sediment count) or by determination of the number of red blood cells per millilitre of urine excreted (chamber count).

The most common method of screening patients for haematuria is haemoglobin dipstick. A sample is recorded as positive when any haemoglobin is present. The haemoglobin dipstick method is easy to use, inexpensive and does not require the presence of intact red blood cells. Dipstick testing for haematuria has a limited specificity (between 65% and 99%); therefore, an initial positive result by this method should be confirmed by microscopic evaluation of the urinary sediment (Messing *et al.,* 1987; Woolhandler *et al.,* 1989; Sutton, 1990). Because haematuria is intermittent in nature, repeat testing increases the sensitivity of the haemoglobin dipstick test.

Microscopic haematuria has been defined as three or more red blood cells per high power field on microscopic evaluation of urinary sediment from two of three properly collected urinalysis specimens (Grossfield *et al.,* 2001). Patients with risk factors for significant disease (*Table 6.1*) should undergo a thorough evaluation for any degree of haematuria. The prevalence of asymptomatic microscopic haematuria in the general population ranges from 0.19% to 21% (Golin and Howard, 1980; Mohr *et al.,* 1986; Sultana *et al.,* 1996; Khadra *et al.,* 2000). Mohr *et al.* (1986) reported that asymptomatic microhaematuria occurred in 13% of the general population and only 0.4% had urothelial neoplasia. The incidence of malignancy in patients over 50 years is higher, however. Sultana *et al.* (1996) found that 5% of patients older than 50 years with asymptomatic haematuria had an underlying malignancy. The incidence increased to 10% if there were associated symptoms.

Table 6.1 Risk factors for significant disease in patients with microscopic haematuria

Age >40 years
Smoking history
Occupational exposure to bladder carcinogens
Associated irritative lower urinary tract symptoms
History of pelvic irradiation
History of urological disease

Screening for haematuria in the general population is not recommended because the positive predictive value (PPV) is too low. It may, however, be reasonable for a high-risk population, such as those exposed to bladder carcinogens such as cigarette smoke, aniline dyes or aromatic amines (Kirkali *et al.,* 2005). The risk of bladder cancer among these high-risk patients is two- to eightfold higher than in normal population after correcting for age, gender and race.

Symptoms that may be caused by bladder cancer include bladder irritability, i.e. urinary frequency, urgency and dysuria. This is a relatively infrequent but important presentation of bladder cancer, and is usually associated with carcinoma *in situ* (CIS) or high-grade bladder cancer (Utz and Farrow, 1984). Late symptoms and signs of bladder cancer include flank pain (due to ureteral obstruction), lower extremity oedema, a pelvic mass, weight loss or bone pain.

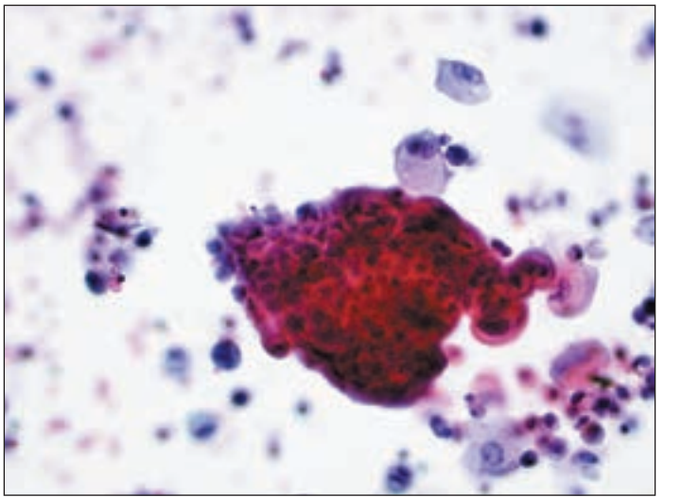
Urinary cytology

Urinary cytopathology (UC) or cytology is the microscopic examination of voided urine or a bladder wash specimen for malignant urothelial cells. UC is used primarily to monitor patients with a history of bladder cancer for the detection of recurrences. UC is highly tumour-specific (>90–95% specificity in most studies), but the sensitivity reported in various studies ranges from 11% to 76% (average 40%) (Bastacky *et al.* 1999). The overall low sensitivity of cytology to detect bladder cancer is almost exclusively due to its inability to detect low-grade bladder tumour (sensitivity 15–20%; Bastacky *et al.,* 1999). Owing to cost and low yield, UC is therefore not particularly suited for screening the general population. Examination of a voided urine or bladder barbotage specimen for exfoliated cancer cells is more accurate when a high-grade cancer is present (Murphy, 2000). It is especially useful for patients treated with topical agents, as the effects of therapy may confound cystoscopic examination. Cytology may identify the presence, although not the location, of a high-grade urothelial carcinoma located in the urethra, prostatic ducts, or in the upper tracts.

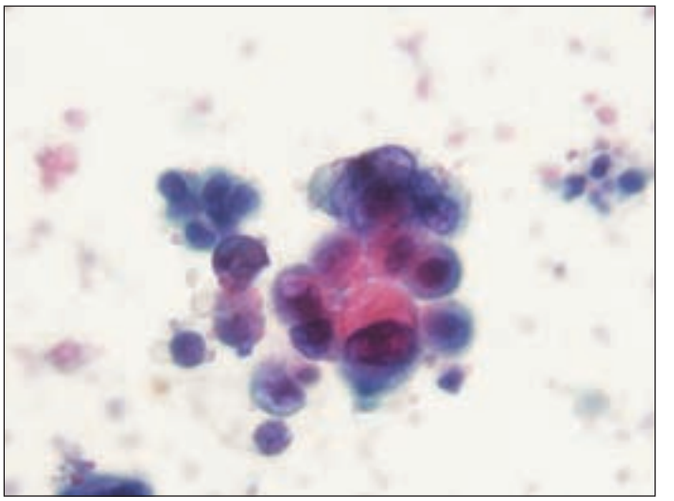
UC can assist the urologist in the timing of cystoscopy during patient monitoring. Patients being observed after the diagnosis of a papillary urothelial neoplasm of low malignant potential (PUNLMP) or non-invasive low-grade carcinoma who have no recognizable tumour cells in their urinary specimens can undergo cystoscopy at longer intervals than patients with tumour cells in their UC (Soloway *et al.,* 1990). UC interpretations can be of prognostic value. Patients treated with topical therapy who have high-grade cancer cells in their urine are more likely to require a cystectomy (Kirkali *et al.,* 2005).

Terminology

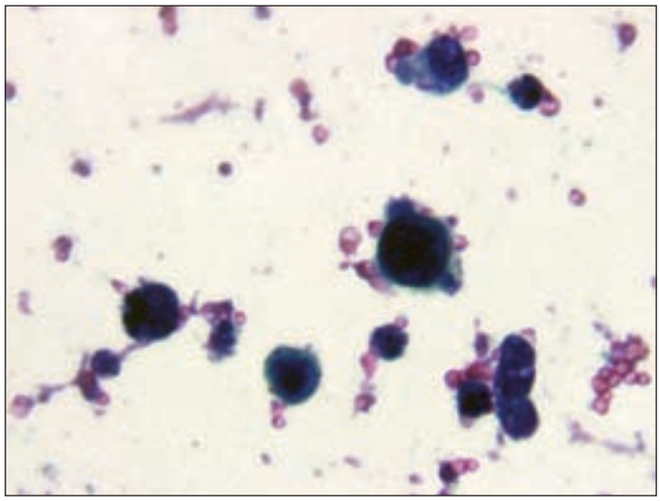
Because the features used to classify urothelial neoplasms histologically may not be present in the cytological sample (namely, the stalk), Murphy (2000) has recommended the following terminology to communicate the cytopathological interpretation: (1) positive, consistent with low-grade neoplasm (**6.1**); (2) positive, consistent with high-grade neoplasm (**6.2** and **6.3**); (3) suspicious for high-grade neoplasm; (4) dysplastic



6.1 Clusters of cells from low-grade urothelial carcinoma. The background is clean and inflammatory cells are not present (urine cytology, Papanicolaou stain, ×40).



6.2 Clusters of cells from high-grade urothelial carcinoma. Here some of the cells are vacuolated and pleomorphic (urine cytology, Papanicolaou stain, ×40).



6.3 Isolated cells from high-grade urothelial carcinoma representing *in situ* urothelial carcinoma (urine cytology, Papanicolaou stain, ×40).

cells, rule out low-grade neoplasm; (5) negative, neoplastic cells not identified; and (6) unsatisfactory, insufficient cells for interpretation. The histological correlates of these cytological diagnoses are noted in *Table 6.2*.

The term *suspicious* is used to describe cells that have features of a high-grade neoplasm, but there are too few for an unequivocal interpretation. Those who have studied asymptomatic, high-risk individuals have discovered that factors other than a developing neoplasm can cause cells in a urinary specimen to appear neoplastic (Farrow and Utz, 1982; Crosby *et al.*, 1991). It is also best to be cautious with the interpretation of a few malignant-appearing cells in specimens from untreated individuals because high-grade urothelial neoplasms in such cases should shed numerous cells into the urine. Dysplastic cells warrant attention, but in many cases, they are not considered diagnostic.

Diagnostic yield of urinary cytopathology

The value of UC in the detection of urothelial neoplasms depends on a variety of factors. One variable affecting the sensitivity of UC is the type of specimen from which interpretations are made. Voided specimens may occasionally be hypocellular and degenerated. They may also contain significant amounts of skin and vaginal contamination, particularly in female patients. Catheterized urine and bladder washes typically contain more cells and less contamination and, as such, have a 20% higher sensitivity (Gregoire *et al.*, 1997; Glas *et al.*, 2003). Properly performed, a bladder washing should include the residual urine collected when the catheter or other instrument is introduced plus a vigorous lavage done after a cystoscopy. Neither random urine specimens nor bladder washings contain tumour cells in every specimen. Malik and Murphy (1999) found that 23% of washings from patients with biopsy-proven, high-grade urothelial carcinomas in their bladders contained no tumour cells. This forms the basis for the recommendation by some authorities that UC specimens should be obtained on three separate days (Badalament *et al.*, 1987).

False-positive cytology results are uncommon. Some patients have positive urine cytology detected with no clinically demonstrable disease. These patients are more likely to have a small urothelial neoplasm that was missed at cystoscopy. There are several reports of patients with positive cytology with normal findings at cystoscopy and upper tract evaluation that required months for histological correlation (Farrow *et al.*, 1977; Murphy *et al.*, 1984). Most recurrences are evident clinically within 3 years of a detectable positive cytology, and therefore close monitoring of the patient (every 3–6 months) during this period is recommended (Schwalb *et al.*, 1994; Dalbagni *et al.*, 1999). Cytological specimens obtained immediately in the post-operative or post-intravesical therapy period may also result in a false-positive reading due to cautery artefacts, inflammation or degradation of cells from instrumentation (Muller *et al.*, 1985).

Other factors that may affect the diagnostic yield include: (1) definition of a cytohistological correlation (whether an immediate or a delayed histological correlation); (2) grade of tumour; (3) whether the correlation is cystoscopic only; (4) number of cytopathologists involved and their interaction with each other as well as their involvement in the data analysis; (5) types of cases (primary neoplasms, persistent or recurrent neoplasms); (6) case mix (the percentage of neoplasms versus negative results will affect the specificity and the predictive value); (7) presence or absence of topical therapy; and (8) histopathological classification used for correlation.

In summary, UC is best applied for the follow-up of patients following a diagnosis of a high-grade urothelial neoplasm. Given adequate sampling and ≥3 specimens, up to 90% of high-grade urothelial carcinomas can be detected by cytology, and the PPV is >90%. UC is less valuable for the detection of low-grade urothelial neoplasm and can be used for monitoring patients who have low-grade non-invasive urothelial neoplasms to detect any high-grade tumours that might develop. Given an adequate sample, the PPV for an

interpretation of high-grade neoplasm in a UC is so high that it can almost never be considered falsely positive. In contrast, the PPV for interpretations of low-grade neoplasm and 'dysplastic cells, rule out low-grade neoplasm' is approximately 60%, high enough to warrant a cystoscopy but not selected site biopsies.

The cellular features of urothelial neoplasms

The cellular features of urothelial neoplasms have been described and illustrated in numerous publications (Malik and Murphy, 1999; Murphy, 2000). Because the features used for histological distinctions may not be present in the disaggregated cells of cytological samples and because it is not always possible to distinguish glandular neoplasms from urothelial tumours, the most accurate approach to classification in this area would seem to be separation on the basis of degree of cytological anaplasia (*Tables 6.2* and *6.3*).

Table 6.2 Histological correlates to cytologic diagnoses

Low-grade cytology	High-grade cytology
Dysplasia	Carcinoma *in situ*
Grade 1 TCC	Some grade 2 TCC
Some grade 2 TCC	Grade 3 TCC

TCC = transitional cell carcinoma

Table 6.3 Cytological features evaluated for the diagnosis of malignancy

Arrangement of cells, size, shape and number
Cytoplasm
Nuclear morphology and size
Nuclear cytoplasmic ratio (N/C)
Chromatin (coarseness, irregularity)
Nucleoli

High-grade neoplastic cells (**6.2**) may be numerous or sparse, depending on the type of specimen, the approach to collection, and the previous application of topical therapy. The key diagnostic changes are nuclear pleomorphism and coarsely granular, irregularly dispersed chromatin. Large nucleoli may appear in high-grade neoplastic cells but are rarely numerous and not essential for interpretation. Occasionally, cells may be small, with degenerated nuclei lacking chromatin detail, but the increased nuclear–cytoplasmic ratios and peculiar nuclear shape of these cells tend to reveal their nature. Importantly, nearly all high-grade neoplastic cells contain all of the diagnostic features listed in *Table 6.3*.

The cells of low-grade urothelial tumours lack many features associated with malignancy, such as nuclear pleomorphism, coarsely clumped chromatin and large nucleoli (**6.1**). In tissue specimens, low-grade urothelial neoplasms are recognized as neoplastic primarily because their cells are arranged on delicate fibrovascular stalks. Similar cells in a flat urothelium cannot be recognized as neoplastic in histological sections and are often termed *dysplasia*. In other words, it is not the cells, but the arrangement of the urothelium, that allows the pathologist to diagnose a low-grade urothelial neoplasm.

Low-grade urothelial neoplasms are composed of cells lacking many features of malignancy. They can be construed as lesions composed of dysplastic cells on delicate fibrovascular stalks. It is the stalk, rather than the cells, that allows histological classification of these tumours as neoplasms. When disaggregated in urinary samples, there is little difference between the cells on stalks and similar cells that might occupy flat areas of urothelium. Therefore, low-grade and dysplastic cells will be described together.

Low-grade/dysplastic cells are often numerous in urinary specimens. The abnormally high number of cells is often the most important clue to the presence of a low-grade carcinoma or PUNLMP and should be reported as 'numerous cells, a very low-grade neoplasm cannot be excluded', even if the cells themselves appear relatively normal. Neoplastic cells tend to be loosely clustered. They have markedly eccentric nuclei and increased nuclear–cytoplasm ratios. The nuclei are irregular, a feature usually manifested by a single notch, crease or shallow depression. The nuclear chromatin is more granular than normal but evenly dispersed. Large nucleoli are not a feature of these cells but are typical of the reactive or regenerative elements from which they must sometimes be distinguished. Importantly, all of the features listed in *Table 6.2* are not necessarily present in every cell.

Limitations in the use and interpretation of urinary specimens

Consultations based on urinary specimens have been extremely beneficial in certain clinical situations, primarily

to identify high-grade neoplastic cells in the bladders of patients being monitored for persistent or recurrent disease. The use of UC has limitations in the following areas: (1) screening the asymptomatic population; (2) detection of renal parenchymal carcinoma; (3) detection of prostatic adenocarcinoma; (4) localization of a neoplasm; (5) detection of a non-aggressive neoplasm; (6) detection of adenocarcinomas and squamous cell carcinoma of the urinary bladder; (7) detection of a non-urothelial neoplasm; (8) detection of neoplasms with little or no surface components.

Summary

The cytopathological assessment of urinary specimens is a valuable means to detect tumour cells in patients suspected of harbouring a bladder cancer. Despite its limitations, this approach is currently the single most efficacious way to monitor patients for clinically important disease after cystoscopy.

Urine markers

Although the ideal use of a urine-based marker for the diagnosis of bladder cancer has not been determined, several tests have been approved for use by the US Food and Drug Administration (FDA). These include the bladder tumour antigen (BTA), the BTA stat (Polymedco Inc., Redmond, WA, USA), the nuclear matrix protein 22 (NMP22) (Matritech, Newton, MA, USA), and UroVysion (Abbott Molecular/Abbott Laboratories Inc., Des Plaines, IL, USA).

BTA stat

The BTA stat is a point-of-care test approved by the FDA as an adjunct to cystoscopy for monitoring bladder cancer recurrence. This test detects the presence of human complement factor H-related protein in the urine. In a side-by-side comparison of tumour markers, BTA stat was found to have a much higher sensitivity for high-grade tumours (74%) than for low-grade tumours (25%). Its specificity was 77% (Lokeshwar *et al.,* 2002).

NMP22

The NMP22 is a point-of-care test and detects elevated nuclear mitotic apparatus protein (**6.4**). The NMP22 test is designed to measure NMP22 levels in a patient's urine by a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) that uses two monoclonal antibodies (**6.4**).

6.4 NMP22 positive test. Note positive reading indicated by a red line in both the control (C) and test (T) windows.

The sensitivity and specificity of NMP22 has been evaluated in many studies. A study evaluating the detection of bladder cancer with this test and cytology found the NMP22 to have a specificity of 86% (Gutierrez Banos *et al.,* 2001). In studies that have compared the sensitivity of NMP22 according to tumour grade, the test has lower sensitivity to detect low-grade tumours (Gutierrez Banos *et al.,* 2001; Ponsky *et al.,* 2001). However, in most studies, the sensitivity of the NMP22 test for detecting intermediate- and high-grade tumours varies between 50% and 70%, and 70% and 100% respectively.

UroVysion test

The UroVysion test is comprised of a multicoloured fluorescence *in situ* hybridization probe set approved by the FDA for the detection of bladder cancer. It involves the staining of exfoliated cells in urine with four denatured fluorescent centrometric chromosome enumeration probes. These detect chromosomes 3, 7 and 17 and a locus-specific probe for 9p21. The cells are observed under a fluorescence microscope. The set criteria for detecting bladder cancer by the UroVysion test are ≥5 cells with a gain of ≥2 chromosomes, ≥10 cells with a gain of one chromosome, or ≥20% of cells

with a loss of 9p21 locus. In various studies, the sensitivity of the UroVysion test is between 69% and 87% (Lokeshwar *et al.*, 2004, 2005). The test has excellent sensitivity to detect CIS and high-grade tumours (range 83–100%). It is useful as an adjunct to cytology because it maintains the specificity but increases the sensitivity (45.8% vs 72.22%) (Halling *et al.*, 2000; Sokolova *et al.*, 2000).

Immunocyt test

The Immunocyt test is based on the visualization of tumour-associated antigens in urothelial carcinoma using fluorescein-labelled monoclonal antibodies. The monoclonal antibodies M344 and LDQ10 are directed against sulphated mucin glycoproteins and a Texas red-linked monoclonal antibody 19A211. Specific technical requirements for this assay are a high-quality fluorescence microscope and a centrifuge. In several studies, the sensitivity of Immunocyt varies between 38% and 100%, and the specificity ranges between 75% and 90% (Pfister *et al.*, 2003; Hautmann *et al.*, 2004). The test appears to have a similar sensitivity in detecting low-grade, low-stage tumours (i.e. 18–100%) and high-grade, high-stage tumours (77–100%). Immunocyt, with an average sensitivity and specificity of approximately 80%, is superior to conventional urine cytology and is clearly among the most promising diagnostic markers for bladder cancer.

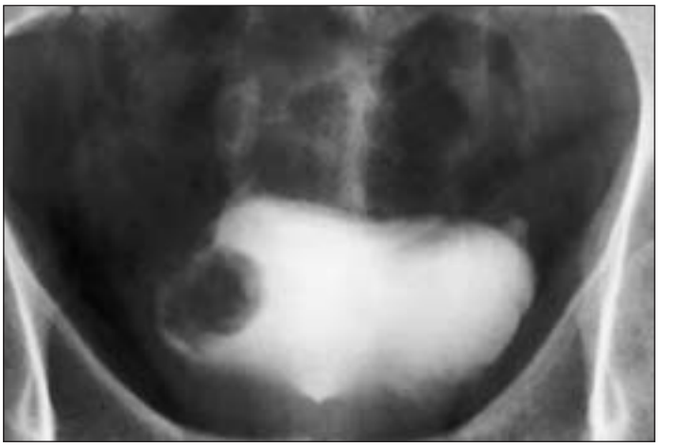
These and other urine-based markers under development can provide advantages over cytology. An ideal protocol for the adjunctive use of ≥1 of these tests in combination with cystoscopy and cytology will require further studies and discussion among opinion leaders.

