HANDBUCH DER UROLOGIE

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XV

SUPPLEMENT

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UROLOGY IN CHILDHOOD

BY

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WITH 218 FIGURES

SPRINGER-VERLAG

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Foreword

Volume XV "Urology in Childhood" was written in 1956/57 and was the first in the series of the Encyclopedia of Urology to appear. This present volume has been constructed as a supplement and the original intention was to deal only with those subjects in which there have been significant advances during the intervening sixteen years. As the work has proceeded, however, it has become evident that there is no aspect of paediatric urology which has not been developed, and no topic which has not been illuminated by many contributions to the literature. Indeed, there has been such a copious flow of publications devoted to children's urinary tract disease that a full review is no longer possible within the compass of a volume of this size: the decision as to what should be left out has therefore been a matter of the greatest difficulty. The choice has been inevitably arbitrary and many omissions are regretted. The attempt has been made, however, to report the most notable developments of the subject, and perhaps the greatest change in the practice of paediatric urology has been the full integration with paediatric nephrology. The team approach to infant disease in particular has led to greatly improved results. I have been fortunate to have Dr. T. M. BARRATT associated with me in my urological unit, and I have therefore invited him to contribute rather extensively to this volume on aspects of nephrology which are now essential equipment for the paediatric urologist. Also on the medical side the endocrine problems associated with adrenal cortical hyperplasia are now a matter for a specialist, and I have therefore included a valuable chapter on this subject by Dr. G. H. NEWNS, paediatrician and endocrinologist at The Hospital for Sick Children. The study of chromosome anomalies is now a specialty in itself and could easily have occupied the whole volume, but the relevant data have been ably summarised by Professor POLANI and Dr. SINGER. The neuropathic bladder associated with myelomeningocele requires treatment integrated with the total management of these disabled children, and I have therefore invited Mr. H. B. ECKSTEIN, a paediatric surgeon particularly concerned with this subject, to contribute a chapter. In the discussion of neoplastic disease I am grateful to Dr. J. BOND, Tumour Research Fellow at The Hospital for Sick Children, for her assistance in indicating the place of radiotherapy and chemotherapy.

The purely urological subjects have remained my personal responsibility, and inevitably the selection of topics reflects my own particular interests. As before no attempt has been made to describe operative techniques, though in some cases I have included a brief discussion on the choice of available procedures for particular circumstances. In each chapter extensive references have been given, including where possible review articles, but complete coverage of the literature is now only obtainable by computer and I believe that a statement of personal views based on the experience of a large paediatric urological unit is of equal value.

I would like to acknowledge my indebtedness to many of my colleagues, particularly on the radiological side, for their assistance, to my registrars for helping in the clinical work and for reading through the drafts of many chapters.

The illustrations are from many sources, but most in my section have been produced by the Department of Medical Illustration in the Institute of Urology, and I am grateful to Miss F. M. WADSWORTH, the artist, for her drawings, and to Mr. R. E. BARTHOLEMEW, the photographer, for the reproductions.

Figures 64, 65, 67–75, 77–79 have been previously published in the British Journal of Urology [**44**, 417–433 (1972)] and are reproduced by the kind permission of the Editor.

Finally I would like to express my gratitude to my secretary for her indefatigable efficiency and to my wife for her forbearance with my preoccupation.

London, February, 1974 D. INNES WILLIAMS

Contents

A. The Nephrological Background to Urology

T. M. Barratt

With 1 Figure

B. Acute Renal Failure

T. M. Barratt

With 2 Figures

C. Chronic Renal Failure in Children

T. M. Barratt

With 2 Figures

D. Hypertension in Childhood

T. M. Barratt

With 6 Figures

E. Glomerular Disease and Haematuria

T. M. Barratt

With 3 Figures

F. Renal Anomalies

D. Innes Williams

With 18 Figures

G. Urinary Tract Infection

T. M. Barratt

H. Localised Inflammatory Lesions

D. Innes Williams

With 3 Figures

I. The Female Urethra in Recurrent Infections

D. Innes Williams

With 2 Figures

J. Vesico-Ureteric Reflux

D. Innes Williams

With 15 Figures

K. Ectopic Ureter

D. Innes Williams

With 9 Figures

L. Ureteroceles

D. Innes Williams

With 18 Figures

M. Obstructive Uropathy: The Functional Disorder

D. Innes Williams and T. M. Barratt

With 5 Figures

N. Obstructive Uropathy: The Upper Tract

D. Innes Williams

With 23 Figures

O. Obstructive Uropathy: The Bladder

D. Innes Williams

With 14 Figures

P. Obstructive Uropathy: The Urethra

D. Innes Williams

With 19 Figures

Q. The Prune Belly Syndrome

D. Innes Williams

With 7 Figures

R. Urinary Incontinence

D. Innes Williams

With 4 Figures

S. Neuropathic Bladder

H. B. Eckstein

With 10 Figures

T. Epispadias and Exstrophy

D. Innes Williams

With 9 Figures

U. Urolithiasis

T. M. Barratt and D. Innes Williams

With 9 Figures

V. Neoplastic Disease: The Kidney

D. Innes Williams with the assistance of J. Bond

With 5 Figures

W. Neoplastic Disease: The Lower Urinary Tract

D. Innes Williams with the assistance of J. Bond

With 9 Figures

X. Congenital Adrenal Hyperplasia

G. H. Newns

With 4 Figures

Y. Sex Chromosome Anomalies and Intersex States

P. E. Polani, S. M. Kohlinsky and J. D. Singer

With 21 Figures

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A. The Nephrological Background to Urology

T. M. Barratt

With 1 Figure

The ultimate goal of the urologist is the preservation of function of the kidneys. In this chapter, some aspects of renal function and metabolism of children will be considered which are relevant to the clinical practice of paediatric urology.

I. Development of Renal Function

1. Morphological and Biochemical Aspects

The formation of nephrons is essentially complete by the 36th week of gestation (Potter and Thierstein, 1943). The nephrogenic zone is in the outer cortex, and the superficial cortical nephrons are the last to be formed. On the basis of the DNA content Widdowson et al. (1972) reported that the kidney of the full term infant contains about 17 per cent of the adult number of cells; these cells are 70 per cent of the adult size. Net DNA synthesis stops at the age of six months, and subsequent growth of the kidney is due to increase in cell size rather than cell number. These events have been closely studied in the developing kidney of the rat: the DNA complement is complete by six weeks of age (Winnick and Noble, 1965). Interestingly, uninephrectomy before this age increases the DNA content of the remaining kidney, whereas older rats respond by increase in cell size alone with no change in cell number (Karp et al., 1971).

Microdissection studies (Fetterman et al., 1965) have shown that the mean glomerular diameter in the neonate is approximately half that in the adult, whereas the proximal tubule is only about 10 per cent of the adult length: the data suggest that morphological development of the proximal tubule lags behind that of the glomerulus.

On histological examination the neonatal glomerulus is characterised by a prominence of cuboidal epithelial cells lining the glomerular basement membrane. It is unlikely that they limit glomerular filtration rate (McCance, 1962) but they may account for the limited permeability of the neonatal glomerulus for macromolecules (Arturson et al., 1971). The cells of the juxtaglomerular apparatus are also prominent, and it has been suggested that they may cause some obstruction to the flow of blood in the afferent arterioles (Jäykkä, 1961), and be responsible for the high renal vascular resistance of early life.

2. Renal Function before Birth

The kidneys secrete urine from the third gestational month. In mid-term there is little reabsorption of glomerular filtrate, and the urine flow rate is high (Ale-

XANDER and NIXON, 1961); towards term there is increased salt and water reabsorption so that the urine flow rate falls (MCCANCE, 1972). The only known function of the foetal kidney is the maintenance of amniotic fluid volume. Renal agenesis results in oligohydramnios and consequent intra-uterine compression deformities (POTTER, 1946), whereas mothers of children with nephrogenic diabetes insipidus occasionally have excess amniotic fluid. The contribution of the kidney to foetal homeostasis must be small, for infants with renal agenesis are born with a normal concentration of blood urea; the human placenta is an efficient kidney. Nothing is known of the endocrine functions of the kidney—the synthesis and secretion of renin, erythropoietin and 1: 25-dihydroxycholecalciferol—during intra-uterine life.

3. The Neonatal Kidney

By adult standards, the glomerular filtration rate (GFR) is low in infants (BARNETT, 1940; EDELMANN and SPITZER, 1969). This conclusion is reached whether GFR is related to surface area or kidney size. As nephron formation is complete before birth, GFR per nephron is clearly lower in the infant than the adult. Glomerular surface area in the neonate is 25 per cent of the adult level (FETTERMAN et al., 1965), yet GFR is only 5 per cent of the mature value.

Renal plasma flow measured by para-aminohippurate (PAH) clearance is also low in the neonate (WEST et al., 1948), even allowing for the low extraction of PAH (CALCAGNO and RUBIN, 1963). In the piglet, and probably also in the human, there is a high renal vascular resistance at birth (GRUSKIN et al., 1970). It seems, therefore, that the full anatomical potential for glomerular filtration is not realised due to vascular restraints. It is also probable that the distribution of renal blood flow is different in early life, with a greater fraction perfusing the juxtamedullary nephrons (EDELMANN and BARNETT, 1972).

If glomerular function is poorly developed in the neonate, then proximal tubular function appears even more immature, and the advantage, in teleological terms, of restrained glomerular filtration is the prevention of overperfusion of poorly developed reabsorption mechanisms. Thus, tubular maxima for both PAH secretion (WEST et al., 1948) and glucose reabsorption (TUDVAD, 1949) are low in relation to GFR, the renal bicarbonate threshold is low (EDELMANN et al., 1967c) and there is decreased reabsorption of filtered aminoacids (BRODEHL and GELLISSEN, 1968). During water loading the urine flow rate expressed per 1.73 m^2 body surface area is less in infants than in adults (AMES, 1953), but the fraction of glomerular filtrate excreted is increased, indicating diminished proximal reabsorption of sodium and water; the diuretic response under these conditions is limited by the low GFR.

The maximum urinary osmolality attained after water deprivation or administration of anti-diuretic hormone is less in infants than in adults; this, however, is largely due to the low rate of urea excretion, for the concentration of non-urea solute is similar (EDELMANN et al., 1966), and the apparent defect is less on a high protein diet (EDELMANN et al., 1960).

Normal infants have, by adult standards, a mild metabolic acidosis due to a reduced bicarbonate threshold (EDELMANN et al., 1967c). After the first few days of life, the ability to acidify the urine is normal (HATEMI and MCCANCE, 1961; EDELMANN et al., 1967b), but the excretion of titratable acidity is low due to low phosphate excretion, and ammonia excretion is reduced in proportion to GFR. Therefore "the infant excretes hydrogen ion during health at a rate close to maxi-

mum. During acidosis only a modest increase in acid excretion is observed, resulting in rapid development and persistence of acidaemia in response to only a small additional load of hydrogen ion" (EDELMANN and SPITZER, 1969).

Ninety-two per cent of healthy infants pass urine in the first 24 hours of life, and 99 per cent have micturated by 48 hours (SHERRY and KRAMER, 1955). After this stage, the urine flow rate rapidly rises to about 100 ml/kg body weight/day.

4. Maturation of Renal Function

After birth, renal function develops rapidly, and, on a surface area basis, reaches mature levels by the age of 2 years. From a study of premature infants, BARNETT et al. (1948) concluded that it was the duration of extrauterine life rather than body size which was the principal determinant of the development of renal function in early life. There is some evidence that both glomerular and tubular functions are increased in infants fed high protein diets (CALCAGNO and LOWE, 1963; EDELMANN and WOLFISH, 1968), but the effect has only been demonstrated in prematures.

II. Metabolic Aspects of Young Children

1. Body Size

Certain considerations arise when comparing the effects of impairment of renal function in individuals of different body size. The surface area/weight ratio, which is inversely proportional to height, is approximately 3 times greater in the neonate than in the adult. Some parameters of physiological importance correlate (not necessarily in a causal manner) in healthy individuals with body surface area, others with body weight. Amongst the former are basal metabolic rate, GFR, and the dietary intakes of protein and water, whereas total body water and muscle mass (hence creatinine production) are weight-related (BARRATT, 1973). In as far as many metabolic processes are related to surface area, there is perhaps some justification for the rather arbitrary convention for referring GFR estimates in pathological circumstances to that standard, for equivalent reductions in GFR thus corrected in individuals of different size result in a similar threat to homeostasis. For example, the rate of urea excretion in infants on cow's milk and in older children is approximately proportional to surface area, in turn related to the square of body height. Urea is distributed in the total body water, proportional to weight, in turn related to the cube of body height. Hence urea excretion per 100 ml total body water, which is an estimate of the rate of rise of blood urea concentration should renal function cease, is inversely proportional to body height: the evolution of the uraemic state is more rapid in small individuals.

2. Growth

The growing infant synthesises about 1 G protein per kg body weight per day (FOMON and MAY, 1958; FOMON, 1961) and in doing so, incorporates water, phosphate, potassium and other substances into body tissues. Nitrogen retention for

growth relieves the kidney of some of its excretory load; McCance (1959) has described growth as "the third kidney". An adequate calorie intake is essential, however, for the protection by anabolism of nephrectomised puppies from the development of uraemia, hyperkalaemia or hyperphosphataemia (McCance, 1959).

3. Diet

A consideration of paramount importance in the metabolism of young children with renal disease is the difference in composition of the diet of the infant receiving human breast milk or a cow's milk formula (Table 1).

Table. 1. Representative dietary intakes and urinary excretion of infants receiving cow's milk and human breast milk, and of adults expressed per kg body weight per day

Per kg body weight per day	Infants		Adults
	Cow's milk	Human breast milk	
Water (ml)	150	150	30
Sodium (mEq)	4	1	1
Potassium (mEq)	5	2	1
Chloride (mEq)	4	2	1
Calcium (mg)	200	50	15
Phosphorus (mg)	150	23	20
Magnesium (mg)	18	6	4
Protein (G)	5	2	1
Calories	100	100	40
[a]Renal solute load (mOsm)	33	13	7
[b]Urine osmolality (mOsm/l)	330	130	280
[c]Net Hydrogen ion excretion (mEq)	6	1	1

[a]Calculated from the formula of Ziegler and Fomon (1971).
[b]Assuming a urine volume of 100 ml/kg body weight/day in the infant and 25 ml/kg body weight/day in the adult.
[c]From Fomon et al. (1959).

The standard intake of 150 ml/kg body weight/day of human breast milk provides a protein intake of 2 G/kg body weight/day, whereas cow's milk provides 5 G/kg body weight/day. The intakes of sodium, potassium, calcium, chloride and phosphorus are similarly substantially greater with cow's milk. The aggravation of uraemia, hyperkalaemia and hyperphosphataemia in infants with acute renal failure by cow's milk is obvious, but a more subtle and often more deleterious effect is the renal water loss induced by the high solute load in infants with restricted ability to concentrate the urine.

Solute excretion is determined by the diet, and can be approximately estimated as follows (Ziegler and Fomon, 1971):

$$\text{Solute load (mOsm)} = 4 \times \text{dietary protein (G)} + \text{dietary Na (mEq)} + \text{dietary K (mEq)} + \text{dietary Cl (mEq)}.$$

Fat and carbohydrate do not contribute to excreted solute, for they are entirely metabolised to carbon dioxide and water. A typical solute excretion of the

infant on cow's milk is thus 33 mOsm/kg body weight/day, and on human breast milk 13 mOsm/kg body weight/day. With conventional milk intakes of 150 ml/kg body weight/day urine volume averages 100 ml/kg body weight/day, and the osmolar concentration of the urine is therefore 330 mOsm/l in the cow's-milk-fed infant and 130 mOsm/l in the breast-fed infant. An infant who is unable to concentrate his urine to 300 mOsm/l will necessarily be in negative water balance on an intake of cow's milk of 150 ml/kg body weight/day: he does not have effective thirst control, and if the capacity to control the osmolality of the urine is impaired, both limbs of the osmolar homeostatic mechanism are lost. For such an infant cow's milk is as sea-water for a shipwrecked sailor, and may cause dangerous hyperosmolar states.

III. Body Fluids

1. Water and Electrolyte Physiology

a) Sodium and Water

Total body water (TBW) can be estimated by measuring the volume of distribution of antipyrine or deuterium oxide. It amounts to 780 ml/kg body weight in a full term infant, falling to 600 ml/kg body weight in the adult (Friis-Hansen, 1961). Extracellular fluid (ECF) is more difficult to define with precision: it is usually estimated as the volume of distribution of a small anion such as bromide or sulphate whose intracellular concentration is taken to be negligible. The bromide space is about 46 per cent of TBW in infants, and 40 per cent in adults (Cheek, 1961).

The distribution of water between intracellular and extracellular phases is determined by osmotic forces. Sodium and its attendant anion are the principal determinants of extracellular fluid osmolality. Therefore, in states of salt and water (saline) depletion, it is principally ECF volume which is diminished, resulting in circulatory collapse, whereas with pure water depletion it is the intracellular phase that is contracted and the organ principally affected is the brain. Conversely with pure water excess intracellular volume is expanded, causing the syndrome of water intoxication, whereas saline excess expands ECF volume and leads to hypertension and oedema.

The concentration of sodium in the extracellular phase is determined by the relative amounts of sodium and water in the body. A normal serum sodium concentration is quite compatible with severe saline depletion or overload if there are equivalent changes in body water. Conversely, hyponatraemia may either imply water excess with normal body sodium (dilutional), sodium depletion with normal body water (depletional) or, most commonly, a mixture of those two states. The diagnosis of the salt status thus depends more upon physical signs than on laboratory tests, and the most important observation is the blood pressure.

It is convenient to classify states of dehydration as hypotonic, isotonic or hypertonic, depending upon whether the serum sodium concentration (and hence osmolality) is low, normal or high. Particular attention should be given to the hypertonic, hypernatraemic state (Finberg and Harrison, 1955; Finberg, 1969). Infants with water-losing renal disease are at greatest risk, for they may be unable to make up their urinary losses by drinking. The contraction of intracellular volume particularly affects the brain, because of the volume restraints imposed

by the skull. In severe states, intracranial or subdural haemorrhage may occur, due to tearing of subtentorial veins. Convulsions are common, and may also happen during rehydration as the serum sodium concentration is falling towards normal. One quarter of the infants who have been exposed to a serum sodium concentration over 160 mEq/l have residual neurological sequelae (MACAULAY and WATSON, 1967).

b) Potassium

Potassium is the principal intracellular cation. If potassium excretion is impaired, as in advanced renal failure, extracellular potassium concentration rises and leads to cardiac dysfunction, as detailed on p. 19. With renal or gastrointestinal potassium losses, serum potassium is initially maintained at the expense of intracellular potassium, which leaves the cell in exchange for hydrogen ion, resulting in extracellular alkalosis and intracellular acidosis.

c) Hydrogen Ion

Metabolism of a normal diet generates hydrogen ion in excess of bicarbonate, principally from the breakdown of organic phosphate and sulphates. This hydrogen ion is excreted in the urine as titratable acidity and ammonium ion, and amounts to about 1 mEq/kg body weight/day in the breast-milk fed baby, but as much as 6 mEq/kg body weight/ day in the cow's-milk fed infant (FOMON et al., 1959). Failure to excrete hydrogen ion results in a metabolic acidosis with a fall in plasma bicarbonate concentration.

2. Principles of Parenteral Fluid Therapy

Parenteral fluid therapy is only indicated if the oral route is inadequate. The fluid should be given intravenously, and other routes, e. g. subcutaneous, are now obsolete. The establishment and care of intravenous lines in infants requires some skill, and it is particularly important to avoid unnecessary venous cutdowns. Intravenous fluid administration equipment for use in small children should always include a burette which accurately measures the amount of fluid delivered.

The prescription of parenteral fluid therapy should be considered under the following headings: rapid correction of hypovolaemia; deficit replacement; maintenance requirements; and provision for abnormal losses.

a) Hypovolaemia

In states of shock, 20 ml/kg body weight of blood, plasma or normal saline should be administered rapidly.

b) Deficit Replacement

An infant who is perceptibly dehydrated has probably lost 50 ml/kg body weight, and one who is severely dehydrated may have lost as much as 100 ml/kg body weight. Sodium deficits in severe hypertonic dehydration are 0–4 mEq/kg body weight, in isotonic dehydration 4–8 mEq/kg body weight, and in hypotonic dehydration 8–12 mEq/kg body weight (DARROW, 1959). These should be replaced over a period of 6 hours, except in the hypertonic states, where slower rates of replacement are usually deemed preferable.

Sodium may be given with chloride ("normal" saline contains 166 mEq/l; "half-normal" saline 77 mEq/l and "fifth-normal" saline 33 mEq/l). If there is a metabolic acidosis, it may be preferable to give the sodium as bicarbonate (8.4% $NaHCO_3$ contains 1 mEq/ml). Sodium lactate is now obselete. It is not usually necessary to give more than 2 mEq/kg body weight of $NaHCO_3$ in the first instance unless there is a severe metabolic acidosis; this amount will usually raise the serum bicarbonate concentration about 6 mEq/l.

Replacement of potassium deficits is not an urgent matter, and should be spread out over several days. An adequate urine flow should first be present, and not more than 5 mEq/kg body weight/day given. The concentration of potassium in the infusate should not exceed 40 mEq/l.

c) Maintenance Requirements

The intravenous requirements for maintenance of fluid balance in infants with normal renal function are 120 ml/kg body weight/day with 1–2 mEq/kg body weight/day of both sodium and potassium. About half this amount is required in the first few days of life, and after surgical operations (Wilkinson, 1955; Rickham, 1957, 1969). It must be emphasised, however, that infants with abnormal kidneys may not have the usual antidiuretic and antinatriuretic response to surgery, and that the customary practice of maintaining such infants "dry" in the post-operative period may not be appropriate. This is particularly true of infants undergoing relief of urinary tract obstruction, as detailed on p. 169.

d) Abnormal Losses

Children with water-losing renal diseases may require 200 ml/kg body weight/day, or more. The actual amount is governed by the urine volume, in turn determined by the maximum urinary osmolality and the excreted solute load. In salt wasting states, the sodium intake should also be increased to cover the abnormal losses.

IV. Assessment of Renal Function

1. General Considerations

Measurement of renal function in sick children demands simple techniques: tests necessitating catheterisation or repeated venepunctures for their accurate performance are rarely suitable in clinical practice (Barratt and Chantler, 1973). Nearly all biochemical techniques can be scaled down to use capillary blood samples, and it is now unacceptable for a laboratory to require large amounts of blood necessitating venepuncture for simple biochemical investigations in sick children. Many tests necessitate an accurate timed urine collection, which is usually the major source of error, particularly in children with obstructive uropathy (see Chapter M). Some protection from error may be conferred by simultaneous estimation of creatinine execretion, which rises from 10 mg/kg body weight/day in infants to 20 mg/kg body weight/day at puberty (Graystone, 1968).

Inevitably some comparison has to be made between the estimate of renal function and size of the child. Body surface area has long been considered the most suitable parameter, as discussed above, and after the age of 2 years describes most

of the size-related change in renal function. A causal relationship is not, however, implied: there is no mechanism by which a change in body surface area effects a change in renal function. From a teleological standpoint, a better case can be made for extracellular volume (Friis-Hansen, 1961) or total body water (McCance and Widdowson, 1952). One drawback of surface area (SA) lies in its estimation (Krovetz, 1965). The best nomogram is that of Sendroy and Cecchini (1954) (Fig. 1), but the formula of Dubois and Dubois (1916) is very nearly as good:

$$SA\,(cm^2) = Wt\,(kg)^{0.425} \times Ht\,(cm)^{0.725} \times 71.84$$

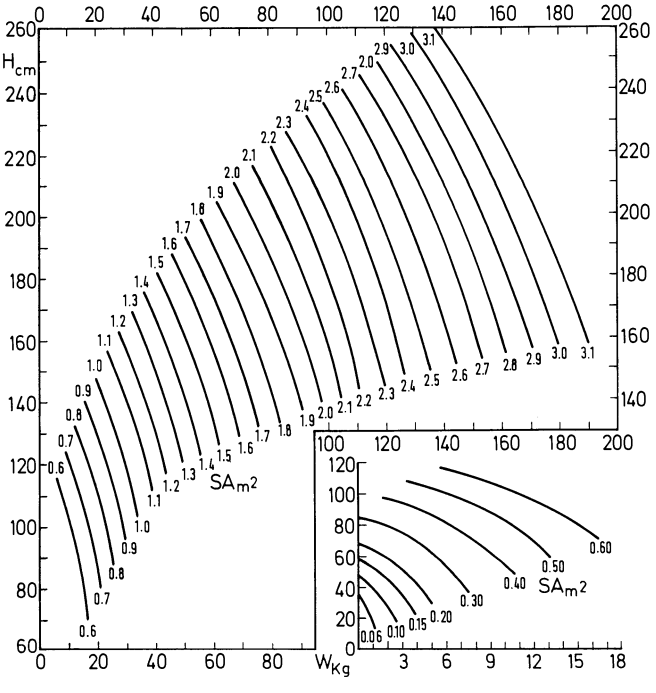

Fig. 1. Nomogram for determination of human body surface area from height and weight. Insert for small children up to 0.60m². From Sendroy and Cecchini (1954). (Reproduced by permission of the authors and the Editor of Journal of Applied Physiology)

2. Glomerular Function

a) Urea

The catabolism of 3 G of protein generates 1 G of urea, which is filtered at the glomerulus and partially reabsorbed by the tubules. The concentration of urea in the plasma is thus determined by the protein intake, the glomerular filtration rate and the extent of tubular reabsorption, and of these the dominant factor is protein intake: assuming that the growing infant synthesises 1 G of protein per kg per day, the urea excretion on a protein intake of 5 G/kg body weight/day (cow's milk) is 1.3 G/kg body weight/day, whereas on a protein intake of 2 G/kg body

weight/day (breast milk) it is 0.3 G/kg body weight/day. Thus the simple expedient of changing the diet from cow's milk to breast milk results in a *fourfold* change in the infant's blood urea concentration. It is, therefore, hazardous to assume that changes in blood urea concentration reflect changes in renal function, particularly in young children.

Nitrogen contributes about half the molecular weight of urea, and therefore the concentration of blood urea nitrogen (BUN) is half that of the blood urea.

b) Creatinine

Creatinine production, and hence excretion, is largely independent of the diet; it is a function of muscle mass and thus indirectly of body weight. The clearance of creatinine is given by formula:

$$C_c = U_c\, V/P_c$$

where C_c = creatinine clearance, ml/min
U_c = urine creatinine concentration, mg/100 ml
P_c = plasma creatinine concentration, mg/100 ml
V = urine flow rate, ml/min

In healthy individuals the clearance of creatinine exceeds the glomerular filtration rate due to tubular secretion (SHANNON, 1935). Over the age of 2 years it is roughly proportional to surface area, and the normal range is 94–142 ml/min/1.73 m^2SA (WINBERG, 1959a). However, the coefficient of variation of replicate estimates of creatinine clearance in the same individual, even under research conditions, is 12 per cent and two estimates therefore must differ by 30 per cent before it can be deemed reasonably probable that a change has actually taken place (CHANTLER and BARRATT, 1972).

In healthy children the excretion of creatinine (U_cV) is related to body weight and its clearance (U_cV/P_c) to surface area. Hence the plasma creatinine concentration is inversely proportional to height, rising from 0.3 mg/100 ml at one year of age to 0.9 mg/100 ml in the adult (WINBERG, 1959; DONCKERWOLCKE et al., 1970). BARRATT and ROSE (1973) found that the glomerular filtration rate could be approximately predicted from the plasma creatinine concentration as follows: GFR (ml/min/1.73m^2 SA) = $0.5 \times$ Ht (cm)/P_c (mg/100 ml).

The plasma creatinine concentration is estimated by the orange colour generated with alkaline picrate. Unfortunately, other substances (non-creatinine chromogens) are also included in the estimate, and the measurement of the true plasma creatinine concentration necessitates prior adsorption onto Fuller's earth or a cation exchange resin (STOTEN, 1968). Autoanalyser methods include a proportion of non-creatinine chromogens, usually equivalent to about 0.2 mg/100 ml. In young children, in whom the true plasma creatinine concentration is low, the non-creatinine chromogens contribute a relatively larger proportion of the result, and estimation of the true plasma creatinine is essential, although technically rather demanding. With these provisos, the plasma creatinine concentration is probably the most satisfactory method for the routine assessment of renal function in children with urological disorders.

c) Glomerular Filtration Rate

Measurement of the inulin clearance is too complex a technique for routine clinical practice. Fortunately, simpler methods are available. If a substance is equilibrated rapidly in its volume of distribution, and cleared from the body only

by glomerular filtration, then the GFR may be estimated from the rate of fall of plasma concentration after a single intravenous injection. Accurate measurement of low concentrations of the substance in plasma is essential, and isotopically labelled compounds are generally the most suitable: ^{51}chromium edetic acid (^{51}Cr-EDTA) (CHANTLER et al., 1969) or ^{131}iodine-iothalamate (COHEN et al., 1969) have both proved satisfactory. Several mathematical analyses are possible, but the simplest only requires two blood samples, 2 and 4 hours after the intravenous injection (BARRATT and CHANTLER, 1973). The half-time ($T\frac{1}{2}$) of the exponential disappearance is determined by plotting the plasma concentrations on a semilogarithmic scale, and an estimate of the volume of distribution (V_D) obtained by dividing the administered dose by the extrapolated zero-time plasma concentration. The GFR can then be calculated:

$$\text{GFR (ml/min)} = V_D \frac{0.693}{T\frac{1}{2}.}$$

Using ^{51}Cr-EDTA, CHANTLER and BARRATT (1972) observed the coefficient of variation of replicate estimates of GFR in the same individual to be 3.5 per cent. The administered radiation dose is small, about 0.1 per cent of that absorbed during intravenous urography, and the method has great potential in paediatric urological practice, for it permits precise quantitation of renal function without the necessity for timed urine collection.

Effective renal plasma flow (ERPF) may be derived in a similar manner from the plasma clearance of radio-iodine-labelled hippuran (COHEN et al., 1971), but the assumptions involved are less secure as the hippuran disappears from the plasma very fast. External counting may be used with a single blood sample to calibrate the curve.

d) Individual Kidney Function

Bilateral ureteric catheterisation to determine individual renal function is difficult to perform in children, particulary if the investigation necessitates accurate measurement of the rate of urine flow. Another possibility is to measure the function of each kidney whilst the contralateral ureter is obstructed by external compression (HAMBY et al., 1968); the method has not been widely applied to children.

If the kidneys are drained seperately it is always prudent to take the opportunity of measuring the function (creatinine clearance) of each kidney independently, for the information may influence subsequent surgical decisions.

At the present time, isotope renography appears to have the greatest potential for assessment of individual renal function (BRITTON and BROWN, 1971). The rate of uptake of radiohippuran by each kidney is proportional to its ERPF and is reflected in the slope of the second phase of the renogram. The accuracy of the method is improved if the intravascular radioactivity, assessed with a prior injection of ^{131}I-human serum albumin, is differentiated from the isotope taken up by the kidney (computer-assisted blood background subtraction; CABBS renography; BRITTON and BROWN, 1971). The most flexible system, however, is to record the output of a gamma-camera on magnetic tape and then analyse areas of interest at leisure later (HOLROYD, GLASS and CHISHOLM, 1972); this technique eliminates error due to faulty positioning of the probes.

3. Tubular Function

a) Measurement of Urine Concentration

It is the osmolality of the urine that is relevant, and its measurement with contemporary osmometers is an easy matter requiring only small volumes of urine. The specific gravity correlates poorly with the osmolality (EDELMANN et al., 1967c), and its measurement should be abandoned.

In response to water deprivation, normal children aged 2–16 years achieve a urine osmolality of 1127 ± 128 (SD) mOsm/kg (EDELMANN et al., 1967c). The osmolality of the overnight urine is 1089 ± 110 (SD) mOsm/kg, and further water deprivation only results in an increment of osmolality of about 10 per cent: examination of the overnight urine provides therefore a simple screening test for disorders of urinary concentrating capacity. During water deprivation tests, the child should not be allowed to lose more than 3 per cent of the body weight, care needs to be exercised that infants with water-losing renal diseases are not dangerously dehydrated.

Failure to concentrate the urine in response to water deprivation may be due to lack of antidiuretic hormone or resistance to its action: the alternatives may be discriminated by the administration of intramuscular vasopressin tannate in oil (0.1 units/kg/body weight). The test is best carried out in the water depleted state to avoid the danger of water intoxication in young infants. WINBERG (1959b) reported the maximum urinary osmolality after pitressin over the age of 3 years to be 1069 ± 128 (SD) mOsm/kg, and should be consulted for normal data for younger children.

b) Acidification of Urine

Hydrogen ion is secreted by the proximal tubule, and neutralises filtered bicarbonate; distal tubular fluid is essentially bicarbonate-free, and net hydrogen ion excretion can then take place, principally in the form of dihydrogen phosphate ($H_2PO_4^-$) and ammonium ion. Three types of defect of hydrogen ion excretion have been recognised (RODRIGUEZ-SORIANO and EDELMANN, 1969). In the first, proximal renal tubular acidosis, there is a quantitative defect in proximal hydrogen ion excretion, but urinary acidification occurs normally when the filtered load of bicarbonate falls during a metabolic acidosis; this defect may occur in isolation (RODRIGUEZ-SORIANO et al., 1967), be part of the Fanconi syndrome, or be secondary to renal dysplasia. In distal renal tubular acidosis (WRONG and DAVIES, 1959), there appears to be an inability to establish a hydrogen ion gradient across the tubular epithelium, and an acid urine is never produced; this defect is accompanied by nephrocalcinosis and urinary calculi (see p. 290). Finally, in uraemia, although the urine can be acidified, there is a diminished availability of hydrogen ion acceptor (HPO_4^{--} and ammonia) and total hydrogen ion excretion is therefore impaired.

The critical observation is the relationship between the plasma bicarbonate concentration and the urine pH. Care must be taken that an adequate urine specimen is examined, particularly that it is not infected (especially with urea-splitting organisms such as Proteus), that it is processed immediately by the laboratory, and that a hydrogen-ion electrode rather than indicator papers is used to measure pH.

Most infants and children pass acid urine during the night. If the child is not acidotic, then the observation of a pH of 5.3 or less in the overnight urine excludes

a defect of hydrogen ion excretion. This simple screening test should always be done before more elaborate assessments of hydrogen ion secretion are undertaken.

In patients with distal RTA, the urine pH never falls below 6.1. In proximal RTA the bicarbonate threshold is low, and the urine pH, although inappropriately alkaline during a mild metabolic acidosis, does in fact fall to 5.3 or less during a severe acidosis.

Ammonium chloride may be used as a mild acidotic stress (WRONG and DAVIES, 1959): the administration of 75 mEq (4G NH_4Cl) per square metre body surface area was used by EDELMANN et al. (1967b), and the urine pH should under these, circumstances fall to 5.3 or less.

c) Proximal Tubular Function

Proximal tubular dysfunction may result in renal glycosuria, generalised amino-aciduria, hypophosphataemic rickets and low molecular weigth ("tubular") proteinuria with increased urinary lysozyme excretion.

B. Acute Renal Failure

T. M. Barratt

With 2 Figures

I. Introduction

There are many differences between the clinical patterns of acute renal failure in infants and in older children (Barratt, 1971), and in this chapter emphasis will be placed upon the younger child. The important factors which determine the special features of renal failure in early life are the physiological characteristics of small body size (Barratt, 1973), maturation of renal function (Edelmann and Spitzer, 1969), growth-directed metabolism (McCance, 1959) and the particular susceptibility of the infant kidney to certain disorders.

II. Pathogenesis of Acute Renal Failure

Secretion of urine depends upon the integrity of the blood supply to the kidney, the normal function of the renal parenchyma and the patency of the urinary passages. There is thus merit in the time-honoured classification of acute renal failure as pre-renal, renal or post-renal. Episodes of acute deterioration of function may afflict kidneys that were previously normal, or may be superimposed upon pre-existing renal disease, and may be rapidly reversible, partially reversible or irreversible.

1. Pre-Renal Factors

Renal hypoperfusion may be the consequence of central or peripheral circulatory failure; the latter is the result of hypovolaemia due to loss of blood, plasma (albumin) or extracellular fluid (saline). The appropriate renal response to hypoperfusion is the production of small volumes of urine of high urea concentration and osmolality but low sodium concentration; there is avid tubular reabsorption of salt and water from a trickle of glomerular filtrate. The finding of a urine: plasma urea ratio of greater than 5 and osmolality ratio greater than 1.2 with a urinary sodium concentration less than 20 mEq/l ("good quality urine") suggests that kidney function will return rapidly if renal perfusion is restored.

The infant with renal failure is usually saline-depleted on arrival in hospital; saline-overload is uncommon unless there is complete anuria. The saline depletion may result from extrarenal losses, as for example with diarrhoea and vomiting (perhaps itself the consequence of a urinary tract infection), or from renal losses in infants with kidneys unable to conserve salt and water adequately, and is often the event that precipitates renal failure. The plasma sodium concentration may be low, normal or high, depending upon the relative magnitudes of salt and water losses, and the diagnosis is based upon the physical examination rather than on laboratory findings (Wrong, 1971). Saline depletion can usually be recognised by

diminished skin turgor, poor peripheral circulation, and, if the data are available, evidence of recent weight loss, but the physical signs may be less obvious if there is hypernatraemia due to predominant water losses (FINBERG, 1969). The arterial blood pressure may be difficult to estimate in infants, but is an essential observation in the assessment of salt and water balance, for hypertension virtually excludes saline depletion.

2. Renal Factors

a) Acute Tubular Necrosis

Acute tubular necrosis may follow any period of prolonged renal hypoperfusion, or may be due to nephrotoxins. Saline depletion following gastroenteritis is a common cause, particularly in tropical countries (GORDILLO-PANIAGUA, 1967), and acute tubular necrosis is likely if oliguria persists in spite of volume replacement. It may be superimposed upon other renal disease, as, for example, a complication of the hypovolaemia of the nephrotic syndrome (CHAMBERLAIN et al., 1966) or of saline depletion due to renal losses. Sometimes no cause is found. The oliguric phase is shorter in children than in adults, and may occasionally escape notice. In hypercatabolic states the urine volume may be relatively normal, but contain insufficient urea to prevent uraemia. A dense prolonged nephrogram may be observed during the oliguric phase (FRY and CATELL, 1972), and probably indicates continued glomerular filtration with leakage of tubular fluid (BANK et al., 1967) (Fig. 2). During the recovery phase there may be inappropriate losses of salt and

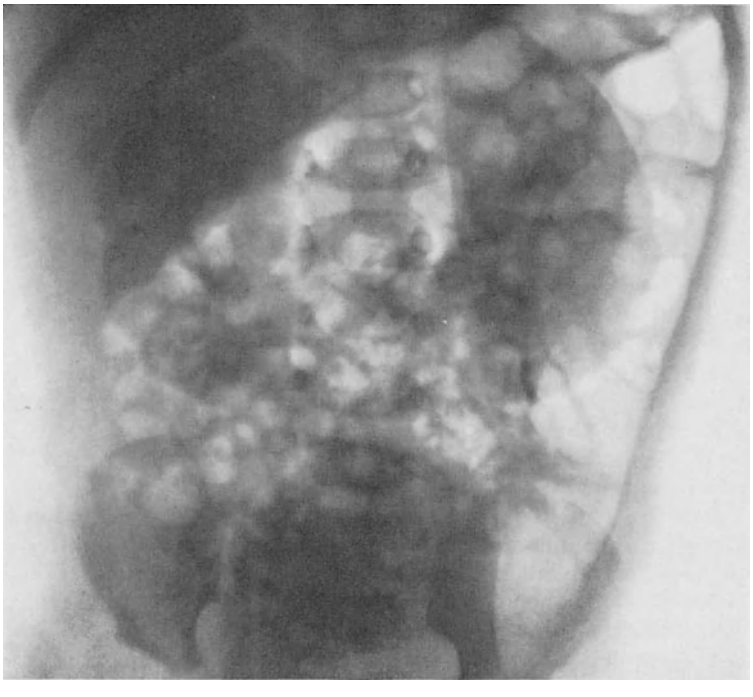

Fig. 2. A dense nephrogram persisting 20 hours after injection of contrast medium in a child of four months with acute tubular necrosis complicating gastroenteritis

water, but this has been over-emphasised in the past, and more commonly diuresis at this stage consists of the appropriate excretion of excess fluid retained during the oliguric phase.

b) Renovascular Accidents

The infant kidney is particularly prone to venous infarction, as either frank renal venous thrombosis or medullary necrosis. This susceptibility may be related to the high renal vascular resistance in early life (GRUSKIN et al., 1970). Most cases of renal venous thrombosis occur in the first two months of life (MCFARLAND, 1965; JOHNSTON, 1968); intra-uterine thrombosis with an infarcted kidney at birth has been described (ZUELZER et al., 1951). Many cases are associated with perinatal asphyxia, particularly in infants of diabetic mothers (AVERY et al., 1957); others follow periods of renal hypoperfusion. The thrombosis originates in the small intrarenal veins and progresses centripetally, but does not appear to propagate to the other kidney (JOHNSTON, 1968); rarely the thrombosis appears to originate in the inferior vena cava (VERHAGEN et al., 1965). Sometimes a similar pathological process also affects the adrenal glands, resulting in adrenal haematomata. There is often evidence of a generalised coagulation disorder with thrombocytopaenia (BELMAN et al., 1970). The clinical picture is of a firm enlarging kidney, haematuria and proteinuria, usually in a sick infant, though occasionally the constitutional disturbance is mild. The nephrotic syndrome has only rarely been reported in children with renal vein thrombosis (FEINERMAN et al., 1957);

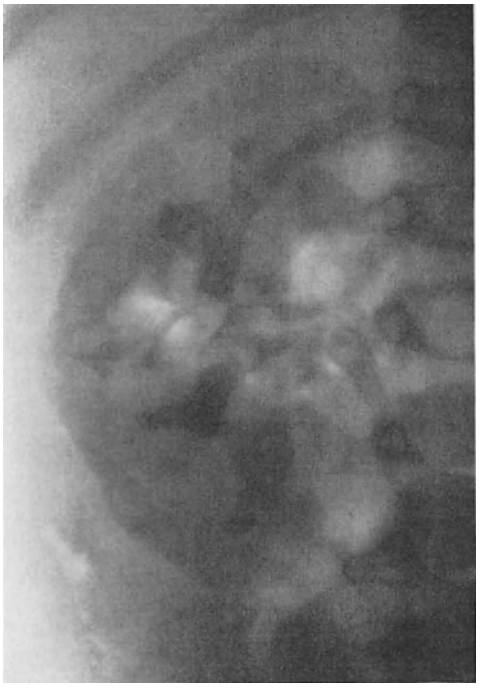

Fig. 3. Medullary necrosis complicating gastroenteritis in a child of three months. Note the heavy opacification of the renal pyramids and a normal pyelogram

here the thrombosis may be secondary and related to the susceptibility of nephrotic patients to thrombo-embolic complications (LIEBERMAN et al., 1968). Uraemia may be due to underlying renal hypoperfusion or associated tubular necrosis, and does not necessarily imply bilateral involvement. Even bilateral cases may have some recovery of function (MCFARLAND, 1965). Thrombectomy has only rarely appeared beneficial (LOWRY et al., 1970) and routine nephrectomy is not necessary in the acute stage (JOHNSTON, 1968; BELMAN et al., 1970); on balance it seems that the risks involved in the radiological definition of the problem and in surgical intervention outweigh the likely benefit in the majority of cases. The value of anti-coagulant or fibrinolytic therapy has not been established. The kidney after venous thrombosis shrinks, and may in later years be responsible for hypertension. At this stage, it may be difficult to distinguish from other varieties of small kidney.