Imaging of bladder cancer at initial diagnosis

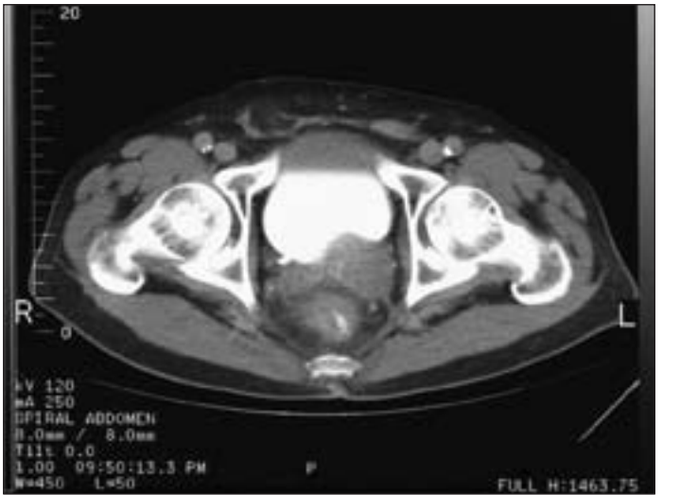
Evaluation of the upper urothelial tract

All patients with haematuria must have their upper tracts evaluated. Excretory urography (intravenous urography, IVU) was traditionally performed as the initial work-up for haematuria. More recently, many institutions have shifted to utilizing computed tomography (CT) as the primary screening modality for the evaluation of painless haematuria. The advent of multislice CT allows for collimation to a slice thickness of 1.25 mm. Coronal reformatted images are then rendered with maximum intensity projection, and volume rendered images of the collecting system, distal ureters, and bladder are performed, which allows for interpretation in both the axial and coronal planes (Wong-You-Cheong *et al.* 1998). The coronal plane allows better visualization of the bladder dome.

Imaging has a limited role in the initial detection of bladder tumour because the tumours are frequently small and confined to the surface. If detectable by imaging, the tumours are appreciated as a filling defect in the bladder on IVU (**6.5**) or as an area of focal or diffuse bladder wall thickening on cross-sectional imaging. On CT and magnetic resonance imaging (MRI), there may be enhancement of a



6.5 Anterioposterior view from an intravenous pyelogram (IVU), which demonstrates contrast within the bladder. Note the large filling defect in the right lateral wall of the bladder. The findings were consistent with transitional cell carcinoma of the bladder.



6.6 Axial CT scan of the pelvis showing an invasive bladder tumour. Note filling defect involving the left posterior wall of the bladder.

bladder tumour with contrast media (**6.6**). Such findings may also be seen in an inflammatory process (infection, radiation or post-chemotherapy), haematomas, fungus balls, cystitis cystica and endometriosis. Ultimately, the diagnosis rests on visual inspection and biopsy.

Staging of the primary bladder tumour

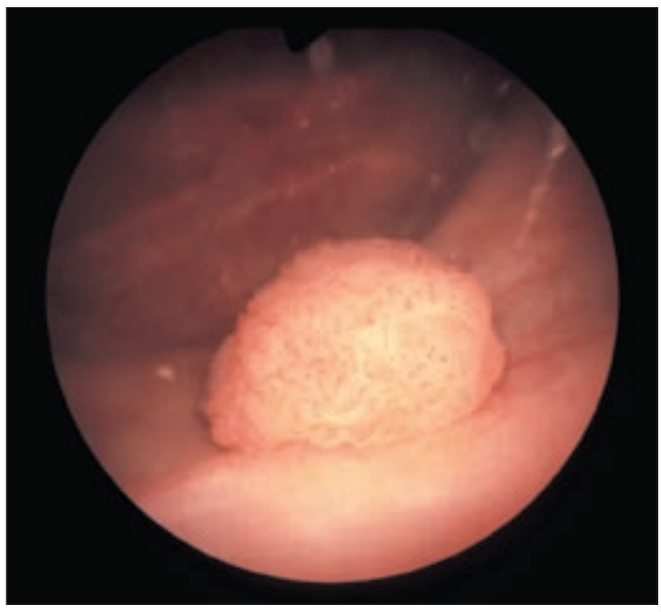
IVU is not useful for staging bladder cancer. However, bladder tumours causing ureteral obstruction usually invade the muscularis propria (Kirkali *et al.,* 2005). Ultrasound is not used for staging because of its limited ability to evaluate the perivesical tissue (Wong-You-Cheong *et al.,* 1998). CT and MRI delineate the perivesical tissue, but staging accuracy is quite variable, ranging from 40% to 98% (Kim *et al.,* 1994; Wong-You-Cheong *et al.,* 1998). MRI is slightly more accurate for staging than CT (Kim *et al.,* 1994). CT and MRI are more useful in distinguishing gross extravesical extension from organ-confined disease. When pelvic imaging is performed after the transurethral resection of a bladder tumour (TURBT), the staging accuracy decreases because post-operative inflammation mimics the appearance of tumour infiltration (Wong-You-Cheong *et al.,* 1998). Ultrafast dynamic MRI sequences may be a more reliable method for distinguishing residual tumour from post-operative inflammation (Kim *et al.,* 1994). These modalities may also detect upper tract transitional cell carcinomas that may occur in 2–4% of bladder cancer patients (Wong-You-Cheong *et al.,* 1998). Currently, MRI and CT are not accurate enough for staging the primary tumour (especially after TURBT), but are used for assessing metastases.

Metastatic evaluation

The most common sites for metastasis for invasive bladder cancer include the regional lymph nodes, liver, lung and bone (Wong-You-Cheong *et al.,* 1998). Both CT and MRI rely on size criteria to detect regional lymphadenopathy. Lymph nodes greater than 1 cm in size are considered clinically suspicious for metastatic disease. As microscopic tumour involvement is not detected by imaging, the accuracy of MRI and CT for staging lymph nodes ranges from 70% to 98% (Kim *et al.,* 1994; Wong-You-Cheong *et al.,* 1998; Paik *et al.,* 2000), with a false-negative rate of 20 40% (Paik *et al.,* 2000). The usual metastatic evaluation for invasive bladder cancer includes chest radiography, liver function tests and an alkaline phosphatase (Kirkali *et al.,* 2005). Abdominal and pelvic imaging (CT or MRI) is often reserved for patients with abnormal liver function tests, locally advanced cancer based on bimanual examination (i.e. clinically T3–T4), or high clinical suspicion of metastasis (Wong-You-Cheong *et al.,* 1998). A routine bone scan is unnecessary but should be performed if there is an unexplained elevation of the alkaline phosphatase or bone pain (Kirkali *et al.,* 2005).

Cystoscopy

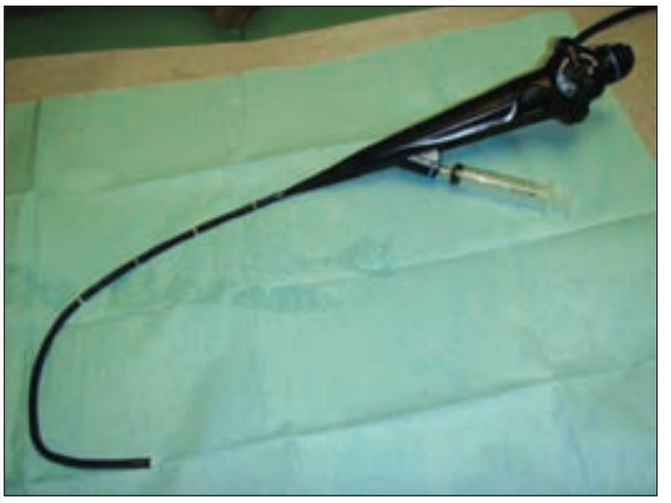
Flexible cystoscopy is often the first investigation for the patient suspected of having bladder cancer (Young and Soloway, 1998). Modern flexible cystoscopes permit almost painless inspection of the urinary bladder (**6.7**). Under intraurethral lidocaine anaesthesia, the urethra and bladder are inspected. The flexible cystoscope provides equivalent visualization to that provided by the rigid cystoscope and is well-tolerated (Soloway, 1985; Young and Soloway, 1998). The precise location of any abnormalities can be documented using photography or a bladder diagram (Young and Soloway, 1998). A thorough endoscopic evaluation is critical. The entire urethra and bladder should be inspected. The bladder should be gradually distended to allow differentiation of true pathology from simple folds, but overdistention must be avoided because this can obscure subtle findings, such as CIS. A bladder wash can be sent along with a voided cytology at this time (Soloway, 1985). A bimanual examination should be performed at the time of the office cystoscopy or immediately before TUR.



6.7 Papillary transitional cell carcinoma of the bladder viewed at cystoscopy.

Appearance of the tumour

Cystoscopic examination of the bladder remains the best approach to identify suspicious lesions in the lower urinary tract (**6.8**). In most cases, a skilled urologist can recognize bladder cancer by inspection, but a biopsy must be performed to establish the diagnosis and define the grade and stage. Information, such as number, size, shape and location of tumours, is easily obtained. Cystoscopically, the appearance of the bladder tumour can be classified according to characteristics of the surface and the base of the tumour. Experienced urologists may be able to predict, with reasonable accuracy, the grade and stage of a tumour by its gross appearance (Crosby *et al.,* 1991). Approximately 70% of urothelial tumours are papillary, 10% are nodular and 20% are mixed.



6.8 Modern flexible cystoscope with biopsy forceps in working channel.

In contrast to the importance of pathological staging of a tumour by the TUR specimen, the issue of whether additional prognostic information can be obtained from the information provided by cystoscopy has been reviewed by various authors (Lutzeyer *et al.,* 1981; Pagano *et al.,* 1987; Abel *et al.,* 1988; Lutzeyer *et al.,* 1981; Whelan *et al.,* 1993). Pagano *et al.* (1987) reported that 73% of 200 patients with Ta and T1 bladder tumours had solitary lesions, 12% had between three and five tumours, and 16% had more than five tumours. They found that those with multifocal tumours were more likely to have a subsequent tumour. Abel *et al.* (1988) studied 107 patients with Ta and T1 bladder cancer. Of this group, 65 (61%) were solitary and 42 (39%) multiple. Of 65 patients with a single tumour, 49 (75%) were pTa compared with 64% of patients who had multiple tumours. Lutzeyer *et al.* (1981) reported progression rates in solitary pTa and pT1 tumours of 18% and 33%, and in multiple pTa and pT1 tumours of 43% and 46%, respectively.

Whelan *et al.* (1993) divided patients into three groups based on the diameter of the tumour: <1 cm, 1–3 cm, and >3 cm. They found no correlation between the size and grade. In addition, the progression of the tumour was not influenced by the size of the tumour.

Fluorescence endoscopy

Traditional white light cystosopy is operator-dependent and may miss a flat lesion. A flat neoplastic urothelial lesion, such as dysplasia or CIS, can be concealed in normal-appearing mucosa or non-specific inflammatory-appearing mucosa. The value of routine random biopsies, which were initially recommended when flat lesions were suspected, was challenged by Witjes *et al.* (1998), who showed in an analysis of 1026 patients that biopsies of normal-appearing mucosa were of little value and rarely impacted the planned treatment.

There is a risk of overlooking a high-grade papillary tumour. Grimm *et al.* (2003) reported that after TUR of a 'superficial' bladder cancer, residual tumour was identified in 33% of cases at repeat resection. In 28% of the patients with fractional resection of T1 urothelial carcinoma, residual tumour was found at the margins of the resected area.

Fluorescent photodetection using 5-aminolaevulinic acid (5-ALA) was first described in 1994 (Kriegmair *et al.* 1994). 5-ALA is a precursor of haem biosynthesis. After intravesical instillation, 5-ALA induces selective enhancement of protoporphyrin IX with a strongly fluorescent dye in the mucosa of neoplastic lesions. The fluorescence is excited with blue light (375–440 nm) and becomes visible using an observation filter in the eyepiece of the endoscope for colour contrast enhancement (Kriegmair *et al.* 1999).

Photodetection using 5-ALA has a high sensitivity for detecting early stage bladder cancer, ranging from 87% to 96%. Specificity is less because of inflammatory lesions (Kriegmair *et al.,* 1996; Jichlinski *et al.,* 1997). These lesions are found especially after intravesical chemotherapy, bacille Calmette-Guérin treatment, and endoscopic resection (Fillbeck *et al.,* 1999). Photodetection is recommended primarily for evaluation of the untreated urothelium or if the mucosa has healed after the treatment. Measurement of 5-ALA-induced fluorescence improves the specificity by 30% without affecting the sensitivity (Zaak *et al.,* 2001a).

In some reports, flat neoplastic lesions that were missed during white light endoscopy were identified by using 5-ALA photodetection. In comparison with white light cystoscopy, 5-ALA photodetection found up to 53% more patients with CIS (Zaak *et al.,* 2002). Sixty-three patients with positive cytology and a negative standard white light cystoscopy underwent photodetection. In 51 (81%) patients, cytological findings were verified by fluorescence endoscopy detecting the malignancy within the bladder. Results in the 12 remaining patients from this group did not show fluorescence, and no cancer was found. In all of these cases, neoplastic disease of the upper urinary tract was excluded by retrograde pyelography (Zaak *et al.,* 2001b). To improve the diagnostic quality of the procedure, an ester of aminolaevulinic acid, hexaminolaevulinate, was developed and evaluated in a multicentric study. Photodetection with hexaminolaevulinate identified 28% more patients with CIS than did standard cystoscopy (Schmidbauer *et al.,* 2004).

Photodetection of neoplasias that were missed with light cystoscopy resulted in a change in treatment strategy in 9% (Filbeck *et al.,* 2002a). In three prospective randomized studies, it has been shown that the risk of residual tumour after TUR of urothelial carcinoma is significantly decreased by 5-ALA fluorescence endoscopy (Riedl *et al.,* 2001; Filbeck *et al.,* 2002b; Kriegmair *et al.,* 2002).

A large study (211 patients) was conducted in 19 European urology centres (Filbeck *et al.,* 2003). Of the 39% of patients with CIS, 96% of the lesions were detected with hexyl aminolaevulinate (HAL) cystoscopy. This compared favourably with standard rigid cystoscopy, which identified only 77% of the lesions; two of the cases missed by HAL cystoscopy were detected with standard cystoscopy, and the third was detected on a random biopsy. The false-positive detection rate was 13% for HAL cystoscopy and 10% for standard cystoscopy. Cytology results were positive in 85% of the patients with CIS in whom cytology was available. All of the cytology-negative cases were detected with HAL cystoscopy, but only seven of eleven were detected with standard cystoscopy. The safety profile was reported to be excellent; only three minor reactions were attributed to HAL.

Fluorescence cystoscopy may be superior to conventional white light endoscopy. The risk of residual tumour after a TURBT is reduced by fluorescence-guided resection. This may lead to a lower recurrence rate, as has been shown in the first phase 3 trial. The results of an ongoing US prospective randomized trial are awaited.

TURBT

A TURBT provides diagnostic information and is therapeutic. The goals of TURBT are to determine the stage and grade of the tumour (diagnostic) and to resect or fulgurate all grossly visible tumour (therapeutic). As with other surgical procedures, attention to detail and skill are required to accurately and safely remove all evident tumour from the bladder. The technique for TURBT is based mainly on surgeon experience. Bimanual examination should be performed before and after TURBT.

Bladder wash cytology may be obtained before TURBT by irrigating normal saline solution through a catheter, cystoscope sheath, or resectoscope sheath (barbotage). A bladder wash cytology detects CIS in almost all cases (Murphy *et al.,* 1984), even when the urothelium appears normal and obviates the need for routine bladder biopsies (Soloway *et al.,* 1990). During barbotage, the bladder wall can be drawn against the sheath, causing urothelial trauma that may mimic the appearance of CIS. Therefore, it is best to perform the bladder wash after inspection of the bladder, although the urine collected immediately on cystoscope introduction should also be sent for pathological review if there is a possibility of a high-grade tumour.

We begin endoscopy with urethral dilation under direct vision using an optical dilator and a 0° or 12° lens (Soloway, 1988). A 27Fr or 28Fr continuous flow resectoscope is then placed, and a full endoscopy is performed with a 70° lens. Continuous flow allows the operator to more easily maintain proper bladder filling and avoid bladder distention. Maintaining the bladder at 50–75% capacity is recommended to diminish the risk of bladder perforation and excitation of the obturator nerve and to facilitate identification of CIS (Soloway *et al.,* 2002).

After full inspection with a 70° lens, the 0° or 12° lens should be replaced and the bladder again evaluated. We prefer the 12° lens for resection, although a 30° lens may be used. All tumours should be completely resected as much as possible. The coagulation current should be minimized to avoid cautery artefact on the removed tissue. At times, tumours in difficult locations may be better accessed by digital manipulation via the vagina or rectum or by suprapubic pressure. In patients suspected of having a tumour stage T1 or higher, muscle must be included in the specimen to allow adequate pathological assessment of the extent of invasion. A bladder wall (angled) loop facilitates attaining the proper depth of resection for tumours located on the posterior and lateral walls, whereas the right angle (90°) loop assists with resection

at the bladder neck and trigone. In patients with an obvious low-grade papillary tumour(s), muscle is not necessary. The resection of large tumours should be orderly, with resection beginning at one edge of the tumour and progressing to the other side and from superficial to deep (Soloway and Patel, 1992). Resecting into the fat has little benefit. Perforation of the bladder should be avoided. The risks of perforation do not justify any theoretic benefit, such as improved accuracy of staging. The roller ball should be used to fulgurate the base of all tumours and any small residual papillary tumours. The bladder should then be reinspected with a 70° lens to ensure complete removal of all tumour. A biopsy should be performed on any suspicious areas of mucosa, such as erythematous patches, using a cold cup biopsy forcep.

A tumour in a bladder diverticulum presents an additional challenge because a diverticulum does not contain muscle. This makes staging more critical but resection more dangerous because perforation is more likely to occur. A biopsy of the prostatic urethra should be considered in patients with a high-grade-appearing bladder tumour or tumour at the bladder neck, irregularity or erythema in the prostatic urethra, positive cytology results and no evident bladder tumour, and those with a previous history of urothelial carcinoma of the prostatic urethra (Soloway and Patel, 1992).

The operative report should include a detailed description of the procedure including: (1) appearance (flat, papillary, sessile), number, approximate size, and location of the tumours (the size of a tumour can be estimated by using the 1-cm width of the resection loop as a reference); (2) location and approximate depth of resection (superficial, into muscle, into perivesical fat); (3) whether all gross tumour was removed or whether residual tumour remained; (4) whether bladder perforation occurred; (5) whether the ureteral orifice was resected or intact at the end of the procedure; and (6) results of the bimanual examination.

Staging and grading

The WHO/ISUP system, now the 2004 WHO classification system, should be used to diagnose bladder tumours (*Table 6.4*). This classification system arose from the need to develop a universally acceptable classification system for bladder neoplasia that could be used effectively by pathologists, urologists and oncologists.

Normal and hyperplastic urothelium

Flat urothelial hyperplasia consists of a markedly thickened mucosa without cytological atypia, and may be seen adjacent to low-grade papillary urothelial neoplasms. There is no evidence regarding its premalignant potential. Papillary urothelial hyperplasia is characterized by urothelium of variable thickness with undulating growth. These lesions lack distinct fibrovascular cores in contrast to papillary urothelial tumours. Papillary urothelial hyperplasia without cytological atypia is thought to be a precursor lesion of low-grade papillary bladder neoplasms because of its frequent association with these neoplasms (Taylor *et al.*, 1996). Papillary urothelial hyperplasia may also be lined by cytologically atypical urothelium ranging from dysplasia to flat CIS and are thought to be a precursor of high-grade papillary urothelial carcinoma (Swierczinski and Epstein, 2002).

Flat lesions with atypia

Dysplasia (low-grade intraurothelial neoplasia) (**6.9**) has appreciable cytological and architectural changes thought to be preneoplastic but fall short of the diagnostic threshold of CIS (Althausen *et al.,* 1976; Farrow *et al.,* 1976). There is some evidence that dysplasia may be a precursor of invasive carcinoma. CIS is a flat lesion that shows nuclear anaplasia similar to that noted in high-grade urothelial carcinoma. *De novo* (primary) CIS accounts for less than 1–3% of urothelial neoplasms, but is seen in 45–65% of invasive urothelial carcinoma. The enlarged nuclei are pleomorphic, hyperchromatic and have a coarse or condensed chromatin distribution (**6.10**).

Papillary urothelial neoplasms: classification

Papilloma

This is a rare, benign condition typically occurring as a small, isolated growth seen primarily in younger patients. On histology, it appears as a normal appearing urothelium lining papillary fronds. The stroma may show oedema and/or scattered inflammatory cells, the epithelium lacks atypia and superficial cells are often prominent. The majority of these lesions, once excised, will not recur.

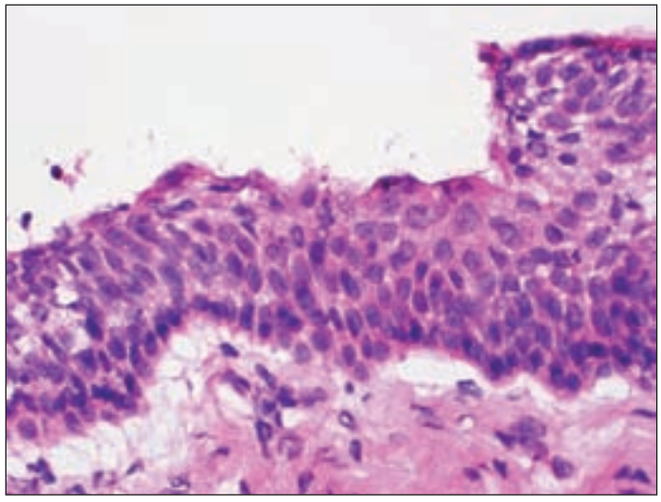
Papillary urothelial neoplasms of low malignant potential

This is a papillary urothelial tumour that resembles the exophytic urothelial papilloma, but shows increased cellular proliferation exceeding the thickness of normal urothelium (**6.11**). The prognosis for patients with PUNLMP is excellent. Recurrences occur, but at a significantly lower frequency than in non-invasive papillary carcinoma (Malmström *et al.,* 1987).

Table 6.4 Features of urothelial neoplasms: World Health Organization/ International Society of Urological Pathologists (WHO/ISUP) 1998

	Carcinoma			
	High-grade	**Low-grade**	**PUNLMP**	**Papilloma**
Configuration				
Papillary	+	+++	+++	+++
Nodular	+++	±	0	0
Architecture				
Normal	0	+	++	+++
Abnormal	+++	±	0	0
Cell distribution				
Even	0	+	+++	+++
Clustered	+++	±	0	0
Superficial cell layer	±	+	+++	+++
Nuclear features				
Pleomorphism	+++	+	±	+++
Fine chromatin	0	+++	+++	0
Coarse chromatin	+++	±	0	0
Even chromatin	±	++	+++	+++
Irregular chromatin	+++	0	0	0
Large nucleoli	+	±	0	0
Mitoses	++	+	±	0

PUNLMP, papillary urothelial neoplasm of low malignant potential; 0, absent/rare; ±, may occur sporadically; +, occurs in some tumours but not constant; ++, occurs in most tumours; +++, characteristic feature, occurring in most or all cases.



6.9 Dysplastic urothelium. There is moderate variability in size of the nuclei, which are hyperchromatic with loss of polarity. These changes do not involve the complete thickness of the urothelium (H&E stain, ×60).

Low- and high-grade papillary carcinoma

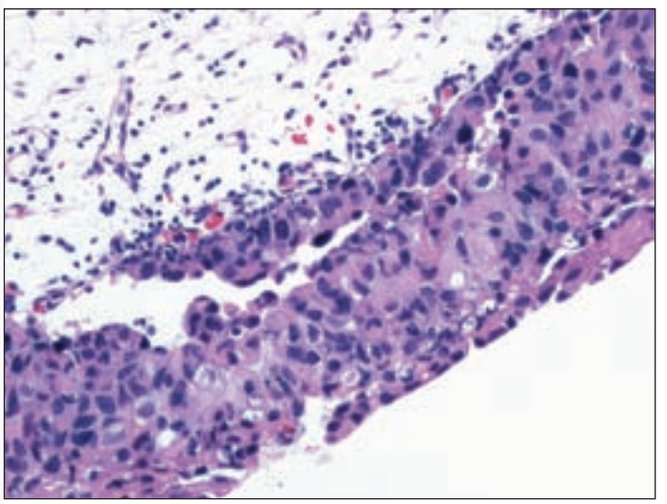
The WHO/ISUP system classifies papillary urothelial carcinoma into only two grades. Low-grade papillary urothelial carcinoma exhibits an orderly appearance but has minimal variability in architecture and/or cytological features that are easily recognizable at scanning magnification (**6.12**). High-grade papillary urothelial carcinomas (**6.13**) are characterized by a disorderly appearance due to marked architectural and cytological abnormalities, recognizable at low magnification. In tumours with variable histology, the tumour is graded according to the highest grade.

The histology of infiltrative urothelial carcinoma has no specific features and shows infiltrating cohesive nests of cells with moderate to abundant amphophillic cytoplasm and large hyperchromatic nuclei. Nuclear pleomorphism may be noted. Nucleoli are highly variable in number and appearance, with mitotic figures and numerous abnormal forms.

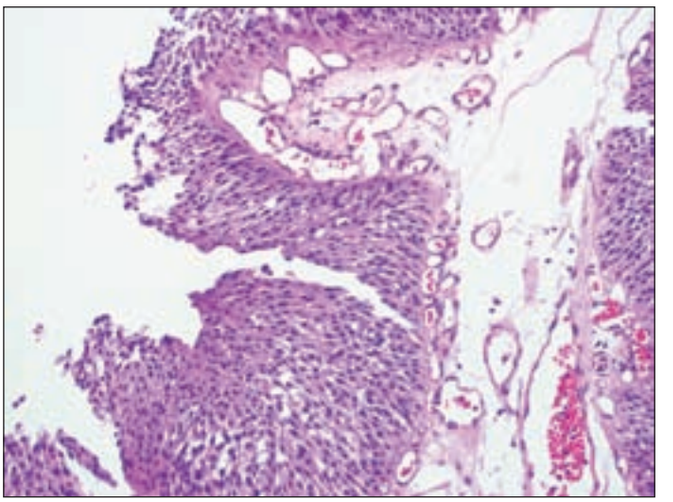
Staging of bladder cancer

Pathological stage is one of the most important prognostic factors in bladder cancer (**6.14**). Accurate staging is critical for patient management. The 2002 TNM (tumour, lymph nodes and metastasis) staging system defines pT1 tumours as those invading the lamina propria, but not the muscularis propria; pT2 tumours as those invading the muscularis propria; pT3 tumours as those invading perivesical tissue; and pT4 tumours as those invading other organ structures (**6.11–6.14**).

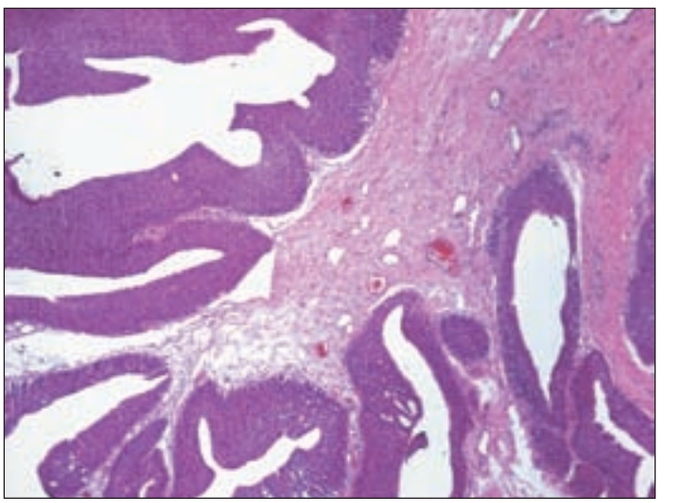
Substaging of T1 tumour (**6.15**) based on muscularis mucosa invasion should not be universally adopted or advocated at this time (Kirkali *et al.,* 2005). For pT1 tumours, the presence or absence of muscularis propria should be reported (**6.12**). For pT1 tumours, pathologists should provide assessment of the depth of lamina propria invasion.



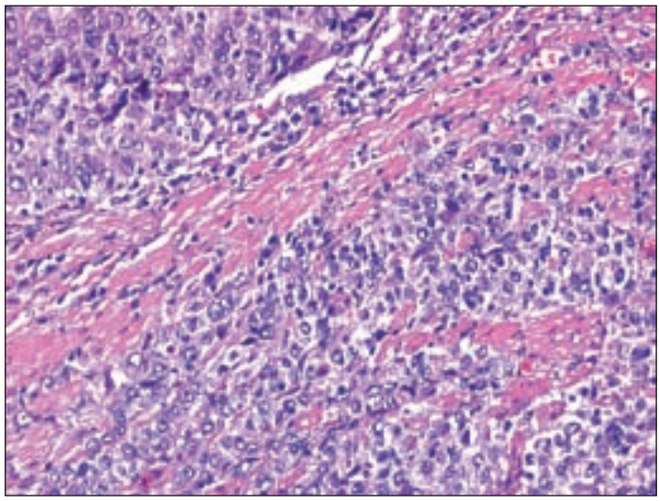
6.10 *In situ* urothelial carcinoma. There is marked variability in size of the nuclei, which are hyperchromatic with loss of polarity. These changes involve the complete thickness of the urothelium (H&E stain, ×20).



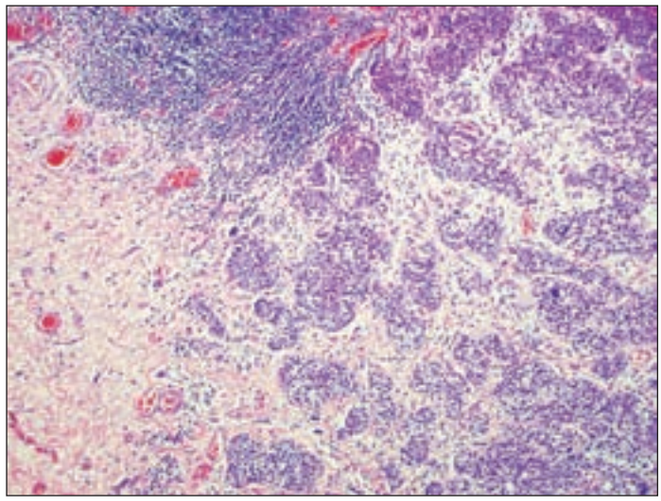
6.11 Papillary urothelial neoplasm of low malignant potential (H&E stain, ×40).



6.12 Low-grade papillary urothelial carcinoma. No invasion into subepithelial connective tissue seen. (AJCC, Ta) (H&E stain, ×10).



6.13 Invasive, high-grade urothelial carcinoma infiltrating muscularis propria. (AJCC, T2) (H&E stain, ×20).

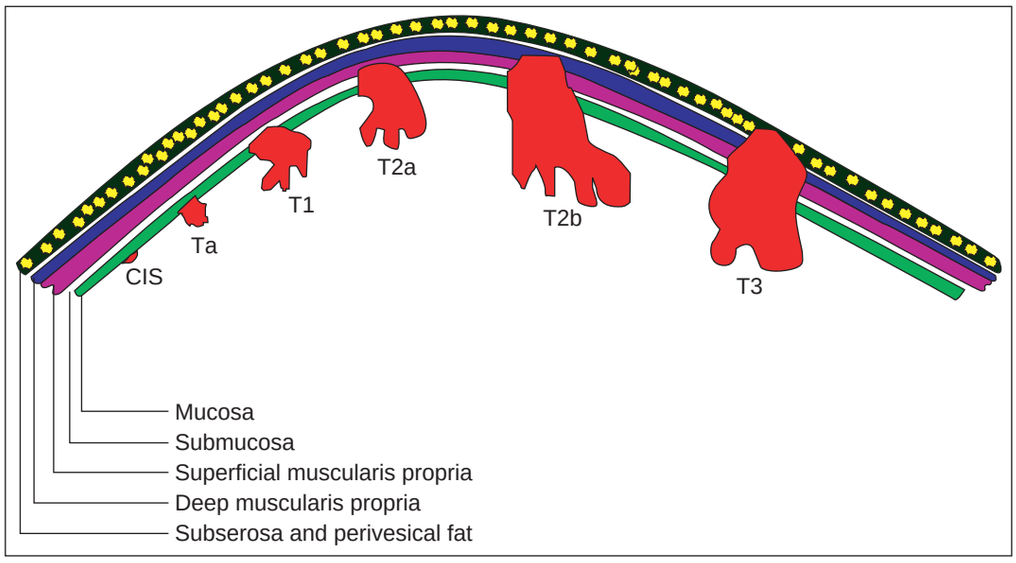


6.15 Invasive high-grade urothelial carcinoma infiltrating into subepithelial connective tissue. (AJCC, T1) (H&E stain, ×20).

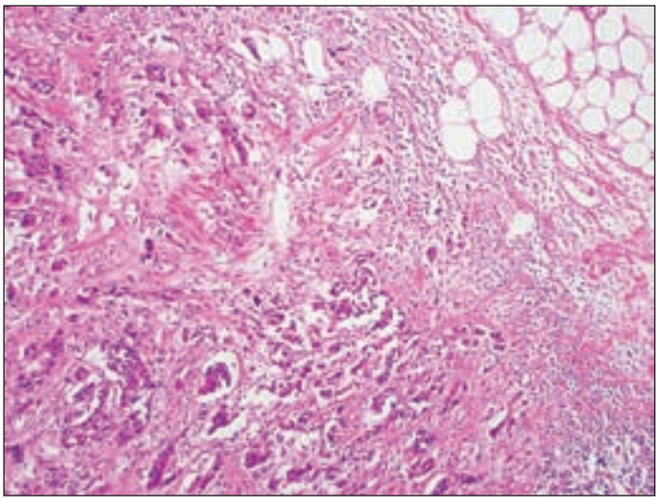
There is little evidence supporting the prognostic benefit of substaging T2 tumours based on the depth of muscularis propria invasion. Thus, distinction between pT2a and pT2b is unnecessary. Tumour size should be included in the subclassification of pT2 tumours. Distinction between pT3a (**6.16**) and pT3b tumours is unnecessary. Subclassification of patients who have prostatic urethral involvement, based on the presence or absence of stromal invasion (**6.17**), is recommended.

Conclusions

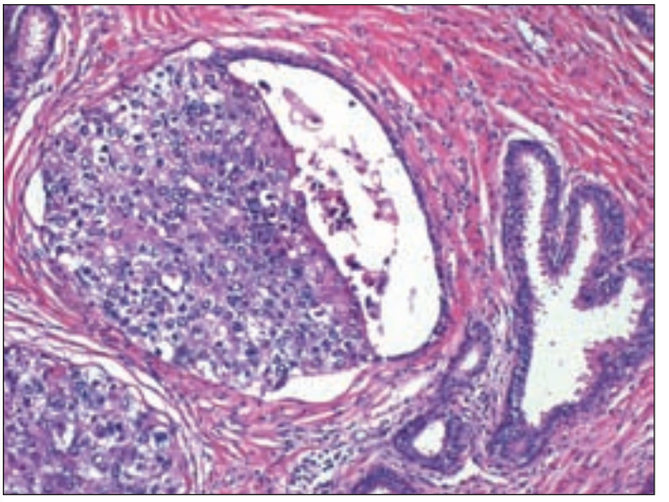
Patients and physicians must recognize the signs and symptoms of bladder cancer so that referrals and evaluations are conducted promptly. Urologists must remember that irritative voiding symptoms are not an uncommon presentation and should consider bladder cancer, particularly CIS, in patients with persistent symptoms.



6.14 Local tumour (T) staging of bladder cancer.



6.16 Invasive high-grade urothelial carcinoma infiltrating microscopically into perivesical adipose tissue (AJCC, T3a) (H&E stain, ×20).



6.17 High-grade urothelial carcinoma invading the prostatic ducts (H&E stain, ×20).

The accuracy of TUR is of the utmost importance in defining the extent of a patient's disease. Cystoscopy, urine cytology, transurethral resection and evaluation of histological section are the mainstays in the diagnosis of urothelial cancer of the urinary tract. Urine cytology has an extremely high specificity for bladder cancer and should routinely be used as an adjunct to cystoscopy in evaluating patients suspected of having bladder cancer. At the time of operative endoscopy, both cystoscopically collected and bladder barbotage specimens should be collected to maximize diagnostic yield if there is uncertainty about the presence of a high-grade urothelial cancer.

Advances in endoscopy, tumour markers and imaging will further improve our abilities to manage this disease. Fluorescence endoscopy appears to enhance the detection of lesions, and future research will reveal the effect of the use of fluorescence endoscopy on prognosis. Numerous tumour markers are under investigation, and several have been approved by the FDA. The optimal use of these markers as adjuncts to traditional evaluation remains to be elucidated. New techniques in imaging, such as dynamic MRI, are expected to improve the ability to stage bladder cancer pre-operatively. The information gained with this imaging may some day prove to be of significant benefit in pre-operative planning and counselling.

References

Abel PD, Hall RR, Williams G (1988). Should pT1 transitional cell cancers of the bladder still be classified as superficial? *Br J Urol* **62**: 235–239.

Althausen AF, Prout GRJ, Dal JJ (1976). Noninvasive papillary carcinoma of the bladder associated with carcinoma in situ. *J Urol* **116**: 575–580.

Badalament TA, Herr HW, Wong GY, *et al.* (1987). A prospective randomized trial of maintenance versus nonmaintenance intravesical bacillus Calmette-Guérin therapy of superficial bladder cancer. *J Clin Oncol* **5**: 441–449.

Bastacky S, Ibrahim S, Wilczynski SP, Murphy WM (1999). The accuracy of urinary cytology in daily practice. *Cancer* **87**: 118–128.

Chang SS, Hassan JM, Cookson MS, *et al.* (2003). Delaying radical cystectomy for muscle invasive bladder cancer results in worse pathological stage. *J Urol* **170**: 1085–1087.

Crosby JH, Allsbrook WC Jr, Koss LG, *et al.* (1991). Cytologic detection of urothelial cancer and other abnormalities in a cohort of workers exposed to aromatic amines. *Acta Cytol* **35**: 263–268.

Dalbagni G, Rechtschaffen T, Herr HW (1999). Is transurethral biopsy of the bladder necessary after 3 months to evaluate response to B.C.G. therapy? *J Urol* **162**: 708–709.

Farrow GM, Utz DC (1982). Observations on microinvasive transitional cell carcinoma of the urinary bladder. *Clin Oncol* **1**: 609–615.

Farrow GM, Utz DC, Rife CC (1976). Morphological and clinical observations of patients with early bladder cancer treated with total cystectomy. *Cancer Res* **36**(7 pt 2): 2495–2501.

Farrow GM, Utz DC, Rife CC, Greene LF (1977). Clinical observations on sixty-nine cases of in situ carcinoma of the urinary bladder. *Cancer Res* **37**(8 pt 2): 2794–2798.

Filbeck T, Roessler W, Knuechel R, *et al.* (1999). 5-aminolevulinic acid-induced fluorescence endoscopy applied at secondary transurethral resection after conventional resection of primary superficial bladder tumors. *Urology* **53**: 77–81.

Filbeck T, Pichlmeier U, Knuechel R, Wieland WF, Roessler W (2002a). Do patients profit from 5-aminolevulinic acid-induced fluorescence diagnosis in transurethral resection of bladder carcinoma? *Urology* **60**(6): 1025–1028.

Filbeck T, Pichlmeier U, Knuechel R, Wieland WF, Roessler W (2002b). Clinically relevant improvement of recurrence-free survival with 5-aminolevulinic acid induced fluorescence diagnosis in patients with superficial bladder tumors. *J Urol* **168**: 67–71.

Filbeck T, Pichlmeier U, Knuechel R, Wieland WF, Rößler W (2003). Senkung des Rezidivrisikos oberflächlicher Harnblasenkarzinome mittels 5-aminolävulinsäure-induzierter Fluoreszenzdiagnostik. *Urologe* **42**: 1366–1373.

Glas AS, Roos D, Deutekom M, Zwinderman AH, Bossuyt PM, Kurth KH (2003). Tumor markers in the diagnosis of primary bladder cancer: a systematic review. *J Urol* **169**(6): 1875–1882.

Golin AL, Howard RS (1980). Asymptomatic microscopic hematuria. *J Urol* **124:** 389–391.

Gregoire M, Fradet Y, Meyer F, *et al.* (1997). Diagnostic accuracy of urinary cytology, and deoxyribonucleic acid flow cytometry and cytology on bladder washings during followup for bladder tumors. *J Urol* **157**(5): 1660–1664.

Grimm MO, Steinhoff C, Simon X, Spiegelhalder P, Ackermann R, Vögeli TA (2003). Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol* **170**(2 pt 1): 433–437.

Grossfield GD, Wolf JS, Litwin MS, *et al.* (2001). Asymptomatic microscopic hematuria in adults: summary of the AUA best practice policy recommendations. *Am Fam Phys* **63**: 1145–1154.

Gutierrez Banos JL, del Henar Rebollo Rodrigo M, *et al.* (2001). Usefulness of the BTA STAT Test for the diagnosis of bladder cancer. *Urology* **57**: 685–689.

Halling KC, King W, Sokolova IA, *et al.* (2000). A comparison of cytology and fluorescence in situ hybridization for the detection of urothelial carcinoma. *J Urol* **164**: 1768–1775.

Hautmann SH, Toma M, Lorenzo Gomez MF, *et al.* (2004). Immunocyt and the HA-HAase urine tests for the detection of bladder cancer: a side by side comparison. *Eur Urol* **46**: 466–471.

Jichlinski P, Forrer M, Mizeret J, *et al.* (1997). Clinical evaluation of a method for detecting superficial surgical transitional cell carcinoma of the bladder by light-induced fluorescence of protoporphyrin IX following the topical application of 5-aminolevulinic acid: preliminary results. *Lasers Surg Med* **20**: 402–408.

Khadra MH, Pickard RS, Charlton M, *et al.* (2000). A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. *J Urol* **163:** 524–527.

Kim B, Semelka RC, Ascher SM, *et al.* (1994). Bladder tumor staging: comparison of contrast-enhanced CT, T1- and T2-weighted MR imaging, dynamic gadolinium-enhanced imaging. *Radiology* **193**: 239–245.

Kirkali Z, Chan T, Manoharan M, *et al.* (2005). Bladder cancer: epidemiology, staging and grading, and diagnosis: 2004 Société Internationale d'Urologie (SIU)/World Health Organization (WHO) Bladder Cancer Consensus Panel Consensus Conference. *Urology* **66**(Suppl. 6): 4–34.

Kriegmair M, Baumgartner R, Knuechel R, *et al.* (1994). Fluorescence photodetection of neoplastic urothelial lesions following intravesical instillation of 5-aminolevulinic acid. *Urology* **44**(6): 836–841.

Kriegmair M, Baumgartner R, Knuechel R, Stepp H, Hofstadter F, Hofstetter A (1996). Detection of early bladder cancer by 5-aminolevulinic acid induced porphyrin fluorescence. *J Urol* **155**: 105–110.

Kriegmair M, Zaak D, Stepp H, *et al.* (1999). Transurethral Resection and surveillance of bladder cancer supported by 5-aminolevulinic acid induced fluorescence endoscopy. *Eur Urol* **36**: 386–392.

Kriegmair M, Zaak D, Rothenberger KH, *et al.* (2002). Transurethral resection for bladder cancer using 5-aminolevulinic acid induced fluorescence endoscopy versus white light endoscopy. *J Urol* **168**: 475–478.

Lokeshwar VB, Civantos F (2004). Tumor markers: current status. In: Droller MJ (ed.). *American Cancer Society Atlas of Clinical Oncology: Bladder Cancer*. BC Decker Inc. Hamilton, Ontario, Canada, pp. 160–205.

Lokeshwar VB, Habuchi T, Grossman B, *et al.* (2005). Bladder tumor markers beyond cytology: International Consensus on bladder tumor markers. *Urology* **66**(Suppl 1): 35–63.