Medullary necrosis in infants may be regarded as a similar lesion in which venous infarction is limited to the medulla (BERNSTEIN and MEYER, 1961; DAVIES et al., 1969; CHRISPIN, 1972) (Fig. 3), and the predisposing conditions are similar. The possibility that radiological contrast media may precipitate the lesion is referred to below (GRUSKIN et al., 1970). In the convalescent phase these infants may have a salt-wasting phase, and the structural sequelae may appear on radiological grounds very similar to chronic pyelonephritis (CHRISPIN et al., 1970).

c) Disseminated Intravascular Coagulation

This term is applied to states in which there is generalised activation of clotting system, with secondary fibrinolysis reflected in the presence of circulating fibrin degradation products (FDP) (ABILDGAARD, 1969). It is the end result of many pathological processes such as septicaemia, and is the underlying mechanism of the haemolytic-uraemic syndrome (GASSER et al., 1955; LIEBERMAN, 1972). This disease presents a more homogeneous picture in children than in adults. It frequently follows a gastrointestinal upset, and is characterised by the acute onset of haemolytic anaemia with erythrocyte fragmentation, thrombocytopaenia, renal failure (GIANANTONIO et al., 1964) and evidence of a widespread coagulation disorder (AVALOS et al., 1970). The disease has a remarkable geographical distribuion and occurs with considerable frequency in South America (GIANANTONIO et al., 1964) and South Africa (KAPLAN et al., 1971). In temperate climates there tends to be a clustering of cases in micro-epidemics (MCLEAN et al., 1966), suggesting an infective disorder, but the aetiological agent has not been identified. It has been pointed out that the disease resembles the Shwartzman reaction produced by endotoxin administration (SHUMWAY and TERPLAN, 1964). There is intravascular coagulation and microangiopathy due to the endothelial deposition of fibrin and resulting in erythrocyte fragmentation and platelet sequestration (BRAIN et al., 1962). The renal lesion (HABIB et al., 1967) is the result of arteriolar and glomerular capillary thromboses. In severe cases there is neurological involvement.

There are uncontrolled reports of a beneficial effect of heparin therapy (GILCHRIST et al., 1969), and the mortality is now quite low, but this may be due to improved care of children with acute renal failure and the recognition of milder cases (LIEBERMAN, 1972). Streptokinase is also said to be beneficial (MONNENS et al., 1972), again on the basis of uncontrolled studies.

In a minority of the survivors there is residual impairment of renal function and hypertension. In the Argentinian patients, however, the incidence of hypertension is higher in cases with a long follow-up (GIANANTONIO et al., 1968).

d) Acute Glomerulonephritis

Acute glomerulonephritis is extremely rare under the age of one year. In later childhood it ranks as a major cause of acute renal failure arising in a child who was previously completely healthy. There may be complete anuria. If even a drop of urine is available for examination, it should be saved as microscopy may reveal the presence of erythrocyte and granular casts, which are virtually diagnostic. In 90 per cent of cases the diagnosis can be confirmed by the finding of a low serum C3 concentration.

e) Pyelonephritis

The role of urinary tract infection in the genesis of acute-on-chronic renal failure, mediated either by saline depletion or by renal parenchymal involvement, has been referred to above. Attention must be particularly drawn to the clinical pattern of overwhelming sepsis in young infants. Males are affected most commonly; the usual infecting organism is Eschericia coli. There is evidence of urinary tract infection, septicaemia and sometimes meningitis. Jaundice of an obstructive pattern may be evident. Disseminated intravascular coagulation is sometimes present. These infants are usually saline depleted, hypernatraemic, hyperkalaemic, acidotic and uraemic. The kidneys may be quite strikingly enlarged, and misleadingly suggest an underlying urological abnormality.

3. Post-Renal Factors

Urinary tract obstruction in childhood is usually congenital in origin, and as such of long standing; acute urinary tract obstruction is relatively uncommon. Nevertheless, many children with congenital urinary tract obstruction present as acute emergencies, having been precipitated into renal failure by urinary tract infection or saline depletion. The subject is further discussed in Chapter M.

III. Diagnosis

Children with acute renal failure are often very sick when first seen; diagnosis and treatment may have to be undertaken simultaneously.

Clues to the underlying pathology of the renal failure may be found in the history. Of particular importance in male infants is the character of the urinary stream, though in infants a significant urethral obstruction may be present with apparently normal micturition (Williams et al., 1972). Diarrhoea and vomiting suggest saline depletion, but may also be a prelude to acute tubular necrosis, renal venous thrombosis or the haemolytic-uraemic syndrome, and may themselves be caused by urinary tract infection or uraemia.

On physical examination, some features suggest maldevelopment of the renal tract: agenesis of abdominal wall musculature, anorectal anomalies, genital anomalies and congenital heart disease. Malformations incompatible with intrauterine micturition result in oligohydramnios, amnion nodosum, pulmonary hypoplasia and compression deformities, particularly talipes and abnormal facies (Bain and Scott, 1960; Potter, 1965). Enlargement of the kidneys and bladder implies infravesical obstruction. Gross enlargement of the kidneys is typical of hydronephroses or the infantile variety of polycystic disease, but the kidneys in

acute tubular necrosis or pyelonephritis may also be palpable. Anaemia and short stature imply renal disease of long duration.

A blood film may reveal erythrocyte fragmentation and thrombocytopaenia characteristic of disseminated intravascular coagulation, or a polymorphonuclear leucocytosis suggestive of infection. Blood cultures are essential. A reduced concentration of the complement component C3 is virtually diagnostic of acute nephritis.

The urine should be examined for the presence of protein, cells and casts and the urine sodium, urea and osmolality estimated.

Uraemia is not a contraindication to intravenous urography; diagnostic information is often obtained but the investigation should be deferred until adequate volume replacement has been achieved. High doses of contrast media are essential, but care should be taken in small children for there are reports of renal medullary necrosis after the use of more than 3 ml/kg body weight in sick infants (MAUER and NOGRADY, 1969; GILBERT et al., 1970; GRUSKIN et al., 1970). The contrast material is a considerable osmotic load (STANDEN et al., 1965), and may aggravate water losses in infants with defects of urinary concentration, so fluids should not be withheld beforehand. Cystourethrography may give valuable information about the kidneys if reflux is present, as well as about the lower urinary tract.

Renal biopsy (see Chapter E) is sometimes of help in establishing the diagnosis, particularly in older children in whom the plain abdominal x-ray suggests that the kidneys are of reasonable size.

IV. Consequences of Acute Renal Failure

During episodes of acute renal failure the major disorders of homeostasis are: saline depletion or overload; osmolar disturbances; hyperkalaemia; metabolic acidosis; hyperphosphataemia; hypocalcaemia and hypomagnesaemia; and the rather ill-defined uraemic state. There may in addition be overwhelming sepsis, perhaps accompanied by disseminated intravascular coagulation, and sometimes the clinical picture is dominated by the cause of the renal failure itself.

1. Saline Overload

The clinical features of saline overload are hypertension, peripheral and pulmonary oedema and cardiac failure. If the state has resulted from the injudicious administration of salt and water, and the child is still passing urine, dietary restriction may suffice. However, if oliguria persists in spite of saline overload, diuretics (frusemide, 1 mg/kg body weight intravenously, increasing to 2 mg/kg and then 4 mg/kg) may be tried. Mannitol is, of course, dangerous in these circumstances and its use has been largely abandoned in favour of the modern potent diuretics. If these measures fail, dialysis is usually necessary. Severe hypertension may result in an encephalopathy with convulsions; under these circumstances it is necessary to lower the blood pressure rapidly, and for this purpose diazeoxide (2 mg/kg body weight intravenously) is a useful drug.

2. Osmolar Disturbances

Both hyponatraemia and hypernatraemia may cause convulsions. The latter is the more serious state for there is a high incidence of residual neurological se-

quelae (MACAULAY and WATSON, 1967). Children with water-losing renal disease (nephrogenic diabetes insipidus, obstructive uropathy, renal dysplasia and cystic disease, the Fanconi syndrome, renal tubular acidosis and hypercalcaemia) are most at risk of developing hypernatraemia, particularly if they are receiving a high solute diet.

3. Hyperkalaemia

Elevation of the serum potassium may cause various arrhythmias or cardiac arrest. There are characteristic electrocardiographic changes with peaking of the T-waves that give warning of an impending disorder of cardiac rhythm. In older children a serum potassium concentration in excess of 6.5 mEq/l requires treatment, but in infants higher levels appear to be tolerated, and it is uncommon in this age group for an arrhythmia to develop until the serum potassium exceeds 7.5 mEq/l.

Calcium ion antagonises the effect of potassium on the heart, and the best emergency treatment of a hyperkalaemic arrhythmia is calcium gluconate (up to 0.5 ml/kg body weight of a 10 per cent solution, diluted and given by slow intravenous injection, with electrocardiographic control). A cation-exchange resin charged with calcium (1 G/kg body weight/day) may be administered orally or rectally, and some protection from hyperkalaemia may be conferred by the correction of a metabolic acidosis. The use of glucose and insulin to reduce serum potassium levels is, however, often attended by troublesome hypoglycaemia, and is best avoided.

The risk of development of dangerous hyperkalaemia is much increased in hypercatabolic states, such as in renal failure complicating open-heart surgery, burns or septicaemia. The provision of an adequate calorie intake, intravenously if necessary (HARRIES, 1971), minimises tissue breakdown and the rate of release of potassium into the extracellular fluid (MCCANCE, 1959).

4. Acidosis

A severe metabolic acidosis may be lethal; it may be suspected clinically if the child is hyperventilating (KUSSMAUL respiration). It is not necessary, however, to achieve the full correction suggested by the SIGGAARD-ANDERSEN (1964) formula [amount of bicarbonate required (mEq) = 0.3 × body weight (kg) × base deficit (mEq/1)], and attempts to do so may result in the administration of a dangerously large sodium load, or provoke tetany in a hypocalcaemic child. In an emergency, sodium bicarbonate may be given in a dose of 2 mEq/kg body weight (2 ml of an 8.4 per cent solution per kg body weight) provided the child is not hypertensive; correction of acidosis in a saline-overloaded child can only be achieved by dialysis.

5. Divalent Ions

The plasma phosphate concentration rises in acute renal failure, particularly if the dietary phosphate intake is high, as in the infant on a cow's milk diet. The calcium phosphate product rises, and metastatic calcification occurs; in infants this is liable to develop in fascial planes rather than in vessels (HARDMAN et al., 1971). There is a reciprocal fall in plasma calcium concentration which may

result in tetany; in infants, however, convulsions are a more common neurological consequence of hypocalcaemia. Acidosis protects the patient from the effects of hypocalcaemia.

Adults with acute renal failure tend to become hypermagnesaemic, but in infants hypomagnesaemia is the rule (GHAZALI et al., 1972), particularly if there is hyperphosphataemia. Hypomagnesaemia should be considered if convulsions persist in spite of adequate correction of hypocalcaemia.

Aluminium hydroxide gel prevents phosphate absorption by the precipitation of insoluble aluminium phosphate in the bowel lumen; the serum phosphate level should be maintained between 4 and 6 mg/100 ml with aludrox in a dosage of about 0.5 ml/kg body weight/day. Acute hypocalcaemic symptoms should be treated with 10 per cent calcium gluconate intravenously (up to 0.5 ml/kg body weight). Hypomagnesaemic states can be corrected with 50 per cent magnesium sulphate (0.1 ml/kg body weight) intramuscularly.

6. Uraemia

The extent to which the features of the uraemic state may be attributed to urea accumulation per se, or to other metabolites whose concentration rises in parallel to that of urea, has not been resolved. The gastro-intestinal symptoms of uraemia — nausea, vomiting and diarrhoea — seem, however, to be directly attributable to urea, for they may be minimised by the use of a low protein diet.

7. Other Features

a) Convulsions

Convulsions may be due to hypertensive encephalopathy, hypo- or hyperosmolar states, hypocalcaemia, hypomagnesaemia or uraemia. If there is septicaemia, meningitis must be considered, and disseminated intravascular coagulation may also have neurological sequelae.

The choice of anticonvulsant in renal failure requires some care. Phenobarbitone tends to accumulate; the most suitable are those metabolised by the liver such as diazepam (0.1 – 0.2 mg/kg body weight intravenously).

b) Sepsis

Septicaemia may spread from a renal focus, particularly in young infants (predominantly male), as the IgM agglutinating antibody response to renal parenchymal infection is not apparent in the first two months of life (HANSON et al., 1970). A septicaemia arising from other sources may also cause renal failure, particularly if complicated by disseminated intravascular coagulation (ABILDGAARD, 1969). Antibiotic therapy in renal failure must be managed carefully in order to avoid toxic accumulation of the drugs, and is further considered in Chapter G.

c) Anaemia

Infection, uraemia, disseminated intravascular coagulation or blood loss may be responsible for anaemia. If the child is saline-overloaded, transfusion cannot be started until the excess salt and water have been removed. Even then, it is safer to limit the transfusion to 10 ml/kg body weight of packed cells, and to retransfuse 24 hours later if an adequate haemoglobin level has not been reached.

The blood pressure should be monitored during the transfusion, and should not rise above 90 mm Hg (diastolic).

V. Conservative Management of Acute Renal Failure

In the adult an intake of 0.25 G/kg body weight/day of protein of high biological value results in the minimum rate of urea production. The minimum protein intake in younger children has not been established, but 1 G/kg body weight/day in the infant over 3 months of age seems satisfactory. This is, of course, substantially less than the protein intake of an infant receiving a diet of cow's milk (5 G/kg body weight/day) or human breast milk (2 G/kg body weight/day), but it is often adequate merely to reduce the protein intake to the latter level.

The maximum benefit of such restricted protein diets may only be realised if an adequate calorie intake is achieved—at least 100 cals/kg body weight/day and preferably more. This may be provided in the form of glucose polymer and lipid, but the carbohydrate content of the diet should not exceed 10 per cent, or diarrhoea may ensue.

Insensible water losses are related to surface area, and hence on a weight basis are greater in the infant than in the adult; about 30 ml/kg body weight/day in the infant (LEVINE et al., 1930) falling to 5 ml/kg body weight/day in the adult.

VI. Dialysis

1. Indications

The decision to treat by dialysis is determined less by arbitrary criteria of blood chemistry than by an assessment of the probable course of the renal failure; it is indicated if the infant is hypercatabolic or if a prolonged period of oliguria is expected, but if a quick return of renal function seems likely conservative management may suffice and dialysis be deferred. In practice, diuretic-resistant saline overload is perhaps the most important indication as correction of acidosis or anaemia, for example, is impossible under such circumstances without dialysis.

2. Haemodialysis vs Peritoneal Dialysis

Until recently there has been little question that peritoneal dialysis is preferable to haemodialysis in the management of children with acute renal failure, although there has always been a small minority of cases in whom, for technical reasons such as a burst abdomen, peritoneal dialysis is impossible. The technical difficulties of infant haemodialysis have been access to the circulation, the large blood volume of the artificial kidney relative to that of the child, and hyperefficient dialysis causing the disequilibrium syndrome. An even greater problem, however, has been that the relative infrequency with which haemodialysis in small children is required has hindered the acquisition of the expertise necessary for the safe use of the artificial kidney by paediatric renal units. The development of maintenance haemodialysis programmes in children has therefore opened the door

to new technical solutions, and some of the problems have now been overcome (AHOLA et al., 1972; KJELLSTRAND et al., 1971). Suitable paediatric arterial and venous shunts are available, and paediatric dialysers which require less than 10 per cent of the infant's blood volume for priming have been developed. It has been found important to relate the efficiency of the dialyser to the size of the child; urea clearances of 2–3 ml/kg body weight/min are satisfactory (KJELLSTRAND et al., 1971). Nevertheless, even with these developments, it is likely that most centres will rely on peritoneal dialysis in the immediate future for the treatment of acute renal failure in children.

3. Peritoneal Dialysis

After early difficulties, peritoneal dialysis has now become established as a satisfactory method for the treatment of acute renal failure in children (SEGAR et al., 1961; LLOYD-STILL and ATWELL, 1966; BARRATT, 1971). It is relatively more efficient in small children than in adults, as the peritoneal surface area/body weight ratio is greater (ESPERANCA and COLLINS, 1966). Its simplicity is a major advantage over haemodialysis, but in spite of its apparent ease, the technique should, where possible, be restricted to specialist centres, for it represents only one aspect of the management of the uraemic child, and moreover, it repays handsomely scrupulous attention to detail in execution that can only be achieved by an experienced nursing and resident medical staff.

a) Setting up Dialysis

Under light sedation and local anaesthesia, and with strict aseptic technique, the peritoneal cavity is first filled with dialysate fluid—about 30 ml/kg body weight—through a small needle. This manoeuvre reduces the risk of perforation of a viscus. The peritoneal catheter itself should be moderately flexible, contain an internal stilette, and have perforations which do not extend more than 3 cm from the tip. In infants it is often more convenient to insert the catheter in the left flank rather than in the customary sub-umbilical position, as it may be difficult to bury the perforations below the peritoneum in the latter site. In infants there is also an increased risk of perforation of the bladder, which is an abdominal rather than a pelvic organ. A small skin incision is made. and the catheter inserted into the peritoneal cavity—it helps if the abdominal wall is made tense by the infant crying—and advanced towards the pelvis.

Some modifications of the standard adult equipment are required for infants; a burette to measure the input volume and a heating coil to minimise heat loss during dialysis. Ideally, the administration set should be manufactured as a single piece, and not improvised from other intravenous equipment, for junctions and three-way taps are a potent source of infection.

b) Dialysis Regime

Commercially available dialysate fluids may be used at all ages. A sodium concentration of 130 mEq/l is usually optimal. Glucose concentration should not exceed 2 G/100 ml; higher concentrations cause such a rapid withdrawal along the osmotic gradient into the peritoneal cavity that hypovolaemic shock may ensue. Potassium should be added in a concentration of 4 mEq/l if the serum concentration is not elevated. Lactate is the usual metabolisable anion, but the sick anoxic neonate may fail to convert it to bicarbonate and hence develop a lactic acidosis; it is then necessary to prepare a dialysate containing bicarbonate instead.

A cycle volume of about 25–50 ml/kg body weight is usually satisfactory, but the amount tolerated varies in different children. Over-distension of the peritoneum is dangerous, for it may cause respiratory embarrassment or, in the infant, apnoeic attacks. Under most circumstances it is convenient and adequate to use hourly cycles, allowing the fluid to run into the peritoneum in 10 minutes, to dwell for 20 minutes and to drain for 30 minutes. On this regime, with a dialysate glucose concentration of 1.4 G/100 ml, the drainage usually exceeds the input by about 10 per cent. Assuming insensible losses of 20 ml/kg body weight/day, this regime permits the infant a fluid intake of about 120 ml/kg body weight/day plus the urine volume. Hypercatabolic states necessitate shorter cycle periods, which are best achieved by shortening the drainage phase, for the efficiency of dialysis is related to the volume of fluid passing through the peritoneal cavity in unit time (Boen, 1964).

Accurate recording of the fluid balance estimated from dialysis input and return is important, but susceptible to cumulative errors; the most useful observations are the child's weight and circulatory status, particularly blood pressure. Conversely, when repeated weighing is difficult, as for example in children on mechanical ventilators, or where other factors influence the cardiovascular signs of hydration, as after cardiac surgery, control of fluid balance may become very difficult. In the latter circumstance, monitoring of the central venous pressure is essential.

c) Complications

Certain difficulties may be encountered; bleeding after insertion of the catheter is usually not as troublesome as it might appear at first, unless the infant is heparinised. If bleeding does occur, it is helpful to add a small amount of heparin (200 i.u./litre) to the dialysate to prevent blockage of the catheter. Bowel perforation is very unusual if the peritoneum is first filled with dialysate, but may occur if the gut is grossly distended, and is probably best managed by surgical exploration in young children. Difficulties in drainage of dialysate are infrequent in small children, probably because the omentum is less well developed and does not wrap around the catheter. Infection is reasonably easy to eradicate in older children, but is more serious in infants, for septicaemia may disseminate from a peritoneal focus; at the first suggestion of peritonitis, antibiotics should be added to the dialysate in a concentration which exceeds the minimum inhibitory concentration of the infecting organism but is less than the toxic blood level.

The dialysis regime should be adjusted to permit a normal diet. Particular attention should be paid to the maintenance of nutrition during peritoneal dialysis. In infants a daily protein intake of at least 2 g/kg body weight and a calorie intake of 100 cal/kg body weight should be provided, as well as additional water soluble vitamins. Protein depletion develops rapidly in small infants, and plasma infusions may be required.

VII. Conclusions

Successful management of young children with renal failure may only be achieved with the co-operation of several paediatric skills. A closely co-ordinated team of paediatric nephrologist, urologist, radiologist, nursing staff, pathologists and dietician, all experienced in and equipped for the management of sick infants, is essential, and any compromise of this arrangement will result in less than optimal results.

C. Chronic Renal Failure in Children

T. M. Barratt

With 2 Figures

I. Introduction

Rapid developments in the techniques of dialysis and renal transplantation during the past decade have led to a reappraisal of their suitability for children (Cameron, 1973), and experience to date suggests that, by the criterion of survival at least, children fare as well as, if not better than, adults on renal replacement programmes. The availability of these methods of treatment leads to new considerations in the management of children with urological disorders, and makes it essential that the paediatric urologist is aware of the current practice of his regional dialysis and transplant centre.

II. Epidemiology of Renal Failure in Children

1. Mortality

Comprehensive statistics on the death rate from renal failure in children are not available. The British Paediatric Association (1969) estimated that between 3 and 5 children aged 0–14 years per million total population die of renal failure each year, but the group is sufficiently heterogeneous that such an overall estimate of incidence is of doubtful value, for renal failure may be only one aspect of a complex disease or constellation of congenital malformations. In a survey conducted for the European Society for Paediatric Nephrology, Schärer (1971) found the incidence of chronic renal failure in children aged 6 months to 16 years to be about 1 per million total population per annum. However, reports from centres which have already developed specific paediatric dialysis and transplantation facilities, such as Paris (Broyer et al., 1972b) and California (Potter et al., 1970a), suggest that a more reasonable estimate of the requirements for dialysis and transplantation in children would be provision for 2 new cases per million total population per annum. A similar estimate is reported for Scotland (Pendreich et al., 1972).

2. Aetiology

Under the age of 5 years congenital disorders—hypoplasia, dysplasia, cystic disease (see Chapter F)—predominate, but nearly half these children have other major congenital abnormalities (Barratt, 1971). Over the age of 10 years, however, glomerulonephritis in one form or another is the principal cause of renal failure in children entering dialysis programmes (Schärer, 1971).

III. Pathophysiology of Chronic Renal Failure

1. Adaptation to Diminishing GFR

The glomerular filtration rate may fall to 50 per cent of normal with barely detectable change in extracellular fluid composition. At 25 per cent of normal the concentrations of urea and creatinine rise outside the normal range, but symptoms are unusual. At 10 per cent, renal failure may be symptomatic, and require dietary control. A glomerular filtration rate in children less than 5 per cent of normal is hardly compatible with survival.

By what adaptive mechanisms is homeostasis maintained in the face of declining renal function ? As GFR, and thus urea clearance, fall, plasma urea concentration rises until excretion again balances production; in one sense the elevated plasma urea concentration in chronic renal failure can be regarded as an adaptive response. It has been proposed that with advancing renal disease some nephrons become completely non-functional, but that the residual nephrons function normally (the "intact nephron" hypothesis; PLATT, 1952; BRICKER, 1969). Although this hypothesis seems implausible in view of the obvious heterogeneity of nephron damage apparent on histological examination, it serves as a reminder that the residual functional nephrons must each carry an increased share of the excretory load, and must therefore reject a greater fraction of their filtered load of water, urea and electrolytes than do nephrons in healthy kidneys. There is thus an osmotic diuresis per nephron, so that the urine has an osmolality close to that of plasma. The principal characteristic of nephrons operating under such conditions is lack of flexibility of function; such kidneys are unable to modulate the composition of the urine in response to homeostatic requirements.

The increase in excretion per nephron is sometimes only achieved at the expense of undesired side effects (the "trade-off" hypothesis; BRICKER, 1972). As an example, the increasing parathormone concentration in chronic renal failure serves to maintain phosphate homeostasis by augmenting phosphate excretion, but only at the cost of bony lesions. Likewise hypertension may be regarded as the trade-off of the chronic volume expansion necessary to maintain sodium balance.

2. Uraemia

Although elevation of the blood urea concentration has been recognised for more than a century (BRIGHT, 1827), its exact role in the genesis of the uraemic state remains unclear. Reduction of the urea concentration by a low protein diet in uraemic patients results in improvement in well-being (BERLYNE and HOCKEN, 1968), in haemoglobin concentration (SHAW, 1968), and in gastrointestinal symptoms. Urea is synthesised in the liver from ammonia derived from protein catabolism. Only about 80 per cent of synthesised urea is excreted in the urine; the remainder is reconverted to ammonia by the action of bacterial ureases in the gut (WALSER and BODENLOS, 1959), and the proportion recycled is greater in uraemic patients. Attempts have therefore been made to develop diets which promote the reutilisation of this ammonia in protein synthesis (GIORDANO, 1963; GIOVANETTI and MAGGIORE, 1964). To this end, it is essential to use protein of high biological value—principally of animal origin—and maintain an adequate calorie intake. In adults, net urea production is minimal on a protein intake of 15G/day. Such diets need careful supervision that they are not deficient in

essential nutrients such as minerals or individual aminoacids. In children the minimum protein intake compatible with growth has not been determined precisely, but the World Health Organisation (1965) suggest 1.8G/kg body weight/day at 3 months falling to 0.9G/kg body weight/day at one year of age.

Other metabolites than urea have been considered responsible for the uraemic syndrome, particular guanidine compounds (GIOVANETTI et al., 1969), though these claims remain open to doubt (BAKER and MARSHALL, 1971).

3. Osteodystrophy

There are three types of bony lesion associated with uraemia: rickets/osteomalacia, osteitis fibrosa and osteosclerosis. The first is due to an acquired resistance to vitamin D, and the second to hyperparathyroidism, but the origin of the third is obscure. All three may coexist.

a) Vitamin D

It is now established that vitamin D_3 (cholecalciferol) after absorption from the gut is hydroxylated in the 25-position by the liver, (STAMP, 1973; DELUCA, 1969) and is then transported to the kidney where it is further hydroxylated in the 1-position (LAWSON et al., 1970), forming 1,25-dihydroxycholecalciferol, which is the active metabolite of vitamin D, and which promotes the absorption of calcium from the intestinal lumen (MYRTLE and NORMAN, 1971). The kidney is apparently the only site of 1-hydroxylation (FRASER and KODICEK, 1970); with severe renal damage there is an acquired resistance to the action of vitamin D, impaired gastrointestinal calcium absorption (STANBURY and LUMB, 1962) which can be reversed by the administration of 1,25-dihydroxycholecalciferol (BRICKMAN et al., 1972). The skeletal consequence is osteomalacia, or, in the child, rickets.

b) Parathormone

Radioimmunoassay techniques have shown that plasma parathormone concentrations are high in chronic renal failure (BERSON and YALLOW, 1966; REISS et al., 1969) though there is some doubt about the identity with parathormone of the immunoreactive material in uraemic serum. The hyperparathyroidism is a secondary response to the hypocalcaemia which develops reciprocally with hyperphosphataemia, and is aggravated by the calcium malabsorption referred to above. Hyperparathyroidism tends to restore phosphate equilibrium by stimulating phosphate excretion, but results in osteitis fibrosa characterised by sub-periosteal cystic erosions. Occasionally autonomous hyperparathyroidism develops, necessitating parathyroidectomy (FINE et al., 1970 b). This situation may be recognised by spontaneous development of hypercalcaemia or by failure to induce healing of the bony lesions with vitamin D without causing hypercalcaemia.

Hyperphosphataemia may result in metastatic calcification, with pruritus or corneal irritation (BERLYNE and SHAW, 1967).

c) Evolution of Osteodystrophy

Radiologically evident osteodystrophy is rare in the first year of life. At onset the lesion is principally rachitic, associated with hypocalcaemia. It may be demonstrable in the knee before the wrist. At this stage it is relatively easy to treat with moderate doses of vitamin D (DENT et al., 1961), and the gait may recover with gratifying speed due to improvement in the associated myopathy. If left

untreated, however, the parathyroid reaction develops, the serum calcium rises, the bony lesion apparently improves transiently but then deteriorates into osteitis fibrosa and becomes much less amenable to vitamin D therapy (Figs. 4 and 5).

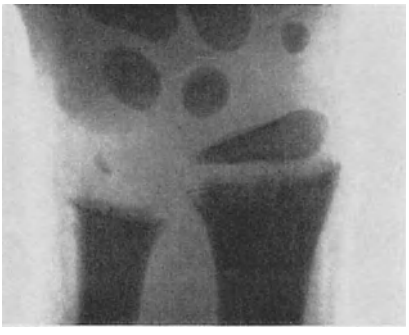

Fig. 4

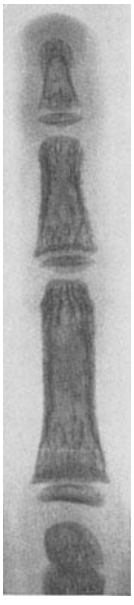

Fig. 5

Fig. 4. Rachitic changes in the wristes of a ten-year-old boy with chronic renal failure due to juvenile nephronophthisis

Fig. 5. Index finger from the same x-ray as Fig. 4 showing sub-periosteal erosions and absorption of the tufts of the distal phalanx indicative of hyperparathyroidism

4. Haematological Consequences

Anaemia is due to failure of erythropoietin production (NATHAN et al., 1971) and impaired iron absorption (LAWSON et al., 1971). There is a haemolytic component that responds to dietary protein restriction (SHAW, 1968) and there may be blood loss due to gastritis or a bleeding tendency secondary to the acquired disorder of platelet function that characterises uraemia (RABNER, 1972). Most patients come to terms with their anaemia, and transfusion should be avoided, for it carries special risks in patients with chronic renal failure: pulmonary oedema due to volume overload; serum hepatitis, which would preclude admission to a dialysis programme; and sensitisation to leucocyte antigens leading to hyperacute transplant rejection.

5. Growth

Growth impairment is usual in children with chronic renal failure. Many factors are involved (WEST and SMITH, 1956): anaemia, infection, acidosis, de-

hydration, osteodystrophy, uraemia and poor calorie intake. Correction of a metabolic acidosis occasionally results in catch-up growth (PRADER et al., 1963). Osteodystrophy has been referred to above. A poor calorie intake seems to be a factor of major importance in many cases (SIMMONS et al., 1971; CHANTLER and HOLLIDAY, 1973).

IV. Practical Aspects of Conservative Management

1. Elimination of Reversible Causes of Renal Failure

There are three major reversible causes of acute-on-chronic renal failure: urinary obstruction, infection and saline depletion. To these may be added hypercalcaemia and nephrotoxins. Of these the most subtle is saline-depletion. As discussed on p. 5 the serum sodium concentration is of little help, and the diagnosis rests on clinical signs rather than laboratory investigations. If the blood pressure is normal, it is always worth increasing the dietary sodium intake to see if renal function improves.

2. Dietary Control

The dietary aspects of the management of chronic renal failure are listed in Table 2. Manipulation of a child's diet is both a major undertaking for the patient

Table 2. Dietary considerations in the management of chronic renal failure

Clinical Feature	Dietary Consideration
Uraemia	Protein
Hypertension	Sodium
Osmolar disturbance	Water
Hyperkalaemia	Potassium
Acidosis	Alkali
Osteodystrophy	Calcium, phosphorus and Vitamin D
Anaemia	Iron and vitamins
Growth failure	All of the above and *Calories*

and his family, and may have far-reaching medical effects. It is important, therefore, that the physician co-operate closely with a dietician experienced in the management of children on restricted diets, and that the diet is constantly reviewed to ensure that the child's *actual* intake (as opposed to recommended intake) is appropriate for his size, maturity and level of renal function. Experience in the management of children with renal failure indicates that common mistakes are unnecessarily severe protein restriction, failure to recognise salt wasting states, and inadequate consideration of the child's changing requirements during weaning.

The dietary protein intake should be reduced to maintain the blood urea con-

centration about 100 mg/100 ml, but it is usually unwise to reduce the intake of protein below 1 G/kg body weight/day. The dietary sodium intake should be related to the blood pressure; allowance must be made for the sodium in any alkali prescribed. If hyperkalaemia is evident the dietary potassium intake should be restricted to 1 mEq/kg body weight/day, and calcium resonium (1 G/kg body weight/day) added if this restriction is inadequate. A calorie intake of at least 100 cals/kg body weight/day should be the goal. A complete vitamin intake should be maintained, and further provision of iron and calcium may be necessary.

3. Medical Complications

Hypertension unresponsive to dietary sodium restriction or diuretics may need treatment as detailed in Chapter D. Acidosis should be treated in the first instance with $NaHCO_3$ 2mEq/kg body weight/day, provided the sodium load is tolerable and hypocalcaemia corrected.

Osteodystrophy should be detected early, and six monthly x-rays of wrist and knee during the peak risk period of 1–4 years of age are necessary in children with a blood urea concentration over 60 mg/100 ml. When radiological evidence of bone disease is present, vitamin D 10,000 i.u./day should be started, and increased slowly till healing occurs. The serum calcium concentration must be monitored. The serum phosphate concentration should be maintained between 4 and 6 mg/100 ml with aludrox (up to 0.5 ml/kg body weight/day).

It is important to give some consideration to the overall effects of multiple prescription in children with chronic renal failure. Such a child may be receiving a diuretic; an antihypertensive agent; an antibiotic; calcium resonium; vitamin D; aludrox; and supplements of iron, calcium and vitamins. Although each item may have a rational indication, the total effect is to burden the child and his family with a complex ritual of administration of medicines that may result in a resistant attitude in the child which interferes with other aspects of treatment, particularly dietary control.

4. Planning for the Future

At some stage in the progress of a child with renal failure the decision must be taken whether the child is suitable for dialysis and transplantation, and if so whether facilities are available for his treatment. There is an optimum stage of the illness for such a decision to be taken—about six months before dialysis is actually required. The critical plasma creatinine concentration is about 5-8 mg/100 ml, the actual level depending upon the rate of progression of the renal disease. If the subject of transplantation is considered too early, the family may be caused unnecessarily protracted anxiety, but if too late, inadequate time may be left for full evaluation of the attitudes of the family and for negotiation with dialysis and transplant units. Many urologists and nephrologists who have responsibility for the care of children with chronic renal failure do not themselves control the admission of patients to dialysis or transplant programmes, and must be careful not to give false promises, either explicit or implicit, that treatment will be available when necessary. Close liason with dialysis and transplantation centres is essential.

V. Regular Haemodialysis

Haemodialysis and transplantation are not competitive, mutually exclusive techniques. Both have a role in the management of the uraemic child, and their proper integration is the cornerstone of successful treatment. In America the emphasis in paediatric renal replacement programmes has been towards live-donor transplantation with only short periods of preparative haemodialysis (FINE et al., 1970a; POTTER et al., 1970b), whereas European programmes have been more strongly orientated to cadaver-donor transplantation, often necessitating prolonged periods of haemodialysis in hospital (BROYER et al., 1972b) or in the home (BOULTON-JONES et al., 1971; BAILLOD et al., 1972).

1. Access to the Circulation

Standard external arteriovenous shunts (QUINTON et al., 1960) can be used in peripheral vessels in children down to 20 kg; in smaller children either special cannulae (BUSELMEIER et al., 1971) are necessary or proximal vessels must be used. Subcutaneous arteriovenous anastomoses (BRESCIA et al., 1966) have been satisfactorily established in children (LINSTEDT et al., 1971), but the necessity for repeated venepuncture hinders their acceptance by the child. The creation of a saphenous vein autograft shunt (MAY et al., 1969; D'APRUZZO et al., 1972) facilitates needling. Limb growth has not been affected by these fistulae.

2. Equipment and Dialysis Routine

Some modification of standard dialysis equipment has proved necessary for younger children. The priming volume has been reduced to less than 10 per cent of the child's blood volume, principally by attention to the size of the blood lines. The urea clearance of the dialyser should not exceed 3 ml/min/kg body weight (KJELLSTRAND et al., 1971). In hospital, the dialysis routine is often dictated by the space available in the dialysis unit, but with home dialysis greater flexibility is possible. BAILLOD et al. (1972) have preferred 6-hour periods on 5 nights each week.

3. Medical Problems

The principal medical problems are growth, sexual maturation and osteodystrophy. An early report from HUTCHINGS et al. (1966) of a pre-adolescent girl who did not grow or enter puberty on dialysis has subsequently been shown to be unduly pessimistic, as this patient was found to have XO chromosomal constitution (GRUMBACH, 1970). Normal growth rates are occasionally achieved, particularly in younger children, but catch-up growth is very rare (CAMERON, 1973). An important factor appears to be calorie deficiency due to anorexia and distaste for restricted diets (SIMMONS et al., 1971).

Recent studies (BROYER et al., 1972a) suggest that sexual maturation can proceed normally, and the onset of menstruation has been reported.

The problems of osteodystrophy are not resolved by haemodialysis (FINE et al., 1972); indeed, the incidence of bony problems increases with the duration on dialysis, and in a recent survey (MEHLS et al., 1972) one fifth of the children on dialysis had obvious skeletal deformities.

A major problem that has emerged in the treatment of chronic renal failure by haemodialysis has been the development of serum hepatitis, placing at risk not only patients but also medical personnel (ROSENHEIM, 1972). For this reason it is important to screen individuals for Australia (hepatitis-associated) antigen and antibody before admission to dialysis programmes, and to be very cautious in the use of blood and blood products in these patients.

4. Psychological Problems

The psychiatric strain on the child of extended haemodialysis is discussed by FRANCIS et al. (1970) and by RAIMBAULT (1973). It is clear that these problems loom large in all published series, and considerable attention must be given to the arrangement of psychiatric support in dialysis programmes. This is especially true of home haemodialysis in which the mother is asked to carry an almost intolerable burden of responsibility for one child, leading to feelings of guilt for neglecting the rest of the family (CAMERON, 1973).

5. Results

By short-term technical criteria, chronic haemodialysis is a reasonably successful treatment of an otherwise fatal illness in childhood, and the actuarial survival at 2 years is 88 per cent (SCHÄRER et al., 1972). There is every reason to believe that the results obtained in adults, with 81 per cent survival at 6 years (MOORHEAD et al., 1970) can be achieved in children.

VI. Transplantation

Renal homotransplantation has now been reported in some 300 children (STARZL et al., 1966; WILLIAMS et al., 1969; GONZALES et al., 1970; LA PLANTE et al., 1970; POTTER et al., 1970a; NAJARIAN et al., 1971; FINE et al., 1971; LILLY et al., 1971; HULME et al., 1972; SCHÄRER, 1972), and experience has now accumulated sufficient to draw some conclusions on the technical aspects of paediatric transplantation, even if psycho-social problems remain unresolved.

1. Recipient Selection

Most centres have restricted transplantation to children at least five years of age and with a usable bladder, though some have not been deterred by lower urinary tract abnormalities (TUNNER et al., 1971). There has been some anxiety about the transmission of recipient disease to the transplant, particularly in cases of glomerulonephritis with crescents (POTTER et al., 1970a) and focal glomerulosclerosis (HOYER et al., 1972). Children anuric after an episode of the haemolytic-uraemic syndrome have been successfully transplanted (CERILLI et al., 1972). Oxalosis has progressed after transplantation (CAMERON, 1973), but in cystinosis the transplanted kidney has not developed the Fanconi syndrome (MAHONEY et al., 1970). Several children have now been transplanted after bilateral nephrectomy for Wilms' tumour (e.g. NAJARIAN et al., 1971).

There are a number of reports of transplantation in children under the age of 5 years (e.g. MARTIN et al., 1969; NAJARIAN et al., 1971; CERILLI et al., 1972), but the suitability of such young children for renal transplantation must at the time of writing remain an open question.

2. Donor Selection

It has proved possible to transplant adult kidneys into children down to about 10 kg body weight. Live-donor transplants, especially from parents, have been commonly used, in spite of the inevitably unsatisfactory HL-A histocompatibility that this policy implies. However, the alternative policy of seeking HL-A identical cadaver kidneys necessitates much longer periods on dialysis. Identical twins and, on average, one in four siblings will have HL-A identity with the patient, but the use of live-donors under the age of 18 years raises severe ethical problems (CURRAN, 1972).

Cadaver kidneys from children have been shown to hypertrophy after transplantation (FINE et al., 1971). The attractive idea of using kidneys from stillborn or anencephalic foetuses has, with the notable exception of the case reported by MARTIN et al. (1969), not proved successful.

3. Technical Aspects

The standard extraperitoneal approach for transplantation in adults is applicable in children down to 35 kg body weight; below this weight the mid-line transperitoneal approach described by STARZL et al. (1964) has proved more satisfactory. Ureteric complications of transplantation, particularly fistulae, have been as troublesome in children as in adults (EDELBROCK et al., 1971).

4. Immunosuppression and Medical Problems

All the fearsome complications of transplantation and of immunosuppressive therapy observed in adults have been reported in children (CAMERON, 1973). In addition, the corticosteroids used may impair growth, but the relationship between growth failure and steroid dosage is irregular (NAJARIAN et al., 1971); catch-up growth is sometimes observed after transplantation, particularly in boys with bone-age less than 12 years (FINE, 1972). In general, osteodystrophy regresses after successful transplantation (FINE et al., 1972). Sexual maturation usually proceeds normally, and there are several examples of successful pregnancies in girls who had received their transplant before puberty (LILLY et al., 1971). Psychological problems remain, however, particularly with the effect of corticosteroid therapy on the facial appearance of adolescent girls.

5. Results

The 2-year graft survival for cadaver donors in children is between about 40 (BARNES et al., 1972) and 55 per cent (SCHÄRER et al., 1972) and for parent donors about 65 per cent (BARNES et al., 1972) (Table 3). These figures are as good as, if not better, than corresponding data for adult patients. They are, of course, less than patient survival; after graft failure the patient may return to dialysis and receive a second graft.

Table 3. Results of renal transplantation in children. Data from Ninth Report of the Human Renal Transplant Registry (BARNES et al., 1972). Graft survival is, of course, less than patient survival: after graft failure the patient may return to dialysis and receive a second graft

Donor	Recipient age (yrs)	Number of Transplants	One year post-transplant		Two years post-transplant	
			Patient Survival %±SE	Graft Survival %±SE	Patient Survival %±SE	Graft Survival %±SE
Parent	0–5	6	30±20	30±20	30±20	30±20
	6–10	51	78±6	70±7	75±7	70±7
	11–20	415	74±2	67±2	68±2	59±3
Cadaver	0–5	30	51±10	40±9	45±11	26±9
	6–10	40	53±8	42±8	45±9	36±8
	11–20	316	65±3	49±3	53±3	41±3

VII. Conclusions

In the absence of precise information on the long-term survival of transplanted kidneys and the severe stress imposed upon the child and his family during treatment by dialysis and transplantation, some authors have questioned the wisdom of submitting any children to these forms of treatment (RILEY, 1964; REINHARDT, 1970). It seems too early to arrive at final conclusions on this point, but it is relevant to compare dialysis and transplantation with other programmes for the treatment of fatal illness in childhood. Both the results of treatment and the quality of life are superior to those achieved in the treatment of leukaemia and other childhood malignancies. It is likely that the financial cost of the two forms of treatment is of the same order. Similarly, renal replacement programmes compare favourably with the current treatment of children with spina bifida. Thus by standards currently applied to other areas of paediatrics, dialysis and transplantation with present-day results seem an acceptable form of treatment for children with end-stage renal failure.

D. Hypertension in Childhood

T. M. Barrat

With 6 Figures

I. Introduction

Arterial hypertension is uncommon in children, but may complicate a wide variety of diseases (Loggie, 1971); in this chapter, attention will be particularly directed to those aspects which the paediatric urologist is most likely to encounter.

Taking the blood pressure is an essential part of the routine physical examination of all children, especially those with urological disorders as they have an increased risk of developing hypertension, particularly after surgery (Berens et al., 1966). It is, however, commonly omitted or incorrectly performed because an accurate recording of the blood pressure in young children demands both patience and skill. As it is one of the more difficult techniques of the physical examination, it should be performed by the doctor, and not delegated to the junior nurse.