Lokeshwar VB, Schroeder GL, Selzer MG, *et al.* (2002). Bladder tumor markers for monitoring recurrence and screening comparison of hyaluronic acid-hyaluronidase and BTA-Stat tests. *Cancer* **95**: 61–72.

Lutzeyer W, Rubben H, Dahm H (1981). Prognostic parameters in superficial bladder cancer: an analysis of 315 cases. *J Urol* **127**: 250–252.

Malik S, Murphy WM (1999). Monitoring patients for bladder neoplasms: what can be expected of urinary cytology consultations in clinical practice? *Urology* **54**: 62–66.

Malmström PU, Busch C, Norlén BJ (1987). Recurrence, progression and survival in bladder cancer: a retrospective analysis of 232 patients with 5-year followup. *Scand J Urol Nephrol* **21**: 185–195.

May M, Nitzke T, Helke C, *et al.* (2004). Significance of the time period between diagnosis of muscle invasion and radical cystectomy with regard to the prognosis of transitional cell carcinoma of the urothelium in the bladder. *Scand J Urol Nephrol* **38:** 231–235.

Messing EM, Vaillancourt A (1990). Hematuria screening for bladder cancer. *J Occup Med* **32**: 838–845.

Messing EM, Young TB, Hunt VB, Emoto SE, Wehbie JM (1987). The significance of asymptomatic microhematuria in men 50 or more years old: findings of a home screening study using urinary dipsticks. *J Urol* **132**: 64–66.

Mohr DN, Offord KP, Owen RA, *et al.* (1986). Asymptomatic microhematuria and urologic disease: a population–based study. *JAMA* **256:** 224–229.

Muller F, Kraft R, Zingg E (1985). Exfoliative cytology after transurethral resection of superficial bladder tumors. *Br J Urol* **57**: 530–534.

Murphy WM (2000). *Urinary Cytopathology*. ASCP Press, Chicago, IL.

Murphy WM, Soloway MS, Jukkola AF, Crabtree WN, Ford KS (1984). Urinary cytology and bladder cancer. The cellular features of transitional cell neoplasms. *Cancer* **53**: 1555–1565.

Pagano F, Garbeglio A, Milani C, Bassi P, Pegoraro V (1987). Prognosis of bladder cancer. I. Risk factors in superficial transitional cell carcinoma. *Eur Urol* **13**(3): 145–149.

Paik ML, Scoleri MJ, Brown SL, *et al.* (2000). Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. *J Urol* **163**: 1693–1696.

Parkin DM, Whelan SL, Felay J, Teppo L, Thomas DB (2002). *Cancer Incidence in Five Continents*. IARC, Lyon.

Pfister C, Chautard D, Devonec M, *et al.* (2003). Immunocyt test improves the diagnostic accuracy of urinary cytology: results of a French multicenter study. *J Urol* **169**: 921–924.

Ponsky LE, Sharma S, Pandrangi L, *et al.* (2001). Screening and monitoring for bladder cancer: refining the use of NMP22. *J Urol* **166**: 75–78.

Riedl CR, Daniltchenko D, Koenig F, Simak R, Loening SA, Pflueger H (2001). Fluorescence endoscopy with 5-aminolevulinic acid reduces early recurrence rate in superficial bladder cancer. *J Urol* **165**: 1121–1123.

Sanchez-Ortiz RF, Huang WC, Mick R, *et al.* (2003). An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. *J Urol* **169:** 110–115; discussion 115.

Schmidbauer J, Witjes F, Schmeller N, *et al.* (2004). Members of the Hexvix PCB301/01 Study group. Improved detection of urothelial carcinoma in situ with hexaminolevulinate fluorescence cystoscopy. *J Urol* **171**: 135–138.

Schwalb MD, Herr HW, Sogani PC, *et al.* (1994). Positive urinary cytology following a complete response to intravesical BCG therapy: pattern of recurrence. *J Urol* **152**: 382–387.

Sokolova IA, Halling KC, Jenkins RB, *et al.* (2000). The development of a multitarget, multicolor fluorescence in situ hybridization assay for the detection of urothelial carcinoma in urine. *J Mol Diagn* **2**: 116–123.

Soloway MS (1985). Flexible cystourethroscopy: alternative to rigid instruments for evaluation of lower urinary tract. *Urology* **25:** 472–474.

Soloway MS (1988). Optical dilator to obviate blind urethral dilatation prior to endoscopic resections. *Urology* **31:** 427–428.

Soloway MS, Patel J (1992). Surgical techniques for endoscopic resection of bladder cancer. *Urol Clin North Am* **19:** 467–471.

Soloway MS, Murphy WM, Johnson DE, Farrow GM, Paulson DG, Garnick MB (1990). Initial evaluation

and response criteria for patients with superficial bladder cancer. Report of a workshop. *Br J Urol* **66**: 380–385.

Soloway MS, Sofer M, Vaidya A (2002). Contemporary management of stage T1 transitional cell carcinoma of the bladder. *J Urol* **167:** 1573–1583.

Sultana SR, Goodman CM, Byrne DJ, *et al.* (1996). Microscopic haematuria: urological investigation using a standard protocol. *Br J Urol* **78:** 691–698.

Sutton JM (1990). Evaluation of hematuria in adults. *JAMA* **263**: 2475–2480.

Swierczinski SL, Epstein JI (2002). Prognostic significance of atypical papillary urothelial hyperplasia. *Hum Pathol* **33**: 512–517.

Taylor DC, Bhagavan BS, Larsen MP, *et al.* (1996). Papillary urothelial hyperplasia: a precursor to papillary neoplasms. *Am J Surg Pathol* **20**: 1481–1488.

Utz DC, Farrow GM (1984). Carcinoma in situ of the urinary tract. *Urol Clin North Am* **11**: 735–740.

Whelan P, Britton JP, Dowell AC (1993). Three-year follow-up of bladder tumors found on screening. *Br J Urol* **72**(6): 893–896.

Witjes JA, v d Meijden APM, Collette L, *et al.* (1998). Long-term follow-up of an EORTC randomized prospective trial comparing intravesical bacille Calmette-Guérin-RIVM and mitomycin C in superficial bladder cancer. EORTC GU Group and the Dutch South East Cooperative Urological Group. European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Collaborative Group. *Urology* **52**(3): 403–410.

Wong-You-Cheong JJ, Wagner BJ, Davis CJ Jr (1998). Transitional cell carcinoma of the urinary tract: radiologic–pathologic correlation. *Radiographics* **18**: 123–142.

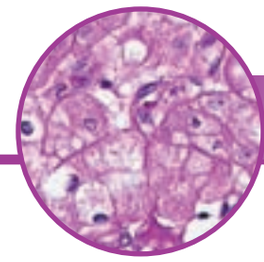
Woolhandler S, Pels RJ, Bor DH, Himmelstein DU, Lawrence RS (1989). Dipstick urinalysis screening of asymptomatic adults for urinary tract disorders. I. Hematuria and proteinuria. *JAMA* **262**: 1214–1219.

Young MJ, Soloway MS (1998). Office evaluation and management of bladder neoplasms. *Urol Clin North Am* **25:** 603–611.

Zaak D, Frimberger D, Stepp H, *et al.* (2001a). Quantification of 5-aminolevulinic acid induced fluorescence improves the specificity of bladder cancer detection. *J Urol* **166**: 1665–1669.

Zaak D, Kriegmair M, Stepp H, *et al.* (2001b). Endoscopic detection of transitional cell carcinoma with 5-aminolevulinic acid – results of 1012 fluorescence endoscopies. *Urology* **57**(4): 690–694.

Zaak D, Hungerhuber E, Schneede P, *et al.* (2002). Role of 5-aminolevulinic acid in the detection of urothelial premalignant lesions. *Cancer* **95**(6): 1234–1238.



Chapter 7

Renal masses

Anthony Koupparis

Malignant renal masses

Introduction

Renal cell carcinoma (RCC) is the most common renal tumour. It accounts for approximately 3% of adult malignancies, 85% of renal malignancies and 2% of all cancer deaths. In 1999 in the UK, 3676 patients were diagnosed with RCC, with just over 2000 dying from the disease in the year 2000. In the USA, approximately 36 000 new cases occurred in 2005, with 12 500 deaths occurring in the same year. RCC is the most lethal of urological tumours, with approximately 40% of patients dying of the condition. Roughly 25% of patients present with locally invasive or metastatic disease. RCC is most commonly sporadic; however, distinct groups of patients have been identified that develop rarer hereditary forms.

History

RCC has a variety of synonyms. It has been termed hypernephroma, due to the fact it was incorrectly thought to arise from the adrenal gland. Its other names include Grawitz tumour after Paul Albert Grawitz, professor of pathology at Greifswald Germany, clear cell carcinoma and nephrocarcinoma.

In 1826 Konig first described the anatomy of kidney tumours. In 1861 Wolcott reported the first nephrectomy; interestingly, he presumed he was operating on a hepatoma. This was followed by the first 'planned' nephrectomy in 1869 by Simon. In 1903 the incorrect term hypernephroma was corrected by Albarran and Imbert, who recognized that these tumours originated from the kidney as opposed to the adrenal glands.

Epidemiology

Overall, RCC affects males twice as commonly as females. There are variations within the histological subtypes; for example, papillary RCC is five times more common in men. In general, RCC usually presents in the fourth to sixth decades of life.

Aetiological risk factors include:

- Smoking.
- Urban residents.
- Low socioeconomic status.
- Renal failure and long-term kidney dialysis.
- Obesity.
- Asbestos exposure.
- Hypertension.
- Anatomical: polycystic and horseshoe kidney.
- Nutritional factors: vitamins A, C and E and fruit and vegetables are protective.
- Genetic factors. Several inherited forms of kidney cancer exist: von Hippel-Lindau (VHL); inherited form of clear cell: hereditary papillary renal carcinoma; inherited form of type I papillary RCC: hereditary leiomyoma RCC; inherited form of type II papillary RCC: Birt–Hogg–Dube syndrome (BHD); risk of developing several different types of kidney cancer, including chromophobe RCC and oncocytoma.

Pathology

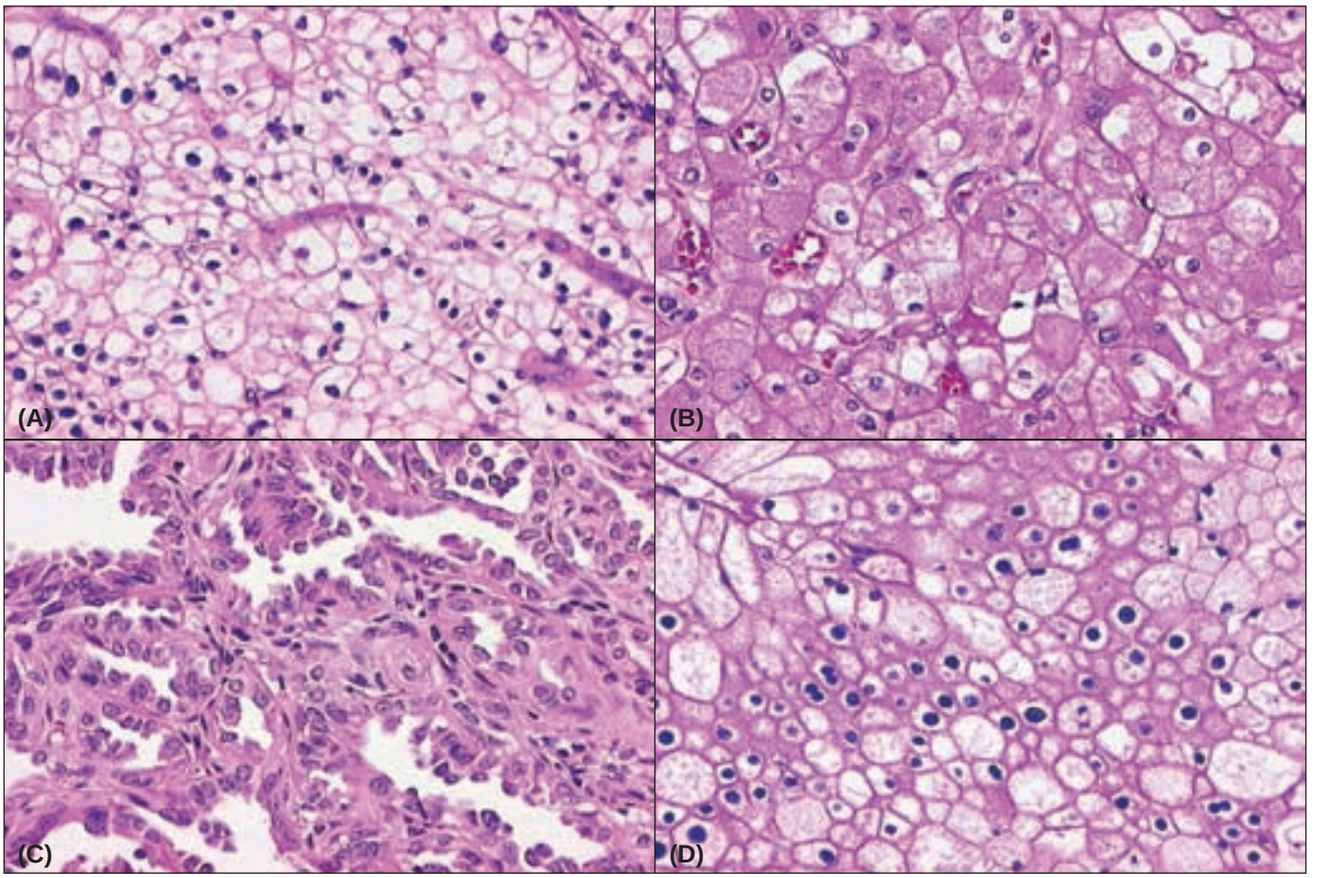
RCC is an adenocarcinoma of the renal cortex, probably arising from the proximal convoluted tubule. Macroscopically, RCCs are typically round and vary in size. They are generally comprised of areas of yellow or brown tumour interposed with areas of haemorrhage and necrosis. They are often surrounded by a pseudocapsule of compressed tissue. Up to 20% contain calcification, and are multifocal. Approximately 25% are cystic, with 2% of cases associated with synchronous or asynchronous bilateral tumours.

Histological classification

- *Conventional:* comprise 80% of RCCs and arise from the proximal convoluted tubule. Microscopically, they can include clear cell, granular cell or mixed types (**7.1**).
- *Papillary:* comprise 15% of RCCs and also arise from the proximal convoluted tubule. Two subtypes of papillary RCC exist: type 1 and type 2. Type 2 cancers are genetically more heterogeneous, have a poorer prognosis, and may arise from type 1 cancers.
- *Chromophobe:* comprise 5% of RCCs and probably arise from the distal convoluted tubule.
- *Collecting duct (Bellini):* comprise <1% of RCCs.
- *Sarcomatoid variant:* rare subtype that exhibits an aggressive behaviour and has a poor prognosis.
- *Medullary cell:* very rare; associated with sickle cell trait or disease and arise from the cortical medullary collecting duct.

Grading

RCCs are assigned a grading according to Fuhrman's criteria proposed in his article the *Prognostic significance of morphologic parameters in renal cell carcinoma* published in 1982 in the *American Journal of Surgical Pathology*. The nuclear grading system is based on nuclear size and shape, number and size of nucleoli, and clumping of chromatin. These characteristics give an indication of how actively the tumour cells are producing protein, and give an important indication of survival.



7.1 (A) Histological slide of a conventional clear cell RCC. Note the round or polygonal cells with abundant cytoplasm. (B) Histological slide of a conventional granular cell RCC. The granular cells have eosinophilic cytoplasm and abundant mitochondria. (C) Histological slide of a papillary renal cell RCC. Microscopically, they consist of eosinophilic cells arranged in a tubular or papillary fashion. (D) Histological appearance of a chromophobe RCC. Note the relatively transparent cytoplasm with a fine reticular pattern which has a plant-cell appearance.

1. Well differentiated.
2. Moderately differentiated.
3/4. Poorly differentiated/undifferentiated.

Staging

Following histological confirmation of the disease, staging is achieved by the 2002 TNM classification (*Table 7.1*).

Genetics

Studies from the early 1980s observed that deletions and translocations of the short arm of chromosome 3 occur in sporadic, non-inherited kidney cancer. Furthermore, loss of a segment of chromosome 3 could be an early event in the development of RCC. This led to an enormous amount of work on hereditary forms of RCC with the hope that observations in these groups of patients might be applicable to RCC as a whole and lead to the development of new treatment strategies for the management of RCC.

von-Hippel Lindau (VHL) syndrome

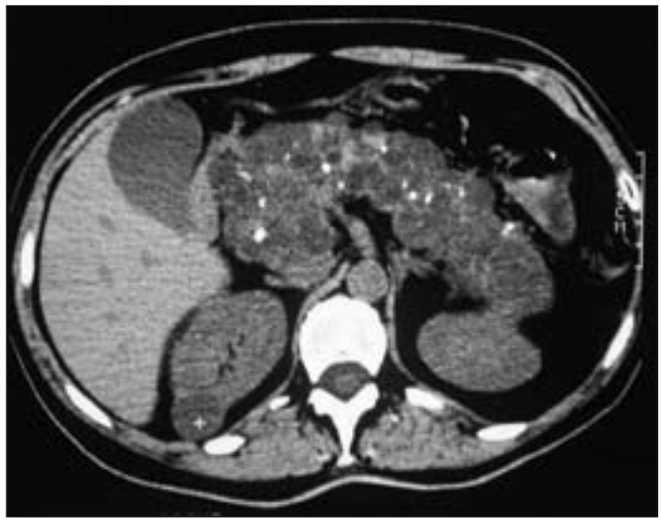
VHL is a rare autosomal dominant cancer syndrome. Affected individuals develop retinal angiomas, haemangioblastomas of the cerebellum and spine, phaeochromocytomas, renal and pancreatic cysts (**7.2**) and in approximately 50% of cases bilateral, multifocal clear cell RCCs (**7.3**). The VHL tumour suppressor gene responsible for this syndrome was identified in 1993. It undergoes a 'two-hit' loss of function whereby both copies of the gene present in the tumour tissue have been inactivated by mutation or loss. Interestingly, defects in the VHL gene appear to be responsible for approximately 60% of cases of sporadic clear cell RCC.

The VHL protein produced in this condition arises from the VHL gene. It functions as a tumour suppressor by binding to transcriptional activators of hypoxia-inducible genes, such as hypoxia-inducible factor-α (HIF-1α) and 2α (HIF-2α), thereby destabilizing them. In particular, the VHL protein promotes the ubiquitination and destruction of HIF-1α. In clear cell RCC, loss of the VHL gene leads to an increase in HIF-1α, resulting in overexpression of proteins normally

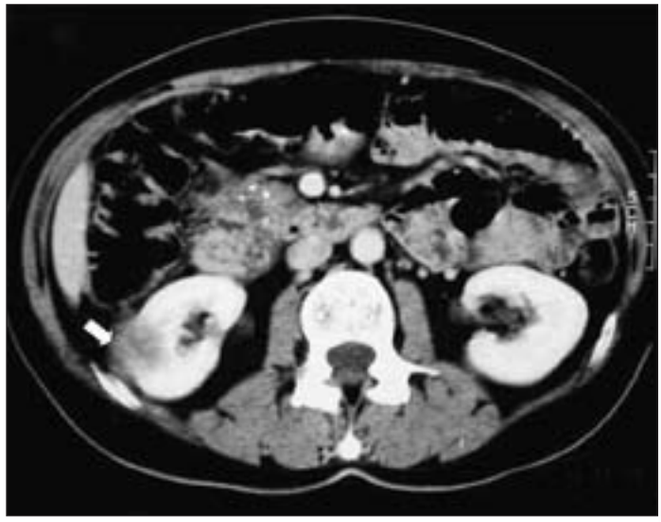
Table 7.1 Summary of TNM for RCC

T1 ≤7 cm; limited to the kidney
T1a ≤4 cm
T1b ≥4 cm
T2 >7 cm; limited to the kidney
T3 Adrenal or perinephric invasion; major vein involvement
T3a Adrenal or perinephric invasion
T3b Renal vein(s); IVC below diaphragm
T3c IVC above diaphragm
T4 beyond Gerota's
N1 Single node
N2 More than one node

IVC = inferior vena cava



7.2 Abdominal CT scan showing multiple pancreatic cysts in a patient with VHL syndrome.



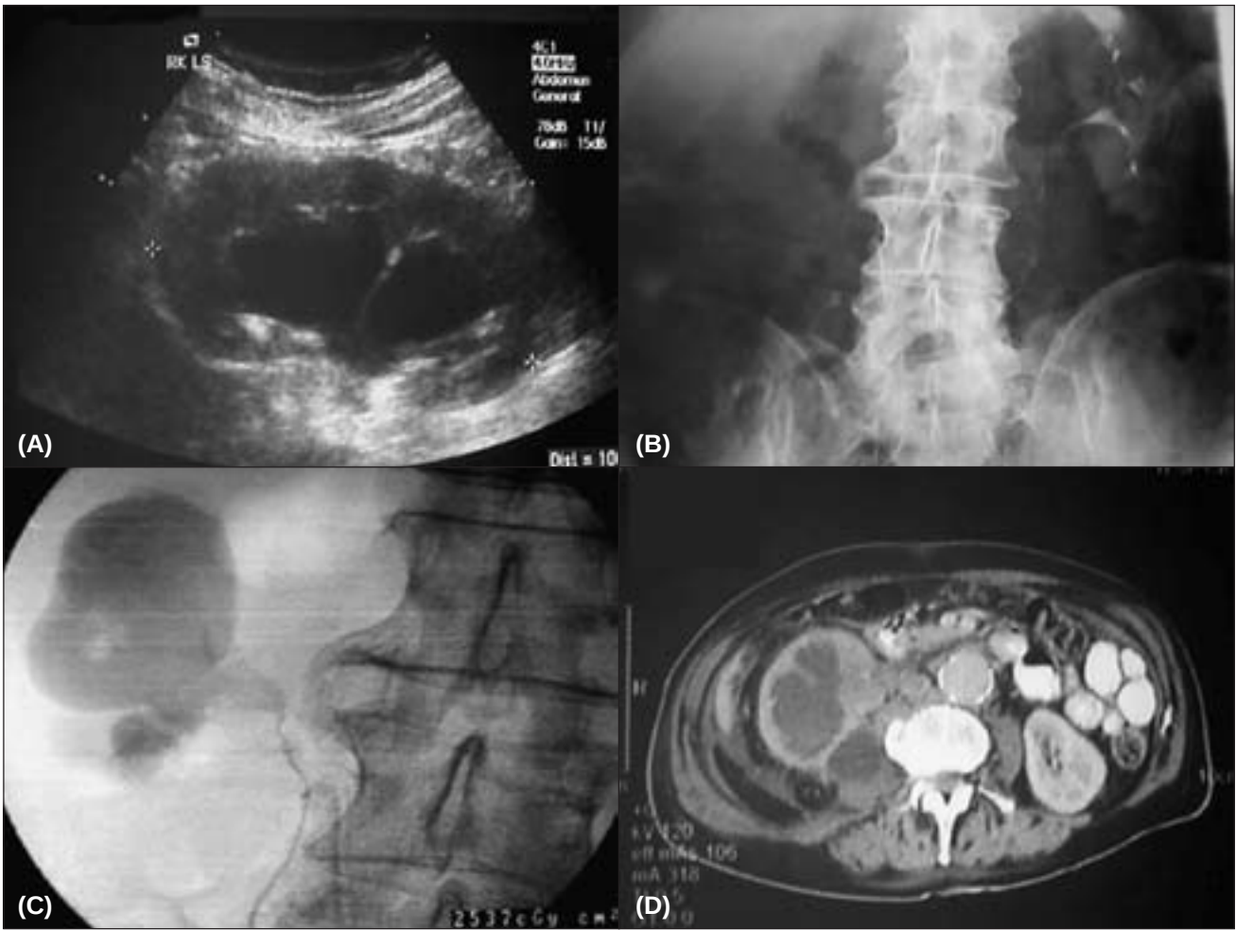
7.3 Abdominal CT scan showing a clear cell carcinoma in a patient with VHL syndrome.

seen with hypoxia, for example, vascular endothelial growth factor (VEGF), transforming growth factor-α (TGF-α) and -β (TGF-β), and platelet-derived growth factor-β (PDGF-β). Increased levels of VEGF, PDGF-β, and TGF-β stimulate tumour angiogenesis resulting in the delivery of additional oxygen and nutrients promoting tumour cell growth. In addition, the increase in TGF-α promotes tumour cell proliferation and survival via activation of the epidermal growth factor receptor.

Hereditary papillary renal carcinoma

Hereditary papillary renal carcinoma is an autosomal dominant condition associated with multifocal, bilateral type I papillary RCCs. The causative gene is the proto-oncogene c-MET, located on the long arm of chromosome 7. The c-MET gene encodes MET, a tyrosine kinase receptor, which is normally activated by hepatocyte growth factor and regulates tyrosine kinase growth hormones and epithelial proliferation and differentiation. In hereditary papillary renal carcinoma the c-MET gene undergoes 'gain of function' mutations, which convert it from the usual autoinhibited state to an activated state. Furthermore, chromosome 7, which contains the mutated gene is then duplicated, which increases the gene dose.

Only a small proportion of sporadic papillary RCCs are associated with mutations in the MET gene. However, it may



7.4 Radiological images from a patient who presented with night sweats, fatigue, weight loss and loin pain. (A) The initial renal ultrasound shows a marked right-sided hydronephrosis. (B) The patient then underwent an intravenous urogram. The 6-hour post-contrast film is shown, demonstrating a complete absence of excretion of contrast from the right kidney. (C) The patient then underwent a rigid cystoscopy and bilateral retrograde examination. Note the hydronephrotic kidney and abnormal appearances of the proximal ureter. (D) A subsequent CT scan of the chest, abdomen and pelvis revealed the diagnosis of metastatic renal cancer. A slice from the abdominal CT reveals a large renal mass invading local structures.

still play a significant part in light of the observation that in 75% of cases of sporadic papillary RCC there is duplication of chromosome 7.

Hereditary leiomyomatosis and renal cell cancer syndrome

This is an autosomal dominant condition in which individuals affected are at risk of developing cutaneous and uterine leiomyomas and papillary RCC. They are primarily type 2 papillary RCCs. Tumours tend to be unilateral, solitary, metastasize early and are the most aggressive of the familial types. It is the gene encoding the Krebs' cycle enzyme, fumarate hydratase, which is lost in this condition.

Birt–Hogg–Dube (BHD) syndrome

BHD is a rare autosomal dominant cancer syndrome in which those affected are at risk of developing fibrofolliculomas (hair follicle hamartomas) of the face and neck, pulmonary cysts and renal tumours. The BHD gene encodes the protein folliculin, a suspected tumour suppressor gene, and is found on the short arm of chromosome 17.

Approximately 15% of affected individuals develop multiple renal tumours. They can be bilateral, multifocal, malignant and can metastasize. Tumours are mainly chromophobe RCCs, or mixed chromophobe–oncocytomas. Occasionally, papillary or clear cell tumours can arise.

Clinical presentation

In the region of 50% of RCCs are detected incidentally with imaging for atypical or unrelated symptoms. Of the symptomatic patients, 50% present with haematuria, 40% present with loin pain, 30% present with a mass, with only 10% presenting with the classic triad of mass, haematuria and loin pain.

Patients can also present with the symptoms and signs of metastatic disease. These include night sweats, fatigue, weight loss and haemoptysis (**7.4**).

Spread

- *Direct:* adrenal gland (7.5% of tumours >5 cm); renal vein; inferior vena cava; right atrium.
- *Vascular:* lung (75%), liver (20%), bone (10%), brain (10%).
- *Lymphatic:* hilar and para-aortic lymph nodes.

10–40% present with paraneoplastic syndromes that can be associated with any stage of the disease. Different types are detailed in *Table 7.2*. Rare presentations include lower limb oedema and varicocoele (due to obstruction of the testicular vein via involvement of the left renal artery).

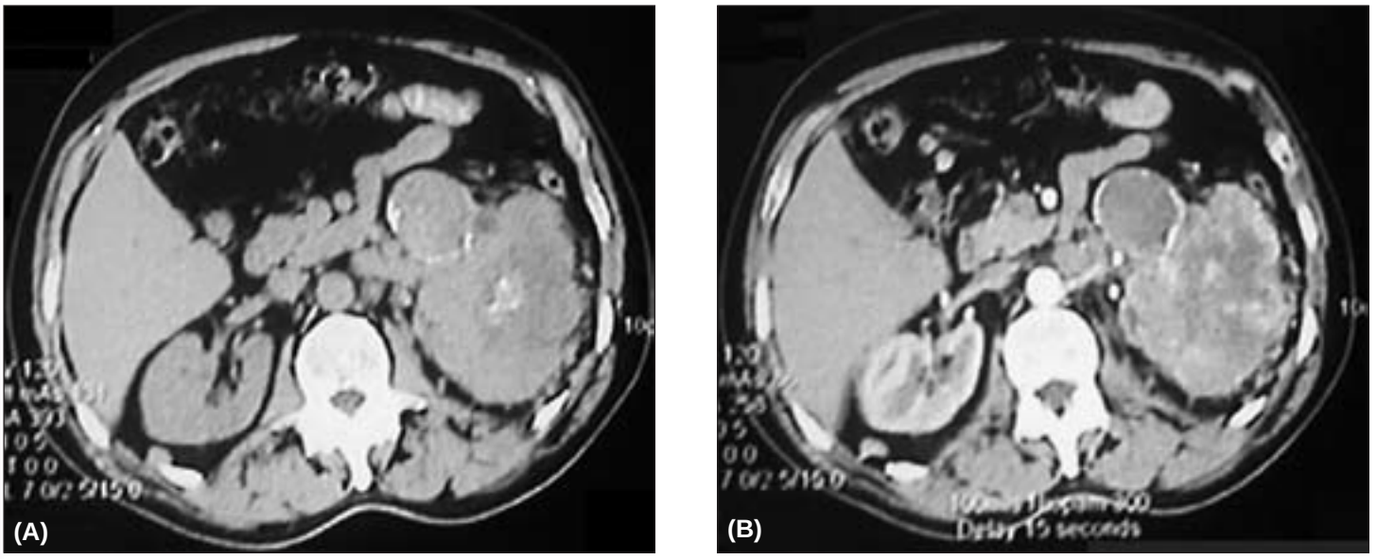
Diagnosis

Full blood count, serum urea, creatinine, electrolytes, calcium and liver function tests are mandatory. These may reveal some of the paraneoplastic syndromes mentioned above. An abdominal ultrasound is often a first-line investigation for a patient with a mass or loin pain. Ultrasound has the ability to distinguish between solid, cystic and complex masses. Following identification of a renal mass, a pre- and post-contrast computed tomography (CT) scan is the method of choice for detecting and staging RCC. Any solid enhancing renal mass is considered a renal carcinoma until proven otherwise. **7.5** is an abdominal CT demonstrating a large left renal mass – note the areas of enhancement on the post-contrast film.

Table 7.2 Paraneoplastic syndromes and causes

Anaemia – secondary to haematuria or anaemia of chronic disease
Polycythaemia – ectopic erythropoietin production
Hypertension – ectopic rennin secretion, renal artery obstruction
Hypoglycaemia – ectopic insulin
Cushing's disease – ectopic ACTH
Hypercalcaemia – ectopic PTH-like substance
Gynaecomastia, amenorrhoea – ectopic gonadotrophins
Staufers syndrome – syndrome of unknown aetiology associated with hepatic dysfunction, fever and anorexia. Resolves in the majority of patients post-nephrectomy. The 1-year survival is 88% and recurrence of the syndrome is associated with recurrence of the tumour

ACTH = adrenocorticotrophic hormone; PTH = parathyroid hormone



7.5 Pre- and post-contrast abdominal CT scan showing a large left-sided renal mass. (A) Pre-contrast. (B) Post-contrast.

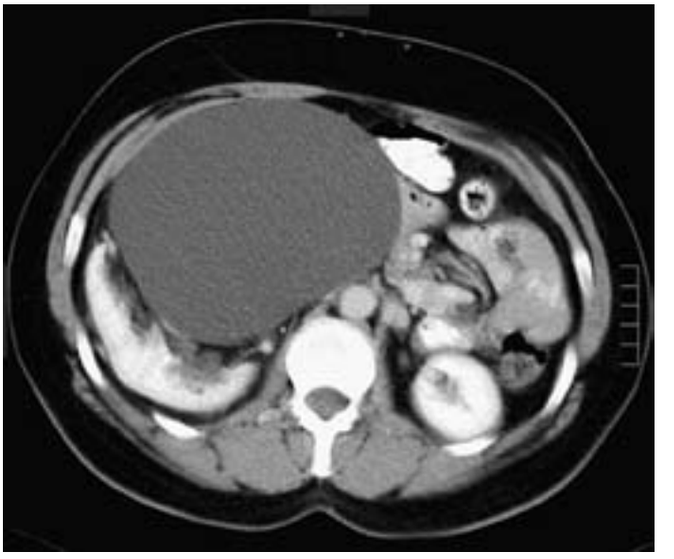
Benign renal masses

At this point it is appropriate to mention benign renal masses. By far the most common are simple renal cysts accounting for approximately 70%. Approximately 50% of people over the age of 50 years have renal cysts. Simple cysts, if asymptomatic, are no cause for concern. They are fluid-filled, non-neoplastic, unilocular, smooth-walled, arise from cortex, contain straw-coloured fluid and can be of considerable size (**7.6**). Furthermore, with imaging studies they appear sharply marginated, round, smooth, homogeneous, thin-walled, non-enhancing and have attenuation values of –10 to –20 Hounsfield units (HU) on CT (**7.7**). However, more complex cysts present a problem. They have been classified according to their malignant potential by Bosniak (*Table 7.3*). Features of cysts that are suspicious for malignancy include:

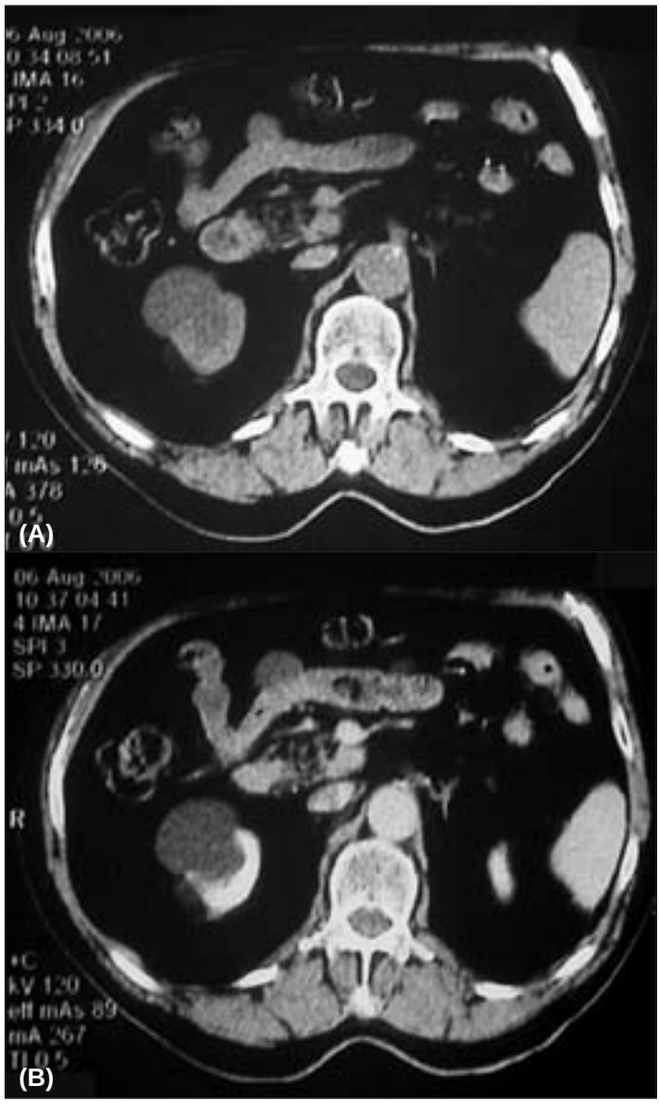
- *Calcification:* small amount in wall or septa may be benign.
- *Abnormal density:* masses with a density >20 HU do not meet criterion for cysts; however, a change of >10 HU before and after contrast studies suggests vascularity.
- *Septations:* especially if irregular and thickness >1 mm.
- *Nodularity:* solid tissue within the cyst wall.
- *Wall thickening*.
- *Small masses*: due to imaging difficulties.

It must be noted, however, that the Bosniak classification is not without its problems. It is good at classifying category I and IV lesions but not definitive for category II and III cysts and problems can arise in diagnosis. As a result, category II and III cysts should be viewed with suspicion and followed appropriately.

Renal oncocytomas account for 3–7% of renal tumours. They are twice as common in males and have a similar age incidence to RCCs. Macroscopically they are usually well-circumscribed, round, encapsulated and have tan/



7.6 An abdominal CT scan demonstrating a large benign renal cyst.



7.7 CT images showing the appearances of the same cyst pre-contrast (A) and post-contrast (B). Note that the cyst does not enhance.

Table 7.3 Bosniak classification

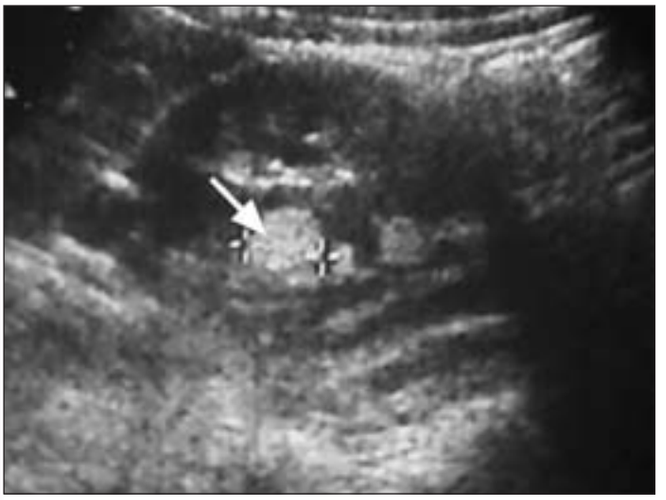
I	Simple benign cyst with hairline thin wall, which does not contain septa, calcification or solid components. Measures as water density and is non-enhancing
II	Benign cyst which may contain a few hairline septa. Fine calcification may be present in the wall or septa. Uniformly high attenuation lesions of <3 cm that are sharply marginated and non-enhancing
IIF	May contain more hairline septa. Minimal enhancement or minimal thickening of wall or septa can be seen. Cyst may contain calcification that might be nodular and thick but there is no enhancement. Lesions are generally well-marginated. Soft-tissue elements are non-enhancing. Includes intra-renal non-enhancing high attenuation lesions of ≥3 cm
III	Lesions are indeterminate cystic masses with thickened irregular walls or septa in which enhancement can be seen
IV	Malignant cystic lesions containing soft-tissue enhancing components

light brown or 'mahogany' appearance and are bilateral in approximately 6% of cases. Microscopically they consist of large, well-differentiated polygonal eosinophilic cells with numerous large mitochondria. They are not known to metastasize and are associated with the loss of chromosome 1 and the Y chromosome.

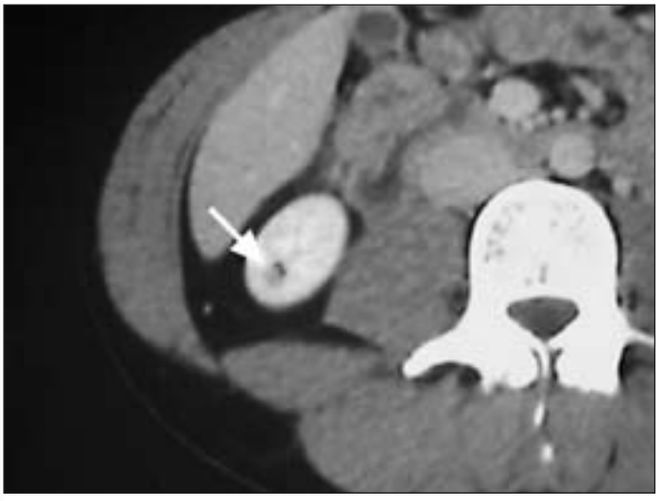
They are an incidental finding in the majority of cases, but can present with loin pain or haematuria. CT scanning can show the characteristic 'spoke-wheel' caused by the central scar, but are usually indistinguishable from a hypovascular RCC. They are generally managed with partial or radical nephrectomy depending on the case and further follow-up is not usually required.

Renal angiomyolipoma is a hamartoma of the kidney (**7.8**, **7.9**). In the majority of cases they occur sporadically, but in 20% they are associated with tuberous sclerosis. This is an autosomal dominant syndrome characterized by mental retardation, epilepsy, adenoma sebaceum and other hamartomas. Approximately 50% of patients with tuberous sclerosis develop angiomyolipomas; these are commonly multifocal and bilateral, and occur at about 30 years of age (**7.10**). Interestingly, solitary angiomyolipomas occur more commonly in the right kidney.

Macroscopically they can appear yellow and grey in colour and have the appearance of a well-circumscribed piece of fat. They are composed of blood vessels, fat and smooth muscle. Microscopically there are abnormal blood vessels, clusters of adipocytes and sheets of smooth muscle cells.



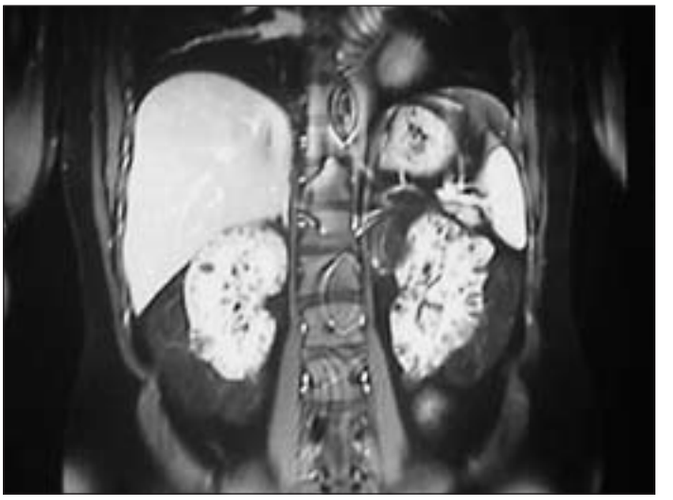
7.8 An ultrasound scan showing the characteristic highly echogenic appearance of angiomyolipomas.



7.9 A slice from a post-contrast CT demonstrating a small, solitary, low-density right sided angiomyolipoma.

They are usually incidental findings but can present with loin pain, mass or haematuria. Approximately 10% present with Wunderlich's syndrome, which refers to a massive, life-threatening retroperitoneal bleed. On ultrasound, angiomyolipomas appear highly echogenic and CT demonstrates a low density fatty tumour whose HUs are <10.

Treatment of these tumours depends on the size. Asymptomatic tumours that are <4 cm are managed with serial ultrasound. Those lesions that are symptomatic or >4 cm are treated surgically or with embolization. A conservative approach should be employed for patients with tuberous sclerosis and bilateral multifocal lesions.