II. The Normal Blood Pressure

Technical aspects of recording the blood pressure are reviewed by Moss and Adams (1962, 1965) and more recently by Loggie (1971). The most common error is to use too small a cuff, which leads to erroneously high estimates of the arterial blood pressure. A useful rule is that the correct cuff is the largest one that can conveniently be applied to the upper arm and that the cuff size should be recorded with the blood pressure reading. The 2.5 cm cuff is almost always too small, even in neonates, and results obtained with its use should be regarded with considerable scepticism. There are reports of inappropriate treatment of normotensive infants after such incorrect estimates of the blood pressure (Hansen and Stickler, 1966). Under one year of age the systolic blood pressure recorded with the 2.5 cm cuff is apparently 20 mm Hg higher than that with the 5 cm cuff (Long et al., 1971). In this age group, the "flush" method (Goldring and Wohlmann, 1952) should be used to confirm the auscultation estimate: by this technique the results approximate to the mean arterial pressure and are apparently less dependent on cuff size (Moss et al., 1957). An atmosphere of calm is essential, for anxiety may elevate both the systolic and diastolic blood pressure of children (Clayton and Hughes, 1952).

Standards for blood pressure in healthy children under conditions of outpatient attendance are given by Moss and Adams (1962) and by Londe (1968) (Table 4.) Even so, it is difficult to decide what constitutes the upper limit of normal blood pressure; if this is taken to be the ninety fifth percentile for age, then inevitably a few apparently normal children will be considered to be hypertensive. In a series of seventy four such children, no aetiological factor related to hypertension could

be discerned in sixty nine (LONDE et al., 1971), but it is not yet clear whether this group represents the expected statistical tail of a normal distribution or the prodrome of essential hypertension in later life.

In the neonate, YOUNG and COTTOM (1966) found the systolic blood pressure in the lower aorta to be 70 ± 8 and diastolic 44 ± 7 mmHg (±SD).

Table 4. Blood pressure standards for normal children as determined under out-patient conditions. From LONDE (1968)

AGE (yrs)	3–5	6–9	10–15
Systolic blood pressure (mmHg)			
Mean—male	89	108	118
female	100	108	118
95th percentile—male	114	125	137
female	118	127	139
Diastolic blood pressure (mmHg)			
Mean—male	58	62	66
female	59	64	67
95th percentile—male	75	76	79
female	75	79	80

III. Saline Dependent Hypertension

In advanced renal failure, hypertension is commonly associated with other features of extracellular fluid volume expansion, namely peripheral or pulmonary oedema, raised jugular venous pressure, cardiomegaly and heart failure. Significant saline overload causing hypertension, may, however be present without any of these clinical features, but recent weight gain is sometimes a useful clue. In this situation, the blood pressure can be lowered by saline removal such as may be achieved by dietary salt restriction, diuretics or dialysis (MERRILL et al., 1961), and satisfactory blood pressure control is associated with a fall in the total exchangeable sodium to normal (BLUMBERG et al., 1967). In some cases with advanced renal failure, however, the hypertension is refractory to saline depletion; these patients have higher levels of plasma renin activity (WEIDMANN et al., 1971) and may require bilateral nephrectomy for blood pressure control. The hypertension of acute nephritis may similarly be dependent on saline overload: treatment with frusemide results in reduction of the duration of the hypertension (RETAN and DILLON, 1969).

The mechanism by which saline overload causes hypertension has not been precisely established. It has been suggested that under such circumstances the arterioles are sensitised to circulating pressor substances (BRUNNER et al., 1972). LEDINGHAM (1971) has reviewed this problem and proposed that the initial result of saline overload is an increase in cardiac output, but that whole body autoregulation then restores cardiac output and tissue perfusion towards normal, leaving hypertension unaffected because of a rise in intrinsic vascular resistance. This sequence has been observed in anephric man following saline loading (COLEMAN et al., 1970).

IV. Renin-Angiotensin Hypertension

1. Renin-Angiotensin-Aldosterone System

Renin is a proteolytic enzyme elaborated by the juxtaglomerular apparatus and acts upon its substrate, an α_2-globulin synthesised in the liver, to form the decapeptide, angiotensin I, which in turn is transformed to an octapeptide, angiotensin II, by a converting enzyme in the plasma and lungs. Angiotensin II has two important biological actions: it is the most potent pressor substance known and it is also an effective stimulus of aldosterone secretion by the zona glomerulosa of the adrenal cortex. Aldosterone causes sodium retention by stimulating sodium/potassium exchange in the distal tubule. For reviews of this complicated subject and its relation to hypertension the reader should consult PEART (1965).

In the experimental animal, it has long been known that the renin-angiotensin system is implicated in the genesis of some forms of hypertension. In the classic experiments of GOLDBLATT et al. (1935), constriction with a clip on one renal artery results in hypertension which is reversible if that kidney is removed within a short period of time. If a longer period is allowed to elapse after the application of the clip the hypertension is not cured by nephrectomy, but is perpetuated by vascular changes in the contralateral kidney. It is disturbing, however, that immunisation of rabbits against angiotensin II, which blocks the action of infused angiotensin, does not protect against renal-clip hypertension (LOUIS et al., 1970), and other mechanisms may be involved.

Understanding of the clinical counterpart of the animal models had to await the development of sensitive specific assays for plasma renin activity and angiotensin II concentration (BOYD et al., 1970). It is now clear that the renin-angiotensin system is involved in a causative or perpetuating role in several varieties of human hypertension: renal ischaemia due to renal artery stenosis, many varieties of parenchymal renal disease especially when the blood pressure is resistant to saline depletion (WEIDMANN et al., 1971), rare renin secreting tumours, namely haemangiopericytoma (ROBERTSON et al., 1967), or occasional Wilms' tumours (MITCHELL et al., 1970) and some individuals with malignant hypertension. In all these situations, secondary hyperaldosteronism with hypokalaemia may develop, due to the stimulation of aldosterone secretion by angiotensin II.

2. Renovascular Hypertension

a) Pathology

Renal artery stenosis and hypertension have been reported in the neonate (ANGELLA et al., 1968; FORMBY and EMERY, 1969; LJUNGQUVIST andWALLGREN, 1962; SCHMIDT and RAMBO, 1965). It is sometimes familial (BERGSTEIN et al., 1971). There is an association between renal artery stenosis and the rubella syndrome (MENSER et al., 1966), idiopathic hypercalcaemia (WILTSE et al., 1966), Marfan's syndrome (LOUGHRIDGE, 1959) and neurofibromatosis (Fig. 6) (HALPERN and CURRARINO, 1965; BOURKE and GATENBY, 1971).

The pathological lesion may be hypoplasia, intimal hyperplasia, fibromuscular hyperplasia, arteritis or external compression. Curiously, the arterial lesion of

Fig. 6. Right renal artery stenosis demonstrated by aortography in a 5-year-old girl with neurofibromatosis and malignant hypertension. She also had an occlusion of the right internal carotid artery at its bifurcation. The hypertension was completley controlled by nephrectomy after a failed attempt at revascularisation

neurofibromatosis is not due to external compression by neurofibromata, but to degeneration. A phaeochromocytoma may compress the renal artery and lead to particularly difficult diagnostic problems (WEIDMANN et al., 1969). The disease is actually or potentially bilateral in some cases and may be associated with coarctation of the abdominal aorta (FISHER and CORCORAN, 1952; SCHMIDT and RAMBO, 1965); this association can also complicate neurofibromatosis or therapeutic irradiation of the abdomen in infancy (COLQUHOUN, 1966). There may be stenosis of a branch of the renal artery (NIALL and MURPHY, 1965; LAMBETH et al., 1960) and occasionally the renal artery is replaced by many smaller vessels (Fig. 7).

Other renovascular abnormalities that have caused hypertension in children, are aneurysm (GROSSMAN and BABBIT, 1967), arteriovenous fistula (LONG et al. 1964) and a corkscrew-like malformation of an intrarenal vessel (LEUMANN et al., 1970).

The kidney distal to an obstructive arterial lesion shows on histological examination, ischaemic tubular atrophy and juxtaglomerular hyperplasia (GOORMATIGH, 1940).

b) Functional Aspects

The ischaemic kidney secretes renin. However, not all cases of renal artery stenosis have elevated plasma renin activity (BROWN et al., 1965) or angiotensin II concentration (CATT et al., 1971); presumably self-perpetuating mechanisms of hypertension are involved analogous to those observed by GOLDBLATT et al. (1934) in experimental animals. The hypertension does not always respond to arterial reconstruction or nephrectomy: the best preoperative prediction of response is not the peripheral venous plasma renin activity, but the differential renal venous

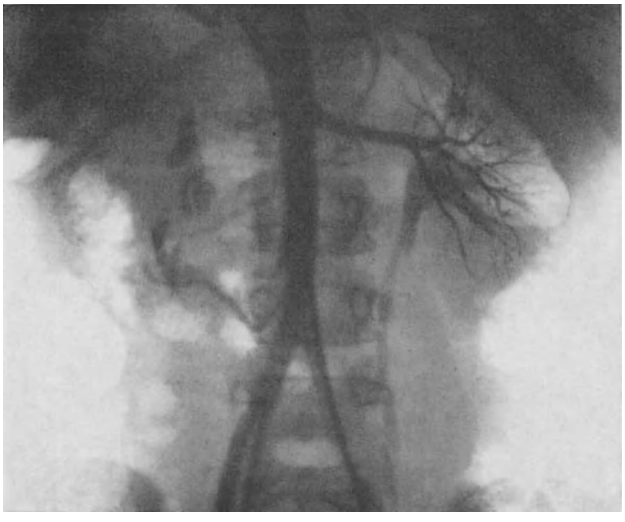

Fig. 7. Left renal arterial anomaly demonstrated by aortography in a 4-years-old girl with malignant hypertension. The left renal artery is replaced by a leash of vessels. Nephrectomy controlled the blood pressure

renin activity (MICHELAKIS et al., 1967; FOSTER et al., 1966). Individuals with high plasma renin activity usually have secondary hyperaldosteronism; in addition to hypokalaemia they are usually hyponatraemic in contrast to patients with Conn's syndrome in whom the plasma sodium concentration tends to be at the upper limit of the normal range.

On the affected side the glomerular filtration rate and renal plasma flow are reduced. There is enhanced fractional proximal tubular reabsorption of sodium and water so that, compared to the contralateral normal kidney, the urine flow rate and sodium concentration are reduced but the urea and creatinine concentration and osmolality are increased (Van GIESEN et al., 1964). This disparity is enhanced during water diuresis, and is the basis of the divided renal function tests described by STAMEY et al. (1960) and HOWARD and CONNOR (1962): the characteristic finding of renovascular hypertension is a decrease of urine flow rate of more than fifty per cent and of sodium concentration of at least twenty per cent on the affected side. The same functional disturbances account for the characteristic appearances of the ischaemic kidney on renography or intravenous urography: there is delayed uptake of the radioactive hippuran or contrast medium because of the diminished renal plasma flow, but the enhanced proximal sodium reabsorption results in increased density and duration of the nephrogram and also increased density of the pyelogram (Fig. 8).

A rare functional disturbance of renal artery stenosis is increased erythropoietin production leading to erythrocytosis (LUKE et al., 1965).

c) Investigation

The key investigations in the diagnosis of renovascular hypertension are the intravenous urogram and the renal arteriogram; all children with unexplained

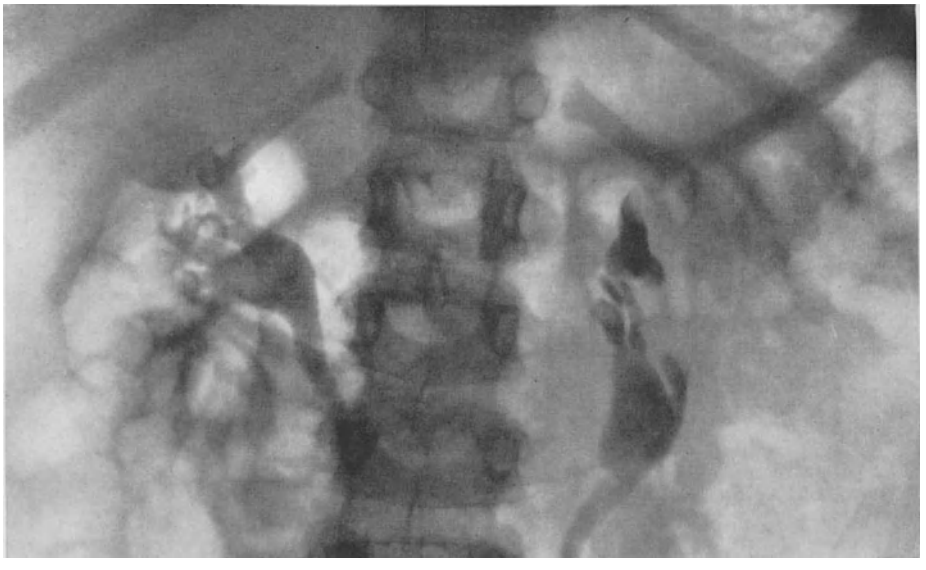

Fig. 8. Intravenous pyelogram of the girl illustrated in Fig. 7: the left kidney is smaller than the right, and the contrast medium is more concentrated

severe hypertension should be examined by both procedures. The incidence of renal arterial lesions in children is low, and there is no systematic experience of the reliability of other methods of diagnosis or assessment in this age group. To some extent, the paediatric problem is different from that of adult medicine: as all children with unexplained hypertension will have renal arteriography, the reliability of screening procedures such as isotope renography in detecting renal ischaemia is less critical. Equally, as the cure rate of the hypertension by arterial reconstruction or nephrectomy is high, the decision to operate is less influenced by preoperative predictions from differential renal function studies or renal venous renin estimations.

The intravenous urogram requires special care, and the radiologist must be consulted first. Films should be taken in rapid sequence in the first few minutes after injection of the contrast medium, as its appearance is delayed on the affected side (MAXWELL et al., 1964). The affected kidney is smaller, has a dense prolonged nephrogram and excretes more concentrated contrast medium than the normal kidney, particularly during a water load. However, the intravenous urogram may be normal in children with renovascular hypertension (LOGGIE, 1971).

Transfemoral renal arteriography in children has a low morbidity in experienced hands; PORSTMAN (1970) reported only five serious complications in two hundred and forty one arteriograms; in three there was transient deterioration of renal function and in two there was occlusion of the femoral artery. Both kidneys and the abdominal aorta must be examined: for this reason aortography is perhaps to be preferred to selective injection into the renal artery, though the latter is essential if branch stenosis is to be excluded. The hypertension should be controlled before aortography.

Differential renal function tests are difficult to perform and are prone to error, particularly in children. The results predict the response to surgery well, but probably not as well as renal venous renin determinations, and recent opinion favours the latter investigation (LOGGIE, 1971), which may conveniently be undertaken at the same time as arteriography.

d) Treatment

Conservative arterial reconstruction is the treatment of choice in children with unilateral disease, and several successes have been reported (HUNTER et al., 1965). However, the technical procedures are not simple, and it is common to have to resort to nephrectomy (CORAN and SCHUSTER, 1968). The latter authors report the cure of hypertension in eight of nine children with unilateral renal artery stenosis.

3. Predominately unilateral Renal Disease

Difficulties commonly arise in the management of hypertensive children with bilateral renal parenchymal disease when one kidney is much more severely affected than the other: the physician must decide whether nephrectomy is likely to result in relief of hypertension or merely in loss of valuable nephrons without blood pressure control. A unilateral hypoplastic, dysplastic or pyelonephritic kidney may contribute little to renal function yet be the cause of severe hypertension. Two special pathological variations deserve mention: segmental hypoplasia (ROYER et al., 1971) and the kidney following renal venous thrombosis (PERRY and TAYLOR, 1940). In segmental hypoplasia (the Ask-Upmark kidney: ASK-UPMARK et al., 1929) hypoplastic and dysplastic changes are confined to one reniculus; the rest of the kidney is normal or exhibits histologically the sequelae of hypertension. The lesion may be the consequence of an arterial occlusion early in development. Hypertension may also follow an episode of renal venous thrombosis, the kidney gradually shrinking over a period of some weeks. Children in whom renal venous thrombosis has been treated conservatively should be followed up for many years in order to have early warning of the development of high blood pressure. It is often difficult to dissect the contributions of dysplasia, pyelonephritis and renovascular accident to the genesis of a unilateral small kidney associated with hypertension.

If the contralateral kidney is apparently normal or preferably hypertrophied, and if it can be shown by blood background subtraction isotope renography that the function of the affected kidney is negligible, then clearly it is reasonable to undertake nephrectomy in the hope that the blood pressure will fall. The pessimism of SMITH (1956), who surveyed the published literature and concluded that only 26 per cent of cases treated by nephrectomy were cured, may not be applicable to the paediatric age group, where the therapeutic yield seems to be somewhat greater. His stringent criteria of a cure remain valid, particularly the requirement that the blood pressure should be normal at least one year after operation. If the disparity of function between the two kidneys is less marked, or if both kidneys show evidence of pathological change, then medical therapy is to be preferred. If medical treatment fails it may be possible to identify the site of inappropriate renin release by renal venous catheterisation and renin estimation. However, no guide lines have been established for deciding which kidneys should be removed, and if there is doubt, a conservative approach should

be adopted, for removal of functioning renal tissue without blood pressure control is unfortunate for an individual whose renal function is already compromised. Furthermore, with some pyelonephritic kidneys the hypertension occasionally subsides after some years of medical treatment.

4. Renal Tumours

Hypertension is occasionally a feature of Wilms' tumour (KOONS and RUCH, 1940; HUGHES et al., 1949) and has been reported to ameliorate following surgery only to return with recurrence of the tumour (BRADLEY and PINCOFFS, 1938). Plasma renin activity may be high (SPERGAL et al., 1969) with secondary hyperaldosteronism and hypokalaemia. In some cases this may be the result of renal ischaemia due to distortion of renal vasculature, but this mechanism does not account for the return of hypertension with metastasis, and in the case of MITCHELL et al. (1970) renin was found in the tumour but not in the surrounding normal kidney tissue. The findings suggest inappropriate renin secretion by the tumour (LEE, 1971).

Tumours of the juxtaglomerular apparatus (haemangiopericytoma) have been described (ROBERTSON et al., 1967) which secrete renin; except for the plasma renin activity, the condition mimics Conn's syndrome and may be extremely difficult to diagnose. In ROBERTSON's et al. (1967) case, for example, the tumour was only discovered on laparotomy and was not visualized by renal arteriography. The youngest case reported was aged 13 years (HODGE, 1971).

V. Corticosteroid Hypertension

1. Aldosterone

Aldosterone is synthesised in the outer zone (zona glomerulosa) of the adrenal cortex (CATHRO, 1969). Its secretion rate is controlled by corticotrophin, angiotensin II and the plasma potassium concentration. The main action of aldosterone is to enhance the sodium/potassium exchange mechanism in the distal nephron leading to sodium retention and urinary potassium loss. Primary aldosteronism, described by CONN (1955), is characterised by mild hypertension, hypokalaemic alkalosis and depressed plasma renin activity; the abnormalities are reversed by the aldosterone antagonist spironolactone. The tumours causing Conn's syndrome are small, so that preoperative and operative localisation is difficult. This syndrome is rare in childhood, but has been described in a few cases (NEW and PETERSON, 1968), and the youngest reported child was three years of age (CAVELL et al., 1964).

The classical picture of Conn's syndrome is well established, but it is not clear to what extent normokalaemic hypertension may be attributed to adrenal adenomata (CONN, 1965). Furthermore, several syndromes have been described (see LEDINGHAM, 1969, for review) which may mimic primary aldosteronism to a greater or lesser extent, and some of these occur in children. LIDDLE et al. (1964) described a family with hypokalaemic hypertension but low aldosterone secretion rates. There are two hypertensive varieties of congenital adrenal hyperplasia. 11β-hydroxylase deficiency (STEMPFEL and TOMKIN, 1966) accounts for about

ten per cent of children with congenital adrenal hyperplasia: there is virilisation with elevated 17-oxosteroid (previously called 17-ketosteroid) excretion and hypertension due to excessive desoxycorticosterone secretion. Deficiency of 17-hydroxylase has been described (BIGLIERI et al., 1966) in adolescent females with hypokalaemic hypertension and deficient secondary sexual development: in this syndrome the 17-oxosteroid excretion is low. In both varieties the cortisol deficiency, corticotrophin excess and aberrant steroid production with its attendant clinical features can be remedied by treatment with cortisol.

2. Cortisol

Glucocorticoid excess may cause hypertension, as for example, in Cushing's syndrome (RAITI et al., 1972) or during treatment with cortisone or prednisone. In younger children the clinical features are usually so dramatic that clinical diagnosis is easy; more difficult are older obese girls who may have a moderately elevated 17-oxogenic steroid excretion and in whom it is not clear whether the apparent hypertension is due to a cuff artefact. In such children the cortisol secretion rate should be measured.

VI. Catecholamine Hypertension

1. Physiology

Adrenaline (epinephrine) and noradrenaline (norepinephrine) are the principal biologically active catecholamines (CATHRO, 1969). Noradrenaline is synthesised from tyrosine by way of dihydroxyphenylalanine (DOPA) and dopamine. Methylation of noradrenaline produces adrenaline.

Adrenaline is the main hormone of the adrenal medulla, whereas noradrenaline is the catecholamine liberated by post-ganglionic sympathetic nerves and extra-adrenal chromaffin tissue. There are two types of target organ receptor for circulating catecholamines (AHLQUIST, 1967): α-receptors, blocked by phentolamine, mediate smoothe muscle constriction whereas stimulation of β-receptors, blocked by propranolol, cause smoothe muscle relaxation. Noradrenaline acts essentially on α-receptors, whereas adrenaline stimulates both α and β-receptors.

The catecholamines are metabolised by O-methylation to metadrenaline and normetadrenaline and subsequent oxidation to 3-methoxy-4-hydroxy-mandelic acid (HMMA; syn. vanillylmandelic acid, VMA). HMMA is quantitatively the most important metabolite of infused catecholamines. Occasionally dopamine is secreted by chromaffin tumours: it is metabolised to homovanillic acid (HVA).

2. Pathology

Functioning neural crest tumours in children may result in hypertension due to catecholamine production (CATHRO, 1969). The commonest is the phaeochromocytoma (STACKPOLE et al., 1963), but functioning neuroblastoma and ganglioneuroma also occur (KÄSER, 1966; VOORHESS, 1966). Phaeochromocytomata may arise at any site on the sympathetic chain, but the most common site is, of course, in the adrenal gland. Unusual sites are the renal hilum causing pressure on the renal

artery (WEIDMANN et al., 1969; SERINGE et al., 1968), the bladder, where they may obstruct the flow of urine (COGGIN et al., 1971), in the posterior mediastinum and in the region of the carotid body. Extra-adrenal tumours occur with relatively greater frequency in children than in adults (STACKPOLE et al., 1963).

Phaeochromocytomata are sometimes bilateral and sometimes familial (CONE et al., 1957). They may be associated with neurofibromatosis though, as SAXENA (1970) points out, this relationship is very uncommon in children and such cases as have been described are probably examples of SIPPLE's (1961) syndrome: multiple mucosal neuromata, medullary carcinoma of the thyroid and phaeochromocytoma (LEVY et al., 1970). They have also been described in Von Hippel-Lindau's disease (WISE and GIBSON, 1971) and seem to occur with increased frequency in association with congenital heart disease (REYNOLDS and GILCHRIST, 1966).

Most phaeochromocytomata in children are benign (STACKPOLE et al., 1963) but they may occasionally be malignant.

3. Functional Aspects and Diagnosis

Noradrenaline secreting tumours cause hypertension which in children is more commonly sustained than paroxysmal. Adrenaline secreting tumours are nearly always confined to the adrenal medulla, and have more marked metabolic effects such as weight loss, impaired carbohydrate tolerance, polyuria and constipation. The most useful biochemical screen is, the measurement of the urinary excretion of HMMA. This investigation should be undertaken in all children with malignant hypertension even if there is another apparently satisfactory explanation for the elevation of the blood pressure. Standards for the excretion of HMMA by healthy children have been presented by MCKENDRICK and EDWARDS (1965) and by HAKULINEN (1971). Methyldopa may interfere with some methods of estimation of HMMA. Techniques for the measurement of the urinary excretion of adrenaline and noradrenaline are more complex and normal data are less well established. However, estimation of individual urinary catecholamines does have some value in tumour localisation for, if adrenaline predominates, the tumour is virtually certain to be in the adrenal gland. The estimation of plasma catecholamine concentrations is even more technically demanding (CARRUTHERS et al., 1970), and great care is required to eliminate error. Venous sampling from an inferior vena caval catheter may, however, be of great assistance in localisation of the tumour (LOGGIE, 1971). Patients with malignant phaeochromocytomata and other functioning neural crest tumours also excrete dopamine and homovanillic acid, which are usually not present in excessive amounts in the urine of patients with benign phaeochromocytomata.

If hypertension is due to a phaeochromocytoma administration of an agent which blocks alpha sympathetic receptors will lower the blood pressure. Phentolamine (rogitine) is a short acting alpha-blocker; phenoxybenzamine (dibenyline) has a more sustained action. The phentolamine test should be carefully controlled and requires two people for its proper execution. An intravenous infusion is set up, and the blood pressure recorded each minute. After injection of a saline control, phentolamine is given intravenously in doses of 0.01 mg/kg body weight rising to 0.1 mg/kg body weight. In cases of phaeochromocytoma there is usually a dramatic but short lived response. Severe hypotension should be counteracted by elevation of the feet rather than by the administration of pressor agents. False positive results are common, particularly with severe renal hypertension

or in patients on hypotensive therapy, and the test has only a marginal ancillary value in establishing the diagnosis of phaeochromocytoma.

Occasionally, an intermittently functioning phaeochromocytoma may be suspected in a normotensive individual and under these circumstances a provocation test may be carried out. Three agents have been used: histamine, tyramine (ENGELMAN and SJOERDSMA, 1964) and glucagon (0.01–0.02 mg/kg body weight i. v.; LAWRENCE, 1965). Histamine is rather dangerous and glucagon seems to be the most satisfactory.

4. Location and Treatment

An abdominal tumour may sometimes be palpated, which may occasionally precipitate a hypertensive crisis. A chest X-ray is essential. Careful intravenous urography commonly reveals the site of the tumour, particularly if tomograms are taken a few minutes after injection of the contrast medium when a vascular soft tissue mass may be evident in the adrenal area displacing the kidney. The definitive radiological procedure is aortography (Fig. 9), which should only be undertaken after careful preoperative pereparation (see below) and is preferable to presacral air insufflation. Aortography is always helpful, even if the site of the

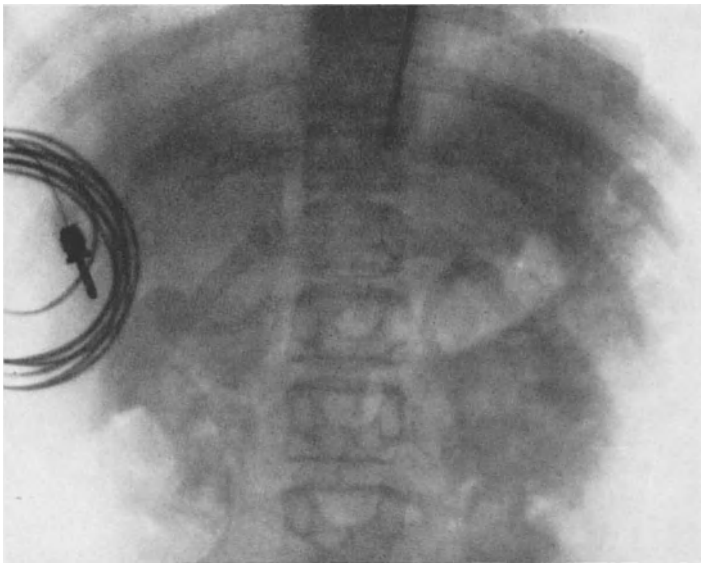

Fig. 9. A large phaeochromocytoma above the right kidney demonstrated by aortography in a girl aged 14 with malignant hypertension

tumour is obvious from the intravenous urogram, for it defines the vascular supply and permits reasonable assurance that the contralateral adrenal gland is normal. This knowledge permits the surgeon to choose a loin approach if he wishes, otherwise a less convenient transabdominal approach may be required to exclude bilateral tumour.

Safe anaesthesia and surgery demand adequate preoperative preparation of the patient. The principle is to control the hypertension by pharmacological means for sufficient time to permit circulatory readjustment (Ross et al., 1967). Sustained catecholamine overproduction results in a contraction of the plasma volume and relative polycythaemia: under these circumstances removal of the tumour will release the vasoconstriction and precipitate hypotension. Phenoxybenzamine is given for three days preoperatively; if tachycardia develops due to unopposed beta-activity, this should be controlled with propranolol (see Ross et al., 1967, for details). During surgery it is essential to monitor the patient with arterial and central venous pressure recordings. Hypertension may develop as

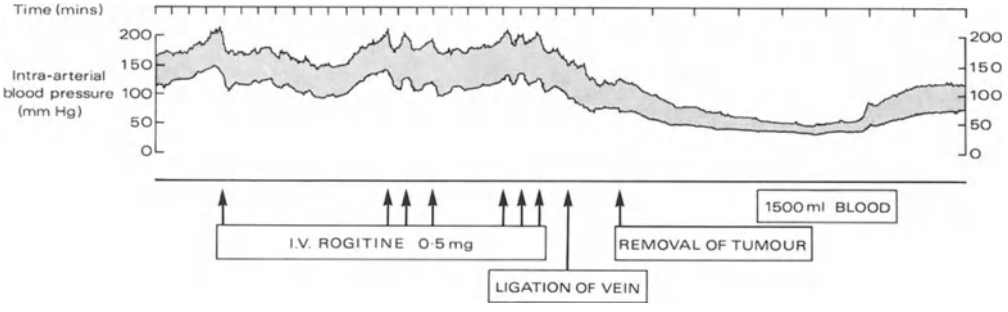

Fig. 10. The blood pressure recorded by arterial catheter during removal of the phaeochromocytoma illustrated in Fig. 9. Although she had been treated for 3 days preoperatively with phenoxybenzamine and propranalol (Ross et al., 1967), α-blockade was incomplete, and severe hypertension, poorly controlled by phentolamine, occurred, particularly when the tumour was handled. After removal of the tumour there was a dramatic fall in blood pressure which responded to blood transfusion

the tumour is handled if the patient is incompletely blocked (Fig. 10), and can be controlled with phentolamine. The hypotension which may develop after removal of the tumour should be treated by blood volume expansion rather than by pressor agents. Alpha-methyltyrosine, which inhibits catecholamine synthesis, has also been used as preoperative preparation as well as in the treatment of malignant phaeochromocytoma (Jones et al., 1968).

It is commonly difficult to decide on histological grounds whether the tumour is benign or malignant, but most phaeochromocytomata in children are benign. Long term follow-up is essential and family members should be screened for the disease.

VII. Essential Hypertension

The diagnosis of essential hypertension should not be made in children without rigorous exclusion of all aetiological possibilities (Rosenheim, 1961), but in most large series there are some hypertensive children who defy diagnosis. For example, in Loggie's (1971) series of forty children with severe hypertension, seven were of unknown cause.

In some adults with essential hypertension, plasma renin activity is low, and this low-renin essential hypertension has also been described in a child (GRUSKIN et al., 1971).

VIII. Consequences of Hypertension

1. Cardiac

Persistent hypertension results in the development of left ventricular hypertrophy, which may be evident on the electrocardiogram before it can be detected clinically or radiologically, and electrocardiographic evidence of left ventricular hypertrophy suggests that hypertension has been present for some weeks. Severe hypertension may cause left ventricular failure and pulmonary oedema, particularly if saline overload is present.

2. Neurological

Headache is common in severe hypertension. Convulsions due to hypertensive encephalopathy may occur: in these circumstances there is almost always ophthalmoscopic evidence of accelerated (malignant) hypertension, namely haemorrhages, exudates and papilloedema. A convulsion may be the first symptom of the illness, and papilloedema may lead to the referral of the patient to a neurosurgeon in the first instance. Papilloedema itself does not result in any symptoms, or at most a slight blurring of vision. It is rare for children to develop cerebral thrombosis or haemorrhage with residual neurological sequelae, but some may present with facial palsy (STILL and COTTOM, 1967).

3. Renal

Deterioration of renal function occurs in the accelerated phase of hypertension. The pathological hallmark of this condition is necrotising arteriolitis, and it is usually but not invariably accompanied by papilloedema (SEVITT et al., 1971). There may be haemotological evidence of microangiopathic haemolytic anaemia (BRAIN et al., 1962). The mechanisms which underlie the vicious circle of endstage renal failure whereby renal disease causes hypertension and hypertension aggravates the renal disease are, however, incompletely understood.

IX. Hypotensive Therapy

1. Indications for Treatment

It is not appropriate to review the pharmacology of hypotensive agents in this text (see NICKERSON, 1970), but certain practical aspects of the treatment of hypertension in children will be discussed. The first problem is to decide which child with high blood pressure should be treated. Malignant hypertension is a

medical emergency, for the necrotising arteriolitis may lead to hypertensive encephalopathy or deterioration of renal function, and the diastolic blood pressure should never be permitted to remain above 120 mmHg, particularly if there is papilloedema. Hypertension due to saline overload is also an urgent problem as left ventricular failure and pulmonary oedema may develop suddenly. It is less clear, however, whether milder degress of hypertension should be treated. Evidence from the Veterans' Administration Co-operative Study Group on Antihypertensive Agents (1970) suggests that the morbidity of adults with mild hypertension (90–114 mm Hg diastolic blood pressure) is reduced by antihypertensive therapy in comparison with placebo. In the absence of other information it seems appropriate to extrapolate these conclusions to the paediatric age group and to treat all children who have persistent elevation of a diastolic blood pressure above 90 mm Hg, particularly if there is electrocardiographic evidence of left ventricular hypertrophy, which adversely affects prognosis (PERERA, 1958). It is certainly prudent to establish control of hypertension before elective urological surgery.

Sensitivity to hypotensive drugs is subject to considerable individual variation and the dosage of each drug must be adjusted to the response of the child. Similarly the susceptibility to side effects is variable and the most suitable drug for one child may not be ideal for another.

2. Acute Hypertensive Emergencies

A combination of intravascular hydralazine and reserpine has long been popular in paediatric practice (ETTELDORF et al., 1956). These authors recommend an initial dosage of 0.07 mg/kg body weight of reserpine and 0.15 mg/kg body weight of hydralazine. Either drug may be used on its own: LOGGIE (1971) recommends a smaller initial dose of reserpine (0.02 mg/kg body weight, whereas a larger dose of hydralazine is often required. Hydralazine has a more rapid onset of action than reserpine, especially if given intravenously, and is remarkably free of side effects over short periods, though prolonged oral administration of high doses causes a syndrome resembling disseminated lupus erythematosus.

Recently diazoxide has been shown to have a very rapidly acting hypotensive effect when administered intravenously in adults (FINNERTY, 1966; MILLER et al., 1969) and children (MCLAINE and DRUMMOND, 1971) (Fig. 11). The initial dose

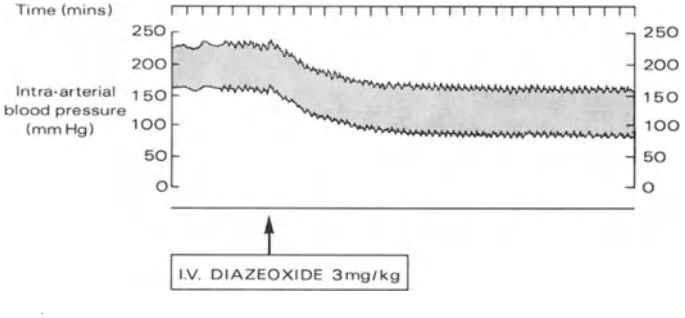

Fig. 11. The blood pressure response, recorded by arterial catheter, to intravenous diazoxide (3 mg/kg body weight) in the patient illustrated in Fig. 6. Note the very rapid control of hypertension

has generally been about 2 mg/kg body weight; up to 5 mg/kg body weight has been used. Care must be taken that the drug is not extravasated during injection, for it is very irritant.

Occasionally, severe renal hypertension unresponsive to other therapy may be ameliorated by alpha-blockade with phenoxybenzamine, and beta-blockade with propanalol is worth a trial in refractory cases provided that there is no evidence of cardiac failure.

3. Saline-Dependent Hypertension

Substantial extracellular volume expansion causing hypertension may be present without overt oedema, and it is always prudent to consider this factor first in the management of hypertension complicating renal failure. Restriction of dietary sodium to 1 mEq/kg body weight day in infants or 15 mEq/day in older children may be sufficient. Acute crises of left ventricular failure and pulmonary oedema are best managed by intravenous frusemide: 1.0 mg/kg body weight is a convenient initial dose, but the current trend is towards larger doses in refractory cases. For oral therapy of milder hypertension, a thiazide diuretic such as hydrochlorthiazide (1 mg/kg body weight day) is superior to frusemide (Anderson et al., 1971). In end stage renal failure the hypertension is sometimes only controlled by removal of salt and water by dialysis.

4. Long Term Therapy

Methyldopa is a very convenient drug (Pritchard et al., 1968). It blocks transmission at adrenergic ganglia by interference with catecholamine synthesis and conversion to the false neurotransmitter α-methyl noradrenaline (Carlsson and Lindquist, 1962). It also depresses plasma renin activity (Weidmann et al., 1971) and does mot adversely affect renal function (Mohammed et al., 1968); hence it is well suited for the management of the child with hypertension due to renal disease. For oral administration an initial dosage of 5 mg/kg body weight/day is satisfactory, and may be increased up to 25 mg/kg body weight/day, though children are apt to be lethargic at these higher dosages. Rapid intravenous administration should be avoided as it may provoke hypertension (Feldman et al., 1967). Its use is occasionally complicated by the development of an autoimmune haemolytic anaemia (Worrledge et al., 1966). The other adrenergic blocking agents—guanethidine, bethanidine and debrisoquine—cause more marked postural hypotension and side effects than methyldopa, but may be added if the control with methyldopa is inadequate. The most suitable drug and its dosage varies in different individuals.

X. Summary

Childhood hypertension is a complicated subject which the paediatric urologist may encounter only occasionally. At risk of being dogmatic, it may be helpful to summarize the preceding discussion with a few simple comments.

a) Recording the blood pressure is part of the routine examination of all children, especially those with urological disorders. Particular attention should

be paid to the blood pressure after urological surgery, as severe hypertension sometimes develops at that time.

b) The correct cuff to use is the largest one that can conveniently be applied to the upper arm.

c) Essential hypertension should not be diagnosed in children without rigorous exclusion of all other possibilities: a renal arteriogram should always be undertaken if the diagnosis is not apparent.

d) The most important investigation is the intravenous urogram, which needs to be carefully planned in conjunction with the radiologist.

e) In the absence of diuretic therapy, hypokalaemia suggests hyperaldosteronism, either primary or secondary to increased renin secretion.

f) The blood pressure of patients suspected of having a phaeochromocytoma must be controlled with phenoxybenzamine before aortography or surgery.

g) In most children with unilateral renal ischaemia, successful revascularisation or nephrectomy cures the hypertension. The relative predictive merits of renal venous renin estimations and divided renal function studies have not been established in children, but the latter are technically difficult.

h) A conservative approach to patients with asymmetrical bilateral parenchymal renal diease is indicated unless one kidney is obviously not contributing significantly to overall renal function.

i) Malignant hypertension is a medical emergency and the diastolic blood pressure should never be permitted to remain above 120 mm Hg.

j) Hypertension in the presence of renal failure should be assumed to be due to salt and water overload and initial therapy should be directed to sodium depletion by dietary restriction and diuretics.

E. Glomerular Disease and Haematuria

T. M. Barratt

With 3 Figures

I. Introduction

The glomerulus is an ultrafilter, which, in disease, may become blocked, leaky or both. It is the degree of block, i.e. reduction of glomerular filtration rate, which usually determines the outcome of the illness, but it is commonly the leak of substances normally restrained by the glomerular filter, viz. protein and erythrocytes, that first draws attention to the presence of renal disease. As haematuria may result in the child with glomerulonephritis being referred to the urologist in the first instance, the emphasis of this chapter will be on those glomerular diseases in which haematuria is the dominant clinical feature.

II. Mechanisms of Glomerular Injury

Two immunopathogenetic mechanisms of nephritis have been recognised (Unanue and Dixon, 1967; Lewis and Couser, 1971). In the first, originally described by Masugi (1934), anti-kidney antibody fixes to glomerular basement membrane, and causes renal damage by the activation of the complement system, attraction of polymorphonuclear leucocytes and localised deposition of fibrin. Antibody can be detected by immunofluorescent techniques as a smooth, linear deposit on the glomerular basement membrane, but is difficult to demonstrate in serum unless bilateral nephrectomy has been performed, for circulating antibody is rapidly fixed by the kidney. Auto-immune renal disease of this type is believed to occur in Goodpasture's (1919) syndrome, characterised by nephritis and lung haemorrhage, but is otherwise very rare, especially in children.

The second variety of immune damage results from the deposition of circulating soluble antigen-antibody complexes in the kidney. In this system, the antibody does not in general have a special affinity for renal tissue, and the kidney is involved as an "innocent bystander" of an immunological reaction. Both antigen and antibody can be detected by immunofluorescent microscopy as a coarse granular deposit, and by electron microscopy as electron-dense humps on the epithelial side of the glomerular basement membrane. In human disease the prototype is serum sickness, but soluble immune complexes are being implicated in the pathogenesis of an increasingly wide range of glomerular diseases, including post-streptococcal nephritis (Michael et al., 1966), malarial nephropathy (Allison et al., 1969), the nephritis of disseminated lupus erythematosus (Koffler et al., 1971), of congenital syphilis (McDonald et al., 1971) and subacute bacterial endocarditis. An example which the paediatric urologist may

encounter is the nephritis associated with bacterial colonisation of ventriculo-atrial shunts used in the treatment of hydrocephalus (BLACK et al., 1965). It is thought that pathogenic processes of this sort underlie much human nephritis, particularly in children; currently the major problems are the identification of the antigens involved and the relevant characteristics of the affected individual's immunological response (SOOTHILL and STEWARD, 1971).

For some human glomerular disease, however, the evidence for immunopathogenesis remains insecure. Relapse of the steroid-sensitive nephrotic syndrome, or of the recurrent haematuria syndrome are often precipitated by an upper respiratory tract infection, suggesting immunological disease, but the mechanisms involved have not been elucidated.

III. Methods of Investigation

1. Haematuria

The addition of even small amounts of blood to urine causes obvious macroscopic haematuria. In an adult, the blood flow through a single glomerulus is approximately 1 ml/day; this amount is easily detectable by the unaided eye after dilution in a representative 24-hour urine volume of 1000 ml. The use of benzidine derivatives in the detection of blood in the urine has been abandoned due to their carcinogenic properties, and the most convenient test is now HEMASTIX[1] These are strips impregnated with a buffered mixture of organic peroxide and ortho-tolidine. The peroxidase-like activity of haemoglobin, myoglobin and some of their degradation products catalyses the oxidation of ortho-tolidine to a blue derivative. The test is more sensitive to free haemoglobin and myoglobin than to intact erythrocytes; it gives an indication of the amount of haemoglobin present, but the minimum concentration of erythrocytes detectable cannot be specified because the degree of haemolysis is variable. Administration of vitamin C may result in false negative results.

The presence of haematuria should be confirmed by microscopic examination of a fresh uncentrifuged urine specimen. As well as distinguishing between haematuria and haemoglobinuria or myoglobinuria, microscopy may reveal the presence of red cell casts, which immediately points to a parenchymal source of bleeding and eliminates the necessity for urological investigations other than intravenous urography.

In the past, following the work of ADDIS (1949), considerable attention has been paid to quantitation of erythrocyte excretion rates. Normal children excrete less than 250000 red blood cells per 12 hours (EDELMANN and BARNETT, 1972). However, in children with haematuria there is such marked temporal variation in erythrocyte excretion rates that precise quantitation does not contribute much more than can be learned from the use of simpler methods such as Hemastix.

2. Proteinuria

Protein is present in normal urine; albumin constitutes about one quarter to one half of the total urinary non-dialysable solids, and excretion rates from 6 to

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31 mg/day in the healthy adult have been reported (BERGGÅRD, 1970); the distinction between normal and pathological urine in this respect is thus quantitative and not absolute. Pathological proteinuria may be due to increased glomerular permeability, ("glomerular proteinuria") or to decreased tubular reabsorption of proteins normally present in the glomerular filtrate ("tubular proteinuria") though other mechanism are possible (HARDWICKE et al., 1970).