7.10 This 3-D CT reconstruction from a patient with tuberous sclerosis. Note the bilateral, large angiomyolipomas.

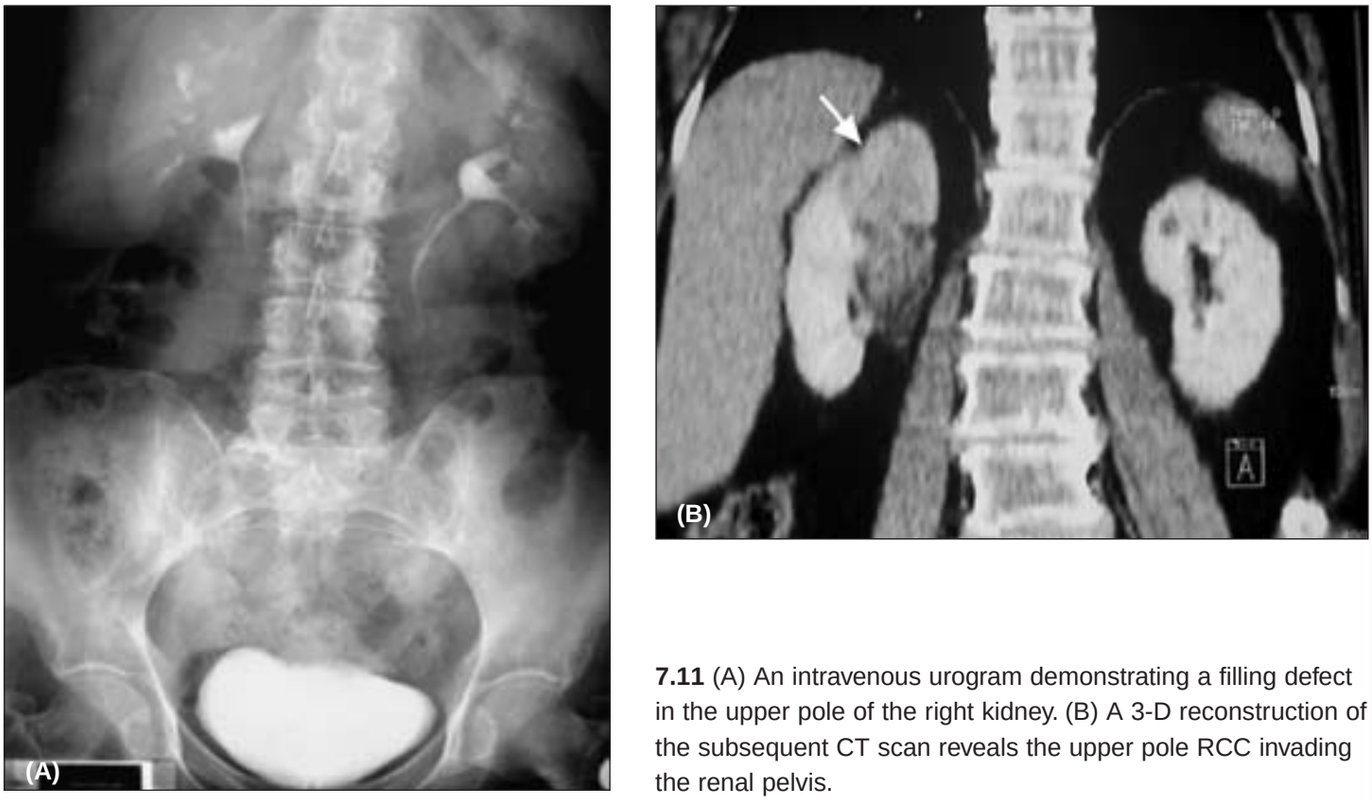
Other benign lesions include cortical adenomas, fibromas, lipoma, myomas, lymphangiomas and haemangiomas.

Other imaging investigations employed to assess RCCs include magnetic resonance imaging and also renal arteriography. Magnetic resonance imaging is of use in assessing tumour invasion of the renal vein or inferior vena cava and is particularly useful in those with a history of contrast reactions or renal insufficiency. Arteriography is sometimes employed to obtain further information about the renal vasculature especially in the setting of nephron-sparing surgery or anatomical abnormalities such as horseshoe kidneys. The traditional intravenous urogram has essentially been superseded by the use of ultrasound and CT (**7.11**), however some RCCs are still identified in this way.

Treatment

Surgery

Open radical nephrectomy is traditionally the standard treatment for localized RCC. It was described by Robson in 1963. By definition, this includes excision of Gerota's fascia, including the contained kidney and perirenal fat. The aim is to excise the tumour with an adequate margin avoiding dissemination of malignant cells. The ipsilateral adrenal gland is often removed with larger tumours and regional lymphadenectomy may sometimes be performed; however, this is controversial.



7.11 (A) An intravenous urogram demonstrating a filling defect in the upper pole of the right kidney. (B) A 3-D reconstruction of the subsequent CT scan reveals the upper pole RCC invading the renal pelvis.

Laparoscopic nephrectomy has now largely superseded open surgery, particularly for tumours less than 7 cm. Laparoscopic procedures are associated with reduced morbidity and hospital stay while maintaining oncological safety.

A further option, particularly for smaller tumours situated away from the hilum, is partial nephrectomy. Partial nephrectomy performed for tumours <4 cm in size demonstrates recurrence-free rates and survival rates similar to radical nephrectomy.

Minimally invasive treatment

As previously mentioned, over recent years there has been an increase in the incidental detection of renal tumours. Many of the tumours are asymptomatic, some are benign, and others have a slow growth rate and a variable malignant potential. As a result, enthusiasm for minimally invasive approaches to small renal tumours in patients for whom more traditional surgical approaches may not be appropriate has increased. Any surgical treatment for renal tumours has to adhere to the principle of tumour excision with a wide margin. Furthermore, the surgeon must be able to monitor and precisely target the area to be ablated to assure complete tumour destruction and preservation of surrounding vital structures. As a result, ablative technologies, such as percutaneous radiofrequency ablation (RFA) and cryotherapy, are being employed and appear to offer a promising alternative to surgical approaches.

Cryotherapy

Ablation of normal renal tissue occurs at –19.4°C, whereas ablation of cancer cells occurs at –40°C. Cryotherapy produces tissue temperatures as low as –190°C by exploiting the Joule–Thompson, which refers to the temperature drop that occurs when compressed gas expands. Usually, compressed argon gas is allowed to expand through a small orifice at the end of the cryoprobe, producing temperatures well below those required to ablate normal renal tissue and cancer cells. The histological result of cryoablation is a confluent coagulative necrosis within the cryolesion, with eventual fibrosis and scarring. Cell destruction occurs through the thawing forces of water flow from extracellular to intracellular space as a result of the formation of intracellular ice. Renal cryoablation can be accomplished using an open surgical technique, a laparoscopic approach, or via a percutaneous procedure. The ice-ball achieved with cryoablation technology can be

readily identified and actively observed with ultrasonography (usually during a laparoscopic or open surgical approach) or with axial magnetic resonance imaging or CT (usually during percutaneous procedures).

Most commonly, a 'double-freeze' cycle (freezing beyond the margins of the tumour, thaw and second freeze cycle) is used to increase the size of the cryolesion with either active or passive thawing after each cycle. The ice-ball is extended to approximately 10 mm beyond the margin of the tumour to incorporate the 'indeterminate zone' (the outer few millimetres of the ice-ball that are not ablative) and a margin of normal renal parenchyma to optimize oncological control. With cryoablation, real-time ultrasonographic monitoring of the growing ice-ball allows the surgeon to visualize the ablative process, and ensures that the ice-ball extends beyond the targeted area in every dimension.

Radiofrequency ablation (RFA)

RFA probes achieve temperatures that exceed the required 70°C for complete tissue ablation. They are inserted as one needle and deploy up to 10 umbrella-like wire electrodes into the tissue when activated. RFA probes deliver a monopolar alternating current of 400–500 kHz to the renal tissues. An expanding sphere of coagulative necrosis forms around each electrode. As with cryoablation, RFA can be delivered via an open or laparoscopic surgical or percutaneous approach. Contemporary imaging methods allow for precise positioning of the RFA probes. The procedure may also vary by the number of RF cycles, although two cycles is most typical.

Metastatic RCC (mRCC)

Even in the presence of metastatic disease, nephrectomy may be indicated to control symptoms including haematuria, pain, paraneoplastic syndromes and compression of adjacent viscera. In addition to this, there has been a median survival of 10 months' benefit demonstrated for cytoreductive nephrectomy prior to interferon-α in patients with good performance status. Furthermore, solitary metastasis can be excised in patients with advanced RCC. Much of the clinical experience with medical treatment of RCC is with clear cell. Response rates for chemotherapy alone are very low. RCCs express the multiple drug resistance protein P-glycoprotein and are therefore resistant to most chemotherapies.

Immunotherapy

RCC is a particularly immunogenic tumour. It expresses a variety of antigens, and the observations of complete regression, stabilization and complete responses to immunotherapy support the value of immunomodulatory therapies. Immunotherapy aims to boost tumour antigenicity or host surveillance.

Interferon-α

Immunotherapy with interferon-α is beneficial for patients with metastatic RCC who have a good performance status. It provides a response rate of 6–15%, a 25% decrease in the risk of tumour progression and a modest survival benefit of 3–5 months.

Interleukin-2

Treatment with interleukin-2 is associated with more side effects than interferon-α and shows response rates ranging from 7–27%. Currently, no data exist to demostrate that either treatment is more effective than the other.

Tyrosine kinase inhibitors

Significant advances in the treatment of mRCC have occurred in recent years. As a result of work on genetic forms of RCC, sporadic clear cell RCC is associated with inactivation of the VHL protein and an accumulation of HIF. This result in an overexpression of VEGF and PDGF, neoangiogenesis and the development of cancer. Recently, several antiangiogenic/tyrosine kinase inhibitors have been developed including Sunitinib, Sorafenib and Temsirolimus.

Phase III trails have demonstrated a modest 3-month survival benefit with Sorafenib when compared to placebo in patients who have failed to respond to prior systemic immunotherapy. A phase III trail has recently evaluated Sunitinib as first-line monotherapy versus interferon-α, showing an 11-month progression-free survival benefit. Finally, Temsirolimus has demonstrated a survival benefit in poor-risk patients with mRCC when compared with interferon-α.

The role of these drugs is still being considered, and certainly in the UK, funding issues exists. However, several other antiangiogenesic drugs are under investigation and the European Association of Urology recommends that these drugs are considered as first-line or second-line treatment in patients with mRCC.

New therapies

Stem cell transplant

Allogeneic stem cell transplantation performed after a non-marrow ablative regimen produces a marked graft-

versus-tumour effect, and has been shown in some studies to produce significant responses. Attempts to increase treatment specificity are aimed at identifying tumour epitopes that initiate the graft-versus-tumour response. The problems include the need for a haplotype-matched sibling donor and also severe graft-versus-host reactions that can be limited with courses of immunosuppressive agents.

Tumour vaccines

These represent a potential method of enhancing host immunity. They require further research but may be improved with the simultaneous administration of cytokines.

Target antigens

Stem cell or vaccine therapies aim to identify tumour antigens involved in the immune response. For example, the G250 renal cancer antigen identifies as CA9. Notably, the CA9 gene is a target for HIF and is overexpressed in VHL-related clear cell carcinoma.

Follow-up of renal cell carcinoma

The aim of follow-up is to identify postoperative complications, monitor renal function and to detect the presence of local or distant recurrence. There is no consensus on which investigations should be used; however, most protocols include a combination of examination, blood tests, chest X-ray and CT scanning. Follow-up protocols should take into account the risk of developing metastasis or recurrence and historically, the anatomical stage has been considered to be the most important factor. However, a combination of clinical and histopathological factors better predict tumour recurrence than stage alone. Systems proposed by the Mayo clinic and also the UCLA Integrated Staging System use such factors to stratify patients into low-, intermediate- and high-risk for recurrence. This allows appropriate follow-up to be arranged.

Prognosis

Staging is the most important prognostic indicator for RCC (*Table 7.4*). Variations exist between the histological subtypes; for example, papillary RCC metastasizes less commonly than clear cell; however, the survival rate, if it does metastasize, is worse for papillary RCC than for clear cell RCC.

Table 7.4 Five-year survival

T1 90–100%
T2 60–95%
T3a 60–70%
T3 b/c 50–80%
T4 or N+ 5–30%
M+ 5–30%

Further reading

Bosniak MA (1986). The current radiological approach to renal cysts. *Radiology* **158**:1–10.

Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM; TARGET Study Group (2007). Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* **356**(2):125–134.

Fuhrman SA, Lasky LC, Limas C (1982). Prognostic significance of morphologic parameters in renal cell carcinoma. *Am J Surg Pathol* **6**:655−663.

Hudes G, Carducci M, Tomczak P, *et al.* (2006). A phase 3, randomized, 3-arm study of temsirolimus (TEMSR) or interferon-alpha (IFN) or the combination of TEMSR + IFN in the treatment of first-line, poor-risk patients with advanced renal cell carcinoma (adv RCC). 2006 ASCO Annual Meeting Proceedings. *J Clin Oncol* **24**:18S.

Latif F, Tory K, Gnarra J, *et al.* (1993). Identification of the von Hippel-Lindau Disease Tumor Suppressor Gene. *Science* **260**:1317–1320.

Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA (2007). Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* **356**(2):115–124.

Chapter 8

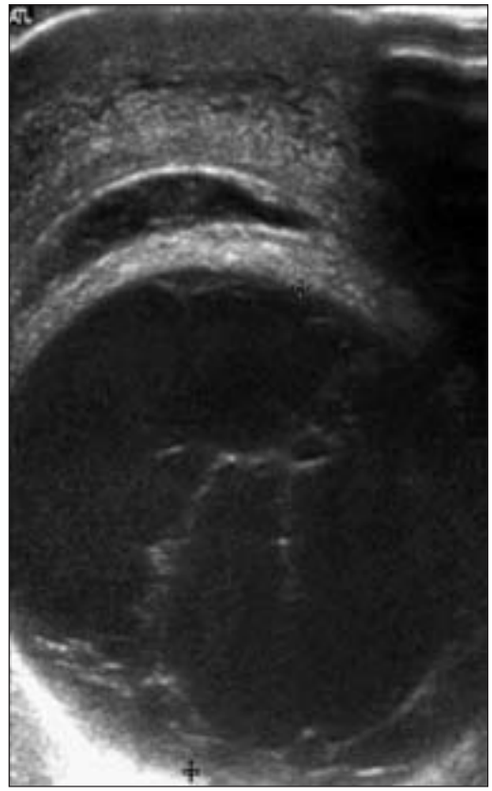
Scrotal Swellings

Angela Cottrell

Benign swellings

Epididymal cyst

An epididymal cyst is a cystic swelling of the epididymis. Clinically, the patient may complain of a swelling in the scrotum that gets larger over time. Examination of an epididymal cyst will reveal a swelling that you can 'get above', which is separate from the testis. When transilluminating the cyst its appearance has a classical description of a 'Chinese lantern'. If the patient has minimal symptoms, conservative management is appropriate. Aspiration is not appropriate as the cysts are frequently multiloculated. Surgical excision is appropriate if symptomatic (**8.1**).



8.1 Ultrasound scan of epididymal cyst.

Hydrocoele

A hydrocoele is an abnormal collection of fluid between the visceral and parietal layers of the tunica vaginalis that surrounds the testis (**8.2**). It is the most common benign testicular mass, affecting 1% of males. The tunica vaginalis produces approximately 0.5 ml of fluid a day and the fluid accumulates due to an imbalance of production and absorption.

Causes of hydrocoele

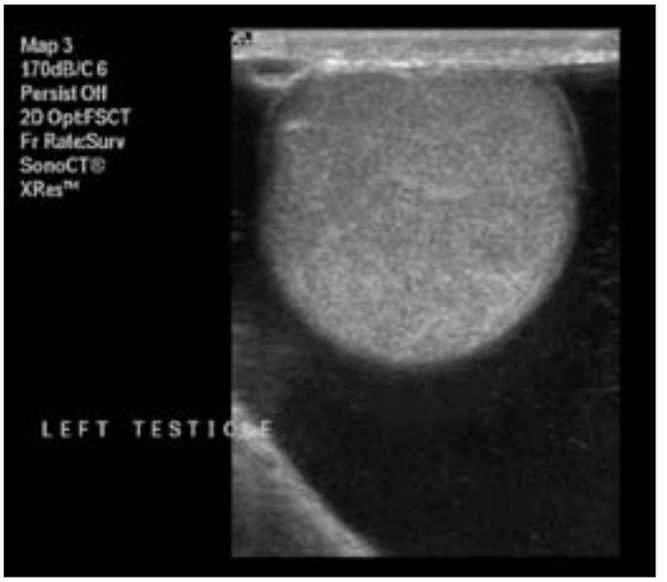
- *Congenital:* patent processus vaginalis.
- *Acquired:* primary (idiopathic); secondary (i.e. trauma, infection, tumour).

The patient may give a history of a swelling in the scrotum. On examination of the scrotal swelling it is not usually possible to palpate the testis through the hydrocoele fluid collection. The surface of the swelling is smooth. It is possible to 'get above' the mass and it transilluminates.

Simple aspiration of a hydrocoele may achieve symptomatic relief of a tense hydrocoele; however, this is not definitive treatment as the fluid is likely to re-accumulate. Surgical intervention may include Lord's plication technique or Jaboulay procedure involving excision of the hydrocoele sac. The hydrocoele fluid is then absorbed by scrotal lymphatics. In a child, the patent processus vaginalis may be ligated.

Varicocoele

A varicocoele is an abnormal dilation of the veins of the pampiniform plexus, which is present in 15% of men. The



8.2 Ultrasound showing hydrocoele.

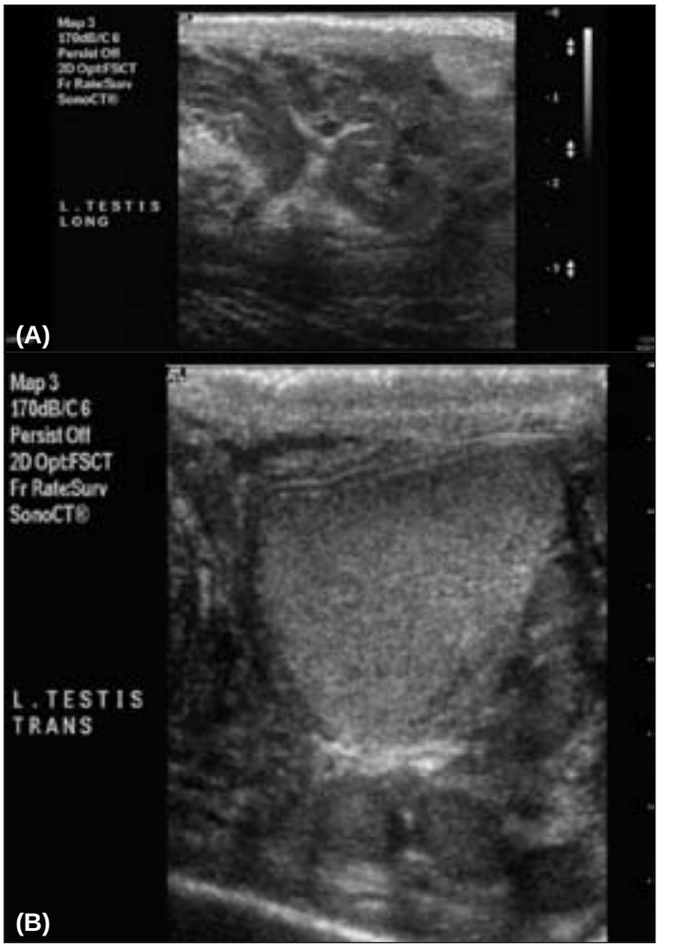
patient may complain of a scrotal swelling and discomfort or dragging sensation in the scrotum. On examination it is possible to get above the mass. It is not possible to transilluminate the mass and characteristically it feels like a 'bag of worms'. It increases in size when standing.

Varicocoeles are more common on the left side (90%) than the right due to the drainage of the left testicular vein into the left renal vein at an angle of 90°. Varicocoeles may arise secondary to a left-sided renal mass extending into the renal vein and causing back pressure on the testicular vein. It is therefore necessary to perform an ultrasound scan of the renal tract once a varicocoele has been identified to exclude renal pathology (**8.3**).

Treatment options, if the patient is symptomatic include open or laparoscopic ligation or embolization of the varicocoele (**8.4**, **8.5**).

Acute epididymo-orchitis

Acute swelling of the epididymis or testis is most commonly infective in aetiology. Pathogens may be viral (e.g. mumps, orchitis) or bacterial. Pathogens usually arise from the bladder or urethra, however, and may rarely be secondary to systemic illness such as tuberculosis. In younger men, the most common pathogens are those from sexual transmission including *Chlamydia trachomatis* or *Neisseria gonorrhoea*. In older men, urinary tract pathogens are more frequent and bladder outlet obstruction may increase the risk of infection.



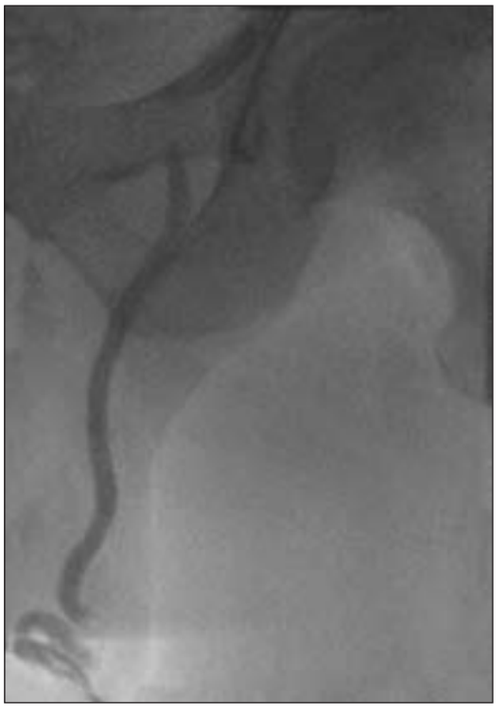
8.3 Ultrasound scan showing left varicocoele: (A) longitudinal and (B) transverse view.

The man may present with a short onset (usually) unilateral testicular pain and may have a history of recent sexual activity. Examination may reveal a hot, tender testis or epididymis and the overlying skin may be erythematous (**8.6**).

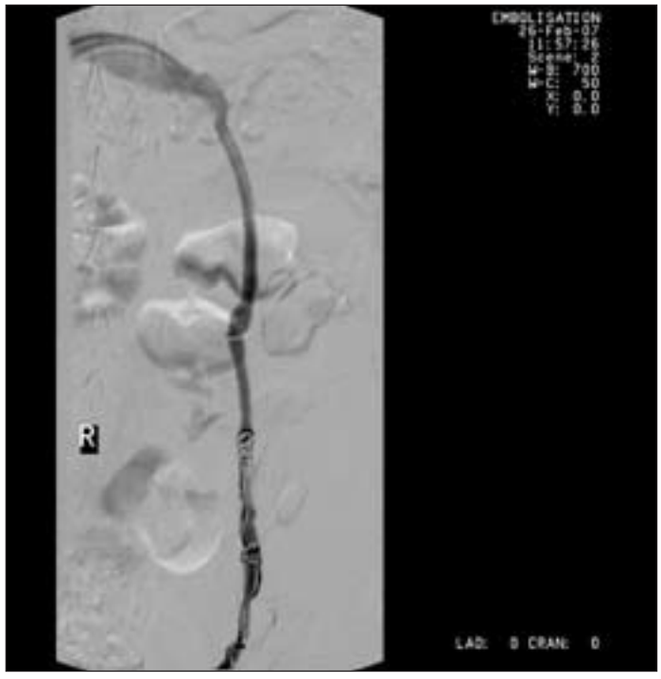
An appropriate broad-spectrum antibiotic should be used. A young sexually active man should be empirically treated with a fluoroquinolone antibiotic, which has good penetration of the urinary tract, and if the causative pathogen is *C. trachomatis*, should continue with doxycycline for 2 weeks. The sexual partner should also be treated.

Testicular cancer

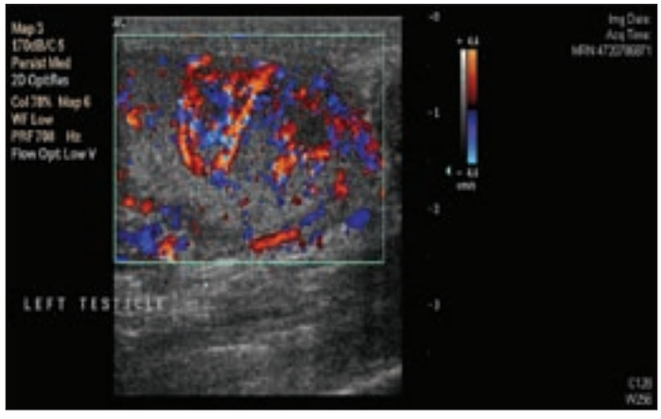
Testicular cancer is the most common tumour in men aged 20–50 and comprises 1% of male neoplasia. Incidence



8.4 Venogram demonstrating left varicocoele.



8.5 Embolization of left varicocoele.



8.6 Ultrasound of testis showing hyperaemia suggestive of epididymo-orchitis.

is increasing, with approximately three to six new cases per 120 000 men per year. Cure rates, however, are high: approximately 95% of low-stage cancers may be cured.

Germ cell tumours occur most commonly between the ages of 20 and 45. Lymphoma is more common in men over the age of 60. Testicular cancer is more common in men with a history of cryptorchidism, both in the affected and contralateral testis.

The patient may present with a history of a scrotal swelling. This is usually painless but may be associated with an aching sensation. A history of trauma may lead to self-examination and finding a lump. A partner may have discovered the lump. At a late stage, systemic features may be reported such as weight loss or lymphadenopathy. A detailed history may also elicit risk factors for testicular cancer.

Examination of the scrotum may reveal a unilateral, hard, non-tender irregular testicular mass. Associated structures may be involved such as the epididymis or overlying skin. Further examination may reveal signs of systemic disease such as lymphadenopathy or cachexia, or gynaecomastia.

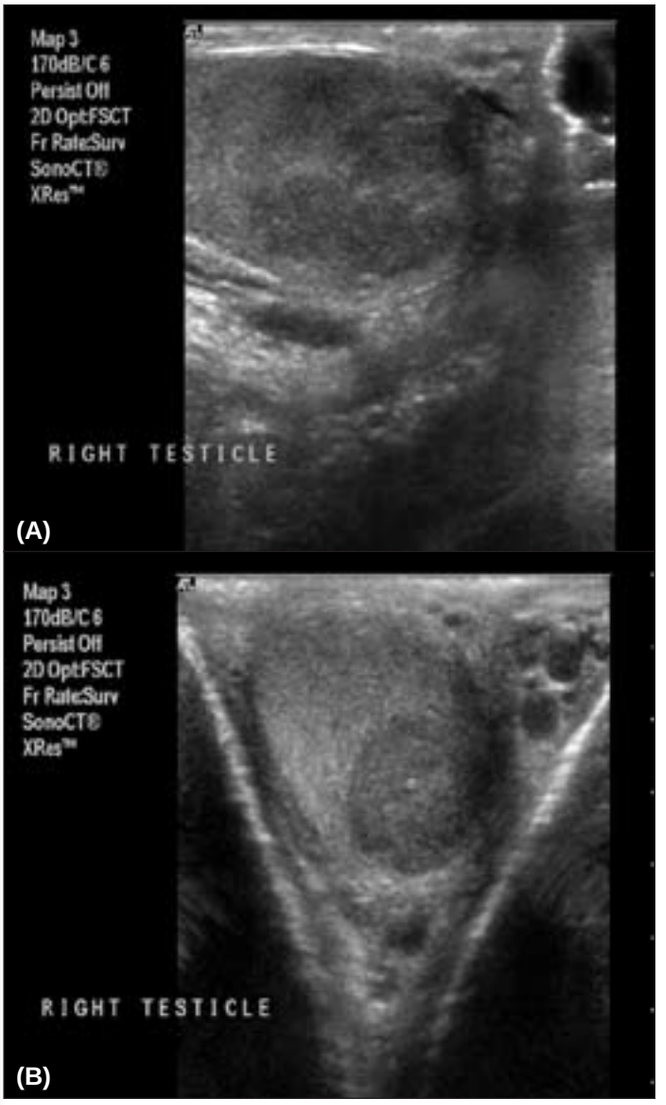
The first-line investigation of choice is scrotal ultrasound, which carries a sensitivity of approximately 100% (**8.7**). For staging purposes, a computed tomography should be performed of the chest and abdomen. If there are symptoms suspicious of bony or brain metastases, bone scan or computed tomography of the head may be performed. Serum tumour markers should be performed and play an important part in diagnosis, prognosis and in monitoring the response to treatment, and are necessary to adequately stage the disease. Tumour markers most commonly measured are α-fetoprotein (AFP), human chorionic gonadotrophin and lactate dehydrogenase. Tumour markers may be raised in approximately 51% of testicular cancers and 90% of patients with advanced disease.

The majority of testicular tumours are germ cell tumours (90%). Other tumours affecting the testes may be sex cord stromal tumours (3%), e.g. Leydig or Sertoli cell, or other tumours such as metastatic deposits, or lymphoma.

Germ cell tumours are subdivided as shown in *Table 8.1* and *Table 8.2*.

Treatment of testicular tumour

Radical orchidectomy is performed via an inguinal approach. The testis, epididymis and cord are removed.



8.7 Ultrasound of right testis showing mass: (A) longitudinal and (B) transverse view.

Table 8.1 Germ cell tumour classification

Seminoma (48%) (**8.8**, **8.9**)
Non-seminomatous germ cell tumour (42%)
- Teratoma (**8.10**)
- Yolk sac tumour
- Choriocarcinoma
- Mixed non-seminomatous germ cell tumour

Mixed germ cell tumour (10%)

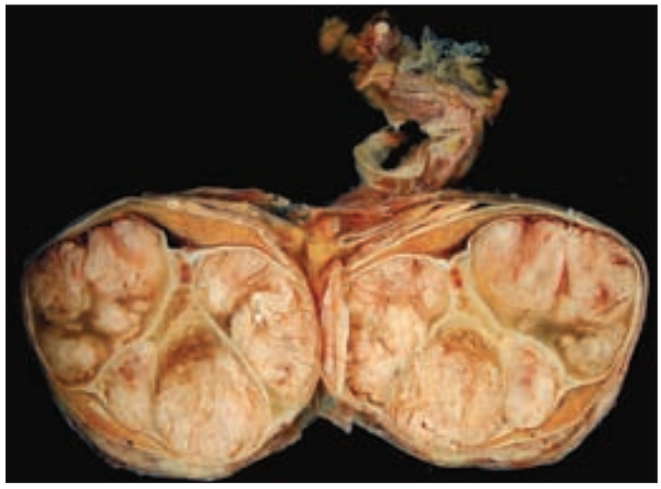
Testicular tumours are staged using the TNM classification and, in addition, serum tumour markers are used.

Table 8.2 TNM classification of testicular tumours

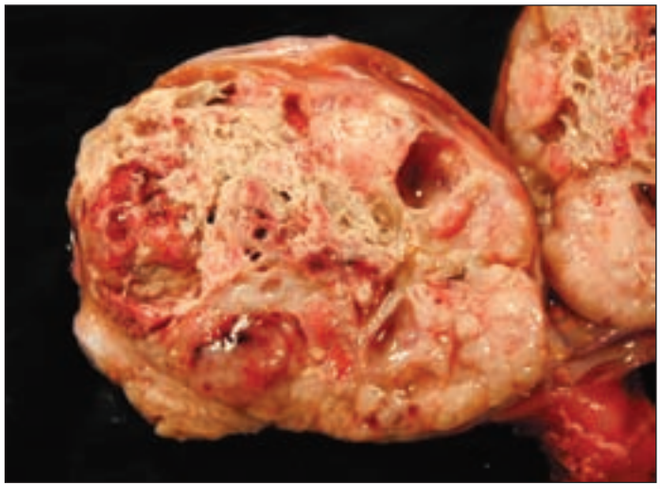
T	(Pathological)
Tx	Primary tumour not assessed
T0	No evidence of primary tumour
Ta	Intratubular germ cell neoplasia (carcinoma *in situ*)
T1	Tumour limited to the testis and epididymis without vascular invasion; tumour may invade tunica albuginea but not tunica vaginalis
T2	Tumour limited to testis and epididymis with vascular invasion, or tumour extending to tunica vaginalis
T3	Tumour invades spermatic cord with or without vascular invasion
T4	Tumour invades scrotum with or without vascular invasion
N	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases with lymph node ≤ 2 cm or multiple lymph nodes ≤ 2 cm
N2	Metastases with a lymph node 2–5 cm or multiple lymph nodes collected size 2–5 cm.
N3	Metastases with lymph node mass >5 cm
M	
Mx	Distant metastases cannot be assessed
M0	No distant metastases
M1a	Non-regional lymph node or pulmonary metastases
M1b	Distant metastases other than to non-regional lymph node or lungs.
S	(Serum tumour markers)
Sx	Markers not available
S0	Markers normal
S1	LDH 1–1.5 times upper limit of normal, hCG <5000 mIU/ml
S2	LDH 1.5–10 times upper limit of normal, hCG 5000–50 000 & AFP 1000–10 000
S3	LDH >10 times upper limit of normal, hCG > 50 000 & AFP >1 000 000

Subsequent management depends on tumour type and prognostic factors determined by the International Germ Cell Cancer Collaborative Group and whether the tumour is metastatic. Patients with non-seminomatous germ cell tumours with no evidence of metastasis are managed by chemotherapy. Those with good, intermediate and poor prognosis metastatic disease also undergo chemotherapy, followed by retroperitoneal lymph node dissection. Patients with non-metastatic seminomas undergo radiotherapy. Those with metastatic disease may undergo radiotherapy, chemotherapy or retroperitoneal lymph node dissection.

8.9 Macroscopic appearance of seminoma.



8.8 Macroscopic appearance of spermatocytic seminoma.



8.10 Macroscopic appearance of teratoma.

References

Naber KG, Bergman B, Bishop MC, Bjerklund-Johansen TE, Botto H, Lobel B, Cruz FJ, Selvaggi FP (2001). EAU guidelines for the management of urinary and male genital tract infections. *Eur Urol* **40**: 576–588.

Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohen-Cedermark G, Horwich A, Klepp O, Laguna MP, Pizzocaro G (2005). EAU Guidelines on Testicular Cancer.

Reynard J, Brewster S, Biers S (2005). *Oxford Handbook of Urology*. Oxford University Press, Oxford.

Investigation of Erectile Dysfunction

Matthew Hotston

Introduction

Erectile dysfunction (ED) is defined as 'the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse' (NIH Consensus Development Panel on Impotence, 1993), and was believed to have affected over 150 million men in 1995 worldwide, accounting for at least 1 in 10 men in Western countries. Despite the introduction of novel treatments for this condition, this figure is still expected to rise to over 320 million by the end of 2025 (Ayta *et al.,* 1999). It is therefore essential that the clinician performs an appropriate, thorough and directed investigation of a patient presenting with ED to ensure the maximum chance of success in subsequent treatment (*Table 9.1*).

Table 9.1 Clinical assessment of erectile dysfunction

History	Medical
	Psychosocial
	Sexual
Physical examination	
Laboratory tests	

Each consultation should commence with a full clinical history, including sexual, psychosocial and medical, a physical examination, and routine laboratory tests. Following this, confirmation or further evaluation can be pursued with additional diagnostic approaches. Throughout all the following investigations described, it is essential that the physician creates an atmosphere of calm, empathy and responsiveness, so that the patient can cooperate openly and fully. It must be emphasized that there is no standard approach to investigating ED, and so it is essential to appreciate and understand the tests available to gain a successful outcome. The extent of investigation needs to be tailored to the individual's wishes. The following is a concise approach to initially managing the patient in the clinic setting, followed by a description of diagnostic studies currently available.

Patient assessment

Clinical history

The clinical history is the most important part of the diagnostic evaluation of the patient with ED. ED may represent an early marker of cardiovascular disease and even depression, which can then be addressed appropriately (Montorsi *et al.,* 2003a). The initial focus should address whether the patient does have ED, and not a dysfunction of libido, ejaculation or orgasm. Various questionnaires have been formulated to aid the physician in this manner, as well as determining its severity. The most commonly used is the International Index of Erectile Function (IIEF; *Table 9.2*).

This is composed of 15 questions (full version), which can be completed prior to consultation (Rosen *et al.,* 1997). Specifically, it is important to determine the time of onset and duration, the particular situations where occurring, and the intensity of the problem. This is in order to classify the nature of ED, so any further diagnostic evaluation can become more focused. Essentially, ED can be of psychogenic or organic cause, or indeed mixed, which is thought to be currently the most common aetiology (Melman and Gingell, 1999). Those of an organic nature tend to report an insidious onset of symptoms, which is not situational, with poor or absent nocturnal and morning erections. Directed questions can include assessment of the quality of the

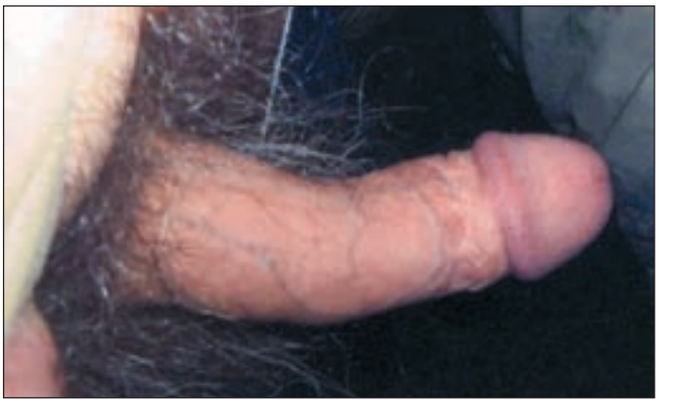
Table 9.2 IIEF-5 scoring system (abridged version)

	Score				
Over the past six months:	**1**	**2**	**3**	**4**	**5**
1. How do you rate your confidence that you could get and keep an erection?	Very low	Low	Moderate	High	Very high
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always
4. During sexual intercourse how difficult was it to maintain your erection to the completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always

The IIEF-5 score is the sum of questions 1 to 5. The lowest score is 5 and the highest score 25.

erection. A reduction in penile rigidity (normally expressed as a percentage of their best) and sustainability may indicate a haemodynamic component, particularly veno-occlusive dysfunction. Pain or deformity of the penis may indicate Peyronie's disease (Roddy *et al.*, 1991) (**9.1**).

A full current and past medical history should be acquired, in order to elucidate relevant risk factors. This should involve a cardiovascular, neurological, metabolic and hormonal, and psychiatric history. Any past history of surgery and trauma, including complications, should be noted. A drug history is important, as there are many medications, such as antihypertensives (diuretics, β-blockers) that can cause impotence (Slag *et al.*, 1983). Recreational drugs in the form of cigarette smoking, alcohol, marijuana and cocaine, are also associated with ED. Common causes of arterial insufficiency that can be identified include diabetes, hypertension, smoking, hyperlipidaemia and previous pelvic surgery. Corporal veno-occlusive dysfunction may occur due to previous injury or surgery to the penis, Peyronie's disease, as well as diabetes and hyperlipidaemia leading to changes in the fibroelastic properties of the corporal tissue (Roddy *et al.*, 1991).



9.1 Peyronie's disease.

Physical examination

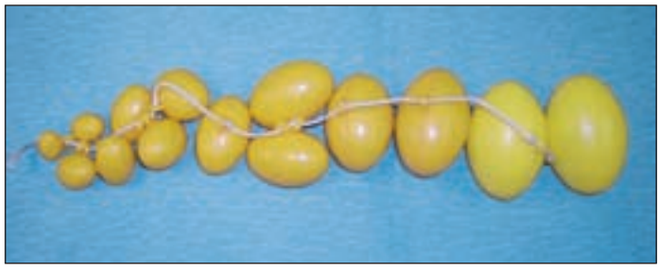
A full physical examination is mandatory, to assess for any direct causes, as well as any associated risk factors. The external genitalia should be examined for general sensation and anatomical deformities, such as Peyronie's plaques.

A rectal examination may reveal prostate cancer, prostatitis and reduced anal sphincter tone. The bulbocavernosal reflex can also be performed. The endocrine system should be assessed in the form of general thyroid status, looking for gynaecomastia (**9.3**) and small testes, suggesting hypogonadism (**9.4**).

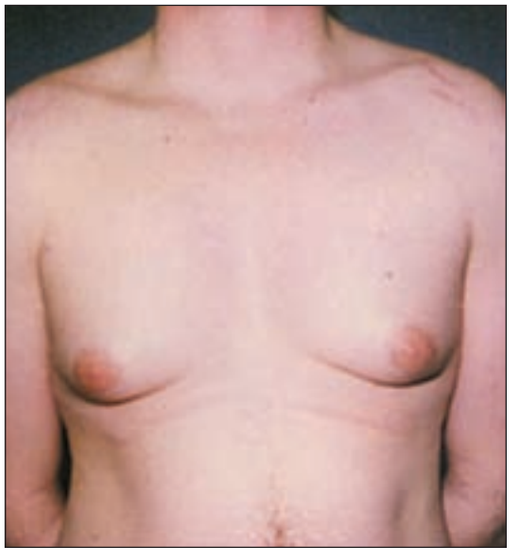
The patient's vascular status should be sought through blood pressure measurement, peripheral pulses and any evidence of peripheral vascular disease (**9.5**).

Laboratory tests

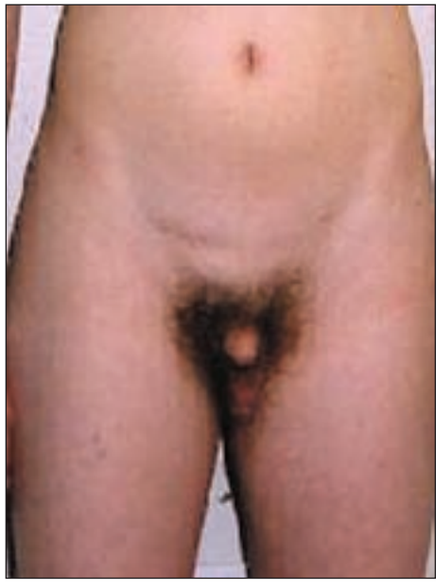
Most patients should be offered basic laboratory tests, such as baseline haematological and biochemical blood tests, lipid profile, and a random blood plasma glucose sample. Other tests can be directed through clinical suspicion, such as liver function tests, serum testosterone, prolactin, thyroid function, follicle-stimulating hormone and luteinizing hormone tests.