The use of boiling or salicylsulphonic acid for the detection of proteinuria has been superceded by ALBUSTIX[2]. These are paper strips impregnated with tetrabromophenol blue buffered in citrate at pH 3.5. Protein in urine, particularly albumin, binds with the dye and causes a colour change by displacement of the transformation range of the indicator. False positive results may be obtained in urine of high pH, otherwise there is a good correlation between the Albustix reading and the urine albumin concentration (RENNIE et al., 1967). Proteinuria present during standing, but not during recumbency (orthostatic proteinuria) is in general not pathological.

Screening tests depend upon the concentration of protein in urine, and are thus affected by variation in urine flow rate. A better estimate of glomerular function may be obtained by measuring the sieving coefficient (relative concentration in glomerular filtrate and plasma water) of a molecule of a size normally just restrained by the glomerular basement membrane. For this purpose, the albumin/creatinine clearance ratio is the most suitable approximation for clinical use (BARRATT et al., 1970).

Further delineation of glomerular permeability in states of heavy proteinuria is achieved by a consideration of the relative clearances of proteins of varying molecular size ("differential protein clearances"; "selectivity of proteinuria") (HARDWICKE et al., 1970). If the clearance of a larger protein is substantially less than of a smaller one, the proteinuria is said to be highly selective. The ratio of the clearance of IgG (molecular weight 166000) to albumin (molecular weight 70000) is a convenient estimate of selectivity, and may be used to characterise the nephrotic syndrome: if less than 10 per cent, minimal histological abnormality and steroid response are almost certain, whereas if greater than 20 per cent, steroid resistance and significant histological abnormality are more probable (BARRATT and MACAULAY, 1973).

3. Complement

The complement system is a complex array of eleven plasma proteins, activated in a cascade manner by antigen-antibody reactions, amplifying the effect of the antibody. In the classic system, complement is demonstrable by its role in the lysis of erythrocytes by anti-erythrocyte antibody. The third component of complement, C3, which can be identified on electrophoresis of plasma as β_{1C}-globulin, is the component present in the greatest concentration (76–190 mg/100 ml: OGG et al., 1968), and is easily measured by immunochemical techniques. The term serum complement is sometimes loosely and incorrectly used to describe the concentration of the third component, C3.

Depression of serum total haemolytic complement has long been recognised as characteristic of acute nephritis. The C3 concentration is also reduced, and in the typical case returns to normal levels within a few weeks (WEST et al., 1964). Low C3 levels are also observed in patients with active lupus nephritis, and

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persistently low levels characterise a variety of nephritis with the histological appearance described as membrano-proliferative (WEST et al., 1965; OGG et al., 1968).

4. Renal Biopsy

a) Background

The introduction of percutaneous renal biopsy in 1951 by IVERSEN and BRUN, its widespread application in adults (KARK and MUEHRCKE, 1954) and its use in children (VERNIER et al., 1958; DODGE et al., 1962; WHITE, 1963) have led to a new understanding of paediatric renal pathology, particularly in the field of glomerulonephritis. Considerable skill, which may only be achieved by continued experience, is required both for the safe collection and reliable interpretation of renal biopsy material. For this reason, the technique should be restricted to centres which undertake at least 25 renal biopsies per year and which have the services of a pathologist with an informed interest in the histology of renal disease.

b) Equipment

Most investigators use the Silverman needle (Fig. 12). It is essential to have FRANKLIN's modification (KARK and MUEHRCKE, 1954), in which the pointed tip of each hollowed prong is filled with silver solder, obviating the need for rotation of the needle. The instrument has been further modified by WHITE (1962): a particular improvement of this model is the use of aluminium alloy to reduce the weight, and the length of the biopsy may also be adjusted. These needles have a limited life, and should be discarded after some 10–20 biopsies. Great care is required during cleaning so that the inner prongs are not distorted.

Good results have been obtained with a disposable modification, the Vim Tru-Cut[3] (KARK, 1968). Beginners find the technique easier to learn with this needle than with the standard Silverman model.

The safety of the procedure and the quality of the biopsy are much improved if the kidney is located during the procedure by fluoroscopy using an image intensifier (EDELMANN and GREIFER, 1967), and adequate tissue should be obtained by these techniques in at least 95 per cent of cases.

c) Indications and Precautions

It is not appropriate to specify precisely the indications for renal biopsy; as information accumulates on the various forms of glomerulonephritis, so the need for histological definition of the lesion in each particular child varies. At this stage a rough guide is that persistent proteinuria unresponsive to corticosteroid therapy should be investigated by renal biopsy, particularly if associated with haematuria, whereas children with intermittent proteinuria or with recurrent haematuria without proteinuria are unlikely to have severe glomerular lesions, and can usually be managed without resort to renal biopsy.

It is unwise to attempt percutaneous renal biopsy in a solitary functioning kidney, or in a child with a haemorrhagic diathesis. Hypertension should be controlled before biopsy, and the risks are increased in the uraemic state. A urogram should be obtained before the biopsy and bleeding time, clotting time

3 Travenol Laboratories

and platelet counts checked. The child's blood group should be ascertained, and blood cross matched beforehand. Informed parental consent must be obtained.

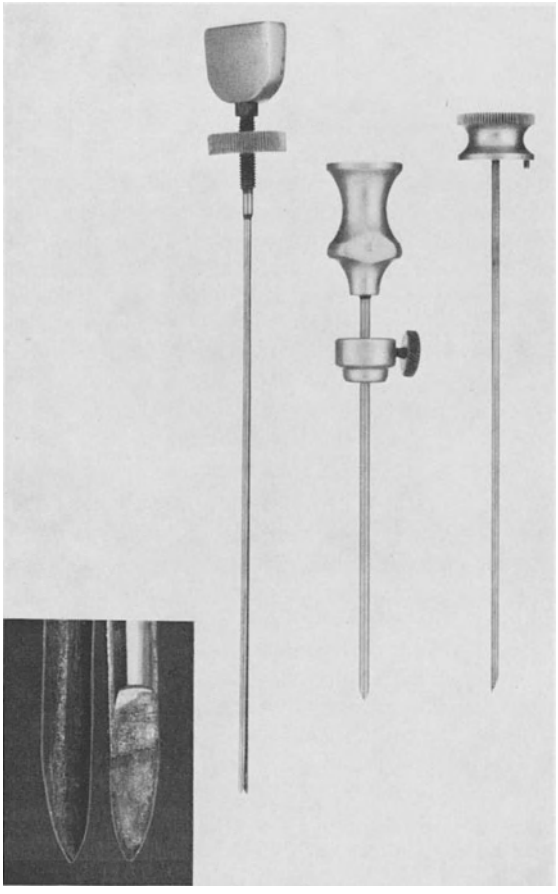


Fig. 12. The Silverman needle as modified by FRANKLIN (KARK and MUEHRCKE, 1954) and WHITE (1962). Insert shows FRANKLIN's contribution: the in-filling of the hollow ends of the prongs so that they occlude and cut the biopsy when covered by the outer needle

d) Technique

Local anaesthesia with sedation is satisfactory in most cases, although in younger or particularly apprehensive children general anaesthesia may be preferable. The child lies prone on an X-ray table with a radiolucent cushion under the abdomen. An intravenous injection of contrast medium is given, and the kidneys located on the television screen during the nephrographic phase 2–3 minutes later. The biopsy site is selected in the lower pole about 1 cm from the margin of the kidney. A small skin incision is made and the biopsy needle with stilette in situ is inserted (Fig. 13a). It is safer if the child does not breathe whilst the needle is advanced into the kidney. The tip of the needle should just penetrate

the renal capsule—this can be felt more easily with the standard Silverman needle than with the sharper disposable model—and its position is then checked fluoroscopically (Fig. 14). If the needle is in the kidney, its tip will move exactly

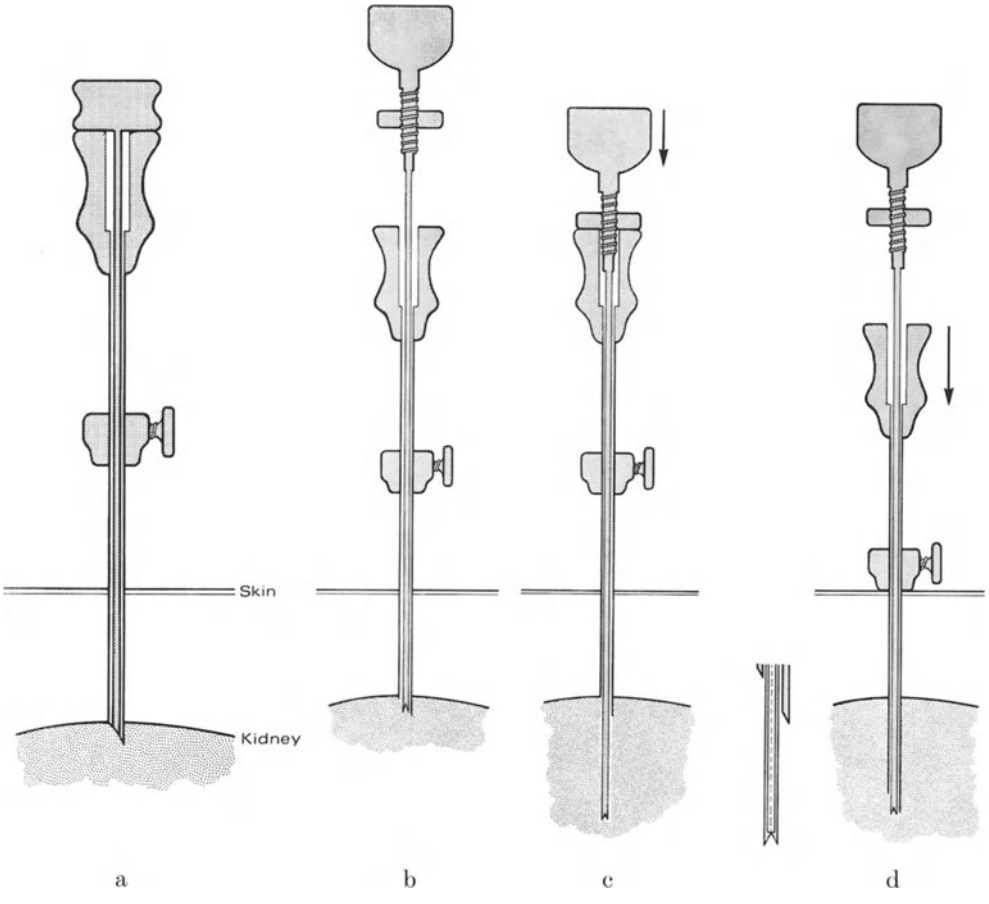


Fig. 13a—d. Stages in renal biopsy. a The needle with the stilette in situ is inserted just through the renal capsule. b The stilette is removed and the prongs inserted. c The prongs are advanced into the renal tissue. d With the prongs fixed, the outer needle is advanced to cover the tips of the prongs and cut the biopsy

synchronously with the renal shadow during respiratory excursions. The stilette is then removed and the prongs inserted until the resistance of the renal tissue is felt (Fig. 13b). The prongs are advanced into the kidney (Fig. 13c) and their top is then held still whilst the outer needle is advanced downwards to cover the prongs and cut the biopsy tissue (Fig. 13d). An adjustable skin stop guides the depth to which the outer needle should be inserted. This manoeuvre is the most difficult of the whole procedure: a common error is to withdraw the prongs rather than advancing the outer needle, or to fail to cover the prongs with the

outer needle before withdrawal from the kidney. This results in traumatising the biopsy specimen and tearing the kidney with an increased risk of haemorrhage.

Only one kidney should be biopsied and not more than four attempts at biopsy of that kidney should be permitted at one session.

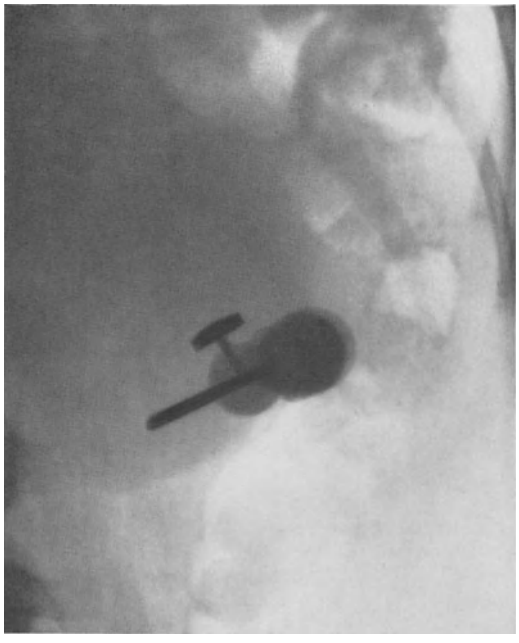


Fig. 14. It is safest and easiest to perform the biopsy during the nephrogram phase of excretion urography with a television monitor. After Fig. 13a the position of the needle is checked radiologically

e) Post-Operative Care and Complications

After biopsy the child should remain in bed for 24 hours. The pulse and blood pressure should be observed regularly and a high fluid intake maintained.

The most common complication is haemorrhage, either retroperitoneal or into the urinary tract, where it may cause clot colic. In experienced centres the incidence of haemorrhage requiring transfusion is low, somewhat less than one per cent (EDELMANN and GREIFER, 1967). Occasional cases of infarction of the kidney have been described, necessitating nephrectomy (MUECKE and MARSHALL, 1969), and in KARK's (1968) survey the mortality was 0.07 per cent. Intrarenal arteriovenous fistulae have been reported following needle biopsy (DE BEUKELAER et al., 1971), and may sometimes be suspected by the detection of a bruit over the affected kidney. In some instances these fistulae have regressed spontaneously, and they should therefore be managed conservatively.

There is no doubt that the incidence of complications is less in experienced hands.

f) Specimen Handling

It is an advantage to have a dissecting microscope available in the biopsy room so that the presence of glomeruli may be immediately ascertained. The biopsy specimen requires special handling and the pathologist should always be consulted beforehand. For light microscopy the tissue should immediately be placed in special fixatives. The sections should be cut 2 μ thick or less and several histological stains are required. The presence of immunoglobulin, complement or fibrinogen in glomeruli may be demonstrated by immunofluorescence using fluorescin conjugated antisera. For this purpose, snap-frozen biopsy material is required. Further diagnostic information may be obtained by electron microscopy, or by light-microscopic examination of ultra-thin sections of tissue embedded in epoxy resin as for electron microscopy (EASTHAM and ESSEX, 1969). The range of techniques required for the complete examination of renal biopsy specimens is thus wide, and it is doubtful if renal biopsy should be performed in centres without access to these methods.

g) Normal Appearances and Terminology

In the normal glomerulus the afferent arteriole feeds the glomerular capillary tuft, which invaginates Bowman's capsule. The capillaries are lined by endothelial cells mounted on a basement membrane; epithelial cells with spreading foot processes are to be found on the capsular side. The capillary tuft is supported by a mesangium; mesangial cells appear morphologically similar to endothelial cells but do not come into contact with the capillary lumen. In young children epithelial cells are more prominent than in the mature glomerulus. The term proliferation is applied to states in which there is an increase in the cellular content of the glomerulus, and is qualified by the predominant cell involved, e.g. mesangial or endothelial. These changes may be diffuse, affecting all glomeruli, or focal, leaving some glomeruli intact. The term membranous glomerulonephritis is used for those conditions in which there is thickening of the glomerular basement membrane. The histological classification in current use is reviewed by WHITE (1971).

IV. Syndromes of Glomerulonephritis

1. The Acute Nephritic Syndrome

The acute nephritic syndrome consists of the sudden onset of haematuria, proteinuria, oliguria, oedema, hypertension and uraemia, though not all these features need be present. Indeed, percutaneous renal biopsy in family contacts of patients with acute nephritis may reveal histological evidence of the disease without any of these clinical features (DODGE et al., 1968). The disease is commonly preceded ten days earlier by an upper respiratory infection with a beta-haemolytic streptococcus of Lancefield group A and Griffiths type 12; occasionally other varieties of streptococci or sites of infection are involved.

In the acute phase, severe illness may be complicated by hypertensive encephalopathy, heart failure or acute renal failure. Confirmation of the diagnosis may be found in the elevation of serum antistreptolysin-"0" titre, and depression of total haemolytic complement and C3. A renal biopsy is rarely necessary to establish the diagnosis but will reveal a diffuse exudative (infiltration with poly-

morphonuclear leucocytes) and proliferative lesion. Later biopsies in the healing stage show mesangial proliferation alone (EARLE and JENNINGS, 1959).

In prospective studies of proven cases of post-streptococcal glomerulonephritis who do not die in the acute stage, complete recovery is the rule (DODGE et al., 1972), though episodic haematuria may persist for some months. Evolution into chronic glomerulonephritis seems to be more characteristic of those cases of the acute nephritic syndrome in whom streptococcal involvement is not apparent: for example patients with membrano-proliferative glomerulonephritis may have an acute nephritic episode early in the course of their illness.

2. The Nephrotic Syndrome

The state of heavy proteinuria, hypoproteinaemia and oedema, from any cause, is termed the nephrotic syndrome (BARRATT and MACAULAY, 1973). Depletion of plasma albumin results in a reduction of plasma colloid osmotic pressure, seepage of fluid into the interstitial space with resultant hypovolaemia, which activates mechanisms of renal conservation of sodium, aggravating oedema, but may also result in circulatory collapse (EGAN et al., 1967) and thromboses of major vessels (LIEBERMAN et al., 1968) including the renal vein.

Two major varieties of the nephrotic syndrome can be discerned in children. In the first, more common in boys than girls, and in younger than older children there is highly selective (see p. 52) proteinuria, sensitive to corticosteroid therapy and no histological abnormality of the glomeruli apparent on light microscopy. This pattern accounts for 80–90 per cent of nephrotic children in temperate climates, and has been variously called idiopathic nephrotic syndrome, lipoid nephrosis, "minimal change" nephrotic syndrome or steroid-sensitive nephrotic syndrome. The last term is the most useful, for it makes no assumption about histology or pathogenesis; steroid-responsiveness and "minimal change" correlate so well that routine renal biopsy is not necessary in this group. Of the steroid-responders, one third never relapse, one third relapse occasionally and one third relapse frequently and develop steroid toxicity.

A much more sustained remission can be obtained in these patients with cyclophosphamide than with steroids (BARRATT and SOOTHILL, 1970) but toxicity problems have not been resolved: chemical cystitis with haematuria due to mucosal telangectasia and bladder fibrosis have been reported (JOHNSON and MEADOWS, 1971), with the possibility of neoplasia (WORTH, 1971), but perhaps the most worrying is the testicular atrophy and azöospermia reported in some adult patients who have received the drug (FAIRLEY et al., 1972). Most patients in this category eventually stop relapsing, and progression to chronic renal failure is uncommon.

In other patients, less selective proteinuria is associated with corticosteroid resistance. There is often a prior history of the acute nephritic syndrome, and there may be haematuria, hypertension, uraemia or hypocomplementaemia: any of these features suggest that it would be prudent to determine the histological appearances by biopsy before embarking on corticosteroid therapy. The steroid-resistant group is heterogeneous, and is most conveniently classified by histology (CHURG et al., 1970). There are to be found "minimal change" lesions apparently identical to those of the steroid-sensitive group; focal glomerulosclerosis, often first evident in juxta-medullary glomeruli and sometimes missed on early, superficial biopsies; mesangial proliferative glomerulonephritis, with appearances similar to healing post-streptococcal glomerulonephritis; membranoproliferative

glomerulonephritis, many of which have persistent hypocomplementaemia (West et al., 1965); advanced chronic glomerulonephritis; and, uncommon in children, membranous glomerulopathy. Steroid resistant minimal change nephrotic syndrome appears to respond to cyclophosphamide; in other histological groups this drug has not proved effective (Barratt, 1972), nor has azathioprine (Abramowicz et al., 1970). However, the nephrotic syndrome associated with mesangial proliferative glomerulonephritis and with Henoch-Schönlein disease (Meadow et al., 1972) may slowly improve independentally of therapy.

3. Persistent Proteinuria

The development of the nephrotic syndrome implies that the protein loss exceeds the body's capacity for synthesis. In some children with glomerulonephritis, however, the loss of protein is insufficient to cause the nephrotic syndrome, but it is perhaps artificial to make a distinction on these grounds alone. Proteinuria may be found on routine examination of an asymptomatic child. Provided orthostatic proteinuria can be excluded, persistent proteinuria is always abnormal, and should be investigated by renal biopsy, even if asymptomatic, for it is now possible to give a reasonably precise prognosis from the histological appearances (Cameron, 1973).

4. Recurrent Haematuria

One of the most frustrating varieties of glomerular disease in children is the syndrome of recurrent haematuria (Ayoub and Vernier, 1965), sometimes misleadingly referred to as focal glomerulonephritis. In this syndrome, episodes of haematuria are often precipitated by upper respiratory infection (without the 10 day delay characteristic of acute nephritis) or exercise, and may recur over many years. Haematuria may be brisk, and during attacks abdominal pain is sometimes also present. Males are more commonly affected, and onset under the age of one year is distinctly uncommon. Renal function is not impaired and there is no proteinuria between attacks—indeed proteinuria is the most useful clue to the presence of more serious varieties of glomerulonephritis that need to be defined by renal biopsy. The disease subsides after some years and does not in general progress to chronic renal failure.

On histological examination many such patients have focal glomerulonephritis (Heptinstall and Joekes, 1959); the term implies that the damage is restricted to a few glomeruli. However, in children in about half the cases it is not possible to detect any histological abnormality by light microscopy (Glasgow et al., 1970). Iron stains may, however, demonstrate haemosiderin in the tubules, indicating a glomerular origin of the haematuria. Immunofluorescent studies have demonstrated the depostion of IgA and C3 in the mesangial cells in many of these patients (Berger et al., 1971; McEnery et al., 1971).

Urological disease, particularly tumour, stone and hydronephrosis must of course be excluded before the diagnosis of benign recurrent haematuria can be entertained. Urinary tract infection may present with haematuria. In the subsiding plases of acute nephritis and also of Henoch-Schönlein purpura there may be episodic haematuria. The Henoch-Schönlein syndrome is characterised by colicky abdominal pain with melaena, arthropathy, a purpuric skin rash and nephritis. The histological appearances do have some similarities to those of "focal glomerulone-

phritis": glomeruli are often unequally affected (MEADOW et al., 1972) and there are usually mesangial depos ts of IgA and C3 (LEVY, 1972). A further differential diagnosis of recurrent haematuria to consider is familial nephritis (MCCONVILLE et al., 1966). In the classic variety described by ALPORT (1927), males are most severely affected, and there is associated deafness and sometimes also ocular abnormalities. Another medical cause of recurrent haematuria is sickle-cell disease.

All children with recurrent haematuria should be examined by careful excretion urography, which should perhaps be repeated after two years if the haematuria persists. The diagnostic yield from cystoscopy in children with a normal urogram is very low; we do not routinely undertake this investigation unless the haematuria is particularly troublesome or there are other features pointing to lower urinary tract disease. Similarly, we do not routinely investigate by renal biopsy children with recurrent haematuria without proteinuria, for it is rare to find serious glomerular pathology in this group.

5. Acute and Chronic Renal Failure

These complications of glomerulonephritis are discussed in Chapter B and C.

V. Conclusion

Presented with a child with haematuria, the urologist should search for evidence of glomerular disease. This may be found in the history, on physical examination or, on simple investigation (particularly examination of the urine for protein or casts). The child with recurrent haematuria without proteinuria and with normal excretion urography is unlikely to have a serious parenchymal or urological disorder. The finding of normal renal histology on light microscopy does not exclude a glomerular cause of haematuria.

F. Renal Anomalies

D. Innes Williams

With 18 Figures

I. Introduction

The renal parenchymal anomalies, hypoplasia, dysplasia and cystic disease, present in a bewildering variety of forms either alone or as part of multiple congenital anomaly syndromes. Clearly these changes can occur in response to a number of factors, either genetic or environmental. Many of the conditions are well recognised to be inherited, but it has been shown experimentally that ureteric obstruction can produce cystic dysplasia (Bernstein, 1968). Cystic disease has been induced in new born rabbits by diphenylamine derivatives (Crocker et al., 1972), by nordihydroguaiaretic acid, an antioxidant used in edible oils (Goodman et al., 1970) and by Prednisolone (Percy et al., 1967). Multicystic kidney has been found in association with congenital cytomegalovirus infection (Plotkin and Pasquariello, 1969). As might be expected with so many possible influences involved, the pathological distinction between one form of cystic disease and another, or between cystic disease and dysplasia, is often blurred. The classical contributions of Osathanondh and Potter (1964) are the most important recent attempt to establish a reliable pathological classification and are indispensible to a serious study of the pathogenesis, but the clinico-pathological disease patterns are more important to the urologist and it is with these that this chapter is concerned.

II. Absent Kidney

Bilateral renal agenesis is a rare but well recognised condition, usually associated with a minute or absent urinary tract and often with the typical facies described by Potter. It is, of course, incompatible with prolonged survival, but death in these cases is usually due to pulmonary hypoplasia. Absence of a foetal urine flow results in oligohydramnios: the chest is compressed by the uterus and the lungs have no opportunity to expand. The same complications and the same facies can be observed in association with complete urethral obstruction and with bilateral multicystic kidneys.

Unilateral agenesis is associated with an absent or short ureter and is seldom clinically distinguished from a very small dysplastic kidney. This type of disease is ordinarily accompanied by contralateral enlargement: the investigations of Seipelt et al. (1970) suggest that this is due to hypertrophy of nephrons rather than a large nephron population. On many occasions there are also anomalies of the solitary kidney and its ureteric drainage, particularly when the kidney is ectopic.

III. The Small Kidney

The normal size for a child's kidneys have been set out by HODSON, and variations, either unilateral or bilateral, are of importance. There are, however, a great many causes for diminution in the size of a kidney and precise diagnosis is difficult. Even the distinction between a congenital and an acquired disease is often obscure. Anomalies of development are frequently complicated by infection or ischaemia, while the onset of a serious acquired disease may be insidious or pass unnoticed in an illness affecting other systems. However, the final function of the small kidney and its role in hypertension or urinary infection are of more importance to the clinician than its pathogenesis. In the investigation of these cases the differential renal studies are most valuable, but often difficult to obtain. Ureteric catheter collections are unsatisfactory in childhood and seldom employed in the very young; they may give localisation of infection, but are unlikely to provide useful renal function studies. At times upper tract drainage procedures employed for suspected obstruction, such as nephrostomy or ureterostomy, may permit accurate investigations. ERICSSON (1970) has employed the method of occluding one ureter by an externally applied pressure on one side of the abdomen and estimating inulin clearance by collecting the urine which can only reach the bladder from the opposite kidney. The process is later repeated for the other side. There are obvious sources of error in such collections, but good correlation with other methods of study is claimed. Isotope renograms might be expected to provide a useful assessment of the differential contribution of the kidneys, but in many cases the data are insufficiently precise and a certain amount of guesswork is necessary. Gamma camera renograms may give more accurate information in the future. In practice, therefore, the differential function of the kidneys must often be guessed from a combination of factors, including the radiologically observed size and concentrating ability. In our clinic it is accepted that a pathological kidney which contributes less than 10 per cent of total renal function is better removed, and clearly any very small kidney associated with hypertension should be excised. In other unilateral cases, and in all bilateral cases, the choice usually lies between medical treatment alone and the addition of some conservative surgical procedure, such as reflux prevention in the pyelonephritic group.

1. Unilateral Hypoplasia

The term "hypoplasia" implies that the kidney is congenitally small, but otherwise not abnormal. In the unilateral case the opposite kidney is hypertrophied and the hypoplastic one retains a normal histological architecture. Radiologically this "miniature" kidney has a normal, though small, pelvi-calicine pattern and a normal ureter (Fig. 15). It is difficult to distinguish from the small kidney associated with arterial stenosis, but in the absence of hypertension no further investigation or treatment is required.

2. Bilateral Oligomeganephronic Hypoplasia

In bilateral disease there is an overall shortage of nephrons and the few present undergo great hypertrophy. Microdisection studies by FETTERMAN and HABIB (1969) demonstrate that there is a disproportionate enlargement of the proximal

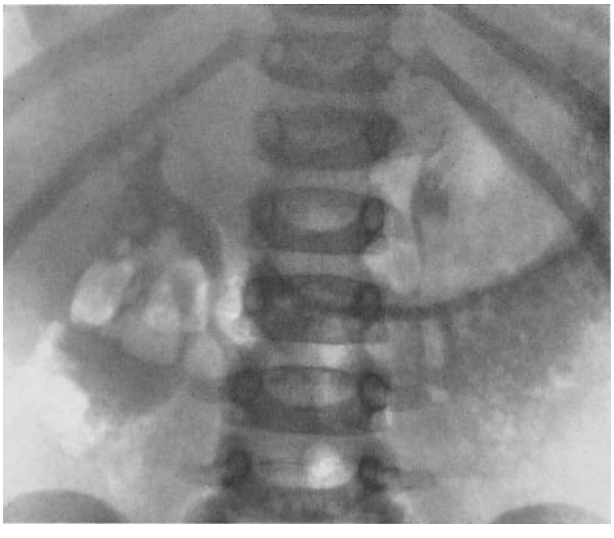


Fig. 15. Renal hypoplasia; miniature kidney. Intravenous urogram in a boy of 2 years with sterile urine and normal blood pressure. The left kidney is very small but the calices are well formed

tubules relative to the glomeruli. The clinical syndrome associated with this anomaly is now well recognised: it has been reviewed with full bibliography by SCHEINMAN and ABELSON (1970) and by CARTER and LIRENMAN (1970). It is a nonfamilial condition presenting early in childhood with vomiting and dehydration, polyuria, hyposthenuria, salt wasting, mild proteinuria and uraemia. Radiologically the kidneys are small (Fig. 16) but normal in shape; concentration in the pyelogram is poor, but the urinary tract is normal. With correction of the electrolyte balance the condition may be stabilised with only a moderately elevated blood urea. Many features of this syndrome are similar to those of nephronophthisis, but the oligomeganephronic hypoplasia is not familial, it is evident from very early infancy and is not necessarily progressive.

3. Segmental Hypoplasia

The localised contraction of a segment of a kidney, particularly when associated with hypertension, is often described as segmental hypoplasia or the Ask-Upmark kidney. It seems likely, however, that this contraction is due to an arterial anomaly and not to hypoplasia in the sense used in relation to the two previous conditions (REUTERSKIOLD and WILBRAND, 1972).

4. Dysplasia

Dysplasia is a histological term implying that the kidney contains primitive renal elements and tissues normally foreign to the kidney. The precise microscopic features accepted as dysplastic are a matter of dispute amongst pathologists. There is, however, general agreement that the presence of cartilage or of primitive

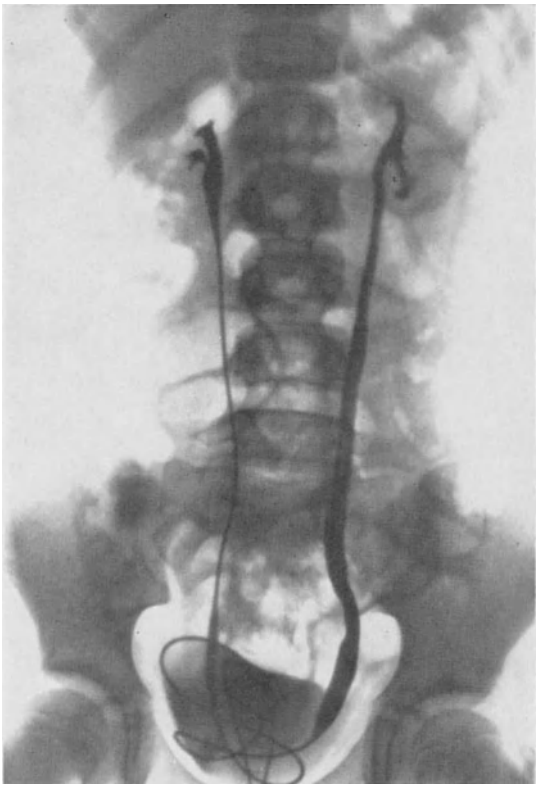


Fig. 16. Bilateral hypoplasia: retrograde pyelogram in a child of 5 years with hypertension and raised blood urea

straight tubules surrounded by cuboidal epithelium and extending far out into the cortex are indisputable evidence of the disorder. Cysts are frequently present, but may vary in size from the microscopic to the enormous, and the disorder described later in this chapter as multicystic kidney is an extreme example of renal dysplasia. The subject has recently been reviewed by RISDON (1971), who finds that almost all the cases in his series were associated with an abnormality of the urinary tract. Other writers, such as ERICSSON and IVEMARK (1958), have suggested that dysplastic tissue can occur in otherwise normal kidneys and render them liable to infection, but our experience would not support this hypothesis. Renal dysplasia occurs in three clear-cut conditions:

a) Dysplasia Associated with an Atretic Impermeable Ureter

In these cases the kidney may be enlarged and multicystic or minute and mainly fibrous. In either variety, infection of the dysplastic kidney is uncommon but contralateral urinary tract anomalies are often encountered and can be productive of serious disease.

b) Dysplasia with Patent Ureter

The ureter is patent but anomalous: it may be ectopic, obstructed or refluxing. In the case of the ectopic ureter, the upper pole of the kidney drained by that ureter is often involved in dysplasia, whereas the lower pole is normal. Diagnosis of these cases is largely concerned with the ureteric anomaly and heminephrectomy is the usual operative procedure, so that the histological abnormality is of no great importance. Where a single ureter is present the whole kidney is dysplastic and usually contracted (Fig. 17). The renal pelvis is often large and atonic with

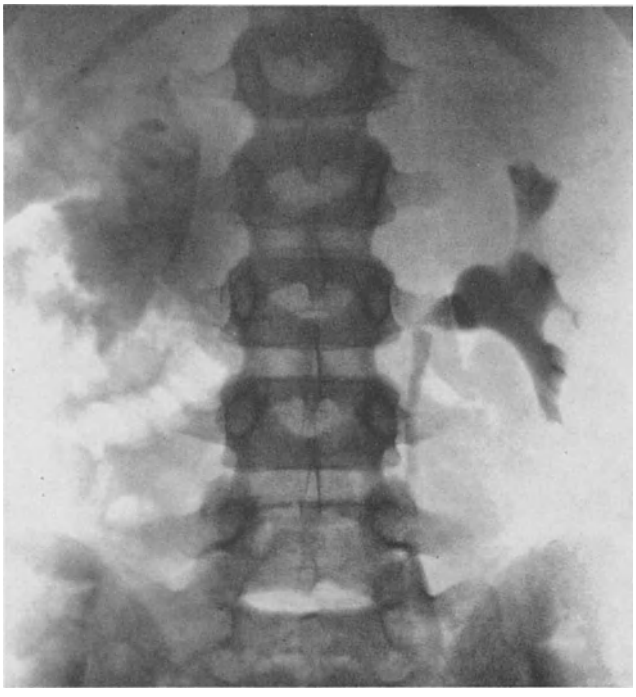


Fig. 17. Unilateral dysplasia with normal ureter. Intravenous urogram in a child of 8 years with severe hypertension from which she ultimately died. The right kidney is minute with clubbed and irregular calices. There has been some pyelonephritic complication of her original dysplasia

a kinked pelvi-ureteric junction, but seldom a well defined obstruction as in classical hydronephrosis. A characteristic radiological appearance (Figs. 18–19) is a small kidney with a cluster of closely packed clubbed calices lying above a vertically disposed dilated renal pelvis. This type of dysplasia is frequently complicated by reflux, infection and pyelonephritis. Hypertension may occur, but whether it is due to the congenital or acquired factor is not clear. In bilateral disease there is a problem of renal failure, often with salt wasting. The treatment demands careful biochemical control, but seldom any surgery in infancy. Later in childhood recurrent infection may require operation for reflux prevention, and pyeloplasty may be considered if there is a suggestion of pelvi-ureteric ob-

struction. In general, however, these cases must be treated conservatively and may ultimately come to renal transplantation.

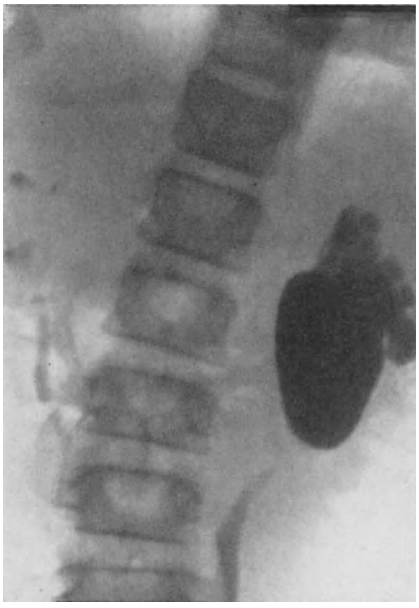


Fig. 18

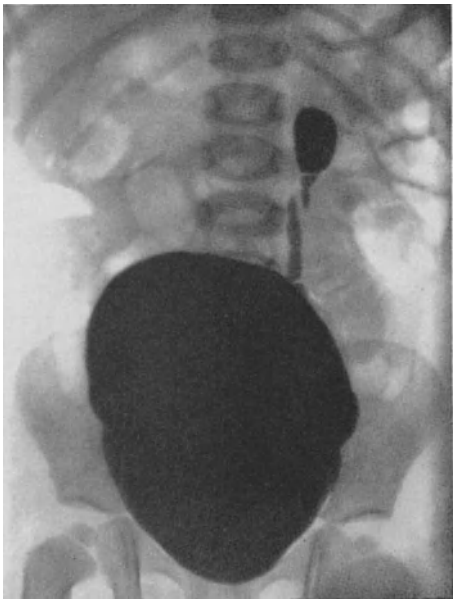


Fig. 19

Fig. 18. Dysplasia of the left kidney with complicating pyelonephritis and pyelonephritic scarring of the right kidney. Micturating cystogram in a boy of 9 years whose original investigations had been undertaken in early infancy. The right kidney, which had been normal, exhibits pyelonephritic scarring. The left kidney shows dysplastic changes with dilated vertically disposed renal pelvis and clubbed calices

Fig. 19. Dysplasia of the left kidney. Cystogram in a 3 year old child showing reflux into a functionless left kidney, represented only by a cap of fibrocystic tissue surmounting a slightly dilated renal pelvis

c) Dysplasia with Urethral Obstruction

In neonates with urethral valves or with other severe congenital urethral obstruction, cystic dysplasia of the kidney is present (Fig. 20). Cortical cysts predominate. The presence of cystic dysplasia has clearly a bad influence on prognosis, but the treatment of the child is essentially the treatment of obstruction and of the biochemical disorder.

Cystic dysplasia may thus be seen in a variety of urinary tract anomalies. It is, in general, not familial and not associated with any abnormality of liver function. Experimental work by BERNSTEIN (1968) suggests that the ureteric disorder is primary and the parenchymal one secondary, but inter-relationships between the two are likely to be complex. It must be emphasised that dysplasia is a histological diagnosis: it may be suspected from the clinical features and the radiological appearances, but many anomalous kidneys present a gross "dys-

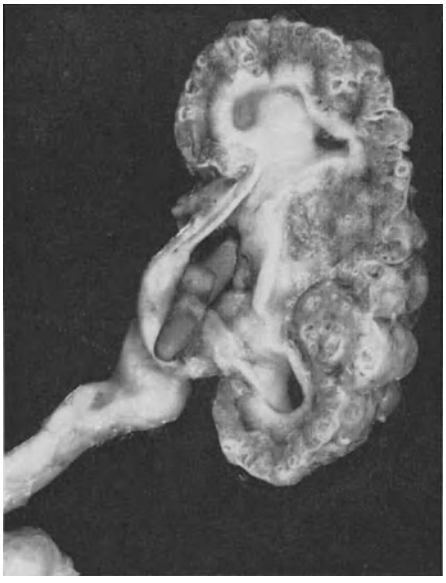


Fig. 20. Dysplastic kidney with urethral obstruction. Post mortem specimen in a child dying from urethral valves showing multiple cysts in the renal substance. (A nephrostomy tube is present in the renal pelvis)

morphism" associated, perhaps, with defects of function without possessing histologically dysplastic elements.

The term dysplasia has also been applied to another distinct condition, nodular dysgenesis, in which there is a focal hyperplasia of tubules in the medullary zone. It has been suggested that these represent the precursors of polycystic disease (MIRANDA et al., 1971).

5. Renal Vein Thrombosis

Renal vein thrombosis occurring in the neonatal period may be severe and fatal, but mild unilateral examples are often followed by recovery (BECK and MARSHALL, 1968). The affected kidney contracts, sometimes to a minute and functionless remnant densely adherent to surrounding tissue, or sometimes to a small functioning kidney similar to the unilateral hypoplasia with well formed calices and a normal ureter (Fig. 21). Such a kidney may be responsible for hypertension, however.

6. Renal Artery Stenosis

Renal artery stenosis can be responsible for some diminution in the size of the kidney (Fig. 22). Where one side only is affected the difference is usually easily measurable and other radiological features assist in the diagnosis. There is a later appearance of the pyelographic shadow, but ultimately a denser medium in the pelvis. In childhood the commonest causes of fibro-muscular hyperplasia and the angiographic findings in the various types have been described by KINCAID (1966). Hypertension is common and is the feature which leads to investigation. Nephrectomy or arterial reconstruction is required.

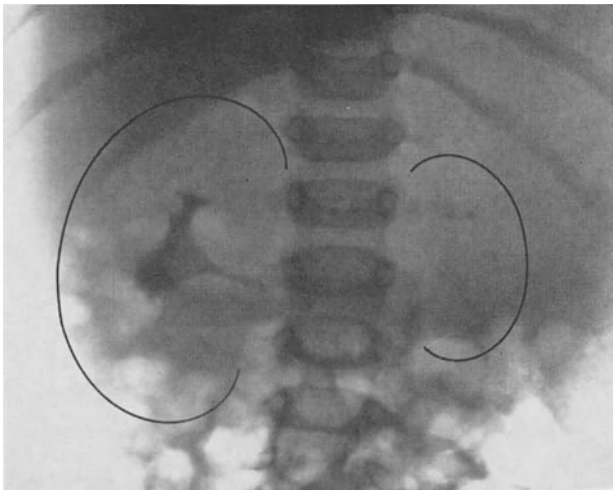


Fig. 21. Contracted kidney following renal vein thrombosis. Intravenous urogram in a boy of 1 year who had a well documented left renal venous thrombosis in the first month of life. The left kidney is very small but functions sufficiently well to produce a pyelogram

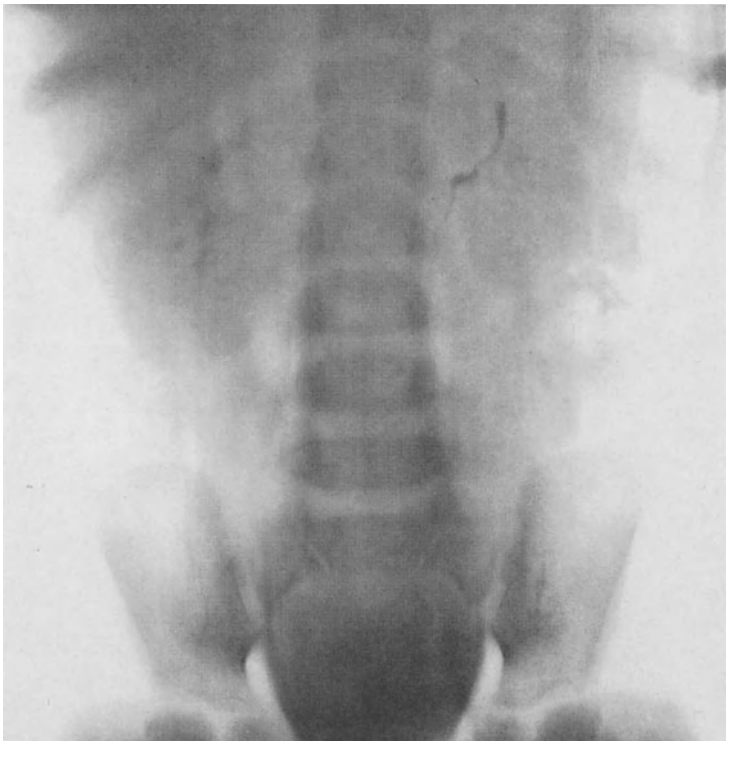


Fig. 22. Renal artery stenosis. Intravenous urograms in a child with severe hypertension. The left kidney is smaller than the right but otherwise normal. Renal artery stenosis was found and the blood pressure returned to normal after nephrectomy

7. Medullary Necrosis

Medullary necrosis occurring in infancy may leave a kidney whose growth is impaired and has clubbed irregular calices with atrophy of the papillae. Medullary necrosis in the acute form is described by CHRISPIN (1972), occurring with acute episodes of gastroenteritis, septicaemia or exsanguination, and in the early phases is characterised by heavy opacification of the medullary zone during intravenous pyelography. The later appearances are not entirely characteristic and closely resemble pyelonephritis (Fig. 23).

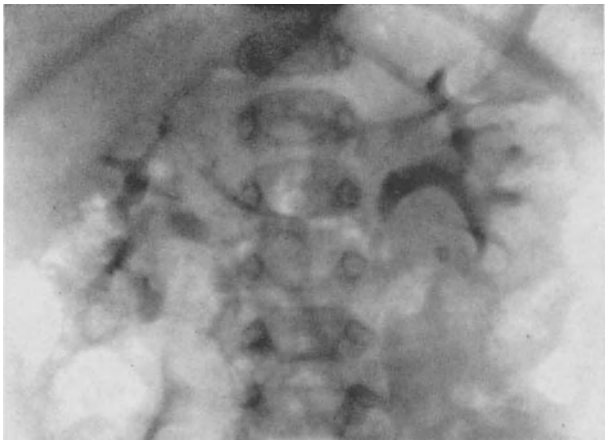


Fig. 23. Medullary necrosis. Intravenous urogram in a 7 month old infant who had at the age of 3 months a uraemic episode following gastro-enteritis. Urograms at the time showed heavy opacification of the medulla. The illustration shows the late effects with clubbing of the calices, easily mistaken for pyelonephritic scarring

8. Pyelonephritis

Pyelonephritis is much the commonest cause of a contracted kidney in later childhood (Fig. 24). As described in Chapter J it is almost always associated with reflux and sometimes with other congenital anomalies, such as renal dysplasia. Characteristically the scarring is irregular, there is a patchy loss of parenchyma with clubbing and elongation of the calices, and a superficial puckering of the surface. In some cases, however, the kidney appears to be more evenly affected and the calices more regularly blunted, though some would say that these examples are due to concomitant obstructive or arterial disease.

9. Obstructive Atrophy

Obstructive atrophy can cause a regular shrinkage of the kidney with loss of parenchyma and blunting of the calices, but a smooth renal outline (HODSON, 1972). This is most evident after an acute but correctable obstruction (Fig. 81), but may also be seen in cases of urethral valves treated early in infancy, and possibly in some examples of sterile reflux from a normal bladder.

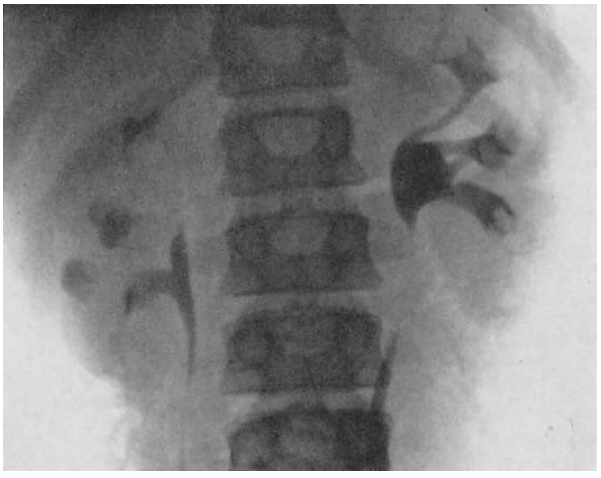


Fig. 24. Pyelonephritic contraction. Intravenous urogram in a child of 9 years with right sided reflux. The right kidney is irregularly contracted with clubbed calices approaching the surface of the kidney in the mid-zone

10. Post-Irradiation Atrophy

Post-irradiation atrophy occurs in children treated for nephroblastoma and other malignancies where the surviving kidney has not been adequately screened (SAGERMAN et al., 1969).

IV. Multicystic Kidney

The multicystic kidney is an extreme form of dysplasia associated with an atretic ureter. The cysts are relatively few in number and large. They are loosely bound together by scarcely recognisable renal tissue and the mass bears no resemblance to a normal kidney (Fig. 25). The upper end of the ureter and renal pelvis are obliterated and may not be found at all, but the lower ureter may be patent and not infrequently allows reflux (Fig. 97). Multicystic kidneys are functionless, and if the opposite one is normal they are harmless, though one causing hypertension has been described (JAVADPOUR et al., 1970). Other abnormalities are common: multicystic kidney may be found at autopsy on children dying of multiple anomalies (SCHRODER et al., 1970), and it is often found with other disorders of the urinary tract. PATHAK and WILLIAMS (1964) found in a series of 20 that the opposite kidney was normal or hypertrophied in only 7; 2 had small dysplastic contralateral kidneys with reflux and renal failure, one had bilateral multicystic disease and died at the age of seventeen days with anuria. In 11 cases the opposite kidney was hydronephrotic with obstruction of the upper or lower end of the ureter, or most characteristically with a mid-ureteric atretic segment very similar to, though less extreme than, the ureteric lesion on the multicystic side (Fig. 97). In 3 of the hydronephrotic cases cystic changes were present in the functioning kidney. FLANNAGAN and KOZAK (1968) found only 7 contralateral

anomalies in 22 cases, but it is clear that the risk to the child is from this contralateral lesion. Treatment of the obstructive disorder is discussed on p. 184.

A palpable mass in the abdomen of a newborn child is the most common presentation of multicystic kidney. Its coarse lobulation and the absence of other signs often suggest the diagnosis. Radiologically it is functionless, but with very large doses of opaque medium in infants producing total body opacification the avascular cysts may be demonstrated as translucent spaces. On cystogram or retrograde pyelogram an absent or blind-ending ureter is found. Other urinary tract anomalies, such as fused kidney or the changes associated with prune belly may be present. Direct cyst puncture is possible, and injection of opaque medium outlines the cyst. Most of these kidneys are removed surgically, though this operation is never urgent and is often perhaps unnecessary, except for final diagnosis.

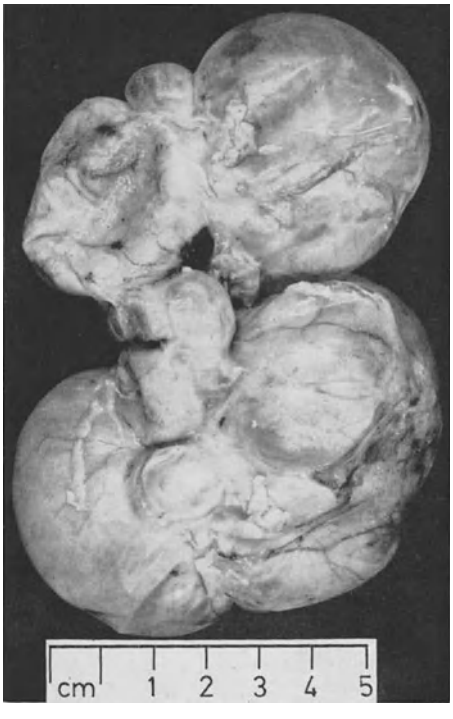


Fig. 25. Multicystic kidney. Specimen removed from an infant with normal contralateral kidney

V. Infantile Polycystic Kidney

Of all forms of cystic disease the childhood polycystic disease of kidney and liver is the most widely recognised and best defined. Osathanondh and Potter (1964) use the term "hamartomatous" to describe it, but this nomenclature has not gained general acceptance and fails to emphasise the importance of the hepatic

as well as the renal anomaly. The topic has been well described from the genetic and pathological viewpoint by BLYTH and OCKENDEN (1971). The cystic change is bilateral and symmetrical, it is not associated in any consistent way with other anomalies of the urinary tract but is invariably accompanied by cysts in the liver. In the kidney there is a uniform distribution of radially arranged fusiform cysts; they are lined by cuboidal or low columnar epithelium and produced by dilatation of the distal convoluted tubules and collecting tubules (Fig. 26). The glomeruli are normal. In the liver there is a proliferation and dilatation of the portal bile ducts associated with a variable degree of periportal fibrosis. BLYTH and OCKENDEN (1971) describe four types of this childhood disease related to the number of nephrons involved. In the perinatal group the kidneys were very large indeed and the child was stillborn or died very shortly after birth. In these at least 90 per cent of renal tubules were affected by cystic dilatation. In the neonatal group, bilateral large kidneys were again the presentation and were associated with renal failure, but only about 60 per cent of the renal tubules were affected. They died six or more weeks after birth. It seems likely that more of these could be saved by careful treatment. In the infantile group large kidneys were present, often with palpable hepatic enlargement, and though chronic renal

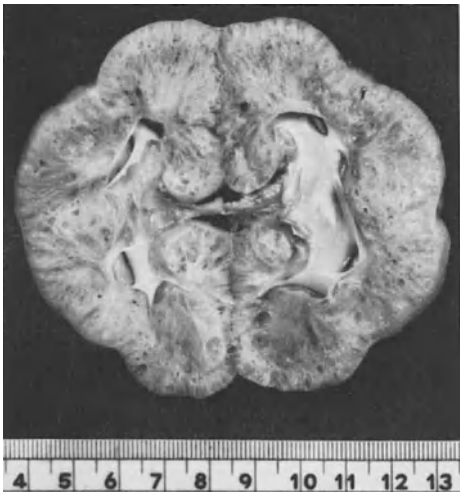


Fig. 26

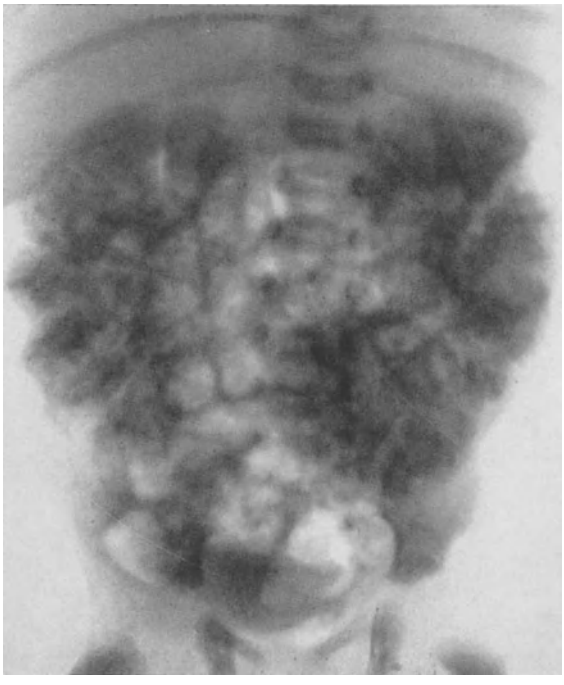


Fig. 27

Fig. 26. Infantile polycystic kidney. Specimen removed at autopsy from a child dying shortly after birth

Fig. 27. Infantile polycystic kidney. Intravenous urogram in a newborn infant with gross bilateral renal swellings. The opaque medium outlines multiple minute tubular cysts throughout the renal parenchyma

failure was present, systemic or portal hypertension was the cause of the symptoms and sometimes of death. These children lived into later childhood and in them only about 25 per cent of the renal tubules were affected. In the juvenile form, hepatomegaly was the presenting sign and many of these children would formerly have been diagnosed as having congenital hepatic fibrosis, but some 10 per cent of their nephrons were affected by cystic change. This form is sometimes described as renal tubular ectasia. Genetic studies showed that where siblings were affected all members of the family fell into the same clinico-pathological group, and it was suggested that a different gene mutation was responsible for each group. The inheritance pattern was that of an autosomal recessive.

The clinical presentation of the neonatal and infantile form leaves little doubt as to the diagnosis and it is confirmed radiologically. Pyelogram (Fig. 27) shows opacification of multiple elongated cystic spaces throughout the parenchyma. The opaque medium takes some hours to appear in this situation and will remain for twenty-four hours or longer before going on to outline the urinary passages. In the older children and adolescents with predominantly liver signs, high dose pyelograms will again show opacification of the cystic spaces. Again these are likely to be elongated and radially arranged, but are predominantly in the medulla. It is important, however, that this disorder should be differentiated from sponge kidney as seen in adults, and from medullary cystic disease described in a later section. Renal biopsy and liver biopsy are easily accomplished and will give a definitive diagnosis, but the radiological appearance is so characteristic that renal biopsy is seldom necessary.

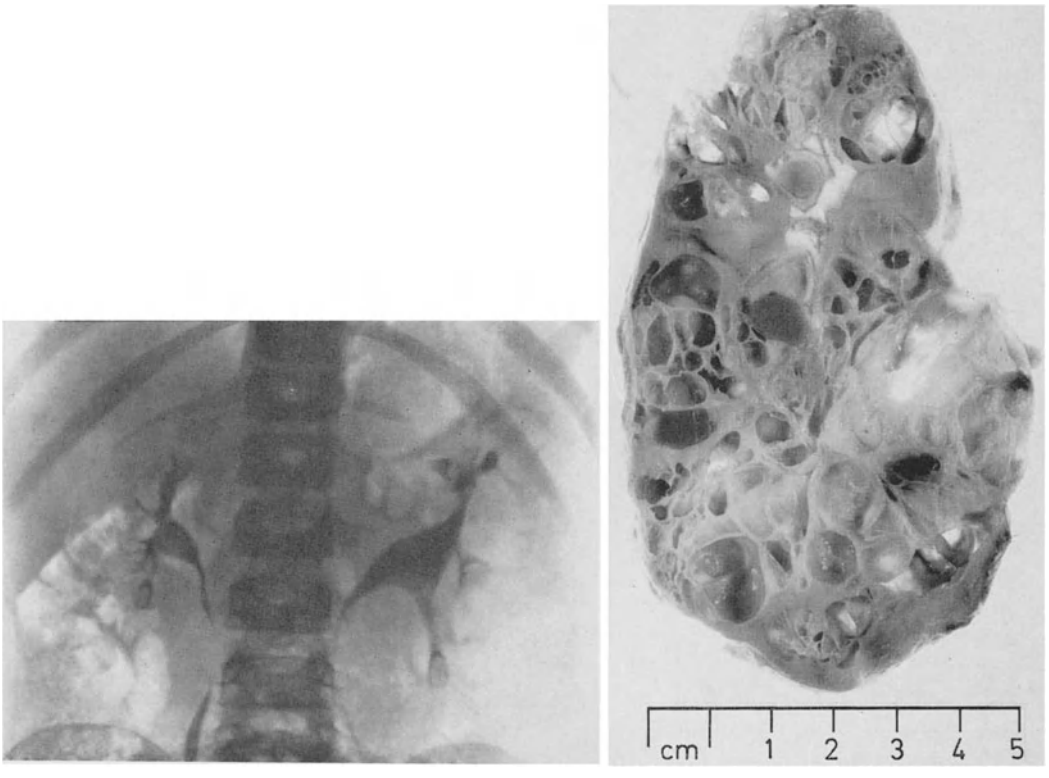
Treatment of the perinatal cases is of no avail, though the somewhat less severe forms can be successfully managed in the early months by attention to their electrolyte requirements and by restricting the protein intake. Many of them go through a salt losing phase in early infancy, but later develop salt retention and hypertension. In the children who progress well the cysts do not appear to enlarge, and sometimes the kidneys seem to be smaller, at least in proportion to the size of the child. Renal transplantation may well prove to be a suitable treatment in the older surviving children provided that the liver disease is not too serious.

VI. Adult Polycystic Kidney

The familiar adult form of polycystic disease has a different pathology and a different form of inheritance from that found in infancy. Rounded cysts of greatly varying size are found throughout the renal parenchyma; they may arise from collecting tubules, from proximal convoluted tubules or from Bowman's capsules. All cysts are said to be in continuity with the tubules in the first place, though this continuity may be lost with later expansion, and it is notable that in contrast to the infantile cases the cysts are not opacified in intravenous urograms. The disease is usually bilateral, although often asymmetrical, and in childhood apparently unilateral cases occur. Liver involvement has been recorded in approximately one third of cases. The inheritance pattern is that of a dominant gene and different generations of the family are frequently involved. Blyth and Ockenden (1971) record this type in childhood and indicate that one autosomal gene with variable manifestations in the heterozygote is responsible.

Adult type polycystic disease has been found in the stillborn foetus, but has also presented clinically with renal enlargement in later childhood. This may be unilateral and the diagnosis between cystic disease and renal tumour may be

difficult to establish. The pyelogram shows the characteristic enlargement of the kidney with stretching of the calices (Fig. 28), and in the nephrogram phase multiple translucent areas corresponding to the cysts. Arteriographically these avascular areas may be shown up more clearly. Unfortunately in the consideration of differential diagnosis a nephroblastoma tumour mass may also be somewhat avascular. Nephrectomy has at times been performed for unilateral disease and in at least one of these children a ten year follow-up has shown no change in the opposite apparently normal kidney. In general, however, the disease is bilateral, though possibly asymmetrical in its incidence, and surgery should be confined to the treatment of complications.



a b

Fig. 28 a and b. Unilateral polycystic kidney of the adult type. a Intravenous pyelogram in a boy of 9 years with haematuria and left renal enlargement. The calices are elongated and distorted by large cysts. b Nephrectomy specimen. Polycystic disease with complicating haemorrhage in the upper pole

Parents suffering from adult type polycystic disease not infrequently wish to know if their children are similarly affected, but the early diagnosis may be difficult to establish. In childhood an entirely normal urogram cannot rule out very early disease. Later on the appearance of translucent areas in the nephrogram should give some indication of the prognosis.

VII. Medullary Cystic Disease: Nephronophthisis

It is usually believed that the two conditions described under these names represent variations on a single rare disease process: a familial disorder, probably due to an autosomal recessive gene and characterised by a progressive renal failure and anaemia. The topic has been well reviewed by GIBSON and ARNEIL (1972), PEDREIRA et al. (1968), and GISELSON et al. (1970). Characteristically several siblings are affected by polyuria and hyposthenuria with progressive uraemia. There is no proteinuria and no abnormal urinary deposit. Changes are not always evident at birth, but have an onset after a few years. Anaemia is a common feature of the children and a few are hypertensive. Radiologically the kidneys show poor concentration of opaque medium in organs of normal size, but with very large doses of medium SPICER et al. (1969) and SIAO et al. (1970) were able to demonstrate the medullary translucent areas in the nephrotomogram.

The progress of this disease is towards renal failure with progressive tubular atrophy and ultimately death. In a few cases there has been an associated retinitis pigmentosa.

VIII. Medullary Sponge Kidney

Although a common and well recognised condition in adults, this disorder is very rare in children. It has been recognised by DELL'ADAMI and BORRELLI (1965) and by SNELLING et al. (1970): in older children and adolescents rather more cases have been described. A familial incidence is unusual. Pathologically there are elongated tubular cysts in the pyramids of the medulla, but not in other parts of the kidney, and often only a few pyramids are involved. The disease may be unilateral or bilateral, and in a number of cases it has been associated with hemihypertrophy of the body (HARRISON and WILLIAMS, 1971). Complicating calculus formation within the dilated tubule (Fig. 29) is responsible for most of the symptoms, which are due to recurrent passage of stones. Some cases have hypercalciuria. No general deterioration of renal function occurs except where due to calculous obstruction and infection. The diagnosis is made radiologically, when on intravenous pyelogram the cysts fill forming brush-like projections from the calices. Nephrocalcinosis may be simulated by the appearance of the calculi in the tubules, but the opacification of the cystic spaces during urography is the diagnostic feature. A similar appearance is seen in the rare EMG syndrome (Fig. 30) in severely abnormal children described on p. 78. Treatment in medullary sponge kidney aims at eliminating infection and occasionally removing obstructing calculi. In very rare instances nephrectomy or hemi-nephrectomy may be desirable.

IX. Multilocular Cysts (Cystadenoma)

In this condition a cystic mass is present in the kidney which is clinically and radiologically indistinguishable from tumour. The mass, which frequently replaces the greater part of the kidney, is enclosed within a single capsule, but part of it may project as a tongue-like excrescence into the renal pelvis and down the ureter. The remainder of the kidney is compressed by the tumour and by the consequent

ureteric obstruction (Fig. 31). The disease is unilateral, presenting as a renal tumour and diagnosed only after nephrectomy. There may, indeed, be some difficulty in distinguishing it from a well differentiated form of nephroblastoma (FOWLER, 1971), but the prognosis with multilocular cysts is excellent.

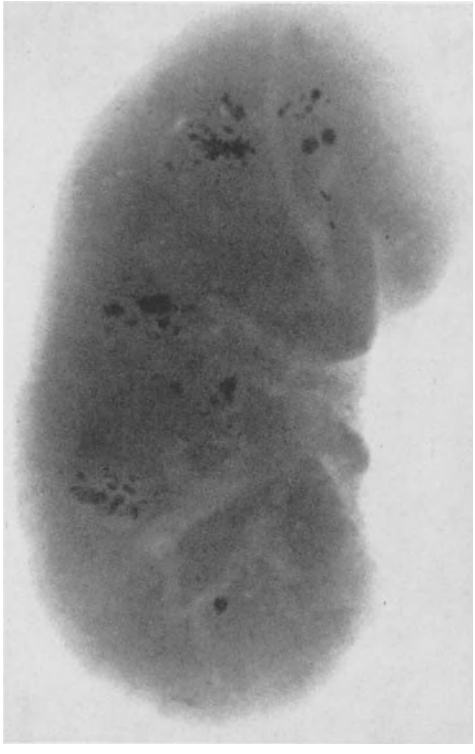


Fig. 29

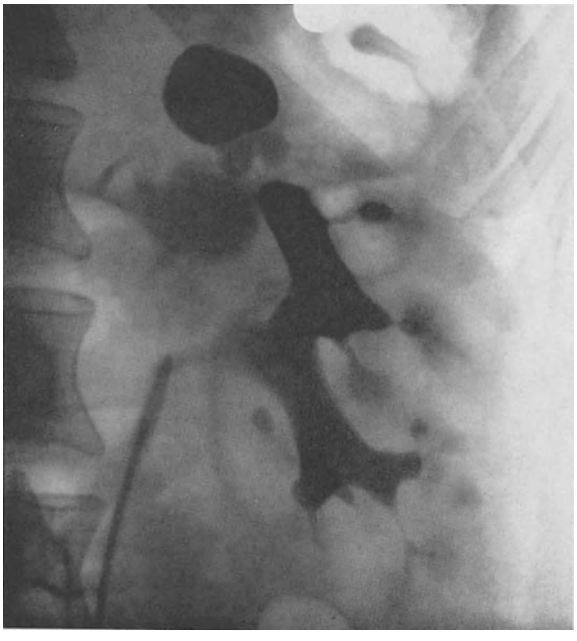


Fig. 30

Fig. 29. Radiograph of excised kidney from a girl aged 17 years with recurrent urinary infection and unilateral changes of medullary sponge kidney showing the distribution of calculi in the cystic dilated collecting tubules

Fig. 30. EMG syndrome. Intravenous urogram in an adult woman showing the combination of collecting tubule opacification as in medullary sponge kidney with multiple spaces having the appearance of caliceal diverticula

X. Serous Cysts

The very common serous cysts found in adult life are very seldom observed in childhood, although a few cases were collected by AHMED (1972). The symptomless mass is felt and urograms demonstrate the large avascular lesion. Cyst puncture is, of course, possible, but in general exploration is desirable in a child since a tumour is a very much more likely diagnosis. The simple cases require only uncapping of the cyst. The lesion has been observed in association with severe

lower urethral obstruction and perhaps in some cases represents an encapsulated extravasation.

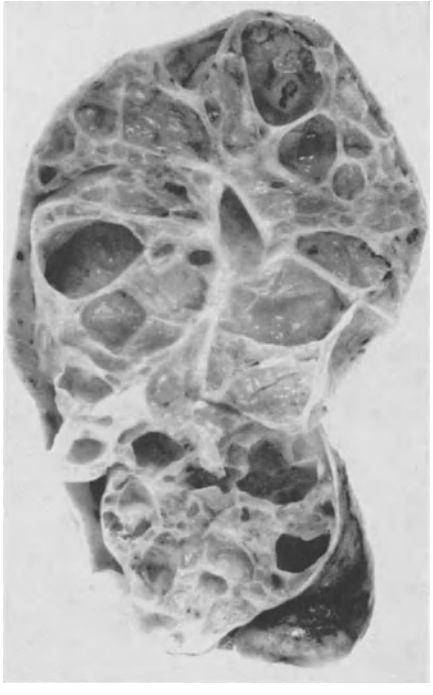


Fig. 31. Multilocular cysts (cystadenoma or lymphangioma). Nephrectomy specimen from a boy with a unilateral nonfunctioning renal mass

XI. Pyelogenic Cysts (Caliceal Diverticula)

Small and usually solitary cystic spaces communicating with the normal calix are not uncommon and are sometimes described as pyelogenic cysts. They are lined by flattened epithelium and, though usually uncomplicated, may contain a stone or be associated with recurrent infection. Often they are found during the routine investigation of a child with abdominal pain or infection, and their relationship to the symptom is obscure. Surgery is seldom required, though in the case of persistent infection a partial nephrectomy or wedge excision of the cyst bearing area may be performed. The differentiation from hydrocalicosis (Chapter N) may sometimes be difficult if the cyst is large.

XII. Microcystic Disease

Cystic dilatation of the proximal tubule is often found in the congenital nephrotic syndrome, particularly in Finnish children, and is referred to as micro-

cystic disease. These children do not enter the differential diagnosis with other forms of cystic disease and are not further discussed in this chapter.

XIII. Cystic Disease and the Multiple Anomaly Syndromes

Cystic disease of one form or another has been described in relation to almost all congenital abnormalities, and the exact pathological details of the kidney are seldom defined. As already remarked, bilateral multicystic kidney may be associated with Potter's syndrome and with the characteristic effects of oligohydramnios. Unilateral multicystic kidney is often found in the prune belly syndrome. In tuberose sclerosis multiple renal cysts or hamartomata are not infrequent on pyelography and they are sometimes the cause of symptoms. Radiologically the kidneys in this disease resemble those of the adult type of polycystic disease with avascular translucent areas in the nephrogram. The diagnosis is made from the associated features of mental deficiency, epilepsy and adenoma sebaceum on the face.

There are rarer multiple congenital syndromes, however, in which a "polycystic kidney" is a feature. Thus in the autosomal trisomy syndromes, which are well reviewed by TAYLOR (1968), polycystic disease is common. In Edward's syndrome (trisomy 18) polycystic renal cortex was found in 15 per cent, in Patau's syndrome (trisomy 13–15) in 33 per cent of cases. The kidney disease was, of course, a relatively unimportant feature of the total syndrome which involves severe growth and development retardation with mental defect. Several other familial conditions believed to be due to an autosomal recessive gene are described in the literature (see appendix). Thus Meckel's syndrome (syn: Gruber, syn: dysencephalia splanchnocystica) is described by HSIA et al. (1971); affected cases had occipital encephalocele, cleft lip, polydactylism, polycystic kidneys and a microgenitalism or ambiguous genitalia. The relationship of this to the oral-facial-digital syndrome described by TUCKER et al. (1966) is not altogether clear. The syndrome described by SMITH, OPITZ and INHORN (1965), and subsequently by PASSARGE and MCADAMS (1967), as cerebro-hepato-renal syndrome is characterised by hypotonia, failure to thrive, jaundice with biliary atresia, abnormal craniofacial development and polycystic kidneys. D'AGNOSTINO et al. (1963) describe an association between polycystic kidneys and the Dandy-Walker syndrome, in which internal hydrocephalus is found with cystic dilatation of the 4th ventricle.

Renal cysts are also recorded in the von Hippel Lindau syndrome with retinal angiomata and cerebellar haemangioblastomata.

The E.M.G. syndrome (exomphalos, macroglossia, gigantism) is a complex anomaly presenting in varying degrees of severity (IRVING, 1970). The features which give it its name are not always the most remarkable: other characteristics are exophthalmos, enlargement of the clitoris and bony abnormality of the metacarpals and phalanges. Some cases have renal failure, and a characteristic urographic appearance is a combination of collecting tubule opacification, as seen in the medullary sponge kidney, with multiple caliceal diverticula (Fig. 30).

XIV. Fused, Ectopic and Dysmorphic Kidneys

The major anomalies of position, form and fusion of the kidneys are well recognised and adequately described. The term dysmorphic is used as a general one to indicate mis-shapen kidneys in various positions, including those with

simple-rotation. All these anomalies will be encountered more frequently in a paediatric urological practice than amongst adults since they are apt to be associated with other congenital abnormalities. Thus, BOATMAN et al. (1972) found other congenital malformations in a third of 96 patients with horseshoe kidney: these included major chromosomal aberrations (e.g. Turner's syndrome) and a variety of cardio-vascular, gastro-intestinal and central nervous lesions. Renal anomalies occur in the Laurence Moon Biedl syndrome: horseshoe kidney and hydronephrosis have presented in our experience. In Fanconi's pancytopaenia, anomalies of renal fusion and rotation are recorded, but multiple urinary tract anomalies may be seen. Polycalicosis has been recorded in the Rubenstein Taybi syndrome (BERAUD et al., 1970).

The dysmorphic kidney may be dysplastic in the histological sense, or may have a normal renal architecture, but in the case of a solitary dysmorphic kidney complications are frequent and may lead to renal failure. Thus, the solitary pelvic kidney has been recently reviewed by SCHULMAN (1970), and his series contains a number in which death was apparently due to renal failure. In the case of this anomaly genital malformations are extremely common, particularly absence of the uterus and vagina in the female. TANENBAUM et al. (1970) have found similar anomalies associated with a solitary crossed renal ectopia; renal failure in these cases will be associated with infection complicating disorders of ureteric drainage. In the case of the pelvic ectopic and crossed ectopic kidneys, ureteric dilatation with or without reflux is common (Fig. 32), but it is unusual to get a pelvi-ureteric

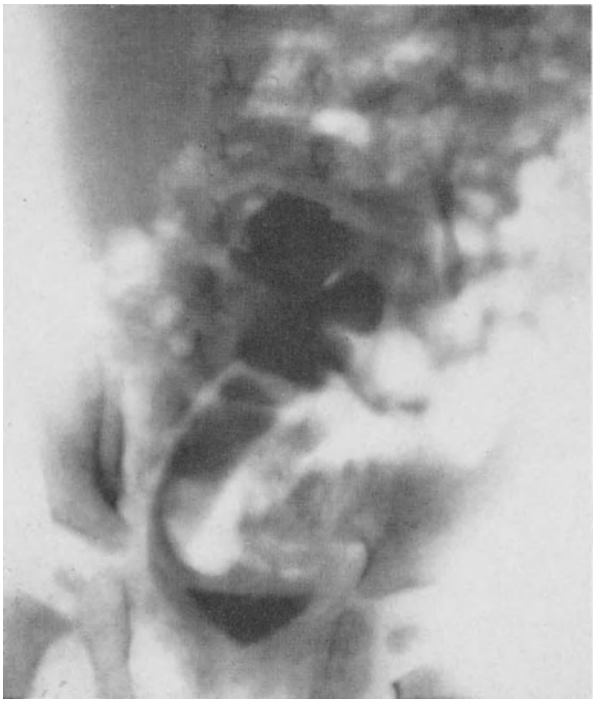


Fig. 32. Crossed renal ectopia with fusion, with dilated ectopic and refluxing crossed right ureter. Intravenous urogram in an infant girl with infection and incontinence

obstruction especially as in many cases a true pelvis is not formed, the ureter splitting into a number of extra-renal calices. In the horseshoe kidney and malrotated kidney in the lumbar region, however, pelvic hydronephrosis is a common complication. Recent studies have placed increasing emphasis on the importance of the anomalous blood supply to these abnormal kidneys. The anatomical arrangements have been discussed by GRAVES (1969) and the radiological studies made by THIEMAN and WIENERS (1970).

G. Urinary Tract Infection

T. M. Barratt

I. Introduction

Urinary tract infection is inextricably interwoven into the fabric of paediatric urology, for it commonly causes the symptoms that first draw attention to the child's illness and to a large extent determines the ultimate prognosis. There have been several symposia in recent years which should be consulted for detailed discussion of the material presented in this chapter (Kass, 1965; O'Grady and Brumfitt, 1968; Stuart, 1969; Kincaid-Smith and Fairley, 1970).

II. Diagnosis of Infection

1. Clinical Features

The classical features of urinary tract infection are too well known to require further elaboration. However, only one third of children found to have persistent bacteriuria during community surveys have symptoms referrable to the urinary tract (Kunin, 1968a). Conversely, only 45 per cent of individuals with frequency and dysuria—the urethral syndrome— prove to have significant bacteriuria on investigation (Mond et al., 1965). Symptoms and signs are therefore unreliable as indications of urinary tract infection and urine culture is always required for confirmation, particularly in view of the implications for radiological investigation and follow up of that diagnosis.

In infants the clinical features may be even more deceptive. Anorexia, vomiting and diarrhoea may mimic gastroenteritis, cause saline depletion and further impair renal function. Jaundice of an obstructive pattern sometimes occurs (Seeler and Hahn, 1969), and other cases are to be found in that all-embracing category of failure to thrive. In this age group, there is a special risk of septicaemia spreading from a renal focus with attendant complications of disseminated intravascular coagulation or meningitis.

2. Significant Bacteriuria

The concept of significant bacteriuria was introduced by Kass (1956, 1957). Bacteria present in the bladder will multiply and, particularly in an early morning specimen of urine, be present in concentrations of greater than 10^5/ml; bacteria acquired during voiding will be present in smaller numbers, less than 10^4/ml. Laboratory methodology for the enumeration of bacteria in urine has been review-

ed by KUNIN (1968b). As significant bacteriuria, i.e. more than 10^5/ml, will only be confirmed on second culture in 80 per cent of cases (KASS, 1962), the definitive diagnostic criteria of urinary tract infection (or persistent bacteriuria) adopted by KUNIN et al. (1964) were significant bacteriuria with the same organism or Escherichia coli serotype in three consecutive urine cultures. Such perfection is expensive and difficult to attain in clinical practice, but is essential for epidemiological surveys, and less elaborate techniques should be regarded as only approximations to this ideal dictated by economic or logistic considerations.

It has been suggested that the diagnosis of urinary tract infection is sharpened if the bacterial excretion rate is considered rather than bacterial concentration in urine (LAMPERT and BERLYNE, 1971), but the effect of this correction is small.

3. Pyuria

Uncentrifuged fresh urine should be examined for leucocytes in a counting chamber: microscopy of the centrifuged deposit is of little value (HOUSTON, 1969). Care must be taken to differentiate renal tubular cells (PRESCOTT and BRODIE, 1964), especially in the first weeks of life (CRUICKSHANK and EDMOND, 1967). Many authors have reported data on the leucocyte excretion in normal children; more than 10 WBC/mm^3 are taken to be abnormal in older children (STANSFELD, 1962), but higher levels are observed in apparently healthy neonates, and LINCOLN and WINBERG (1964b) suggest 25 WBC/mm^3 and 50 WBC/mm^3 as the upper limits in males and females respectively. LITTLEWOOD (1971) reports that 97 per cent of male and 95 per cent of female infants on the sixth day of life have fewer than 5 WBC/mm^3 in their urine. The observed levels of normal leucocyte excretion are, however, very dependent upon the technique of urine collection (vide infra).

Observations of leucocyte excretion must be regarded as of secondary importance to the quantitation of bacteriuria; for example, less than 50 per cent of girls with persistent significant bacteriuria have pyuria (KUNIN, 1970), though the proportion is higher with recurrent or symptomatic infections.

Quantitative leucocyte excretion rates and provocation tests with bacterial endotoxin (PEARS and HOUGTHON, 1959) or prednisolone (LITTLE and DE WARDENER, 1962) have not materially contributed to the diagnosis of pyelonephritis, but have not been systematically evaluated in children.

4. Specimen Collection

No amount of laboratory expertise can overcome inadequate specimen collection. The problem is particularly severe in neonates. Urine samples may be collected in sterile plastic bags, by the clean catch technique, by catheterisation or by suprapubic aspiration. Bag specimens are the least satisfactory due to the high incidence of false positive bacteriuria and pyuria in comparison with clean catch specimens (HOUSTON, 1963). The latter technique makes substantial demands on nursing time and requires obsessional cleansing of the labia in females (LINCOLN and WINBERG, 1964a), but still gives false positive results for both bacteriuria and pyuria in comparison with suprapubic aspiration (NEWMAN et al., 1967). Urethral catheter specimens are not superior to those obtained by a clean catch (MCCARTHY and PRYLES, 1963).

Suprapubic aspiration of the bladder has emerged as the definitive method of urine sampling (PRYLES et al., 1959; NELSON and PETERS, 1965; SACCHAROW and

PRYLES, 1969). In normal subjects urine collected by this method does not contain any bacteria. The technique is simple, though a common error, particularly in neonates, is to insert the needle too close to the symphysis pubis. The complication rate is low, and puncture of organs other than the bladder does not seem to be harmful (WEATHERS et al., 1969). Nevertheless, the technique is hardly suited to the repetitive sampling required in most children with urological abnormalities and should be reserved for occasions when the data obtained by other methods is inconclusive.

Specimens of urine should be refrigerated immediately and transported to the laboratory without delay to minimise bacterial multiplication. Leucocytes are unstable, particularly in alkaline urine, but may be preserved by the addition of boric acid (PORTER and BRODIE, 1969).

5. Screening Techniques

A major impediment to the investigation and management of urinary tract infection in childhood has been the lack of an adequate screening technique for bacteriuria. The ideal method would produce no false negative results and only a limited proportion of false positives. It should be cheap and of such simplicity that it could be undertaken by the parent in the home. Methods based on the bacterial metabolism of triphenyltetrazolium or nitrite, or on urinary catalase activity, have not fulfilled these criteria (SMITH and SCHMIDT, 1962). Bacteria multiplying in the urine consume glucose; subnormal urinary glucose concentrations are a reliable indication of significant bacteriuria (SCHERSTÉN et al., 1967) particularly after incubation at 37° C for 8 hours (MATSANIOTIS et al., 1971) and a test paper has been devised for this purpose (SCHERSTÉN, 1968). The system looks promising, but reports of its reliability in clinical practice have not been published.

Another approach has been to simplify techniques of urine culture by the preparation of glass slides coated in culture media which can be dipped in the urine sample—the dip-slide test (GUTTMANN and NAYLOR, 1967; COHEN and KASS, 1967). A commercially available variant of these systems has been tested by ARNEIL et al. (1970) in paediatric practice and found to be satisfactory.

III. Bacteriology

1. Infecting Organism

In uncomplicated urinary tract infections, Escherichia coli predominates: in the study of KUNIN and HALMAGYI (1962) it was the principal pathogen in 84 per cent of bacteriuric school children. Other organisms were Klebsiella aerogenes, Proteus mirabilis, Staphylococcus albus, Streptococcus faecalis and Pseudomonas pyocyaneus. In recurrent infections or those complicating urological malformations, organisms other than Escherichia coli are found with relatively greater frequency, and mixed infections are common (GOULD, 1968).

The Escherichia genus is antigenically very complex, comprising some 150 O-, 90 K- and 50 different H-antigens. The question arises whether the urinary tract is particularly prone to infection by a restricted number of strains (the

theory of special pathogenecity) or whether the distribution of infecting strains reflects their occurrence in the environment (the prevalence theory). GRÜNEBERG et al. (1968) have reviewed this problem and demonstrated that the distribution of Escherichia coli O-serotypes in the urine of bacteriuric individuals reflected that in their faeces which did not differ from non-bacteriuric controls. These data support the prevalence theory of urinary pathogens and implicate the bowel as the major reservoir of infecting organism. There is some evidence, however, that Escherichia coli strains rich in K-antigen, which is associated with virulence, are commoner in bacteriuric individuals with upper tract involvement (GLYNN et al., 1971).

2. Recurrences

Recurrent infection may be either re-infection with a new strain or relapse of the original strain suggesting incomplete eradication. BERGSTRÖM et al. (1967) report that up to 85 per cent of recurrences are due to re-infection. KUNIN (1970) has presented a similar estimate, and also demonstrated that relapse tends to occur earlier than re-infection: 80 per cent of the relapses but only 50 per cent of the re-infections were detected within six months of the previous episode.

3. Bacterial Variants

Under the influence of many antibiotics and environmental stress bacterial cell wall synthesis may become defective: the resulting organism is larger, pleomorphic and more susceptible to osmotic stress. These variants have been called L-forms, spheroplasts or protoplasts (FEINGOLD, 1960). Using special culture techniques for their detection, GUTMAN et al. (1967) detected L-forms in the urine of 19 per cent of individuals with presumed chronic pyelonephritis. These L-forms may persist in the osmotically favourable environment of the renal medulla. An important therapeutic consideration is that, whilst they lose the antibiotic sensitivity of the parent organism, they become sensitive to erythromycin.

4. Localisation of Infection

For many years clinicians have attempted to differentiate between those infections involving the kidney and those confined to the bladder on the basis of clinical features. The definitive technique is sampling of ureteric urine (STAMEY et al., 1965); by this method WHITAKER and HEWSTONE (1969) demonstrated that 20 per cent of urinary infections in children involved the upper urinary tract. A less exacting technique is to determine whether bacteriuria persists after neomycin bladder washouts (FAIRLEY et al., 1967); equivocal results, however, have been obtained in children (GIRADET and FRUTIGER, 1970). Of the indirect methods of localisation (REEVES and BRUMFITT, 1968), high titres of agglutinating antibody (WINBERG et al., 1963; BRUMFITT and PERCIVAL, 1965) are probably more reliable than the maximum urinary osmolality (WINBERG, 1958; CLARK et al., 1969). The value of the knowledge of localisation may be questioned, but as there is evidence of a lower cure rate if the upper tract is involved (BRUMFITT and REEVES, 1969), these patients should be followed up with greater care.

IV. Epidemiology

1. Neonates

Epidemiological studies of the incidence of urinary tract infection in neonates have been hampered by the limitations of urine sampling techniques discussed above. Nevertheless, all authors are agreed that symptomatic bacteriuria and pyuria are more common in male than female infants. For example, LINCOLN and WINBERG (1964a), using a scrupulous clean catch technique found 8 urinary tract infections in 298 male infants (2.7 per cent) but none in 286 females. They stressed that "asymptomatic" bacteriuric neonates were liable to develop overt illness subsequently.

2. School Children

There is a dearth of epidemiological data on the incidence of urinary tract infection in the pre-school child. This is unfortunate, for it is probably the age at which most pyelonephritic scarring occurs (SMELLIE et al., 1964; ROLLESTON et al., 1970).

The natural history of bacteriuria in school children has been documented by the comprehensive surveys of KUNIN (1968a, 1970; KUNIN et al., 1964). The prevalence of persistent bacteriuria in boys is very low but in girls is 1.2 per cent. To this population are added a further 0.3 per cent per annum so that by the age of 16 years an estimated 4.5 per cent of girls will have been infected. Only one third of bacteriuric girls have symptoms referrable to the urinary tract at the time of diagnosis, but a further third develop symptoms subsequently. The incidence of infection was not related to socio-economic status, and there were only minor differences between white and negro girls.

These studies provide important information on the incidence, unbiased by referral patterns, of associated urological malformation in girls with bacteriuria (KUNIN et al., 1962). Eighteen per cent were found to have caliectasis on the initial intravenous urogram and 4 per cent had one markedly shrunken kidney. Nineteen per cent were found to have vesico-ureteric reflux on the initial cystogram: 35 per cent in the age group of 5–9 years, falling to 11 per cent in those over 15 years of age. Curiously, both caliectasis and vesico-ureteric reflux were almost confined to white girls and their incidence was very low in negro children. Ureteral duplication was observed in 3 per cent of the bacteriuric girls and other urological malformations were very unusual.

All girls with persistent bacteriuria were treated, but within 3 years 75 per cent of the white and a slightly lower percentage of negro girls relapsed. After 3 years of freedom from bacteriuria, the incidence of recurrence falls to about 3 per cent per annum; this, however, is still substantially greater than the risk of normal school girls (0.3 per cent per annum). After a few years the incidence begins to rise again in association with marriage, and 53 per cent of girls who had been observed to have bacteriuria during their school years developed bacteriuria again within 3 months of marriage.