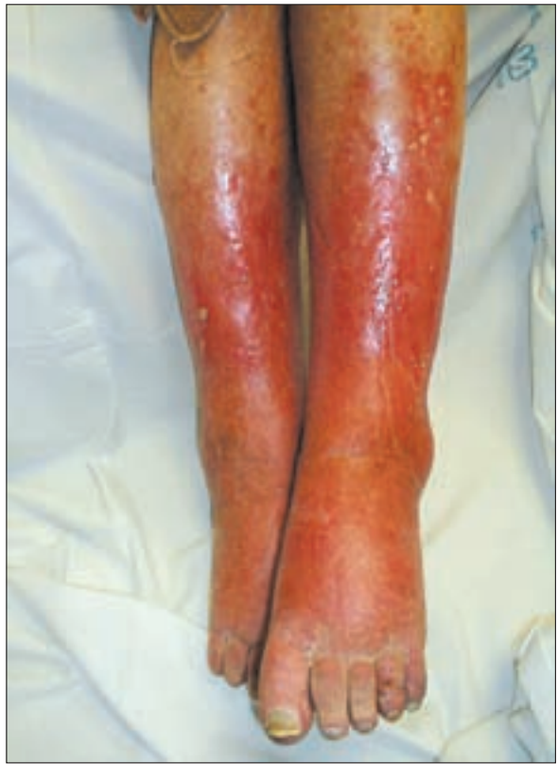
9.2 Orchidometer for measuring testis size.



9.3 Gynaecomastia of hypogonadism.



9.4 Small testes of hypogonadism.



9.5 Signs of peripheral vascular disease.

Non-surgical management of erectile dysfunction

Following a full history and examination, the treatment options can be discussed with the patient. It is reasonable at this point to commence a trial of medical management, provided there are no contraindications. However, it is important to explain that this may be unsuccessful, but that there are further investigative studies that may be of benefit, and surgical approaches for selected cases. The management of ED has changed dramatically from the common use of penile prostheses in the 1970s, to intracavernosal injections, and now the choice of type 5 phosphodiesterase (PDE5) inhibitor medications, and even transurethral therapy (*Table 9.3*). The initial approach should always be to address the patient's lifestyle characteristics. Smoking cessation, diet modification (including reduced alcohol intake), weight reduction (in obesity) and stress management are all simple but effective measures.

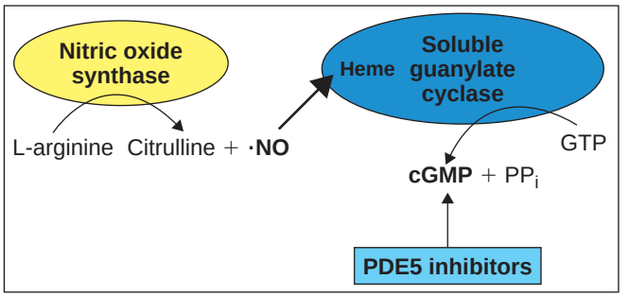
Oral therapies

The World Health Organization suggests that first-line therapy should be in the form of oral therapy, which can be PDE5 inhibitors or dopamine agonists (Jardin *et al.*, 2000). PDE5 inhibitors act on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, inhibiting the breakdown of cGMP (**9.6**). This leads to reduced cellular calcium mobilization, and corporal smooth muscle dilatation results.

There are currently three forms licensed by the FDA (*Table 9.3*). Sildenafil (Viagra) remains the gold standard, although vardenafil has been reported to be more potent, and tadalafil has a longer half-life (Carson and Lue, 2005). Sublingual apomorphine, a selective dopamine agonist, activates neural pathways from the paraventricular nucleus of the hypothalamus (Vitezic and Pelcic, 2002). It can induce an erectile response in 20 minutes, but may lead to emesis, and is not as effective as the PDE5 inhibitors (Gingell 2004). Apomorphine is now off formulary for erectile dysfunction.

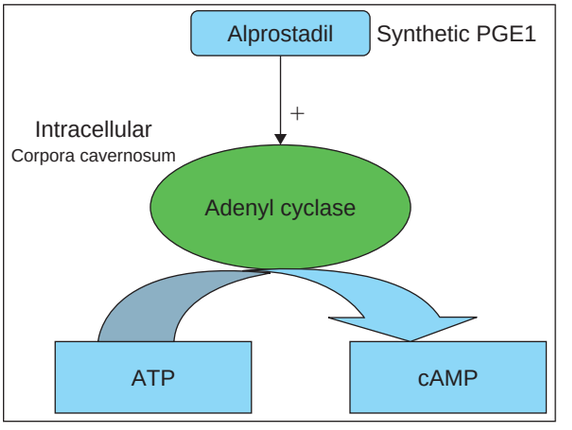
Table 9.3 Options for non-surgical therapies

Oral therapies	*PDE5 inhibitors*	Sildenafil Vardenafil Tadalafil
Intraurethral therapies		Alprostadil
Intracavernosal therapies		Alprostadil Phentolamine Papaverine

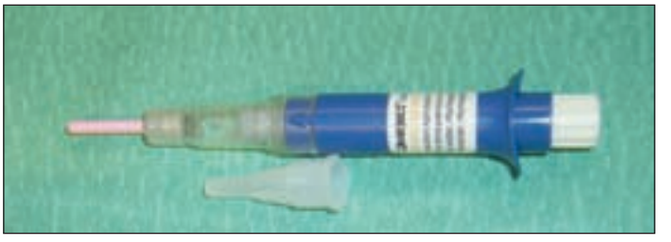


9.6 Action of sildenafil.

Intracavernosal vasoactive agents are available as second-line therapy (Montorsi *et al.*, 2003b). Alprostadil, a synthetic prostaglandin E_1, is very effective (60–90% response) with a short onset of action, when given intracavernosally (**9.7**–**9.9**). However, it has a high dropout rate, due to post-procedure pain and prapism (Fazio and Brock, 2004). This can also be given intraurethrally, which is less invasive, although reports on its efficacy are varied (Padma-Nathan *et al.*, 1997; Leungwattanakij *et al.*, 2001).



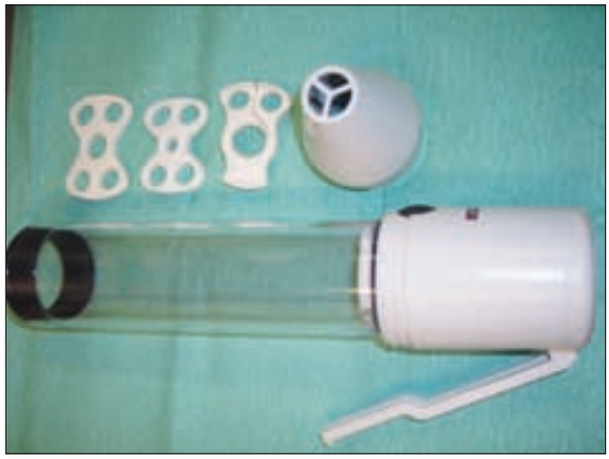
9.7 Action of alprostadil.



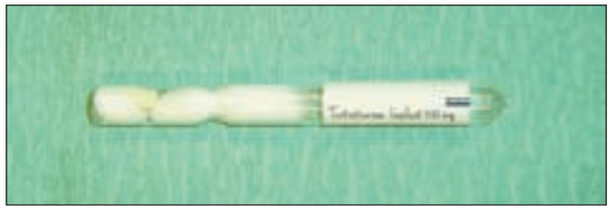
9.8 Intracavernosal administration equipment for alprostadil.

9.9 Intraurethral administration equipment for alprostadil.

Non-pharmacological alternatives include vacuum devices (**9.10**), which appear more acceptable to older patients (Lewis and Witherington, 1997), psychosexual therapy and hormone replacement treatment in those with specific abnormalities, such as hypogonadism (**9.11**).



9.10 Vacuum pump.



9.11 Testosterone pellet.

Further diagnostic tests

Nocturnal penile tumescence

Ohlmeyer *et al.* in 1944 were the first to describe the occurrence of regular cycles of erections during sleep as a normal phenomenon (Ohlmeyer *et al.*, 1944), about 80% of which occur during rapid eye movement (REM) sleep (Lue, 2004). Since then, the assessment of the quality of sleep-associated erections has been traditionally used to differentiate between organic and psychogenic ED (Fisher *et al.*, 1965). The basic nocturnal penile tumescence device measures the maximum penile rigidity, as well as the frequency, duration and magnitude (circumference) of tumescence. One example is the Rigiscan, which can be used on an outpatient basis, comprising two loop transducers applied around the base and tip of the penis, connected to a data-logging unit and microcomputer, so that data are recorded for later interpretation. A positive result tends to indicate organic ED, although false positives and negatives do exist. For this reason, this test is not used routinely.

Pharmaco-test

This is a simple but useful test to differentiate vasculogenic from organic impotence (of other causes). It involves the intracavernosal injection of a vasoactive drug, such as papaverine, prostaglandin E_1, papaverine and phentolamine, or a mixture of all three drugs. A positive erectile response (reflecting an intracavernosal pressure of 80 mmHg or greater) effectively excludes any vasculogenic cause. However, a negative result may occur if the patient is overly anxious. The use of genital self-stimulation, vibratory and visual stimulation can reduce false negative results (Kim, 1999).

Further vascular studies

The complex dynamic process of penile erection requires dilatation of the corporal arterial vessels, and corporal smooth muscle relaxation, leading to raised intracorporeal pressure (from <10 mmHg to around mean arterial pressure), increased by occlusion of the penile venous system (veno-occlusion) (Hanyu, 1988). The aim of the following diagnostic studies is to attempt to differentiate and isolate the area of vascular dysfunction.

Doppler ultrasonography

This can be a useful technique to visualize both the arterial and venous anatomy, as well as performing functional studies. In the flaccid state, the arterial systolic flow is monophasic,

with some diastolic flow. In early erection, both systolic and diastolic flows increase, a dicrotic notch then appears in systole, and diastole subsequently reduces to zero flow (Kim, 2002). The ultrasound can detect anatomical abnormalities such as tunica thickening in Peyronie's disease, vessel wall changes, masses and trauma-related changes.

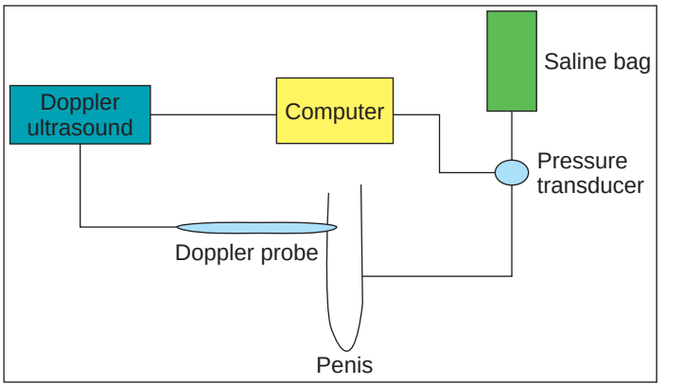
Colour duplex ultrasonography, combining the pharmacotest with ultrasound, can define any arterial dysfunction present. The arterial blood flow can be quantified using peak systolic velocity (PSV), with less than 25 cm/s indicating arterial insufficiency (Kim, 2002). The blood flow acceleration, calculated by dividing the PSV by the systolic rise time (time for systolic to reach its maximum) is also a sensitive marker of arterial function (Oates *et al.*, 1995). Doppler ultrasound can assess veno-occlusive dysfunction, through assessment of end diastolic flow velocity volume (EDV) and calculation of resistance index (RI). The normal EDV is less than 5 cm/s, and any elevation of this is suggestive of venous leak (Benson and Vickers, 1989). An RI (peak flow velocity (PSV)–EDV/PSV) of less than 0.75 is also a reliable indicator of veno-occlusive dysfunction (Lue, 2004).

Cavernosometry and cavernosography

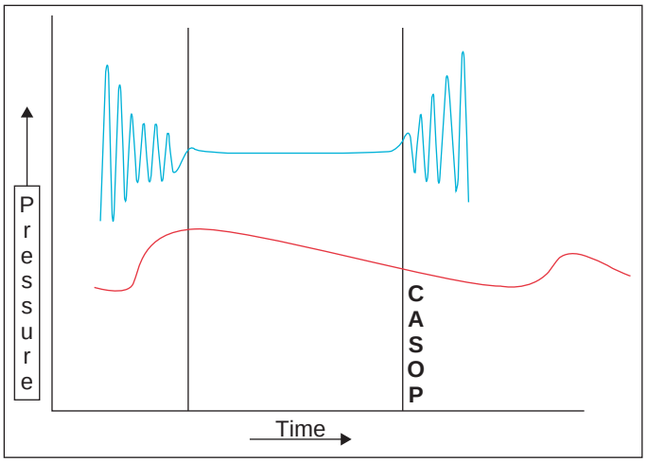
The combination of dynamic cavernosometry and cavernosography is used in patients with suspected veno-occlusive abnormalities, particularly for those requiring venous surgery (Rudnick and Becker, 1992). In cavernosometry, a tourniquet is placed at the base of the penis, and both corpora cavernosae are cannulated. An intracavernosal injection of a vasoactive agent (as described earlier) is administered, to produce complete cavernous smooth muscle relaxation. One of the corpora is connected to a continuous saline infusion pump, and the other is attached to a pressure transducer (pump cavernosometry) (**9.12**).

The normal parameters described by authors are quite varied. Flow rates in a patient with normal venous function should be less than 100 ml/min at induction (Furst *et al.*, 1999), 0–5 ml/min at maintenance (Wespes *et al.*, 1986), and certainly no greater than 10 ml/min (Lue, 2004). Any higher requirements suggest venous leakage. Intracavernous pressure should also be maintainable above 80 mmHg (Sessions and Caeson, 1988). Pressure decay, monitoring the pressure fall over 30 seconds following discontinuation of the saline pump at 150 mmHg, should be less than 50 mmHg (Padma-Nathan, 1989) (**9.13**).

Gravity cavernosometry is a less complex and expensive version of this technique in which the saline is placed at



9.12 Set-up for cavernosometry.



9.13 Cavernosometry traces. CASOP = cavernosal artery systolic occlusion pressure.

certain heights above the corpora, and the pressures within the corpora are continuously measured. The flow rate is determined by the pressure gradient between the infusion pressure and the intracavernosal pressure. The cavernosal arterial patency can be assessed using a combination of cavernosometry and doppler ultrasound. Saline is infused until the cavernosal artery pulsation disappears. The flow is then discontinued, and the intracorporal pressure at which the pulsation returns is recorded. This represents the cavernosal artery systolic occlusion pressure, which should be similar to the brachial artery systolic pressure. Pressure differences greater than 35 mmHg indicate significant arterial insufficiency (Kim, 1999).

Areas of venous leakage can be visualized using cavernosography (Wespes and Schulman, 1993). Dilute contrast medium is infused via the same pump needle, and supine and oblique radiographs can then be taken. A normal

veno-occlusive system should reveal minimal or no venous drainage during erection. Cavernosography in the flaccid state is only indicated for the visualization of penile lesions after a traumatic injury, invasive penile cancer, and priapism (Rudnick and Becker, 1992). Complications from this study are rare; however, those with normal vascular function are at increased risk of prolonged erection (Sessions and Caeson, 1988), which should be treated if persisting for more than 4 hours.

Arteriography

Visualization of the penile arterial tree through selective internal pudendal arteriography is only indicated for those considered for arterial reconstructive surgery or balloon dilatation. Following detection of abnormal arterial function using Doppler ultrasonography, arteriography can then localize and define the vascular lesion. It is a particularly useful tool in the assessment for surgery in young patients with localized trauma (Levine *et al.,* 1990). A Foley catheter is inserted urethrally to decompress the bladder, and an intra-cavernosal injection of a vasoactive agent (such as papaverine or phentolamine) is given (Borge, 1999). The right common femoral artery is cannulated, using the Seldinger technique, and a survey pelvic arteriogram is performed (Wahl *et al.,* 1997). Once the origin of the penile blood supply is identified, the left internal iliac artery is catheterized, and selective imaging is performed (Borge, 1999). Some radiographic contrast agents can cause discomfort at the injection sites, and so a local anaesthetic ± sedation, or even epidural anaesthesia, can be offered (Bahren and Gall, 1988). This also reduces the common problem of arterial vasoconstriction, particularly in combination with intrapudendal injections of vasoactive drugs (Virag *et al.,* 1984). Other problems with this technique include difficulty in differentiating between congenital and acquired variations in arterial anatomy, as well as correlating the findings with the symptoms described (Broderick, 1998). As there are significant risks with this procedure, from exposure to radioactive agents to potential vessel damage, it is largely becoming superseded by non-invasive measures, as previously described.

Further reading

Ayta I, McKinlay J, Krane R (1999). The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU Int* **84**: 50–56.

Bahren W, Gall H (1988). Arterial anatomy and arteriographic diagnosis of arteriogenic impotence. *Cardiovasc Intervent Radiol* **4**: 195–210.

Benson C, Vickers M (1989). Sexual impotence caused by vascular disease: diagnosis with duplex sonography. *AJR Am J Roentgenol* **153**: 1149–1153.

Borge M (1999). Penile arteriography. *Tech Urol* **2**: 81–86.

Broderick G (1998). Evidence based assessment of erectile dysfunction. *Int J Impot Res* **10**(Suppl 2): S64–S73.

Carson C, Lue T (2005). Phosphodiesterase type 5 inhibitors for erectile dysfunction. *BJU Int* **96**: 257–280.

Fazio L, Brock G (2004). Erectile dysfunction: management update. *CMAJ* **170**(9): 1429–1437.

Fisher C, Gross J, Zuch J (1965). Cycle of penile erection synchronous with dreaming (REM) sleep. Preliminary report. *Arch Gen Psychiatry* **15**: 29–45.

Furst G, Muller-Mattheis V, Cohnen M, *et al.* (1999). Venous incompetence in erectile dysfunction: evaluation with color-coded duplex sonography and cavernosometry/-graphy. *Eur Radiol* **9**: 35–41.

Gingell C (2004). Disease overview – erectile dysfunction. *Drugs in Context* **1**(9): 335–348.

Hanyu S (1988). Morphological changes in penile vessels during erection: the mechanism of obstruction of arteries and veins in the tunica albuginea in dog corpora cavernosa. *Urol Int* **43**: 219–224.

Jardin A, Wagner G, Khoury S, *et al.* (2000). *Recommendations of the First International Consultation on Erectile Dysfunction, co-sponsored by the World Health Organisation*. Health Publications Ltd, Plymouth.

Kim SC (1999). Recent developments in the diagnosis of vasculogenic impotence. *Asian J Androl* **1**: 37–43.

Kim SH (2002). Doppler US evaluation of erectile dysfunction. *Abdom Imaging* **27**: 578–587.

Leungwattanakij S, Flynn V, Hellstrom W (2001). Intracavernosal injection and intraurethral therapy for erectile dysfunction. *Urol Clin North Am* **28**(2): 343–354.

Levine F, Greenfield A, Goldstein I (1990). Arteriographically determined occlusive disease within the hypogastric-cavernous bed in impotent patients following blunt perineal and pelvic trauma. *J Urol* **144**: 1147–1153.

Lewis R, Witherington R (1997). External vacuum therapy for erectile dysfunction: use and results. *World J Urol* **17**: 78–82.

Lue T (2004). Male sexual dysfunction. In: *Smith's General Urology*, 16th edition. McGraw-Hill Companies Inc., New York, pp 592–612.

Melman A, Gingell C (1999). The epidemiology and pathophysiology of erectile dysfunction. *J Urol* **161**: 5–11.

Montorsi F, Briganti A, Salonia A, *et al.* (2003a). Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. *Eur Urol* **44**(3): 360–364.

Montorsi F, Salonia A, Deho' F, *et al.* (2003b). Pharmacological management of erectile dysfunction. *BJU Int* **91**: 446–454.

NIH Consensus Conference (1993). NIH Consensus Development Panel on Impotence. *JAMA* **270**: 83–90.

Oates C, Pickard R, Powell P, *et al.* (1995). The use of duplex ultrasound in the assessment of arterial supply to the penis in vasculogenic impotence. *J Urol* **153**: 354–357.

Ohlmeyer P, Brilmayer H, Hullstrung H (1944). Peridisch vorgangge in schlaf. *Pflugers Arch* **248**: 559–560.

Padma-Nathan H (1989). Evaluation of the corporal veno-occlusive mechanism: Dynamic infusion cavernosometry and cavernosography. *Semin Intervent Radiol* **6**: 205.

Padma-Nathan H, Hellstrom W, Kaiser F, *et al.* (1997). Treatment of men with erectile dysfunction with transurethral alprostadil. Medicated Urethral System for Erection (MUSE) Study Group. *N Engl J Med* **336**: 1–7.

Roddy T, Goldstein I, Devine C (1991). Peyronie's disease Part 1 and Part 2. *AUA Update Series, Lesson 1 and Lesson 2* **2**: 1–15.

Rosen R, Riley A, Wagner G, Osterloh I, Kirkpatrick J (1997). The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* **49**(6): 822–830.

Rudnick J, Becker H (1992). Present state of diagnostic management in veno-occlusive dysfunction. *Urol Int* **49**: 9–12.

Sessions R, Caeson C (1988). Diagnostic investigation of impotence. In: *Textbook of Genitourinary Surgery*, 2nd edition. Blackwell Science, Oxford, pp 1333-1351.

Slag M, Morley J, Elson M, *et al.* (1983). Impotence in medical clinic outpatients. *J Am Med Assoc* **249**: 1736–1740.

Virag R, Frydman D, Legman M, Virag H (1984). Intracavernous injection of papaverine as a diagnostic and therapeutic method in erectile failure. *Angiology* **35**: 79–87.

Vitezic D, Pelcic J (2002). Erectile dysfunction: oral pharmacotherapy options. *Int Clin Pharmacol Ther* **40**: 393–403.

Wahl S, Rubin M, Bakal C (1997). Radiological evaluation of penile arterial anatomy in arteriogenic impotence. *Int J Impot Res* **9**: 93–97.

Wespes E, Schulman C (1993). Venous impotence: pathophysiology, diagnosis and treatment. *J Urol* **149**: 1238–1245.

Wespes E, Delcour C, Struyven J, Schulman C (1986). Pharmacocavernosometry–cavernography in impotence. *Br J Urol* **58**: 429–433.

Index