V. Immunology of Urinary Tract Infection

1. Serum Antibody Response

Over the age of two months, infection of the urinary tract sometimes elicits the production of specific agglutinating antibody (NEEDELL et al., 1955). These

antibodies are directed against the O-antigen of the infecting Escherichia coli and are of IgM class (HANSON et al., 1969). Their production in children has been shown to correlate with parenchymal involvement as evidenced by symptoms (ANDERSEN et al., 1965b; ANDERSEN, 1968) or ureteric catheterisation (HEWSTONE and WHITAKER, 1969). Occasionally, the antibody titre suggests renal infection when the urine is sterile (ANDERSEN et al., 1965a): in these cases the appropriate Escherichia coli O-serotype can be identified from the faeces (ANDERSEN et al., 1965c). The titre usually subsides after infection with a half-life of about 8 days (HANSON et al., 1970). With recurrent infection, however, IgG antibodies, which are better detected by immunoprecipitation techniques, are formed. Thus HANSON et al. (1969) demonstrated precipitating antibodies in all of 13 children with recurrent infection, but in only 5 of 20 children in their first known attack, and later confirmed that they were IgG class (HANSON et al., 1971). This phenomenon is unlikely to be the usual secondary response to repeated infection, for most recurrences are re-infection with a new O-serotype, and its significance is not clear.

Whether serum antibodies contribute to the eradication of infection and protection against re-infection, or whether they are an epiphenomenon of the disease process, or whether indeed they contribute to chronicity, has yet to be resolved. However, individuals with hypogammaglobulinaemia are not at special risk of urinary tract infections (Medical Research Council, 1971) so that the protective role of circulating antibody in man is probably slight. Indeed, of the many syndromes characterised by deficiency of immunological systems, only the defective polymorphonuclear leucocyte function of chronic granulomatous disease has been attended by an unusual incidence of urinary tract infection (KONTRAS et al., 1971).

2. Local Antibody Production

Immunoglobulin A is the characteristic immunoglobulin of body secretions; it is locally synthesised (FELDMAN et al., 1971) and found in the urine in conjunction with another protein—the secretory piece—as secretory IgA (BIENENSTOCK and TOMASI, 1968). Secretory IgA concentrations rise in the urine during acute infection (KAUFMAN et al., 1970; UEHLING and STEIHM, 1971) and IgM can also be detected (BURDON, 1970). However, Escherichia coli O-specific antibody in urine is of IgG class (VOSTI and REMINGTON, 1968), and in experimental pyelonephritis, most locally produced antibody is IgG class (LEHMANN et al., 1968; HAND et al., 1970). There is no evidence to date to support the attractive hypothesis that recurrent urinary tract infections are due to a deficiency of local antibody defence systems.

3. Immunological Factors in Chronicity

Bacterial antigen may persist in the kidney after the urine has become sterile. AOKI et al. (1969) demonstrated by immunofluorescence KUNIN's (1963) antigen (which is shared by most strains of Enterobacteriaceae) in 6 of 7 cases of "abacterial" pyelonephritis. Experimentally, COTRAN (1963) showed the persistence of Proteus antigen and antibody in the kidney although the urine was sterile. It is possible that persistent bacterial products in the kidney may elicit a continuing antibody response and inflammation. The role of cell mediated immunity in this situation has not been evaluated.

VI. Experimental Observations

There is a large body of experimental work on urinary tract infection from which only a few topics will be selected for discussion.

1. Urine as a Culture Medium

Normal urine sustains the growth of bacteria: the mean generation time of Escherichia coli is 60 minutes, but is increased at the extremes of physiological urinary pH and at high osmolality (ASSCHER et al., 1966). The persistence of bacteria within the urinary tract, however, is determined not only by their growth rate but also by hydrodynamic factors (O'GRADY and CATTELL, 1966 a, b). O'GRADY et al. (1968) have constructed a mechanical model simulating conditions of bacterial growth in the bladder and have also described analogue and digital computer models: from these the relative influence of bacterial growth rate, urine flow rate, residual volume and frequency of micturition on bacterial colonisation of the bladder can be observed. They do not take into account, however, the intrinsic defence systems of the bladder, whereby organisms are lysed on contact with urothelium (COX and HINMAN, 1961; NORDEN et al., 1968).

2. Haematogenous Pyelonephritis

Intravenous injection of gram-positive bacteria results in pyelonephritis; with gram-negative organisms it is difficult to infect the kidney reproducibly (GORRILL, 1968). Renal localisation is enhanced if the kidney is massaged (BRAUDE et al., 1955) or the ureter obstructed (GORRILL, 1956; GUZE and BEESON, 1956). These techniques differ in their effects: if the kidney is massaged, a larger proportion of the injected bacteria are localised in the kidney, whereas obstruction does not greatly increase the localized infecting dose but renders the kidney more susceptible to a small number of bacteria which multiply rapidly. The medulla is much more prone to infection than the cortex (FREEDMAN and BEESON, 1958), and any injury in that area strikingly enhances the localisation of bacteria (ROCHA et al., 1958). The greater susceptibility of the medulla is attributed to its high osmolality, for water diuresis provides some protection from haematogenous pyelonephritis (ANDRIOLE and EPSTEIN, 1965). Caution must be exercised, however, in extrapolating from one animal model to another or to the human situation (BEESON, 1967).

3. Ascending Infection

It is difficult to induce pyelonephritis reproducibly in the experimental animal by the introduction of bacteria into a normal bladder. ASSCHER et al. (1970) injected Escherichia coli intravesically into rats with the urethra clamped and massaged the bladder: under these circumstances all have vesico-ureteric reflux. Their technique resulted in pyelonephritic scarring and inhibition of compensatory hypertrophy following contralateral nephrectomy. Interestingly, heat-killed Escherichia coli, which did not cause scar formation, also prevented compensatory hypertrophy.

VII. Specific Urological Associations

1. Vesicoureteric Reflux

Reflux is abnormal (Williams, 1965) but is found in approximately 30–50 per cent of children with urinary tract infection (Kunin et al., 1962; Smellie and Normand, 1966). The incidence diminishes with age (Baker et al., 1966), and disappears in 40 per cent of treated children (Smellie, 1966). To account for these observations it has been proposed that with growth the intramural segment of the ureter elongates and the tendency to reflux is thereby diminished (Hutch et al., 1963). Whether reflux by itself is important has not yet been resolved, but there is now abundant evidence that reflux and infection is a potent cause of pyelonephritic scarring (Smellie et al., 1964). A controlled trial of reflux prevention surgery demonstrated a reduction in the incidence of infection and an increase in renal growth in the operated group (Scott and Stansfeld, 1968). It is important to recognise that reflux is not a homogeneous disease; failure to appreciate its variety has been a source of conflicting opinion in the literature (see Chapter J).

2. Minor Urological Abnormalities

There is no doubt that a major factor in the genesis of urinary tract infection is the shortness of the female urethra, but other factors must be involved (Robson and Manley, 1970). Distal urethral stenosis (Lyon and Tanagho, 1965), subclinical neurogenic bladder (Lapides and Costello, 1969) and psychological factors influencing bladder function (Campbell, 1970) have been invoked, and are discussed in Chapter I.

3. Obstructive Uropathy

The susceptibility of the obstructed kidney to infection has been described above. In these patients, urinary tract infection may take a more acute and virulent course. Renal destruction and general ill-health resulting from pyonephrosis may require urgent surgical drainage of the urinary tract.

4. Calculus Disease

The association between urolithiasis and infection with Proteus species is described in Chapter U. Failure to eradicate the infection is the major cause of recurrence of stones (Ghazali et al., 1973). If the stone obstructs the flow of urine, pyonephrosis may supervene, and some cases described by the term xanthogranulomatous pyelonephritis are really examples of this disease (Habib et al., 1968).

5. Catheterisation

The introduction of drainage tubes into the urinary tract carries a high risk of infection. Substantial improvement, however, can be attained by the use of closed drainage systems (Kunin and McCormack, 1966).

VIII. Functional Sequelae of Urinary Tract Infection

1. Acute Infection

The most characteristic disturbance of renal function in acute pyelonephritis is a diminished capacity to concentrate the urine (WINBERG, 1968); this defect is closely associated with renal infection as shown by antibody response or ureteric catheterisation (BRUMFITT and REEVES, 1968). Between attacks, the concentrating capacity returns to normal, unless there is urographic abnormality (APERIA et al., 1970). Glomerular filtration rate is reduced, as is effective renal plasma flow, measured by the para-aminohippurate clearance (CALCAGNO et al., 1968). In recurrent urinary tract infection there is also a sub-clinical defect in hydrogen ion excretion with a diminished bicarbonate threshold, even if the glomerular filtration rate is normal (BERG et al., 1971). Gastrointestinal salt and water losses due to diarrhoea, vomiting and poor fluid intake lead to extracellular fluid volume depletion, often with hypernatraemia due to a predominant water deficit, and metabolic acidosis. Renal function may be still further depressed by septicaemia, especially if it is complicated by disseminated intravascular coagulation (ABILDGAARD, 1969). This propensity of the young infant to dissemination of infection is attributed to the low serum IgM concentration (GITLIN et al., 1963); in the first two months of life, systemic Escherichia coli infections do not elicit the response of agglutinating antibody characteristic of older individuals (HANSON et al., 1970).

2. Chronic Pyelonephritis

There are no functional disturbances that are pathognomic of chronic pyelonephritis. In a study of small diseased kidneys, BERG et al. (1970) found that single kidney glomerular filtration rate could not be predicted from the intravenous urogram, but that depression of glomerular filtration rate correlated best with a history of recurrent infection. Contrasting dysplastic and pyelonephritic kidneys, ERICSSON (1970) suggested that a high Tm glucose/GFR ratio, implying nephron underperfusion, was characteristic of infected kidneys. Both these studies emphasise the importance of urinary infection as a cause of diminished glomerular filtration rate.

There is a strong association between chronic pyelonephritis and hypertension, reviewed in Chapter D. In some of these cases, particularly those with otherwise relatively good renal function, the hypertension is mediated by the renin-angiotensin system and is probably due to ischaemic areas resulting from pyelonephritic scarring.

IX. Chronic Pyelonephritis

1. Pathological Diagnosis

A major limitation to the understanding of urinary tract infection has been the lack of satisfactory pathological criteria for the diagnosis of chronic pyelonephritis (HEPTINSTALL, 1967). The principal features were described by WEISS and PARKER (1939); the gross appearance of the kidney is as important as the micro-

scopic. The hallmark of chronic pyelonephritis is the cortical scar, which, unlike that of hypertension or ischaemia, is associated with dilatation of the underlying calix (SMITH, 1962). The kidneys are irregularly and unequally contracted. On histological examination periglomerular fibrosis and hyalinisation of glomeruli may be seen. Tubular changes are more severe: they are atrophic, sometimes dilated and containing eosinophilic casts (thyroid-like changes) and there are inflammatory cells in the interstitium. As the changes may be focal, a needle renal biopsy is sometimes inadequate to display them satisfactorily.

Some authors (ROSENHEIM, 1963; MACGREGOR, 1970) have drawn attention to what they regarded as another type of pyelonephritic kidney with a smooth, even contraction. The bacterial aetiology of this disease is open to question. In adults a common diagnostic problem is the differentiation of pyelonephritic lesions from those of ischaemia, hypertension or nephrotoxins such as phenacetin. In children, however, it is the distinction between pyelonephritic and dysplastic kidneys that is most troublesome. Some features are highly suggestive of dysplasia: the presence of cartilage cells, sheets of primitive mesenchyme and macroscopic cysts (ERICSSON and IVEMARK, 1958 a, b; BERNSTEIN, 1968). Such kidneys are commonly infected and it may be difficult to decide to which pathological process the renal inadequacy should be attributed.

2. Radiological Diagnosis

HODSON (1965, 1967) has defined the radiological features of chronic pyelonephritis. The small, unequal kidneys grow poorly (for standards see HODSON et al., 1962) and scars with associated caliectasis are typical. Children with pyelonephritic scarring usually have vesico-ureteric reflux (HODSON and EDWARDS, 1960); the scars are usually present from a very early age (SMELLIE et al., 1964; HODSON and WILSON, 1965; ROLLESTON et al., 1970).

3. Bacteriology

In many individuals with a presumptive diagnosis of chronic pyelonephritis the urine is sterile. ANGELL et al. (1968) have doubted the role of infection in such cases. Culture of renal biopsy material is only very occasionally diagnostic if the urine is free of bacteria (JACOBSON and NEWMAN, 1962). The demonstration of bacterial antigen by immunofluorescence in "abacterial" pyelonephritis suggests a new diagnostic approach (AOKI et al., 1969).

4. Natural History of Pyelonephritis

A central, but unresolved, question is the relationship between urinary tract infection of childhood and death from renal failure attributed to chronic pyelonephritis in later life (MACGREGOR, 1970; BARRATT and MACAULAY, 1973). Review of patients 10–20 years after the diagnosis of urinary tract infection in childhood reveals a disturbingly high incidence of severe renal damage, particularly in males (MACAULAY and SUTTON, 1957; STEELE et al., 1963; LINBLAD and EKENGREN, 1969) but there are many sources of bias in such observations, and it is clear that children with urinary tract infection must be regarded as a heterogeneous group with varying prognoses (MACGREGOR and FREEMAN, 1968). MAC-

GREGOR (1970) describes a small group of patients, predominately female, who succumb to "pyelonephritis lenta" in early adult life, and stresses the incidence of vesico-ureteric reflux in them. He also raises a very complex question:

"... an adverse influence becoming steadily more obvious with advancing age is operating upon women to cause a large and disporportionate number of deaths from chronic pyelonephritis in the female sex between 50 and 70 years of age. The necessary deduction seems to be that it is not until this epoch that we witness the final impact of renal damage inflicted by urinary infection in childhood."

The relationship between childhood urinary infection and pyelonephritis in later life has not, however, been established, nor will it be so until epidemiological surveys such as those of KUNIN et al. (1964) have run their full course: the definitive answer to this problem cannot be expected until the end of the century.

X. Treatment

1. Basic Considerations

Medical treatment of urinary tract infection involves measures designed to minimise bacterial colonisation of the urinary tract such as a high fluid intake with frequent micturition and the administration of antibiotics. Table 5 describes

Table 5. Sensitivity to drugs of bacteria causing urinary infections. Res. = resistant to concentrations attainable in urine. Modified from GARROD and O'GRADY (1972)

Drug	Concentration attained in urine (μg/ml)	Minimum Inhibitory Concentration (μg/ml)					
		Escherichia coli	Proteus mirabilis	Klebsiella aerogenes	Pseudomonas aeruginosa	Staphylococcus aureus	Streptococcus faecalis
Sulphonamides	1000	1	8	Res.	50	4–16	Res.
Nitrofurantoin	125	16	200	100	Res.	4	25
Ampicillin	250+	8	4	Res.	Res.	0.04	2
Carbenicillin	2000	5	2.5	250	50	0.5–50	25
Cephaloridine	300	4	4	4 to Res.	Res.	0.1–5	16
Kanamycin	300	2	4	2	64	0.5	64
Gentamycin	50	1–4	2–8	1–2	1–8	0.1–1	8–16
Trimethoprim	50	0.4 to Res.	7.5 to Res.	25 to Res.	Res.	4–30	4–125
Nalidixic Acid	200	3.0–7.5	2.5–20	1.6–50	4.0–500	50	500

the usual sensitivity of common urinary pathogens to currently available antibiotics. There has been considerable controversy as to whether the urinary concentration is an adequate reflection of the efficacy of therapy, or whether the renal tissue concentration is more important. Because of the complex arrange-

ments of fluid compartments within the kidney, the tissue concentration is rather an over-simplified concept, but an approach to estimating antibiotic concentration in interstitial fluid has been made by analysis of renal lymph (COCKETT et al., 1966). If antibacterial activity in the blood were an essential prerequisite for treatment, then, as O'GRADY and GARROD (1972) point out, nitrofurantoin would be of no value, for antibacterial levels are only achieved after concentration of the drug in the urine. It must, therefore, be adequate under many circumstances just to sterilise the urine.

2. The Acute Infection

In acute, uncomplicated urinary tract infections there is little to choose between several antibiotics provided that the organism is sensitive. A sulphonamide is probably still the drug of choice (BRUMFITT and REEVES, 1969) though ampicillin or nitrofurantoin are equally effective (BURKE and STICKLER, 1969), and cephalexin is as effective as ampicillin (DAVIES et al., 1971), but sulphonamides are superior on the grounds of cost or toxicity. Short courses of treatment are adequate: two weeks therapy is as effective as six weeks with sulphonamides (BERGSTRÖM et al., 1968) or with ampicillin or nitrofurantoin (KINCAID-SMITH and FAIRLEY, 1969), and earlier claims (STANSFELD and WEBB, 1954) of the necessity for prolonged therapy have not been substantiated.

Use of the earlier sulphonamides was sometimes complicated by crystalluria, but with the development of more soluble forms, this is now rare. Sulphadimidine is a popular choice, but is rather less potent than sulphafurazole or sulphamethizole, both of which are highly soluble and suited to the treatment of urinary tract infection. The long-acting sulphonamides may cause Stevens-Johnson syndrome and should be avoided (BEVERIDGE et al., 1964).

3. Recurrences

Recurrence after effective treatment is usually due to re-infection with a new strain (BERGSTRÖM et al., 1967), and with prolonged follow-up only about 25 per cent of bacteriuric girls remain free of further infection (KUNIN, 1970). This percentage remains approximately constant for each course of treatment, which permits an elegant mathematical analysis of recurrence, for the percentage remaining bacteriuric declines exponentially with the number of treatment courses. Thus, KUNIN (1970) was able to analyse the factors which influenced recurrence, and found that the rate was higher in white rather than negro girls, and in young rather than older children. Interestingly, the presence of vesico-ureteric reflux did not adversely affect the tendency to relapse.

4. The Emergence of Resistant Strains

Treatment of urinary tract infection with sulphonamides alters the bowel bacteria and subsequent recurrences are usually due to a sulphonamide resistant organism (BERGSTRÖM et al., 1968). Nitrofurantoin does not have this effect on faecal flora (LINCOLN et al., 1970b). Interesting data have emerged on the mechanism of resistance: some bacteria have the capacity to transfer a cytoplasmic factor (R-factor) which confers resistance to one or many antibiotics to a previ-

ously sensitive strain (DATTA, 1969; LINCOLN et al., 1970a). The ability to transfer resistance to sulphonamides is now possessed by 20 per cent of Escherichia coli isolates from women with their first urinary tract infection (BRUMFITT et al., 1971).

5. Maintenance Chemotherapy

Against this background long term chemoprophylaxis seems rather a forlorn hope, and there are scanty controlled data to substantiate its use. RAY et al. (1970) reported a small series in which continuous chemoprophylaxis was superior to ad hoc treatment of infections in children without urological abnormalities, but not with neurogenic bladder. NORMAND and SMELLIE (1965) present considerable anecdotal evidence that low dose long term chemotherapy can prevent the progression of pyelonephritic scarring. In view of the rapid development of resistant organisms in the bowel, it seems improbable that sulphonamide prophylaxis could be effective; indeed, ORMONDE et al. (1969) demonstrated nitrofurantoin to be a more effective prophylactic agent than either sulphadimidine or cycloserine and BAILEY et al. (1971) showed low dose (1 mg/kg body weight) nitrofurantoin to be an effective prophylactic in adults with recurrent bacteriuria. Consideration of the mathematical models presented by O'GRADY et al. (1968) suggests that even slight prolongation of the mean generation time may have a marked effect on bacterial colonisation of the bladder.

6. Antibiotic Therapy in Uraemia

Many problems arise in the treatment of patients with renal failure. For drugs excreted mainly by the kidney, modification of dosage schedules is required to prevent accumulation (KUNIN, 1967; Table 6). As the volume of distribution of the drug is unaltered, the individual doses are unchanged, but their frequency of administration is reduced (O'GRADY, 1971). Kanamycin, gentamycin, colomycin

Table 6. Some aspects of the administration of antibiotics commonly used in the treatment of urinary tract infections

Drug	24 hour dosage (mg/kg)	Oral administration	Modification of dosage in renal failure	Comments
Sulphonamide (Sulphafurazole Sulphadimidine)	100	Yes	+	Avoid in jaundiced neonates
Nitrofurantoin	10	Yes	Do not use	Useful prophylactic at low dose (1–2 mg/kg/day)
Ampicillin	30	Yes	+	
Carbenicillin	150	No	+	
Cephalosporins	30	Yes (Cephalexin)	+	Nephrotoxic (Cephaloridine)
Kanamycin	10	No	++	Nephrotoxic and ototoxic
Gentamycin	3	No	++	Ototoxic
Trimethoprim	8	Yes	+	Synergy with sulphonamides (Sulphamethoxazole)
Nalidixic acid	50	Yes	+	Avoid in neonates

and streptomycin are particularly liable to accumulate in renal failure, and may cause ototoxicity or nephrotoxicity. Schedules for the administration of kanamycin (SØRENEN et al., 1967) and gentamycin (GINGELL and WATERWORTH, 1968) to uraemic individuals have been published. For example, gentamycin should be given parentally in a dosage of 1 mg/kg body weight 8-hourly with a glomerular filtration rate above 70 ml/min/1.73 m^2 SA, 12-hourly down to 30 ml/min/1.73 m^2 SA, 24-hourly down to 10 ml/min/1.73 m^2 SA and 48-hourly or at longer intervals as dictated by blood levels (which should not exceed 10 μg/ml) if the glomerular filtration rate is less than 10 ml/min/1.73 m^2 SA. In advanced renal failure, administration of these agents should be controlled by estimation of the blood level taken just prior to injection to ensure that the concentration has fallen to a low level. Care should be exercised in the choice of antibiotic combinations to ensure that it is feasible to estimate blood levels in the presence of more than one drug.

Some antibiotics are nephrotoxic and may cause further deterioration of renal function: streptomycin, kanamycin, colomycin and cephaloridine. The nephrotoxicity of gentamycin is not well established. The fraction of an antibiotic which has both a renal and an extra-renal clearance that is excreted by the kidney may decrease at low levels of glomerular filtration rate and be insufficient to reach effective concentrations in the urine. As an example, nitrofurantoin is of very little value in the treatment of urinary infection in chronic renal failure (SACHS et al., 1968), yet may accumulate in the serum to cause peripheral neuritis (LOUGHRIDGE, 1962). Tetracyclines should not be administered to uraemic patients: the interference with bowel flora diminishes gastrointestinal urea metabolism and aggravates the uraemic state.

7. Antibiotic Therapy in Neonates

There are some special risks attendant upon the administration of antibiotics to neonates (NYHAN, 1961). Sulphonamides may precipitate kernicterus by displacing bilirubin from its binding site on albumin (ODELL, 1969). Chloramphenicol, now no longer used, is inefficiently conjugated by the neonatal liver (WEISS et al., 1960) and may cause toxicity—the grey syndrome. Penicillins have a prolonged half life in young infants (AXLINE et al., 1967) due to decreased tubular secretion, but toxicity problems are minor. Tetracyclines should be avoided in young children because they cause hypoplasia of the dental enamel.

8. Some New Antimicrobial Agents

Trimethoprim specifically inhibits the bacterial enzyme dihydrofolate reductase, but has little effect on the human enzyme (Symposium, 1969; GARROD and O'GRADY, 1972). It therefore acts in the same metabolic sequence as sulphonamides, and there is synergy between the two agents. Trimethoprim is now only available in combination with sulphamethoxazole, which was selected because its half life is similar to trimethoprim, thus preserving the optimal ratio of the two drugs. REEVES et al. (1971) reported a higher cure rate of hospital urinary tract infection with this mixture than with ampicillin or sulphadimidine, and it has proved to be a very useful addition to the therapeutic armamentarium. The recent report of resistance due to R-factors is, however, disturbing (FLEMING et al., 1972). The drug is useful in infants unless there is jaundice, when it should be avoided because the sulphonamide component may precipitate kernicterus.

Of the cephalosporins (Symposium, 1970), cephaloridine and cephalothin must be administered parentally. There have been some reports of nephrotoxicity of cephaloridine (KAPLAN et al., 1968), but the problem seems to be less with cephalothin. Cephalexin has a similar spectrum to the other cephalosporins, but can be administered orally, and is as effective as ampicillin (DAVIES et al., 1971).

Gentamycin is the latest aminoglycoside antibiotic and has emerged as an important drug in the treatment of patients with gram-negative septicaemia. It has a major advantage over kanamycin in that it is effective against Pseudomonas pyocyaneus. For treatment of this organism, it has sometimes been combined with carbenicillin, but there is evidence that under some circumstances this combination may be antagonistic (MCLAUGHLIN and REEVES, 1971). Gentamycin dosage and its modification in renal failure is discussed above, and the kinetics of gentamycin excretion in infants are reported by MCCRACKEN et al. (1971).

9. Candida

Candida albicans infection of the urine is sometimes a problem in children with urological disorders, particularly if drainage tubes are left in situ. The mycelial masses may obstruct the flow of urine. Under these circumstances, antibiotics should be discontinued, but local irrigation with nystatin is sometimes required.

XI. Conclusion

The volume of information about the natural history and treatment of urinary tract infection has grown so rapidly in the past decade that it has become difficult to decide which techniques are relevant to the clinical practice of paediatric urology. In particular, most of the advances described in this chapter have not been subjected to cost-benefit analysis. For example, a case could be made that every child with a urological malformation should have a monthly quantitative bacteriological analysis of a clean catch urine specimen; but does the information merit the labour of its collection, and materially improve the child's prognosis? In the next decade, it will be as important to study the problems of the delivery of health care by established techniques as to further the basic understanding of the disease process; this generalisation applies with particular force to the management of urinary tract infection of childhood.

H. Localised Inflammatory Lesions

D. Innes Williams

With 3 Figures

I. The Kidney

In contrast to the very common generalised pyelonephritis of childhood, localised renal infections are rare and becoming rarer as antibiotic treatment of primary infections improves. Specific infection with tuberculosis has almost disappeared in children under the age of 12 in Western Europe and North America. Hydatid disease is still seen in some areas, but Actinomycosis is almost unknown. Metastatic pyaemic infections still occur from time to time, however, and present in various guises.

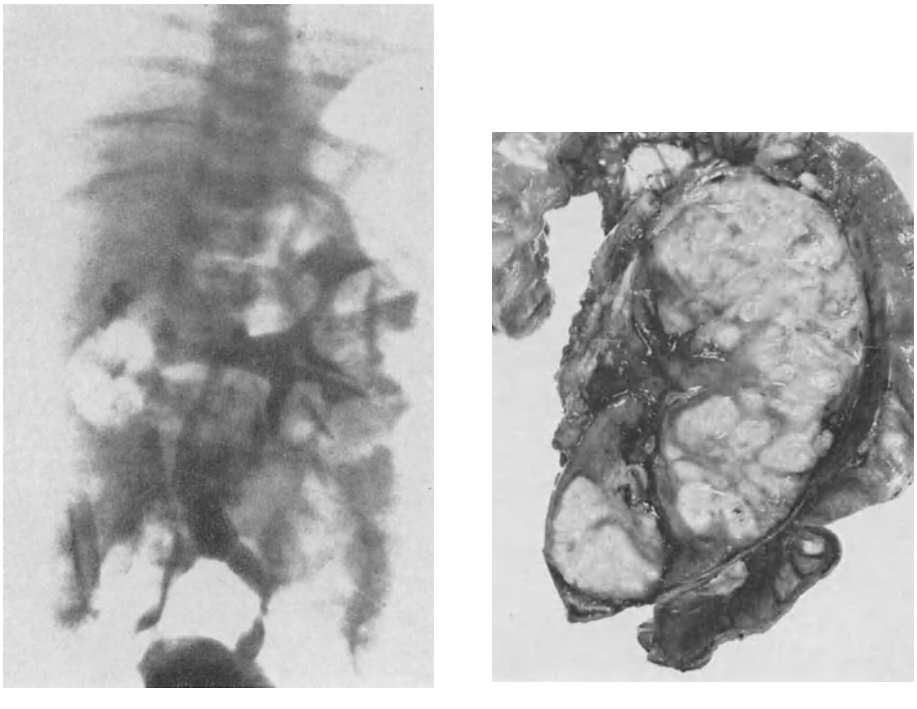
1. Renal Carbuncle

Although acute staphylococcal septicaemia from umbilical sepsis and osteomyelitis is likely to be effectively treated before the kidney is involved, metastatic infections may occur in less evident ways and may progress to severe destruction before they are recognised. Affected children present with a history of some weeks of general ill health and low grade fever, and are found on examination to have a large swelling in one loin. The urine is often free of pus, though it may contain staphylococci, which are the usual cause of the disorder. Intravenous urograms show a greatly enlarged kidney and a deformity not unlike that seen in adult polycystic disease (Fig. 33). Often the renal function is surprisingly well preserved, but where there is massive involvement antibiotics are unlikely to control the infection satisfactorily and nephrectomy will be required for the unilateral disease. In older children the carbuncle may be a solitary one, presenting with chronic pain in the loin, though there is usually some history of fever and some evidence of bacteriuria. Urography shows the presence of a mass in the kidney, strongly suggestive of tumour or cyst (Fig. 34): it is found to be avascular on arteriography and often proves to be a well localised lesion at exploration which will settle down satisfactorily if drained.

2. Xanthogranulomatous Pyelonephritis

The deposition of cholesterol-containing material within an inflammatory lesion in the kidney produces the change of xanthogranuloma, evident to the naked eye as bright yellow crystalline or amorphous material within the inflamed area. On many occasions this has been observed in adults, giving rise to a tumour-like mass in the kidney; the same disorder has been recorded in infants by Ceccarelli et al. (1970), but in the author's experience xanthogranuloma has ordinarily been the accompaniament of pyonephrosis due to stone and associated with proteus

infection. Without stone the tumour-like swelling must be differentiated from neoplasm by arteriography; the central area is avascular, the periphery irregular, but a similar picture may be obtained in some nephroblastomata and entire reliance cannot be placed on these findings. Nephrectomy or partial nephrectomy will be required.



a b

Fig. 33 a and b. Renal carbuncle. Multiple pyogenic abscesses in an infant. a Intravenous pyelogram shows apparently good function in enormously enlarged left kidney. b Nephrectomy specimen showing extensive abscess formation within the renal substance

3. Perinephric Abscess

Staphylococcal perinephric abscess is essentially a complication of renal carbuncle which has ruptured into the perinephric tissues, though the intra-renal lesion itself may have been very small. With better antibiotic control of infection this disorder has become extremely rare. The signs are of pain in the loin and limp due to psoas spasm: later a swelling and an oedematous mass appears in the loin. The urogram shows a loss of the psoas shadow and displacement of the kidney and ureter.

Perinephric abscess as a complication of infected stone disease is not so uncommon; it is almost always due to a proteus infection and the diagnosis is evident radiologically from the presence of the stone.

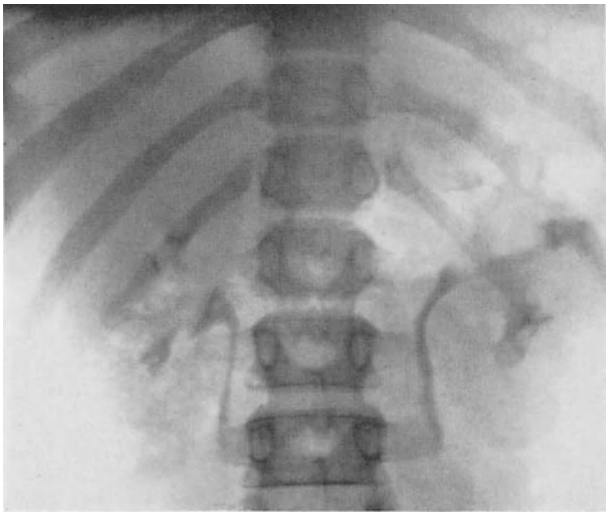


Fig. 34. Renal carbuncle. Intrarenal abscess. Intravenous urogram in a 10 year old girl with left loin pain. The renal sinus is spread out and the calices compressed by an avascular mass. Proved at operation to be an abscess within the renal substance. Uneventful convalescence after drainage

II. The Bladder

The simple cystitis which accompanies the urinary infections of childhood requires no special comment: it is ordinarily associated with frequency and urgency of micturition and some dysuria, but if unaccompanied by upper tract infection it is unlikely to cause pyrexia or more local signs than reddening and oedema of the vesical mucosa. It is a transient phenomenon responding rapidly to chemotherapy. There are, however, a number of variant types of cystitis, acute, sub-acute and chronic, which are ill-defined both clinically and pathologically and variously identified by adjectival appendages reminiscent of dermatological nomenclature.

1. Acute Haemorrhagic Cystitis

This term is suitably used to describe a condition of sudden onset with haematuria, frequency and urgency, often with a good deal of local pain and some pyrexia. Radiologically there is likely to be some irregularity of the spastic bladder wall with a little ureterectasis. MUFSON et al. (1971) investigated 25 children with this type of disease and found sterile urine in about two thirds of them, an adenovirus in 3 and an E. coli in 3. The disease is in many ways comparable with the abacterial pyuria commonly observed in soldiers during World War II, but little seen in adults since that time. It seems certain that a virus infection is responsible for some of these cases, and perhaps for all of them. Almost inevitably the antibiotics are employed in their treatment and in general the symptoms subside in the course of a few weeks. Under the heading of acute haemorrhagic cystitis might also be included rare examples of bacterial infection which appears to involve all layers of the bladder wall, persists for some weeks and leaves a permanently damaged atrophic mucosa and fibrosis replacing much of the muscle.

2. Eosinophilic Cystitis

A number of children, and rather more adults, have been reported as suffering from this disease, but the diagnostic criteria are not always clear-cut and since eosinophilic infiltration of inflamed bladder tissues can occur in a variety of circumstances it is perhaps unsatisfactory to employ the term eosinophilic cystitis to indicate a specific disease entity. Most of the children described as having this disorder have suffered from an acute or sub-acute condition associated with haematuria, frequency and dysuria (WENZL et al., 1964; CHAMPION and ACKLES, 1966). The urine is ordinarily sterile and there is very little fever. Intravenous pyelograms show a small capacity thick-walled bladder with some ureteric hold-up. On cystography and on cystoscopy there may be a localised lesion (Fig. 35), most often on the dome of the bladder with polypoid oedematous bullae not unlike the changes seen in infiltrating tumour. The lesion has at times been mistaken for rhabdomyosarcoma, though the polyps associated with eosinophilic cystitis are much redder and more evidently inflamed. On bimanual examination no more than slight thickening of the bladder wall can be felt. Biopsies show infiltration of the subepithelial layers by eosinophilic cells with plasma cells and interstitial oedema; although the disease may last some weeks, or even months, there is a tendency to spontaneous improvement with restoration of the mucosa to normal.

An allergic basis has been postulated for some of these cases, which may at times show an eosinophilia on blood examination, and attention has been drawn

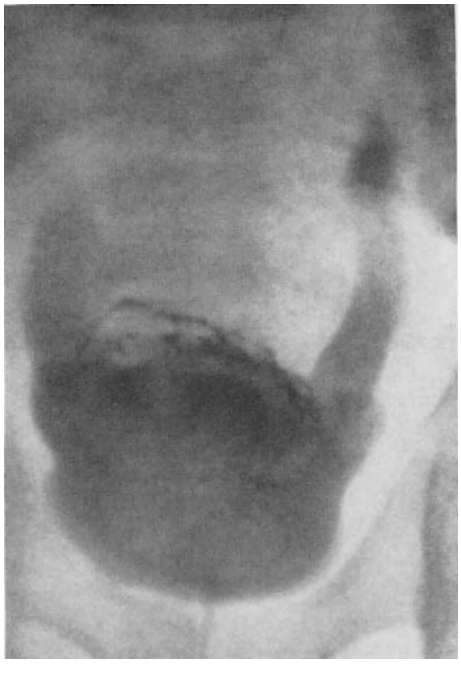


Fig. 35. Eosinophilic cystitis. The cystogram in a boy of 6 with reflux and recurrent infection. The apex of the bladder shows a lobulated filling defect which was associated with a large area of thickened, red and oedematous mucosa, histologically exhibiting the changes of eosinophilic cystitis

to the co-incidence of eosinophilic gastro-enteritis. However, in general the allergen responsible has not been identified. PERLMUTTER et al. (1968) have reported a case in which Toxocara cati antibodies were found and suggested the child had been infected from a domestic pet. Variable eosinophilic infiltration may, however, be found in simple proliferative cystitis and in cases of bladder tumour, particularly where a previous biopsy has been performed.

3. Proliferative and Follicular Cystitis

It is well known that in many cases of chronic or recurrent urinary infection in children, cystic lesions are observed cystoscopically; they are usually multiple, 2–3 millimetres across and most frequently found on the trigone or lateral walls of the bladder. Some are translucent, some opaque with variations in colour from grey through yellow to brown.

Although a cystoscopic diagnosis of "cystitis cystica" is frequently attached to these lesions, biopsy reveals that they may have a number of histological appearances of which cystitis is but one; it appears that various local factors, including chronic inflammation, neoplasia and possibly allergic reactions or immunological responses, may cause the urothelium to become unstable with the resultant appearance of one of the forms of proliferative cystitis. There may thus be proliferation of the epithelial cells into solid nests (Von Brunn's nests), small epithelial lined cysts (cystitis cystica) or the development of mucus-secreting glands in the epithelium (cystitis glandularis). Stromal proliferation also occurs with the development of lymphoid follicles (cystitis follicularis) and in some there is an accumulation of eosinophils as in eosinophilic cystitis.

It is clear that in children the most common underlying cause of urothelial instability is inflammatory. However, cystitis glandularis, which is uncommon in children, must be considered in the context of the exstrophied bladder as possibly pre-malignant. Cystitis follicularis, a form frequently seen in children, may well have an immunological origin but in general the factors responsible are unknown.

Although it is not unusual to find evidence of follicular cystitis in cases of reflux or other anomalies, especially where they are associated with chronic or recurrent urinary infection, it is also seen in children with infections but no other identifiable disorder of bladder function. KAPLAN and KING (1970) made a diagnosis of cystitis cystica in 2.4 per cent of children with urinary infections, but no extensive histological investigation was undertaken. The change did not occur in the very young, but had no specific associations; in general the lesions disappeared when the infections ceased, due to medical or surgical treatment of a urinary anomaly. However, cystitis cystica was apt to be associated with a poor short term prognosis in regard to the elimination of infection. EHRENSPERGER (1970) described these cases as granular cystitis: he observed that although in the superficial layers of the submucosa the infiltration was mainly by lymphocytes, in the deeper layer eosinophils were present, suggesting an allergic factor. The results of treatment were not satisfactory in his series and only 9 out of 30 were cured. He advocated the use of steroids and bladder washouts as well as chemotherapy. FETSCHERIN (1967) has undertaken cytological studies of the urethral mucosa in girls with granular cystitis in order to detect a possible correlation with hormonal activity; no such correlation was observed, however.

Radiologically, proliferative cystitis has been observed by the author as extensive filling defects in the cystogram, and GRIEVE (1967) has published a similar

case. In both instances infection was present from time to time, but was not an invariable factor, and improvement occurred over the course of years.

Thus, although much remains to be learned about it, proliferative cystitis does not seem to be responsible for any specific symptom and its clinical place at present is rather as a prognostic indicator; although it may disappear if the urine is maintained sterile for long periods many children go into puberty with the lesions still present.

4. Pseudo-Membranous Cystitis

On rare occasions cystoscopy in the case of a child with recurrent infection and dysuria reveals a grey membranous deposit on the mucosa in the region of the base of the bladder, somewhat reminiscent of a diphtheritic membrane: this cannot be washed away by irrigation but light application of diathermy will disperse it. It has some tendency to re-form, but local fulguration with long term chemotherapy is ultimately an effective treatment.

5. Malacoplakia

This rare disease is usually seen in adult life, but it has been described in childhood (Opperman, 1924; Morrison, 1944): it is to be regarded as an abnormal tissue reaction to E. coli, and produces a form of chronic cystitis in which there are small, soft, grey-yellow elevations on the mucosa which exhibit histologically the diagnostic appearance of calcospherites, known as Michaelis-Gutmann bodies.

6. Bilharziasis

A child who has been in an area where bilharzia occurs should be suspected of this disease if he is suffering from haematuria. The diagnosis is best made by recognition of the ova in the last drops of urine expelled at the end of micturition, but the characteristic cystoscopic appearance is well described in standard works of urology.

7. Granulomatous Cystitis

Johnson et al. (1967) reported two cases of focal granulomatous cystitis simulating bilharzial disease in children from British Columbia where bilharzia does not occur. They attributed this disorder to an unknown parasite, but noted areas of eosinophilic infiltration between focal granulomata, and they discuss the possible relationship of this disorder with eosinophilic cystitis. It seems likely that an infective origin was responsible.

8. Cystitis Due to Cyclophosphamide

As a complication of the treatment of leukaemia and other forms of malignancy, cyclophosphamide cystitis can be a cause of serious symptoms with profuse haemorrhage and disabling frequency and dysuria. Radiologically a spastic bladder with ureteric dilatation is usual: most cases will subside with treatment, but very severe haemorrhage as seen in the post-irradiation bladder can, at times, demand active intervention.

9. Interstitial Cystitis

Although GEIST and ANTOLAK (1970) have described 21 cases of interstitial cystitis with a variety of complaints, the present author has never seen any child with cystoscopic appearances approaching that seen in the typical Hunner's ulcer of adult life.

III. The Prostate

Prostatitis is, in general, a complaint from which prepubertal boys are mercifully spared, but on rare occasions during the first few weeks of life an acute staphylococcal prostatic abscess may be encountered, causing retention of urine and associated epididymitis. The diagnosis is unlikely to be missed, provided a rectal examination is made, and simple drainage from the perineum leads to cure. It seems likely that these infections are metastatic from umbilical sepsis.

On a number of occasions a peri-prostatic haematoma, later infected to form an abscess, has been encountered (WILLIAMS and MARTINS, 1960). These children are seen during the first two or three weeks of life with urinary obstruction and a boggy mass palpable on rectal examination. On retrospect is seems possible that many of these cases are thermometer injuries: a clinical thermometer roughly introduced into the anus of an infant may well penetrate the anterior wall of the rectum and cause an infected haematoma. Simple drainage should suffice for cure.

IV. The Urethra

A gonococcal urethritis in boys, described by older writers, has not entered the author's experience, and although Reiter's syndrome has been described in children (CORNER, 1950) with urethritis and arthritis complicating dysenteric infection it must be exceptionally rare.

WILLIAMS and MIKHAEL (1971) have described a series of boys in which a mild bulbar urethritis produced urethral bleeding or urethral discharge of a mild degree for long periods. On examination there was often a little meatitis and urethroscopy revealed a fibrinous inflammatory lesion on the mucosa in the bulb of the urethra. No organisms could be cultured from these cases, although some seemed to improve with tetracycline. Nevertheless, minor episodes of urethral bleeding might occur over the course of many months. No definitive stricture has resulted from this type of lesion, though it was suspected as a possible cause in one.

I. The Female Urethra in Recurrent Infections

D. Innes Williams

With 2 Figures

I. Introduction

Recurrent urinary infection in girls is perhaps the commonest disorder for which children are referred to the urologist, and despite the numerous reports of varying but apparently successful methods of treatment it remains a sore trial to many. Some of these cases are found to have clearcut anomalies, such as obstruction, reflux or stone, but the majority are radiologically normal or have very questionable abnormalities. In the absence of reflux there is very little evidence that these infections produce any permanent renal impairment, and most are probably confined to the lower urinary tract, yet they are an important cause of recurrent malaise, loss of schooling and of urinary incontinence. In many centres the investigation and treatment of these children occupies a very large proportion of the time and effort devoted to paediatric urology, and whilst paediatricians are apt to treat children conservatively, amongst the urologists there has been a natural bias in favour of instrumental methods or operative management. There has been a widespread conviction that any procedure which widens the female urethra will cure a substantial proportion and investigations often seemed aimed at providing a scientific basis for these procedures. Only in the last two or three years have controlled studies been reported and it must be admitted that a study of the disorder is a difficult one to control: the symptoms are variable and intermittent. Spontaneous improvement is common, collection of specimens difficult and bacteriological standards variable. Nevertheless it is the hope of all urologists, and the belief of many, that a minor correctable disorder of bladder or urethral function will be found to account for the problem. The possible factors are reviewed in this chapter. It is still possible that the explanation might lie in immunological factors and others beyond the scope of the present author, and all reports should be measured against the known overall incidence of infection and its tendency to spontaneous cure. Thus Kunin et al. (1964) found that 1.2 per cent of schoolgirls had demonstrable infection at any one time, some were mildly symptomatic, others entirely unexpected. Disappearance of infection was often spontaneous or the result of treatment, but recurrence or appearance of infection in other children kept the proportion of the total school population infected at about the same level.

As well as an acquaintance with the limits of normality a balanced view of the problem requires a historical perspective. Over the years there have been a number of dramatic changes in the attitude of urologists towards possible causative factors; new ideas are constantly put forward in publications, but old beliefs although no longer possessing general credence are seldom disproved in the literature. Throughout the 1930's and 1940's the chief factors sought in the investigation of recurrent urinary infections in girls were mucosal or sub-mucosal changes

and evidence of inflamed glands in the urethra. WINSBURY WHITE (1961), who made many contributions on this subject, was a keen advocate of urethroscopy and of the fulguration of projecting polyps and "hillocks" on the bladder neck and trigone. MEREDITH CAMPBELL in 1952 states that urethro-trigonitis is the commonest lesion found in young girls with recurrent infection and believed that intermittent urethral dilatation was the method of choice in treatment, dilatation being of value in opening up gland ducts and massaging out their contents. In the 1950's greater scepticism was expressed in regard to these lesions: polyps at the bladder neck, common enough in women, are not seen in the child and the prepubertal female urethra does not have glands, at least in its distal part. The appearance of cystitis cystica came to be seen as the consequence rather than the cause of infection. At this time mild degrees of obstructive uropathy came to be regarded as the common cause and bladder neck obstruction a very common diagnosis. At first endoscopy was the method of diagnosis and endoscopic resection the common method of treatment, e.g. EMMETT and SIMON (1956). Later with increased use of radiology the importance of reflux became more obvious, but it was often regarded as evidence of bladder neck obstruction and accordingly treated by urethral dilatation or bladder neck revision. The past decade has seen a further shift of emphasis from the bladder neck to the distal urethra, but it is still postulated that an obstructive lesion is the cause of recurrent infection, still to be treated by urethral dilatation or by more radical methods of meatotomy or urethrotomy. Parallel with these developments there have also been suggestions of an abnormality in bladder function, which may not be due to obstruction but to other factors, such as minor neurological lesions or to psychological problems, or to a reflex from a tender inflamed, but not necessarily obstructive, distal urethral ring.

It is perhaps unlikely that a single cause will be found to account for all cases of recurrent infection in girls with normal pyelograms and consequently unlikely that any one form of treatment will be universally successful. Discussing the possible factors concerned it will be useful to consider first the findings of various forms of investigation.

II. Clinical Examination

All grossly abnormal findings exclude the child from the category under consideration, but minor problems may be discovered. Labial fusion is one of these but does not appear to be particularly related to recurrent infections. Anterior prolongation of the urethra is occasionally seen and affects the direction of the urinary stream. Hymenal folds pulling on the urinary meatus may perhaps be of significance in later life, but probably not in childhood. Vulvitis, a simple reddening of the mucosa with minimal discharge, is common and productive of pain on micturition; it is often confused with urinary infection and is perhaps occasionally the cause of it, but somewhat surprisingly in view of the evidence that vulval colonisation by E.coli often precedes urinary infection the urine may remain sterile despite external inflammation. Vulvitis may have a detectable cause, lack of hygiene or excess of it due to the ill-judged use of local antiseptics. The caustic content of additives to produce a "bubble bath" may be responsible. Threadworms are occasionally found. Enquiries into the toilet habits of the child are customary in some clinics but have seldom solved the problem.

III. Measurement of Residual Urine

The presence of residual urine is ordinarily regarded as presumptive evidence of an obstruction, but it may also be due to vesical dysfunction of neurogenic origin. The residue is very small in normal children (STEINERT and HESSE, 1970). Simple catheterisation after micturition is not always reliable because of the possible presence of reflux and because the child has not always had a good uninterrupted opportunity for micturition. The latter criticism also applies to radiological methods. Other methods have used a light radio-opaque substance (Lipiodol in almond oil) in the bladder with check X-Rays 24 hours later to see whether this medium has been voided. MCGREGOR and WYNNE WILLIAMS (1966) used the excretion of phenol red, which is very rapidly put out by the kidney but which will remain a long while in the bladder if residue is present. Radioactive methods may also be employed. Using any of these methods of measuring residual urine it is a common finding that some girls suffering from recurrent infection do retain a small but variable residue in the bladder, perhaps 10–20 ml; by no means all these children have other signs suggestive of obstruction, however, and HOLE (1967) has shown that the results of bladder neck revision or urethral dilatation in this group is often disappointing.

IV. Endoscopy

The observation of trabeculation is important evidence of obstruction or of a neurological disorder, but the observation is a subjective finding and urologists will differ in the importance attached to it. Almost any girl with a great deal of frequency will have mild trabeculation. Prominence of the bladder neck of a degree ordinarily found in male adults is exceptionally uncommon in this group. Cystitis cystica is a feature of many cases of recurrent infection and since it goes along with a longstanding disorder present for a number of years it is likely that they have a bad prognosis, but its exact significance remains unknown. Endoscopy has not been of value in the diagnosis of distal urethral obstruction.

V. Urethral Calibration

The current interest in distal urethral stenosis as a cause of recurrent infection has resulted in great emphasis on calibration performed with bougies à boule, judging the size when the mucosa is pale and tight over the expanded end of the bougie as it is withdrawn. IMMERGUT et al. (1967) showed from an investigation in girls without urinary tract disease that from 0–4 years the mean calibre of the external meatus was 15 Fr; from 5–9 years it was 17 Fr; from 10–14 years it was 21.4 Fr. A similar calibre was found at the membranous urethra where a collagenous ring has been identified as a possible cause of obstruction. Urethrae of significantly smaller calibre than these figures are encountered only very uncommonly and usually in association with some anatomical abnormality. In a further study IMMERGUT (1968) showed that girls with urinary infections had statistically rather larger calibres, but he nevertheless advised urethral dilatation. In the great majority of cases the exact calibration has not been related to the degree of post-operative improvement of the child's symptoms following meato-

tomy, dilatation or urethrotomy. In view of these findings, which can be confirmed from the experience of many urologists, it is clear that there is no stenosis in any way comparable to a stricture in the male urethra. It might well be that functionally the distal urethra could form an obstruction unrelated to its actual calibre when examined under anaesthetic and this possibility will be discussed later.

VI. Radiology

The urethra in the girl has been subjected to very extensive radiological investigations during the past few years, the chief conclusions of which are that the limits of normality are very wide. The outline of the normal urethra may be a simple tubular one (Fig. 36) or it may taper slightly from the bladder neck to the

Fig. 36. A normal urethrogram in the female showing filling of the vagina

external meatus, but many children exhibit a slight collar at the bladder neck, a widened area below and a narrowing again towards the membranous urethra. Any attempts at voluntary restraint of micturition produce a ballooning of the mid-section, which can then be restored to normal on recommencing free flow. At one time the appearance of the "spinning-top" urethra was regarded as evidence of bladder neck obstruction with post-stenotic dilatation (MITCHELL, 1963) but more recently it has been regarded as due to urethral stenosis (Fig. 37). SCHOPFNER (1967) in a very extensive study showed, however, no relationship between the radiological appearance and urethral calibration, or between the urethral outlines and the symptoms or the presence of reflux. KEDAR (1968) attempted some correlation between the form of the urethra and the presence or absence of reflux, but most radiologists have concluded that it is impossible to identify urethral obstruction from the female urethrogram (ALLEN, 1970). The dilatation of the mid-

segment of the urethra has sometimes been interpreted to indicate that a valve is present in the distal urethra, but no valvular structure comparable with that found in male infants is ever discovered.

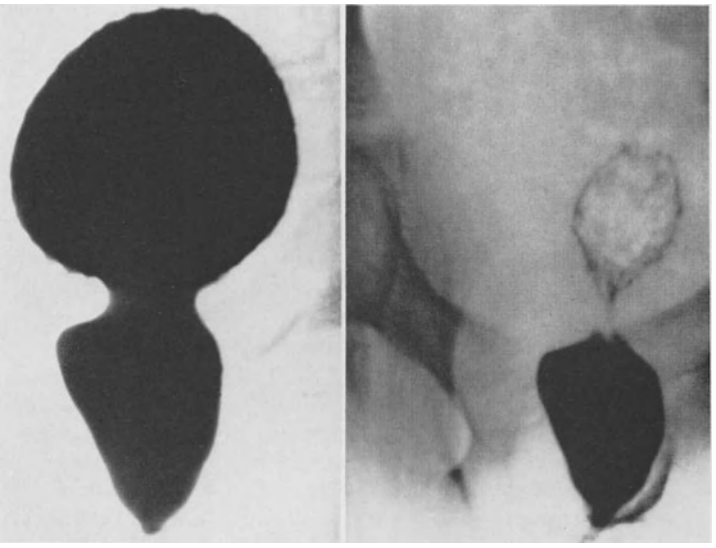


Fig. 37. Micturating cysto-urethrogram showing grossly dilated urethra in a girl with urinary infections. At calibration there was no stenosis of the distal urethra and the appearance may, perhaps, be attributable to external sphincter spasm

VII. Cystometry and Pressure Flow Measurements

It is logical to believe that urodynamic studies will finally settle the diagnosis in cases of doubtful bladder outflow obstruction, but standard reproducible techniques are not yet generally accepted and no firm conclusions have yet been reached in relation to minor obstructions in girls.

Flatmark and Gjertsen (1968) and Flatmark and Knutrud (1969), employing primarily a cystometrographic method found that "bladder hypertension" was present in girls with recurrent pyuria. They noted no change after bladder neck revision but after dilatation or meatotomy the "accommodation pressure" dropped with a small drop in micturition pressure and in bladder capacity indicating, they believe, that an obstruction in the distal urethra had been relieved. Lapides (1962) emphasises the role of the "dysfunctional bladder" in recurrent infections, while Hendry, Stanton and Williams (1973) also comment on a group of girls suffering from recurrent infection but no gross anomaly with an "unstable bladder" exhibiting frequent uninhibited contractions. Campbell (1951), on the other hand, finds a large capacity hypotonic bladder (lazy bladder syndrome) which predisposes to infection and later to upper tract change. It is thus evident that some abnormality of bladder function can be found in many children with recurrent infection, but whether it is the consequence of the infection

or a contributory cause is uncertain. Pressure flow measurements have given satisfactory results in boys. Thus GIERUP and ERICSSON (1971), using opening pressure, maximum voiding pressure and peak flow, found that an obstructive group could be easily defined in the male and that these tests were of diagnostic value. They are, however, very much more difficult to apply in girls and NUNN (1965) investigating girls suspected of bladder neck obstruction found no evidence of a pressure gradient across the bladder neck or in the lower part of the urethra. WHITAKER et al. (1969), in an even more careful study, failed to demonstrate any obstruction in cases of reflux or of recurrent infection.

Many observers believe that the measurement of the lateral pressure upon the urethra is more important than cystometry or flow studies, and all observers agree that the lateral pressure is greatest in the mid-section of the urethra, well below the bladder neck and a little above the external meatus. This is, of course, the site of the external sphincter and of a collagenous ring of tissue. Pressure profile measurements by TANAGHO, MILLER, LYON and FISHER (1971) have shown that the high point of the profile in mid urethra can be lowered by general anaesthesia and abolished by curare. They postulate that the ballooning of the urethra above this level can be due to detrusor pressure associated with asynchronous contraction of the external sphincter causing an interruption of the stream. They correlate this finding with the intermittent flow commonly noted by LYON and SMITH (1963), in girls with recurrent infection using a sound recording device. They believe that some local inflammation in the region of the external meatus could result in tenderness and spasm of the external sphincter, that this, by interrupting the stream, could lead to turbulent flow in the urethra washing bacteria back up from the region of the external meatus into the bladder. The minor external inflammation might thus perpetuate recurrent infections, but the vicious circle could be broken by overstretching the sphincter and thus eliminating the spasm. HENDRY, STANTON and WILLIAMS (1973) also find the high point of the pressure profile in the region of the external sphincter and agree that it can be lowered by anaesthesia, but were unable to confirm that wide dilatation had any permanent effect upon the sphincter muscle, or upon the progress of recurrent infection.

VIII. Results of Treatment

A very important factor in the case for urethral obstruction or spasm as a cause of recurrent infection has been the excellent results which are claimed for urethral dilatation or urethrotomy. However, many of these reports are unsatisfactory and the complaints for which the treatment is undertaken do not lend themselves to well controlled study. Recurrent urinary infection is a diagnosis which might well be applied to a child who has had one brief but definite episode of bacteriuria with another doubtful ill-recorded attack, or at the other extreme to a child suffering from repeated frequent feverish attacks with loin pain and extreme frequency of micturition. It is universally recognised that there is a tendency to spontaneous remission of recurrent attacks often supposed to occur chiefly at puberty when it might be postulated that the increase in calibre of the distal urethra was responsible, but in fact a survey of cases of recurrent infection often shows that remission has occurred earlier in childhood, or has gone on after puberty. It is thus difficult to tell from the literature whether one series is comparable to another and there is no accurate knowledge of the proportion of cases in each year likely to improve spontaneously. No controlled studies of a large

series of bladder neck revisions for recurrent infection are available and the diagnosis of bladder neck obstruction is considered in Chapter O, but KAPLAN and KING (1970) found no benefit from this procedure in simple cases of recurrent infection. The proponents of meatotomy, intermittent urethral dilatation or single wide dilatation and of urethrotomy have all claimed almost equally good results, though such controlled studies as are available do not always support this claim. Papers on the subject are too numerous to list, but examples may be given. KNAPPENBERGER (1963) claimed marked clinical improvement in 90 per cent of girls with recurrent infection as a result of repeated dilatation at six monthly intervals. LYON was one of the original proponents of wide dilatation and has repeatedly reported very good results; he emphasises the need for stretching the collagenous ring in the distal urethra beyond the point of rupture. Ordinarily bougies meet increasing resistance from the urethral wall up to about 24 Fr. then the ring appears to give way and dilatation is easier thereafter. It may be continued to 32–40 Fr. In a recent report LYON and MARSHALL (1971) review 864 children: of 283 with symptoms of cystitis 65 per cent had an immediate and sustained cure, in the long term 86 per cent were improved. Of 297 children with feverish attacks 82 per cent had an immediate cure and the failures were mostly in children with reflux. WEISS et al. (1968) found "stenosis" to be present in 96 per cent of 174 girls, and they cured the infection problem in 70–75 per cent when dilatation was carried to 32 Fr, but only 40 per cent when dilatation went no further than 22 Fr. GRAHAM et al. (1967) in 177 girls had a cure rate of 70 per cent of those without reflux and 49 per cent of those with it.

Meatotomy with dilatation would seem to have a similar effect to wide dilatation with rupture of the distal urethral ring, and HARVARD (1970) reports only 16 per cent of cases not improved by this method. However, FORBES et al. (1969) undertook a controlled prospective study of 37 girls and found that meatotomy had no detectable effect in altering the recurrence rate of infections or the symptomatology. KERR (1969) has advocated chiefly the use of the Otis urethrotome set at about 32 Fr: VERMILLION et al. (1971) followed a group of 106 girls with recurrent infection for two years. In a group treated by urethrotomy together with three months of appropriate drug therapy the cure rate was 78 per cent. However, KAPLAN, SAMMONS and KING (1973) made a blind comparison between dilatation, urethrotomy and medication alone and found no difference in the percent of patients cured in the three groups. There could have been a slight disadvantage to urethrotomy, but possibly the cases of very longstanding recurrent infection were improved by the dilatation techniques. HENDRY, STANTON and WILLIAMS (1973) found overall no difference between children investigated and treated with medication alone from those treated by urethral dilatation plus medication, but if there was a group for which some benefit from dilatation might be claimed it was those children with uninhibited bladder contractions.

IX. Conclusion

Girls with recurrent urinary infections without gross anomalies and with normal pyelograms do not form a homogeneous group and there is no justification for treating all of them by urethral dilatation or urethrotomy. The child whose cystogram is also entirely normal will probably do well on long term chemotherapy and it is doubtful whether endoscopy is justifiable for many of these. In some small volumes of residual urine are present, but this may be due to a failure of

training and of voluntary effort on the part of the child or to a mild outflow obstruction. In these and in children whose infections have already resisted the simple measures of control, cystoscopy is essential and urethral dilatation up to 32 Fr may be performed without risk of harm and with possible benefit for some. Repeated intermittent dilatations are psychologically damaging for the child and no more successful in curing the infections. Urethrotomy is, in general, a surprisingly safe procedure but does entail more hospitalisation and has not been shown to secure any greater benefit than urethral dilatation. Bladder neck revision should not be undertaken except on clear-cut evidence of obstruction at the bladder neck level. The criteria for this are discussed in Chapter O.

J. Vesico-Ureteric Reflux

D. Innes Williams

With 15 Figures

I. Introduction

In the fifteen years since the original volume of this series was written the problem of reflux has occasioned more controversy than any other topic in paediatric urology, and a full review of the subject is therefore required. Reflux undoubtedly justifies a full discussion by the frequency with which it occurs: its reported incidence varies considerably with the thoroughness of the investigation, but Scott and Stansfield's (1968) finding of reflux in 55 per cent of children with recurrent urinary infection is not out of line with other reports. In the great majority of these children reflux is the only detectable abnormality of the urinary tract function, so that it has become customary to speak of primary reflux where there does not appear to be any bladder disorder, but, although a useful clinical classification, this term obscures the issue so often in doubt as to the part played by infection in the aetiology of reflux. Very seldom, in fact, can reflux be treated as a single disease entity; its presence is but one facet of a complex and variable situation and this chapter is therefore concerned with many aspects of urinary tract disorder which may be associated with reflux.

II. The Normal Mechanism

Reflux is such a common finding in children that it is important to re-emphasise that it is an abnormality. In other species it is not necessarily the case: rats reflux with such ease that the phenomenon must occur in the healthy animal at times, while Lenaghan and Cussen (1968) have demonstrated that in pups under the age of two months reflux is common but it ceases spontaneously before the age of six months without having caused any renal damage. In the human child, however, numerous reports have shown that reflux is absent in normal circumstances. Iannaconne and Panzironi (1955) found one case in 50 infants; Iannaconne (1966) no case in 25 neonates. Lich et al. (1964) found no case in 26 neonates; Peters et al. (1967) no case in 66 premature babies. Jones and Headstream (1958) found one case in 100 children, and even the one later turned out to have urinary tract disease. Politano (1963) had no reflux in 50 children; Kjellberg et al. (1957) none in 101 children.

Some doubt on this subject has been raised by the writings of Krepler (1969) who investigated children with urinary infections and mentions a control group in which reflux was present in 33 per cent of children under two years of age and 2 per cent of older children. Nevertheless his controls were not normal children, they were investigated for failure to thrive, for recurrent pyrexia of unknown origin and for suspected malignancy and his evidence does not therefore contradict other

reported findings. It does, of course, indicate that reflux occurs much more readily in the infant than in the older child and that reflux is not necessarily a dangerous or permanent phenomenon, facts which can be confirmed by wide experience.

The intramural ureter upon which reflux prevention depends consists of "an intravesical section" lying immediately beneath the bladder mucosa; an "intramuscular section" which courses through the hiatus in the detrusor muscle and a "juxtavesical section" lying within the fibro-muscular fibres of Waldeyer's sheath. The ureter as it approaches the bladder loses its circular fibres and the intramural ureter is surrounded by only a thin layer of longitudinal muscle: a few of these fibres are inserted into the mucosa at the ureteric orifice, others having formed a decussation over the roof of the intravesical section continue into the trigonal muscle joining with transverse fibres to the opposite side and with longitudinal trigonal fibres passing down as far as the verumontanum in the male and a little below the bladder neck in the female.

Outside this true ureteric muscle there is a space allowing some upward and downward movement of the ureter within the detrusor hiatus. This space was first described by Waldeyer, although his name is more often applied to the sheath of fibromuscular tissue which encloses the space. The muscle fibres bordering this sheath merge upwards with the adventitia of the ureter and downwards with the detrusor fibres. Tanagho et al. (1968) find the muscle of Waldeyer's sheath continuous with deeply placed detrusor fibres extending well down to the bladder neck behind the trigonal layer.

The ureteric hiatus through which the ureter passes is a cleft in the detrusor layer, more or less vertically disposed, with intersecting muscle bundles around it, but the cleft is sometimes not completely filled by the ureter so that there is a weak point in the detrusor muscle layer postero-lateral to the ureter through which a herniation of mucosa sometimes forms the para-ureteric saccule.

Reflux prevention can be due to a passive valvular action or to active muscular contraction; it has been repeatedly observed that the normal human cadaveric bladder does not allow reflux, even though distended to high pressures. This reflux prevention depends upon the intravesical section of the ureter which, lying immediately below the mucosa, is compressed against the firm backing of the detrusor muscle behind it as the bladder pressure rises. Castro and Fine (1969) found, by graduated section of these detrusor fibres, that 5 mm of detrusor backing was adequate to prevent reflux in the normal bladder. Middleton found that the ratio of the length of intramural ureter to diameter averaged 6.7:1 in normal reflux preventing junctions and 0.75:1 in those which allowed reflux. Hutch (1961) records the actual length of the intravesical section which increases with growth from 0.1 cm in a premature child, to 0.7 cm in an infant of one year, 1.15 cm at ten years and 1.45 cm at nineteen years. All these studies emphasise the importance of the intravesical (submucous section) of the terminal ureter which is capable of forming a passive valve and the purely passive system is relied upon in almost all operations aimed at reflux prevention. Yet there is still some evidence that active muscular contraction plays an important part in the normal functioning of the human uretero-vesical junction. Stephens and Lenaghan (1962) maintained that the active contraction of the decussating longitudinal fibres crossing the roof of the intravesical section compresses the ureter and closes it after an efflux has occurred, and Lenaghan (1967) has demonstrated that in dogs unilateral sympathectomy is followed by ipsilateral reflux with asymmetry of the trigone due to muscular relaxation and consequent shortening of the intravesical segment. The situation in man is not necessarily the same, however, and Fryjordet (1968) investigated patients who had had lumbar sympathectomies and found no reflux at all. Tanagho

et al. (1969), also working with dogs, found an intact trigonal muscle to be essential for reflux prevention. Surgical interruption of the continuity between the ureter and trigone consistently resulted in reflux which disappeared after healing. Trigonal muscle stimulation increased the resistance to flow in the intramural ureter by bringing its walls into tight apposition, thus occluding the lumen. This action was impaired if the continuity of ureteric and trigonal muscle had been interrupted. It is, of course, a common observation in clinical cases that damage to the trigonal muscle consequent upon re-implanting one ureter frequently allows reflux to occur post-operatively on the opposite side. Thus, in spite of the post-mortem studies it is difficult to deny the importance of the trigonal muscle in normal human reflux prevention. This importance might lie in its capacity to maintain the length of the intravesical ureter, preventing retraction and therefore keeping a sufficient length to form a passive valve, or it might lie in the active closure of the ureteric lumen. Perhaps both actions are important, for although the rise in pressure which occurs in the bladder at the time of micturition will automatically close a normally placed intravesical section of the ureter, while the bladder pressure is low and the ureteric lumen remains open there may be some back and fore movement of fluid from bladder to ureter. This is, in fact, observed not infrequently in otherwise normal ureters during cine cystography. Some opaque medium escapes back into the lower part of the ureter at a very early stage in filling; it is rapidly returned by ureteric contraction and reflux does not occur again even when micturition takes place at high pressure. It seems that in these cases the intravesical ureter must have failed to close after efflux, allowing a low pressure regurgitation, even though the normal valvular action was present to prevent high pressure reflux.

III. The Pathology of Reflux

A variety of lesions may be responsible for a failure of the normal reflux-preventing mechanism: they are essentially local lesions of the intramural ureter rather than general disturbances of bladder function. Basically there may be a rigidity of the tissues which prevents obliteration of the ureteric lumen, an absence of sufficient length in the intravesical segment or an absence of adequate detrusor backing to an intravesical segment of normal length. All these anatomical defects will produce reflux consistently but the influence of infection and inflammation is not so clearly defined.

1. Reflux Due to Inflammation

It is generally agreed that in childhood reflux not infrequently occurs during an episode of cystitis and ceases after control of infection, but figures on the frequency of this event are hard to obtain since many investigators do not perform cystograms during the phase of active cystitis. King et al. (1968) regarded all cases of reflux in which the intravesical ureter was found to be of normal length and in which infection was present as due to inflammation, and they observed 50 cases in this category, of which 44 ceased spontaneously to reflux at later investigation. Harrow (1967), investigating 90 children with reflux, believed that in 42 the cause was recurrent non-obstructive cystitis. Shopfner (1970), in a radiological study of a very large series, believed that infection alone could have been the cause of reflux in 88 per cent of cases and of these 85 per cent responded to medical treatment alone. Krepler (1969), however, did not find such convincing

evidence that reflux occurred only during infection and LIPSKY (1971) found in an experimental study in dogs that inflammation alone in an anatomically normal ureterovesical junction could not produce reflux, thus contradicting the earlier work of AUER and SEAGER (1937). The mechanism usually postulated to be the cause of reflux in inflammation is oedema of the ureter and rigidity of peri-ureteric tissues, though these findings cannot always be confirmed cystoscopically.

2. Short Intra-Vesical Ureter

It has already been noted that HUTCH (1961) found the intravesical section of the ureter to be much shorter in infants than in older children and it is well known that reflux occurs more readily in the young. For reasons which are seldom evident a persistently short segment may occur as an isolated anomaly associated with reflux, or it may be seen along with ureteric dilatation and a wide trigone with the mega-ureter megacystis syndrome. A permanently dilated fibrotic ureter with reflux from any cause has a short intravesical segment.

3. Para-Ureteric Saccule

The ureteric hiatus in the detrusor muscle may be sufficiently large to allow herniation of the mucosa to occur postero-lateral to the ureteric orifice. Where there is a considerable muscular deficiency this hernia will occur at normal bladder pressures, although it is clearly more apt to develop with increased pressures due

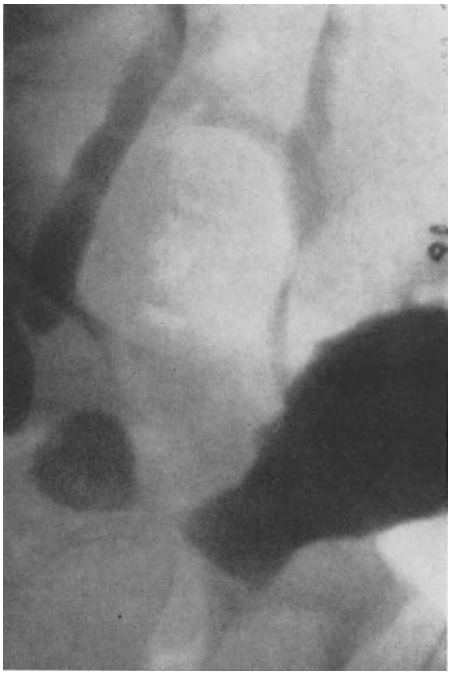


Fig. 38. Reflux with para-ureteric saccule. Micturating cystogram in a boy with recurrent urinary infection

to obstruction or neurogenic dysfunction. In the earlier stages the herniation only occurs during micturition and in the resting bladder some redundancy of mucosa is seen beside the ureteric orifice. In the more advanced condition a saccule is present all the time but it enlarges during micturition (Fig. 38). The enlarging saccule must always pull upon the ureteric orifice, and in many cases the orifice is drawn well out into the wall of the saccule during micturition. In these circumstances the intramural ureter is no longer backed by firm detrusor muscle and therefore allows reflux. However, a ureter with a para-ureteric saccule may on occasions be obstructed but not allow reflux and histologically it may be seen that the ureter and saccule are so closely applied that there is a deficiency of muscle in this area.

IV. Reflux and the Ureter

Reflux may be associated with a normal calibre ureter (Fig. 39) or with almost any degree of dilatation (Figs. 40 and 41) and it is easy to imagine that mechanical back pressure in reflux produces a progressive dilatation of the ureter. Such a hypothesis is hard to substantiate, however, from clinical observation: dilatation

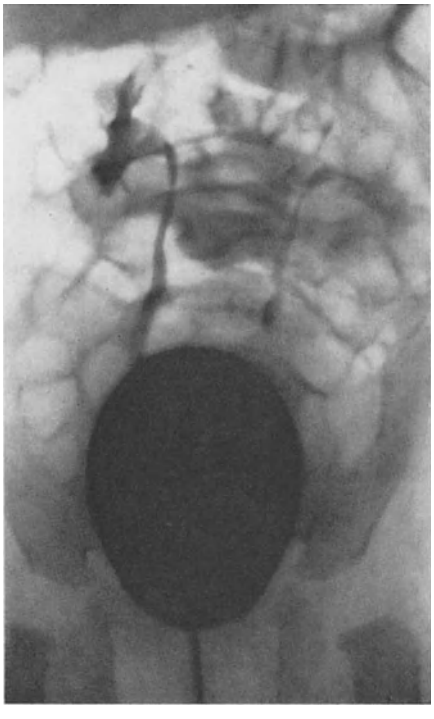


Fig. 39

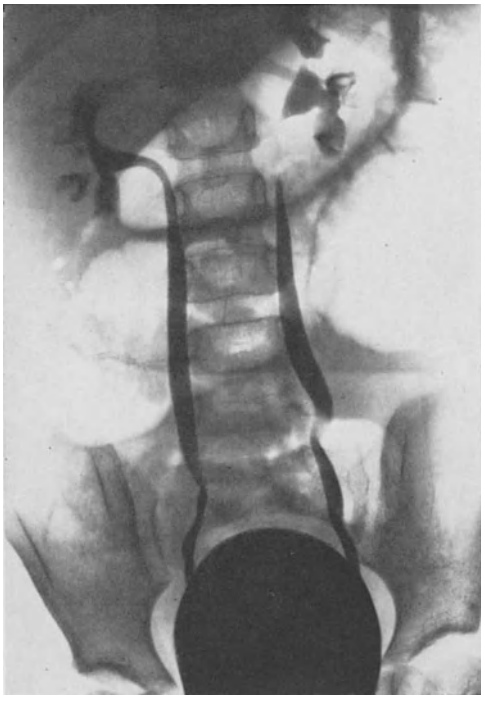
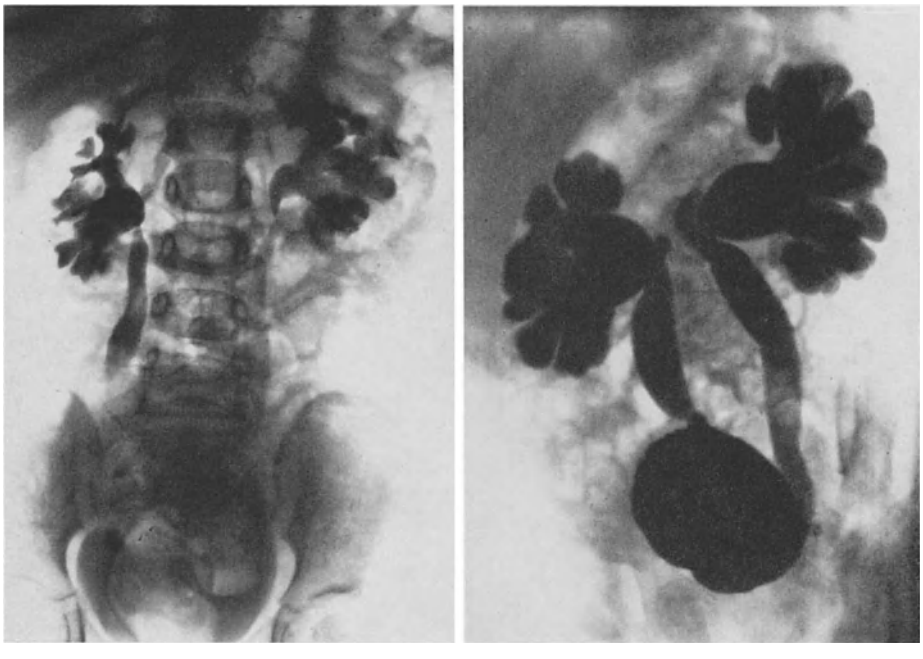


Fig. 40

Fig. 39. Reflux without ureteric dilatation. Cystogram in a male infant with a single episode of urinary infection. Spontaneous improvement can reasonably be expected

Fig. 40. Reflux with minimal ureteric dilatation and pyelographically normal kidneys. Cystogram in a girl with recurrent infection



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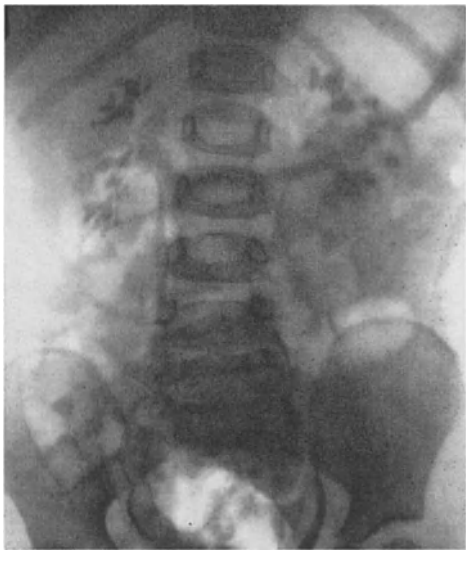


c

Fig. 41 a—c. Reflux with severe dilatation during micturition. a Intravenous urogram in a girl of one year with recurrent infection, showing moderate ureteric dilatation and renal scarring. b Cystogram showing gross dilatation during micturition. c Intravenous urogram a yearlater after control of infection by chemotherapy

may be due to a variety of factors and it is conceivable that ureteric deficiency is the cause rather than the result of reflux. Observation of the ureters in reflux by cine radiology provides some important evidence and many workers have combined this investigation with the measurement of bladder pressures (HINMAN et al.,

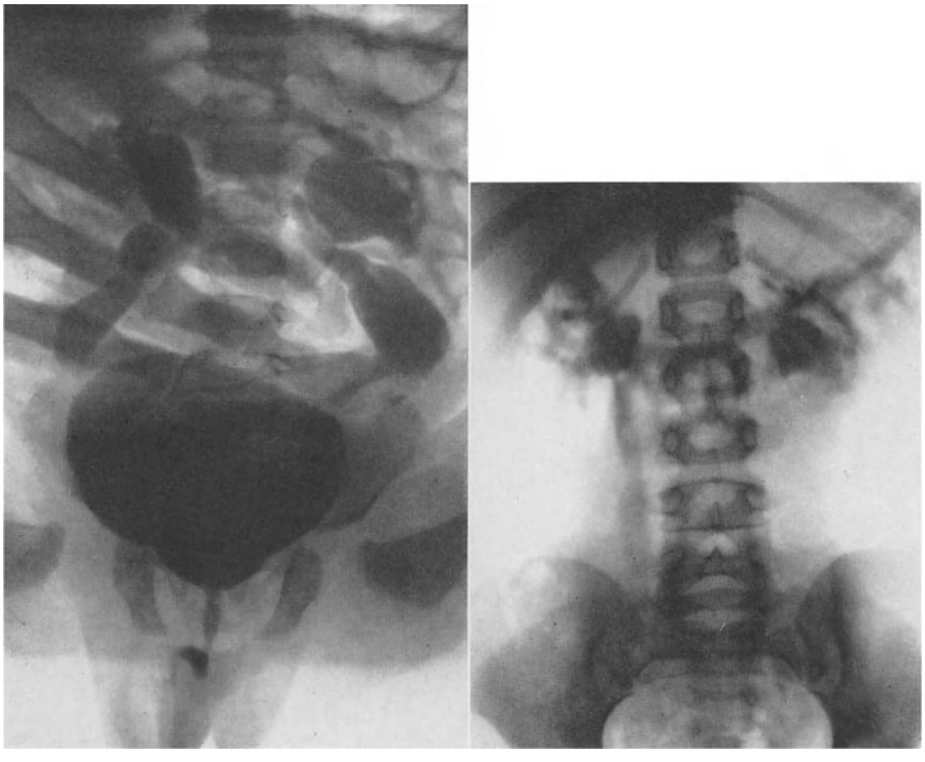
1962 and KREPLER, 1968). MELICK et al. (1966) have attempted to produce a full classification of reflux according to the bladder volume and bladder pressure, but the terminology of many classifications is confusing since reflux which occurs only during micturition is sometimes spoken of as high pressure reflux, while reflux taking place while the bladder is at rest is low pressure reflux. In the latter case, however, there is much less resistance to back flow from the bladder and during micturition the pressure which actually impinges upon the kidney is likely to be much higher and therefore more damaging than in the so-called high pressure reflux.

Certain specific patterns may, however, be described. Reflux may occur on simple bladder filling into a normal calibre ureter. In such instances the ureters appear not to have closed off after efflux, and they are capable of returning the reflux medium rapidly and do not fill again on micturition. In most other mild cases reflux occurs only during micturition and may or may not reach the kidney. In moderately dilated refluxing ureters there is a characteristic appearance and behaviour which distinguishes them from dilated obstructed ureters: the calibre depends very largely upon the state of the bladder. With an empty and relaxed bladder the ureter appears incompletely distended with rather lax folds and kinks, sometimes longitudinal striations in the pelvis and ureter can be discerned indicating corrugation of the mucosa, and a kinking is particularly liable to occur at the pelvi-ureteric junction. During micturition there is a rapid distension of the entire ureter and the renal pelvis with accentuation of the kinking but obliteration of the longitudinal striations. Peristaltic activity is not observed at the height of distension but recovers as the bladder relaxes, though it is seldom as vigorous as in the purely obstructive cases. MELICK and NARYKA (1960) and MELICK et al. (1966) record very low ureteric pressures at rest and believe these ureters are in fact incapable of raising a high pressure in contrast to the obstructive form. KIRKLAND et al. (1971) report that a high base line pressure is more common, but record abnormal pressure readings in almost all refluxing ureters which are capable of any active contraction. REUTERSKIOLD (1970) found most refluxing ureters had a good contractility and failed to find any particular pattern associated with reflux. All would agree that in severe grades of dilatation the ureter is extremely tortuous and often aperistaltic. Moreover it appears that the accurate measurement of bladder pressures has not produced data which can be accurately correlated with renal damage or with the prognosis in reflux cases.

In following the progress of a case of reflux with dilatation it is clearly of vital importance to compare like with like. The range in calibre of the ureter must be estimated using the I.V.P. with an empty bladder and a cystogram at the height of micturition as indicators (Fig. 41). Using these strict criteria an increase of ureteric dilatation is frequently observed in cases of reflux with bladder outflow obstruction, in cases of neurogenic bladder and in some with a severe infection, but with a sterile urine and a normal bladder the ureters do not show a progressive change. In some instances dilatation in an infant appears to become less even though reflux persists: sometimes there is a spontaneous cessation of reflux with improvement of dilatation and straightening of the kinks as growth proceeds, although it may be demonstrated by retrograde pyelography that the ureters are still capable of distension to their former calibre even though the I.V.P. may appear to have returned to something like normal. An improvement in dilatation can also be seen after simple reflux preventing operations, but once again the ureter retains a potential for considerable dilatation.

The surprising lack of documented cases of progressive dilatation in children with normal bladders and sterile reflux makes it difficult to attribute the ureteric

change in reflux to hydrostatic factors. Experimentally VERMOOTEN and NEUSWANGER (1934) found that ureteric dilatation only accompanied reflux in dogs if infection was present: this might, of course, be due to the high pressure in the



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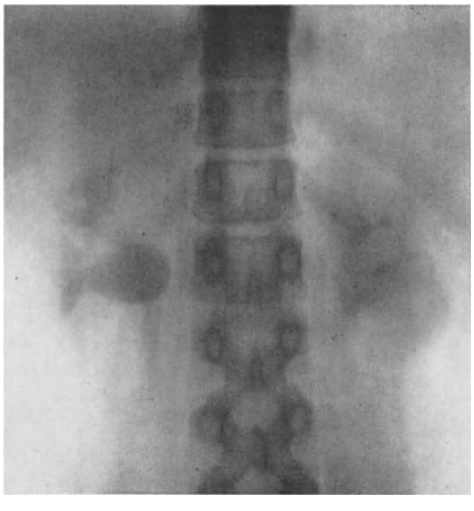


c

Fig. 42a—c. Reflux at birth, followed for 17 years. a Cystogram in a newborn infant with temporarily palpable bladder but no signs of infection. Bilateral reflux with small dysmorphic kidneys. No treatment given. b Intravenous urogram at 8 years of age: the boy remains symptomless and infection free. c Intravenous urograms at 17 years of age: still symptom free and sterile, but blood urea raised to 56 mg/100 ml. The kidneys are small and dysmorphic; there has been no increase of ureteric dilatation, reflux persists

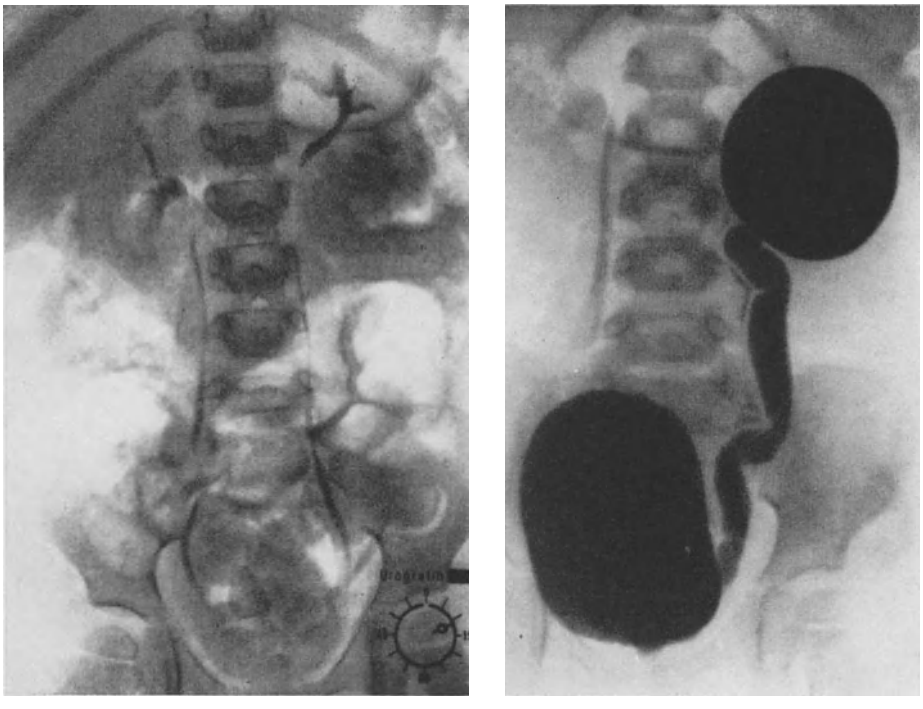
bladder or to the effect of bacterial toxins on the ureteric muscle. TEAGUE and BOYARSKY (1968) have shown experimentally that coliform bacteria and their endotoxins reduce ureteric peristalsis and cause a dilatation even before there has been any inflammatory reaction in the ureteric wall. Thus the dilatation in reflux might be due very largely to infective causes and the effect in a very young infant might be much more severe than would be expected in later life. However, ureteric dilatation can be observed in some sterile cases shortly after birth (Fig. 42) and it is possible that in these we are seeing the effect of a failure of development of the ureter throughout its length as well as at the uretero-vesical junction.

V. Reflux and Hydronephrosis

Many examples of vesico-ureteric reflux exhibit distension of the renal pelvis out of proportion to the dilatation of the ureter suggesting an association between reflux and pelvi-ureteric obstruction (HINMAN and HUTCH 1962). In the writer's series there have been a number of reflux cases subjected to pyeloplasty and these have fallen into two categories. In the first there appears to have been a true pelvi-ureteric obstruction presenting the classical signs of this disease and a clear-cut point of obstruction with a normal ureter below it. Reflux in these cases was sometimes partial, sometimes total, but it appeared to be irrelevant to the problem of obstruction and in several cases ceased spontaneously after pyeloplasty. In the second group there appeared to be no doubt that reflux was the primary disorder and that secondary kinking at the pelvi-ureteric junction was responsible for the appearance of obstruction. The operative findings were different, for although there was some narrowing at the kinked area there was never a clear-cut point of obstruction found in the simple cases. Ballooning of the renal pelvis in these occurred during micturition (Fig. 43) and the dilatation remained for some time after the ureter had emptied largely because of atonicity of the pelvic musculature. Following surgical prevention of reflux this acute dilatation during micturition no longer occurred and the pelvi-ureteric junction was capable of transmitting the normal output of the kidney without difficulty.

VI. Reflux and Obstructive Nephropathy

The persistently raised intrapelvic pressure found in obstructive cases produces a well known effect on the kidney, caliceal dilatation, destruction of nephrons and slowly deteriorating renal function. It is natural to suppose that the brief but repeated period of high intrapelvic pressure associated with free reflux would have a similar effect, though over a much longer time scale. HODSON (1969) has drawn attention to the radiological appearance of progressive destruction of the renal parenchyma due to obstruction, which sometimes occurs without gross hydronephrosis. In this "obstructive atrophy" the kidney is little enlarged, but the renal parenchyma is thinned by progressive distension of the calyces without any of the irregular scarring of pyelonephritis. In a number of older children and adults he finds this picture of obstructive atrophy with reflux but without evidence of obstruction and without history of infection. He therefore postulates that reflux is capable of producing these changes and he suggests that "intrarenal reflux", where backflow takes place into the renal tubules as can occasionally be demon-



a b

Fig. 43a and b. Reflux into duplex ureter with ballooning of lower renal pelvis during micturition. Complete ureteric duplication with both ureters involved in para-ureteric saccule. a Intravenous urogram in a girl with recurrent urinary infection. Good function in the upper pole of a left duplex kidney. Poorly opacified scarring of the lower pole. b Micturating cystogram showing reflux into both left ureters, but severe dilatation of the lower renal pelvis

strated, may be much more damaging, even without infection, than simple reflux into the renal pelvis. ROLLESTON et al. (1970) also believe that sterile reflux alone can produce renal damage, at least in infancy, and note the presence of intra-renal reflux in some children.

In experimental work it has been very difficult to demonstrate this obstructive effect of reflux on renal function. ROSS and THOMPSON (1963) produced reflux in dogs for twelve to twenty-two months but did not observed ureteric dilatation or renal damage in an uncomplicated case. KING and IDRISS (1967) followed dogs for seventeen to twenty months after producing reflux before infection supervened; during that time they noted no change in renal function, although it later deteriorated with infection. LENAGHAN et al. (1972) report similar findings in pups. In clinical practice it has also been hard to document progressive renal damage in sterile reflux cases without obstruction. SARGENT (1964) recorded one man observed with reflux over a twenty-three year period with no change in dilatation or impairment of function. FRIDJOFSSON and SUNDINN (1966) studied adults with iatrogenic reflux and found that the sterile cases had normal renal function. KING et al. (1968) followed several children with sterile urine over a period of two years and found no deterioration of function. Although, therefore, the radio-

logical evidence of late cases is distinctly suggestive it cannot be positively affirmed that sterile reflux alone damages the kidney; if it does so it must be over a long period and then probably in cases where there is free reflux without gross dilatation to damp down the pressure waves.

VII. Reflux and Urinary Infection

It is agreed that reflux can result from inflammatory changes consequent upon urinary infection, but there are many cases in which reflux has an origin in a congenital defect which is later complicated by infection; this event is so common that it may reasonably be supposed that reflux predisposes to infection. This predisposition would be explained by the maintenance by reflux of a residual urine within the urinary tract and a consequence of the theory should be a cessation of episodes of infection after surgical prevention of reflux. Various series have been reported and these will be discussed in a later section. It nevertheless appears that some 25 per cent of children whose reflux is satisfactorily corrected continue to have episodes of infection. As almost all treated children were those in whom medical treatment had failed it seems that surgery is partially, but not completely, effective.

VIII. Reflux and Pyelonephritis

Perhaps the most important observation relating to the natural history of reflux is its association with chronic pyelonephritis. In the child the classical radiological appearances of chronic pyelonephritis are coarse scarring and contraction, a small kidney with an irregular outline and loss of parenchyma in relation to clubbed and distorted calyces, (Figs. 42–46). Radiologically this appearance may be hard to distinguish from the congenitally small and dysplastic kidney discussed on p. 69. Almost 100 per cent of cases with clearcut pyelonephritic scarring will show reflux at some time (Hodson, 1967), or the appearance of the ureter is such as to make it reasonably certain that reflux has occurred in the past. Similar reports come from Scott and Stansfield (1968) and from Hutch, Smith and Osborne (1969). Where the disease is known to be progressive reflux can regularly be demonstrated in addition to infection but by contrast recurrent infection without reflux is not complicated by pyelonephritic atrophy. Occasionally a child with radiological signs suggestive of chronic pyelonephritis may have sterile urine and no history of urinary infection, but in these renal dysplasia or obstructive atrophy have probably been responsible for the renal change. There can be no doubt that it is reflux plus infection which carries the major risk.

The incidence of pyelonephritic scarring in the child population increases with age, but there is only an indirect relationship between scarring and the number of infections. Moreover the radiological appearance of scarring takes some months to develop so that it may be seen for the first time after the infection and reflux have been controlled. Occasionally spontaneous cessation of reflux will occur in a case of pyelonephritic scarring even though clinical infections persist. There is no direct relationship between pyelonephritis and the degree of ureteric dilatation. Severely scarred kidneys may have almost normal ureters and some well preserved kidneys have a grossly dilated renal pelvis.

Fig. 44

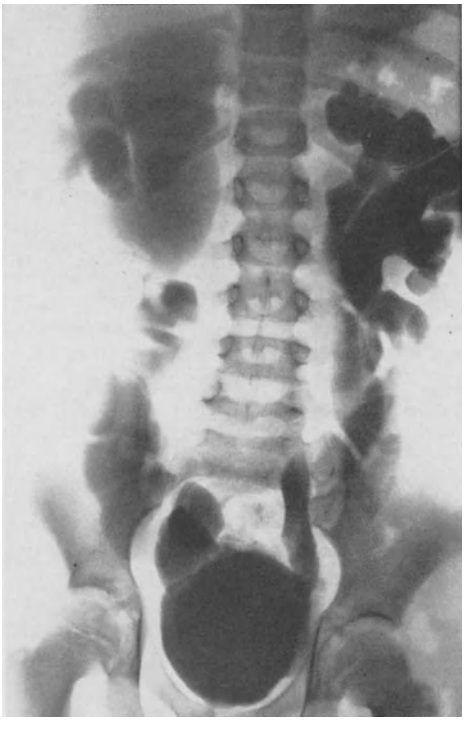


Fig. 45

Fig. 44. Reflux and pyelonephritic scarring. Micturating cystogram in a girl with recurrent urinary infection. The left kidney is severely scarred; on the right there are mild changes, although the reflux appears to be equal

Fig. 45. Reflux with dilatation, obstructive and pyelonephritic changes in the kidneys. Micturating cystogram in a boy of 8 years presenting with enuresis and mild pyuria. Severe dilatation of the ureters with ureteritis cystica in left ureter

There are, of course, many cases of infected reflux with radiologically normal kidneys and the additional factor required for pyelonephritis is unknown. Reflux clearly facilitates the ascent of organisms from the infected bladder and deposits them in the renal pelvis where they can be absorbed into the lymphatics. It may be that the penetration of organisms into the tubular system is required to produce the classical picture of chronic pyelonephritis. Some cystograms do, in fact, show reflux of opaque medium into the renal tubules. There are many gaps in our knowledge but for the present it must be assumed that any child with reflux and recurrent infections runs the risk of developing destructive renal disease.

IX. Spontaneous Cessation of Reflux

It is well known, and often recorded e.g. Baker et al. (1966), that reflux is common in childhood and relatively rare in adults: there is therefore a strong case for supposing that spontaneous cessation of reflux is the rule. Firm conclu-

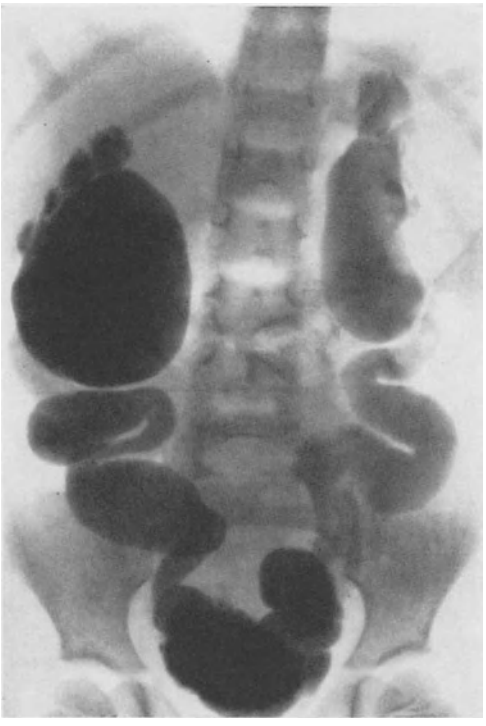


Fig. 46. Reflux with ureteric dilatation and small dysplastic kidneys. Cystogram in a boy of 3 years with infection and uraemia

sions can only be drawn, however, from studies of refluxing cases treated conservatively with accurate monitoring of the rate of spontaneous cessation. Thus SMELLIE (1967) found 61 per cent spontaneous cures in 100 ureters. REISCHAUER et al. (1968) followed 45 cases and found spontaneous cessation in 15, all of which had normal initial pyelograms. STEPHENS and LENAGHAN (1962) followed 69 refluxing ureters for periods of between five and ten years: in 31 per cent reflux ceased, in 29 per cent it improved and in 40 per cent it was unchanged. BLIGHT and O'SHAUGHNESSY (1969) followed 28 patients with reflux but with normal I.V.P's and found recovery in 43 per cent. FISHER and DARLING (1967) compared 50 cases treated medically with 50 treated surgically: 34 per cent of the former recovered spontaneously and none of the uncured cases showed any increase in hydronephrosis. Surgical results were less satisfactory.

The degree of dilatation of the ureter and results were classified by HEIKEL and PARKKULAINEN (1966) who followed 78 patients. In total they had 27 per cent cured and 17 per cent improved, but the most severe degree showed no recovery. O'DONNELL et al. (1969) followed 79 cases with mild or moderate reflux and recorded 39 per cent cured or improved, 48 per cent static and 15 per cent worse, usually with persistent infection. Their most severe grade showed no improvement. EDWARDS (1969) similarly classified cases according to dilatation and found a larger proportion of the milder degrees improving or recovering, but most of the severe dilatations unchanged. It may thus be taken as established beyond

doubt that a child with reflux into normal or slightly dilated ureters has something between a 30 and a 60 per cent chance of spontaneous cessation of reflux. Where severe dilatation is present the chances are less good, but nevertheless individual instances can be shown by most observers to exhibit spontaneous recovery even when the ureter remains dilated afterwards. KING et al. (1968) relate the likelihood of recovery to the appearance of the ureteric orifice and the length of the intravesical segment, as measured cystoscopically. Thus 44 out of 50 cases with a normal anatomy in which they believed inflammation was the cause showed recovery; recovery was much less frequent with a short intravesical segment and in 11 patients with saccule formation there was no improvement at all. These figures could be confirmed from the writer's experience. LYON et al. (1969) have stated that the likelihood of spontaneous recovery may be judged from the appearance of the ureteric orifice, and it is universally agreed that a widely gaping, and certainly a scarred, orifice is unlikely to cease to reflux. Thus recoverability is related to the permanence or otherwise of the local lesion at the ureterovesical junction, and in those cases where there is severe dilatation of the ureter this junction can never be normal. The mechanism of recovery where inflammation was the sole cause need scarcely be discussed further, and the chances of recovery after relief of bladder outflow obstruction are recorded later in this chapter. In many instances, however, recovery must be due to a process of growth and maturation, partly on the basis described by HUTCH (1961), who showed that there was an increase in the length of the intravesical segment of the ureter. Experimentally working with pups, LENAGHAN and CUSSEN (1968) have reported that reflux was very commonly observed at the age of two months but had almost always ceased by the age of six months. This recovery was largely but not entirely related to increasing length of the intravesical segment, the other factor being presumed to be the maturation of the muscular properties of the ureter. They noted that the presence of severe urethral obstruction did not prevent the spontaneous cessation of reflux. In the child the time scale of recovery is uncertain: there are many who have reflux for several years before recovery occurs, even though this is not related to any other event such as puberty. Most will recover in two years or not at all. It may also be remarked that recovery need not necessarily be permanent; reflux may re-appear after an inflammatory episode or later in life during pregnancy. Moreover the cessation of reflux does not necessarily mean that the child is no longer subject to urinary infections or that the ureter has entirely returned to normal.

X. The Clinical Management of Uncomplicated Reflux

Almost all the authors referred to in the bibliography of this chapter have drawn conclusions as to the management of reflux cases, varying from complete conservatism to early operation on the great majority. In this section the present writer attempts a balanced assessment and outlines his personal policy in these cases.

The natural history of the disease already outlined emphasises factors governing treatment.

1. Reflux together with infection is dangerous.
2. Sterile reflux is unlikely to be harmful in the absence of obstruction.
3. Reflux in a normal or slightly dilated ureter has at least a 30 per cent chance of spontaneous recovery.

4. Operation, although ordinarily successful, can never be claimed as entirely free of risk.

The first overall principle in management must therefore be a long term supervision since the children are at risk whether treatment is medical or surgical. They may well develop serious renal damage insidiously and without symptoms demanding urgent attention. Regular reviews of patients by urine cultures and radiological studies are therefore obligatory. This commitment in most communities will fall upon the paediatrician or family doctor, but it is the responsibility of the urologist to ensure that supervision is possible.

The preliminary investigation of reflux cases obviously requires pyelography and cystography. It should preferably also include an estimate of renal function by chemical or isotope method. In all except the mildest cases cystoscopy is desirable both to eliminate complicating factors and to assess the prognosis from the appearance of the ureteric orifices. Urethral dilatation is often included as part of the initial treatment, but as discussed in Chapter I this has little statistical justification. Following the initial investigation the management of most cases with normal ureteric orifices, normal or slightly dilated ureters, should proceed on the expectation of spontaneous cessation of reflux. They may be treated by intermittent or preferably continuous chemotherapy, a discipline of plentiful fluid intake with regular micturition and double voiding if possible should be instituted and if necessary attention should be given to other infections in the body, such as upper respiratory tract, and to vulval hygiene. Urine is cultured at four to eight weekly intervals and pyelograms and cystograms are repeated after one year and again after two years. Many cases will be entirely symptom free and maintain a sterile urine on this regime; if reflux proves to have ceased then follow-up need only be undertaken at less frequent intervals. If it has not, then the full regime should be continued for a further two years. If, despite carefully controlled chemotherapy, infections with fever and evidence of renal involvement continue to occur then operative reflux prevention should be considered: and reflux which persists in girls past puberty is better corrected surgically even if the urine is sterile. Early operation will be advised if the degree of dilatation of the ureter is considerable, Fig. 44–45, or if the condition of the uretero-vesical junction is such that spontaneous cure is unlikely, e.g. short intravesical segment, widely dilated orifice, paravesical saccule. Other factors favouring early operation will be the presence of established pyelonephritic scarring, showing that the condition is potentially serious, and ballooning of the renal pelvis during micturition with possible secondary pelvi-ureteric obstruction. Factors weighing against surgery are early infancy, when both the chance of spontaneous cure and the hazards of operation are greater, and established reflux with enormously dilated aperistaltic ureters. Hypertension is unlikely to be influenced by reflux prevention and should always be controlled medically before surgery of any sort is considered.

Surgery will almost always entail one of the reflux preventing procedures referred to in the next section, but if one kidney is very small, e.g. it contributes less than 10 per cent of total creatinine clearance, or if one ureter is enormous and the other normal, nephro-ureterectomy is preferable. Severely dilated but actively peristaltic ureters should be remodelled at the lower end at the time of re-implantation, and possibly remodelling of the upper end with pyeloplasty will be required later. The most difficult problem is with bilateral gross dilatation with aperistaltic ureters. Reconstructive procedures succeed very poorly in such cases, while cutaneous diversion is much less effective in the refluxing than in the obstructed ureter. Cutaneous ureterostomy is usually sufficient to control infections in the grossly dilated ureters and may thereby improve renal function, but

in the absence of bladder outflow obstruction no functional improvement will be seen in sterile cases as a result of bringing the ureters to the surface. Children with approaching renal failure in such circumstances may be better allowed to remain with an intact urinary tract until such time as a renal transplant becomes inevitable.

In infants with severe dilatation of the ureters a simple vesicostomy, bringing the apex of the bladder to open widely on to the abdominal wall below the umbilicus, may allow free drainage and eliminate infection without compromising later remodelling and re-implantation. It provides an unsatisfactory stoma for prolonged diversion in an older child but can be of value as a temporary measure.

Follow-up is as important as pre-operative investigation. All techniques have an incidence of post-operative obstruction, making pyelography at some time between three and six months obligatory. In general such obstructions are early in onset and late scarring appears to be extremely rare. With regard to persistent infection, WILLIAMS and ECKSTEIN (1961) report that infections continued in 14 per cent of those cases where reflux had been successfully treated, and the majority of those were children with severe pyelonephritic scarring. POLITANO (1963) had a total of 100 patients with 6 failures to prevent reflux and persistent infection in 25. HUTCH (1968) had 31 per cent of patients with some recurrence of infection and HENDREN (1968), 20 per cent. GOVAN and PALMER (1969) comment that only 7 per cent of post operative cases continued to have pyelonephritic episodes, and it is in general the impression that after reflux prevention such infection as occurs is confined to the bladder. In the author's experience this is not invariably the case but there is no doubt that the incidence of progressive pyelonephritic scarring after successful reflux prevention is very small indeed.

XI. Operative Technique

A wide variety of techniques is available for reflux prevention, and although operative details are outside the scope of this work it may be useful to indicate the advantages and disadvantages of the various methods. It is, of course, valuable for every surgeon to develop a routine and employ one method at which he beomes adept, but it is equally important that in special circumstances he should be able to employ other techniques morea pplicable to the particular situation.

Almost all methods of obtaining a valvular uretero-vesical junction depend upon the construction of a terminal segment of submucosal ureter sufficiently long to act as a valve by being compressed against the detrusor muscle by the pressure of the bladder contents during micturition. These methods may be subdivided into re-implantation techniques, advancement techniques and displacement techniques which preserve ureteric continuity.

The re-implantation techniques are best exemplified by the methods described by POLITANO and LEADBETTER (1958) and by PAQUIN (1959). The former was the present author's preferred operation and is applicable to the majority of cases, being particularly well suited to those where the terminal ureter is better excised along with its accompanying saccule. It has a high percentage of success in cure of reflux, 85–95 per cent, and failure is almost always due to poor technique allowing too short a submucous segment (it should be 3–4 cms long) or a failure of healing which allows the ureter to draw back upwards and shorten this segment. Reflux can be prevented in moderately dilated ureters but re-modelling of the

lower end is essential to consistent success in greater degrees of dilatation. It is the author's practice to re-model any ureter which has a diameter of more than one centimetre when deflated and to carry this re-modelling up to the pelvic brim well above the intra-mural segment. The hazards of the operation are largely in the production of obstruction: this can occur by kinking of the ureter outside the bladder, particularly where the implant has been made too high up. Kinking is less likely to occur if the dissection has been carried out extra-vesically as well as intra-vesically so that the ureter can be inspected at the end of the operation and demonstrated to be straight. A very high implant is always in danger of kinking when the bladder is full, though it may well drain when the bladder is empty. Obstruction may also occur from constriction within a very narrow tunnel in the bladder wall, and in others there is stricture of the terminal segment, probably due to avascularity following ruthless stripping of the adventitia. It is rare to see an actual stenosis of the new mucosal junction of the ureter with the bladder unless the uretero-neo-cystostomy has been allowed to remain dry by diversion of the urine at a higher level during the healing period.

The advancement techniques depend upon the construction of a sub-mucosal segment of the ureter downstream from the normal site of the ureteric orifice. In a small trigone this can be very difficult and perhaps impossible bilaterally, but in many cases of reflux a very large trigone is present with the ureteric orifices far apart and advancement is then a simple technique. In cases where a previous re-implantation operation has been undertaken without successful prevention of reflux a high uretero-vesical junction can be brought down to the trigonal level by the advancement method. Bischoff (1957) described an advancement technique depending upon the construction of a ureteric prolongation by burying a strip of mucosa extending downwards from the ureteric orifice toward the bladder neck. This had the significant advantage of leaving the ureter itself in situ, but in fact the method is often associated with poor healing and has not in most hands, e.g. Williams and Eckstein (1965), given adequate reflux prevention. Williams, Scott and Turner-Warwick (1961) described an advancement technique in which the intramural ureter is mobilised along with the bladder mucosa behind it and drawn down over a denuded trigone. This method was developed with a view to avoiding the necessity for tunnelling under the trigonal mucosa, since muscle and mucosa in this area are rather tightly bound together and a tunnel is not easily developed. However, Glenn and Anderson (1967) have shown that the advancement need not necessarily be down towards the bladder neck, it may be medially across the bladder behind the trigone. Advancement techniques are very seldom associated with any form of obstruction and with careful handling they can give efficient reflux prevention.

The displacement techniques have the significant advantage that they maintain ureteric continuity and are particularly appropriate where the blood supply of the ureter may be jeopardised by operative interference higher up: when, for instance, there is a cutaneous ureterostomy to be closed or a pyeloplasty to be performed at the same time as reflux prevention. The original Hutch operation displaced the ureter into the bladder lumen and allowed mucosal growth to cover it over. This method could give efficient reflux prevention but there was some danger of kinking the ureter where it was brought in. The Gregoir technique, well described by Arap et al. (1971) is a more efficient displacement method creating the submucosal space from outside the bladder and reconstituting the muscle layer over it. However, where re-modelling of a dilated ureter is required, or where it is necessary to shorten the ureter by excising the terminal segment, no great advantage can be claimed for this over ordinary re-implantation. Obstruction

may occur with the extra-vesical displacement operation, probably due to excessive mobilisation of the ureter down into the tunnel, or to a very long tunnel with kinking at the upper end, or to haematoma formation.

XII. Reflux in Duplex and Ectopic Ureters

Taking the whole group of duplications, reflux occurs more often than in single ureters and the excess is largely attributable to the complete duplications. AMBROSE and NICOLSON found 27 duplications in a series of 183 refluxing cases, an incidence of 1:7.3, whereas from the known overall frequency of ureteric duplications one case would be expected in every 161 refluxers. The conditions of reflux vary according to the precise anatomy of the duplication and it is therefore necessary to discuss the group under a series of sub-headings.

1. The Bifid Ureter

Although reflux is not uncommonly found in cases of bifid ureter there is very little evidence to suggest that the bifurcation in any way predisposes towards reflux when it is at any point clear of the bladder wall. The refluxed urine enters both limbs of the ureter and pyelonephritic scarring, if present, affects both halves of the kidney although not always to the same extent. The presence of vesico-ureteric reflux does not preclude concomitant uretero-ureteral reflux due to uncoordinated peristalsis. If re-implantation is undertaken for a ureter with a low bifurcation the two branches should be implanted so that they open separately into the bladder to prevent subsequent uretero-ureteral reflux.

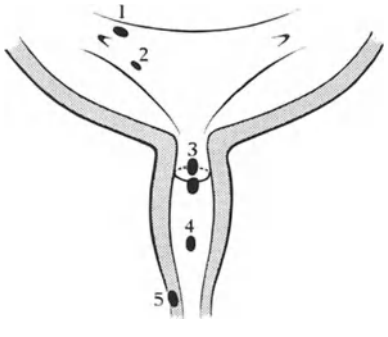


Fig. 47. Diagram showing the possible positions of an ectopic ureteric orifice in relation to their liability to reflux

2. Complete Duplications

Fig. 47 sets out the possible openings for the upper pole (ectopic ureter) in complete duplications. In the rare Type 1. the upper pole ureter lies medial to and on a level with, or even slightly above, the lower pole ureter. Both may function normally but if a para-ureteric saccule is present it will involve both and reflux will occur into both halves of the kidney (Fig. 43).

In the common form of complete duplication, Type 2, the upper pole orifice is usually small and slit-like, opening on the trigone a short distance below and medial to the lower pole. Since the ureters are bound within a common adventitia at their lower end it is clear that the "ectopic" ureter must have a longer intravesical segment than the "orthotopic", and it is therefore no surprise to find that reflux occurs into the orthotopic, but not into the ectopic, ureter. The pathological conditions accompanying this reflux are as varied as in single ureters; short intravesical segment, widely dilated orifice, para-ureteric saccule, and often the contralateral single ureter refluxes as well: this finding was present in 12 out of 26 cases in the writer's series. The salient feature of this group is that the pyelonephritic process often found is strictly limited to the lower pole (Fig. 48), thus confirming the paramount importance of reflux in the development of chronic pyelonephritis in childhood. Occasionally, however, the lower pole is also dysplastic and then the upper pole may possess more calyces than normal, so that a local congenital anomaly of the kidney is present in addition to that of the ureters.

Operative prevention of reflux should be undertaken on the indications already discussed for uncomplicated reflux cases. Since the two ureters are bound closely together at their lower end a re-implantation in these types of duplication may be performed by treating the two ureters as a single unit. If, however, the lower pole ureter is seriously dilated and requires re-modelling it is better to separate the two. A further possibility in this anomaly is to perform a pelvi-ureterostomy at the renal level so that all the urine drains down the healthy upper pole ureter. However, on occasions this ureter is too narrow to take the whole volume of urine and in general the re-implantation techniques are better, except

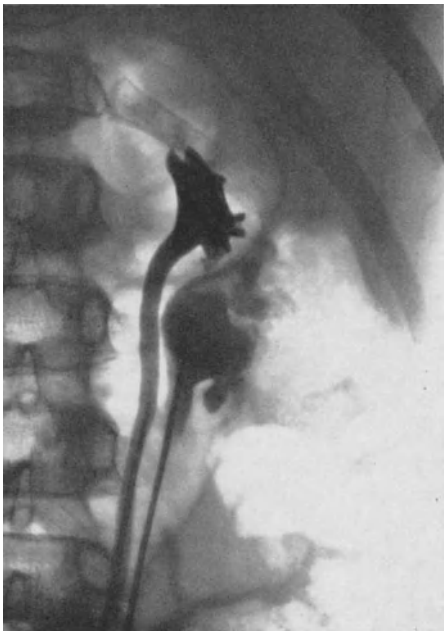


Fig. 48. Duplex kidney with pyelonephritic lower pole. Retrograde pyelogram in a boy with recurrent infection. The upper pole ureteric orifice was in the Type 2 position, the orthotopic orifice allowed reflux. The upper calices are well preserved, the lower scarred and contracted

where the pyelonephritis is far advanced so that hemi-nephrectomy is preferable (JOHNSTON and HEAL, 1971).

When the ectopic ureter terminates immediately above, at or slightly below the bladder neck (Type 3) and there is no complicating ureterocele, reflux into the ectopic ureter is the rule (Fig. 49). This presents a marked contrast with Type 2, and the cystoscopic appearance of this orifice is also different, it is usually wide with relaxed margins and if the bladder is sufficiently distended it gapes. The ectopic ureter itself is usually dilated and the renal element which it drains is pyelonephritic or dysplastic. Although it might be supposed that the long intramural course of this type of ectopic ureter would protect it against reflux this

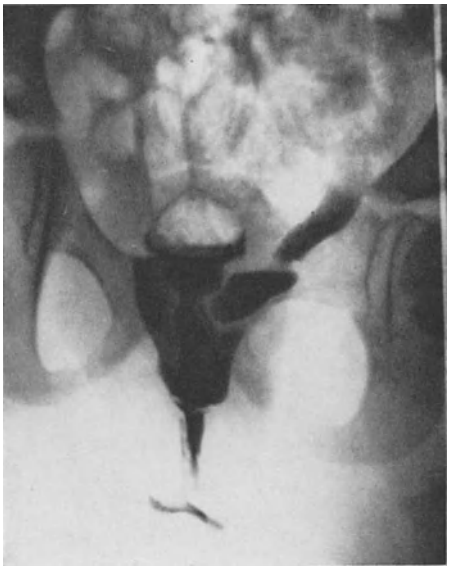


Fig. 49. Urethral ectopic ureter. Micturating cystogram in a girl with recurrent infection but normal continence. The bladder empties completely but reflux occurs into a ureter opening just below the bladder neck. The vagina also is filled with opaque medium

protection fails, both because the muscular system of the ureter is abnormal, because the calibre is wide and because the terminal course is not immediately below the bladder mucosa but deeper within the muscle and adventitia. Most children in this group present with recurrent or persistent pyuria and do not suffer incontinence. Pyelograms show duplication with a defective upper and a normal lower pole, or occasionally, particularly in boys, the ectopic ureter is a single one and no normal renal element is present. A variant on this type is when the orthotopic ureter refluxes as well as the ectopic, perhaps due to saccule formation, and in some such cases enormous dilatation of the lower pole ureter may so dominate the radiological appearance that the small ectopic ureter is overlooked.

In the ectopic ureters hemi-nephrectomy and ureterectomy is almost always the preferable treatment for this group.

An ectopic ureter opening into the lower part of the female urethra (Type 4) usually causes continual dribbling incontinence and does not reflux. The exact

level at which the change occurs from a continent refluxing ureter to an incontinent valvular one is hard to define, although occassionally in bilateral cases one ectopic ureter is above and one below the critical level. Probably, however, all urethral ectopic ureters in the female will reflux if there is meatal obstruction.

An ectopic ureter in the female opening outside the urinary tract (Type 5) obviously cannot be subject to reflux, but in the male where the ureter joins the genital tract reflux into the common terminal duct is usual and is the cause of epididymitis in these cases.

Reflux in association with ectopic ureterocele has many implications and is fully discussed in Chapter L.

XIII. Reflux and Bladder Outflow Obstruction

The response of the detrusor muscle to outflow obstruction is by hypertrophy, with trabeculation and ultimately sacculation of the bladder. The trigonal muscle also undergoes hypertrophy and where it is strong there is some tendency to draw the ureteric orifice towards the bladder neck thus elongating the intravesical segment of the ureter and giving it additional protection against reflux. It is thus not surprising that in a high proportion of cases of urethral valves with gross obstruction no reflux is found. If, however, the trigonal muscle does not respond adequately the process of sacculation of the bladder is likely to involve the ureteric hiatus with consequent outward displacement of the ureteric orifice and reflux. In this situation the ureteric orifice may be cystoscopically invisible, but if seen is often not grossly dilated. Later in the course of the disease, particularly with chronic infection and longstanding obstruction, the ureter itself becomes widely dilated and rigid. In the author's series of infantile urethral valve cases 44 per cent had pre-operative reflux, and of these one third stopped spontaneously after removal of obstruction. In reviewing this group in detail he found the influence of reflux on the course of the disease to be rather less than might have been anticipated. Grossly dilated ureters were found as often without reflux as with it and the overall renal function was slightly better in the reflux cases. However, a number of refluxing ureters were associated with functionless kidneys which ultimately required removal. In other urethral obstructions similar findings may be reported, though the obstruction is seldom as severe as in posterior urethral valves. The rate of spontaneous cessation of reflux after relief of obstruction would obviously vary according to case materia. Thus King et al. (1968) report 31 cases of reflux accompanying unequivocal outflow obstruction in which 14 ceased to reflux after the obstruction had been removed, and of these 11 were cystoscopically normal ureters. It is clear, therefore, that in persistent reflux the causative lesion involved is a local one at the uretero-vesical junction together with the failing muscular activity of the ureter as a whole. In recoverable reflux the simple factor of the intravesical pressure at the time of voiding may be of some importance.

The association of reflux and bladder neck obstruction has often been discussed, but in recent years the concept of bladder neck obstruction as a disease has been severely criticised, e.g. Smith (1969), Scott (1969). Both these authors conclude that there is very little evidence for the existence of such a disease in childhood. It will, however, be evident to all surgeons performing operations for reflux prevention that in some children the bladder wall appears to be of normal thickness, while in others there is well marked hypertrophy of the detrusor

layer with trabeculation although the urethra is urethrographically and endoscopically normal. The bladder neck in these cases is hypertrophied and if no neurological disorder can be demonstrated it is hard to escape the conclusion that some type of obstruction has produced the hypertrophy and that the bladder neck may well be responsible. WILLIAMS and ECKSTEIN (1961) in a series of 276 cases of reflux found 76 in which there was some hypertrophy with severe changes judged by the thickness of the bladder wall in 34 of these. This change was not, however, associated with residual urine and there was no more dilatation of the ureters in this group than in those with thin walled bladders. Bladder neck revision procedures were undertaken where detrusor hypertrophy was found, but there was no difference in the success rate of reflux prevention in cases with or without bladder neck revision. MCGOVERN and MARSHALL (1968), however, report that bladder neck Y–V plasty has improved surgical results and they continue to perform this procedure. RUDHE and ERICSSON (1966) report that their views on bladder neck obstruction in contrast to many other writers have changed very little over the years, and they analyse a series of 45 cases of which 41 were male. The diagnosis was made by conscious micturating cystogram, showing in true lateral views as well as in obliques, an exaggerated intrusion of the muscle of the bladder neck into the urethra on the posterior and lateral aspects. They were not much concerned with the presence of residual urine or trabeculation and the cystoscopic appearance was regarded as of less importance than the radiological. In this group reflux was present in 30 children, of whom 11 were unilateral and 19 bilateral. Upper tract dilatation was present only in those cases with reflux, a fact which seems to minimise the importance of the obstruction itself. After trans-urethral resection of the bladder neck 16 out of 28 patients had a decrease or disappearance of the reflux. They noted that minimal reflux into non-dilated ureters almost always disappeared and that on occasions quite well marked reflux stopped, although it might leave the ureter dilated. Their results were based on a long follow-up and a cessation of reflux must be regarded as reliable, but it has to be compared with the incidence of spontaneous cessation which has reached similar figures. Reflux has frequently been reported in association with distal urethral stenosis: this aspect is discussed in Chapter I, but it may be noted that in general urethral dilatation does not achieve a greater rate of recovery than medical treatment alone.

XIV. Reflux and Megacystis

The mega-ureter megacystis syndrome was first described by the present author in 1954 in relation to infants who had very large capacity bladders capable of emptying completely without residue, but with very free reflux into grossly dilated ureters (Fig. 50). At cystoscopy it could be appreciated that the trigone was wide and that the ureteric orifices were gaping. These children presented with recurrent urinary infections and in many cases passed urine very infrequently, perhaps only twice in twenty-four hours. The volume passed in each act of micturition was considerable but there did not appear to be any difficulty in micturition except during exacerbations of infection. The term 'megacystis' was used in order to distinguish the condition from bladder outflow obstruction in which trabeculation and true residual urine were present. Cystometrographic studies in the author's cases were performed by LEIBOWITZ and O'DONNELL (1957) and showed that the terminal capacity in these cases was considerably greater than observed in normal or in bladder outflow obstruction cases after relief of obstruction. Only

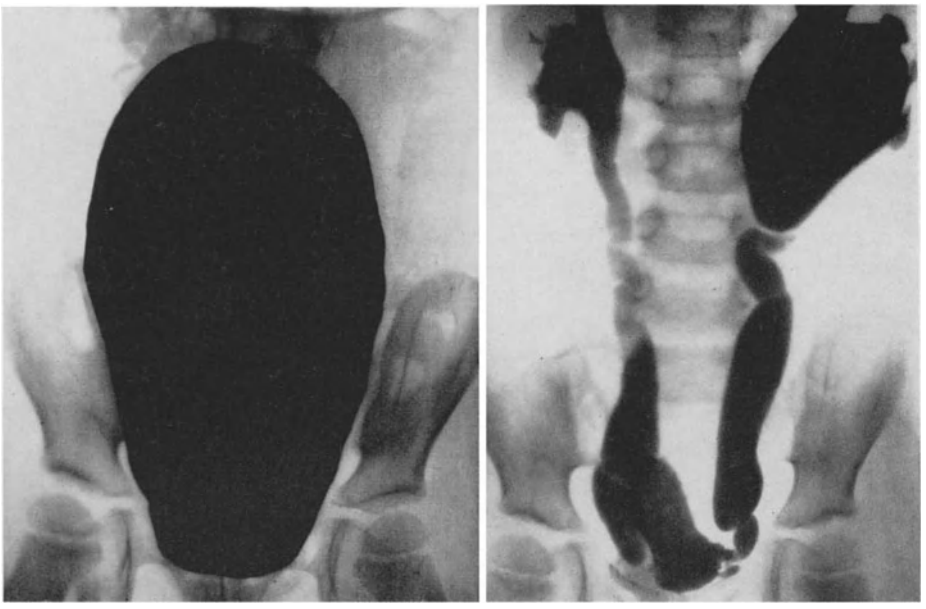


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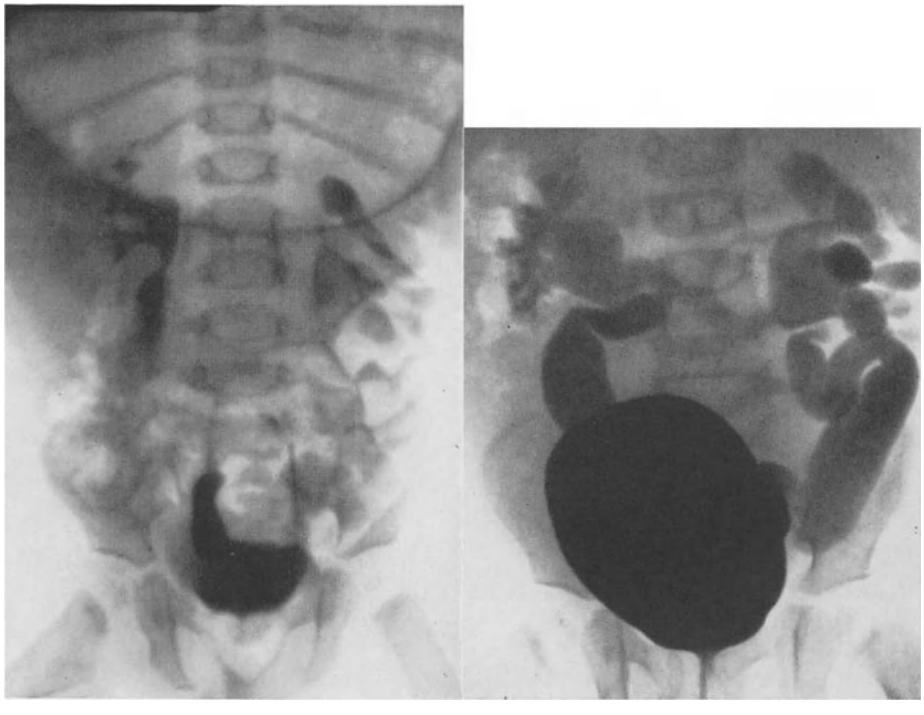
Fig. 50a and b. Mega-ureter-megacystis. A boy of 5 years with recurrent infection. a Cystogram showing an enormous capacity bladder without sensation of fullness. b Micturating cystogram showing satisfactory emptying of the bladder but free reflux into dilated ureters

in the absent abdominal muscle syndrome was there a comparable bladder capacity.

At the time of the initial description the extreme frequency with which reflux occurred in children was not altogether appreciated, nor the extent to which dilatation could occur during micturition only. PAQUIN, MARSHALL and MCGOVERN (1960) later showed that megacystis with reflux need not always be accompanied by dilated ureters; they made accurate measurements of the width of the trigone and the diameter of the ureteric orifice and found both these measurements increased to often as much as twice their normal in the megacystis cases. They felt that the megatrigone was the primary abnormality, the megacystis being relatively unimportant. They noted that the evacuation of the bladder was infrequent and that occasionally the child had difficulty in the initiation of micturition, but that serious symptoms were related only to the reflux and recurrent infections.

It is now clear that the megacystis condition is relatively uncommon compared with reflux as a whole and some doubt has been cast upon the validity of the conception. Nevertheless some children present with very large bladder capacities which differentiate them from ordinary reflux cases and although the serious complications to be faced are those of reflux (Fig. 51) and pyelonephritis, the bladder condition remains. The pathological lesion in the bladder has not been identified. LEIBOWITZ and BODIAN (1963) demonstrated that the ganglion cell population of such bladders is normal, thus contradicting the earlier hypothesis that these bladders were aganglionic.



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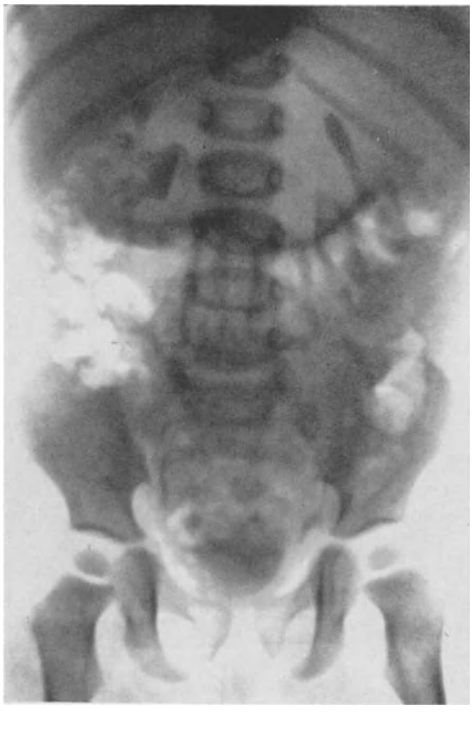

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Fig. 51a—c. Mega-ureter, megacystis. A boy of 1 year with recurrent infection. a pre-operative intravenous urogram. b Micturating cystogram showing gross dilatation of ureters. c The intravenous urogram 3 years after successful reflux prevention

XV. Reflux in Neuropathic Bladder

In the neuropathic bladder of children reflux is common. EDWARD et al. (1969) found that in 71 cases low pressure reflux was present in 25 per cent and high pressure reflux in an additional 34 per cent. They did not, however, find any correlation between reflux and upper urinary tract damage and no difference in the effects of low pressure and high pressure reflux. PELLMAN (1965) found that 30 out of 61 children had reflux and that it was more likely to occur in girls than in boys. Many of these cases developed reflux between the ages of one and three years and it was particularly associated with infection before instrumentation. They found to their surprise that reflux was more common where muscular paralysis was least severe. Some of the bladders were trabeculated but some were not and a flat cystometrogram was characteristic of the refluxing cases. COOPER (1968) carried out an extensive investigation of pressure flow relationships in the neuropathic bladders of children and found that there was no correlation between high bladder pressures and reflux, or indeed between high bladder pressures and upper tract dilatation. Reflux occurred in the infected urinary tracts where bladder pressures remained low.

The effects of reflux in the neuropathic bladder are often similar to those seen in the normally innervated urinary tract. Reflux, once established, is difficult or impossible to eradicate and leads to chronic pyelonephritic atrophy. Ureteric dilatation is often seen with reflux and is frequently worse on the refluxing side, in unilateral cases. However, the dilatation is primarily due to the bladder disorder and may well occur without reflux. The management of neuropathic bladders is discussed in Chapter S.

XVI. Reflux in Vesical Exstrophy

The extroverted bladder obviously cannot reflux in ordinary circumstances, but in epispadias and after reconstruction of exstrophy reflux is common. The pathological junction of the ureter and bladder is responsible and the anatomy and the treatment are discussed in Chapter T.

XVII. Reflux with Renal Dysplasia

It is well recognised that renal dysplasia is often associated with disorders of ureteric or vesical form and function and particularly with reflux. The simplest examples are seen in the cystic dysplastic kidneys. In the multicystic kidney the renal tissue is replaced by a functionless bunch of cysts with an obliterated renal pelvis and upper ureter. The lower part of the ureter in such circumstances often appears normal, yet reflux frequently occurs into it and contralaterally there is often ureteric obstruction or reflux or both. Small but functioning dysplastic kidneys are liable to infection, perhaps because of their intrinsic anomalies (ERICSSON and IVEMARK, 1958) and associated reflux might be attributable to infection, yet the slight atonic dilatation of the ureters in dysplastic cases strongly suggests an muscular anomaly and reflux is often seen in neonatal examples without infection (Fig. 52). In ectopic ureter the association of renal dysplasia with poorly functioning refluxing ureters is well established. Reflux in the prune belly syndrome might be included under this heading as well, but is discussed in Chapter Q.

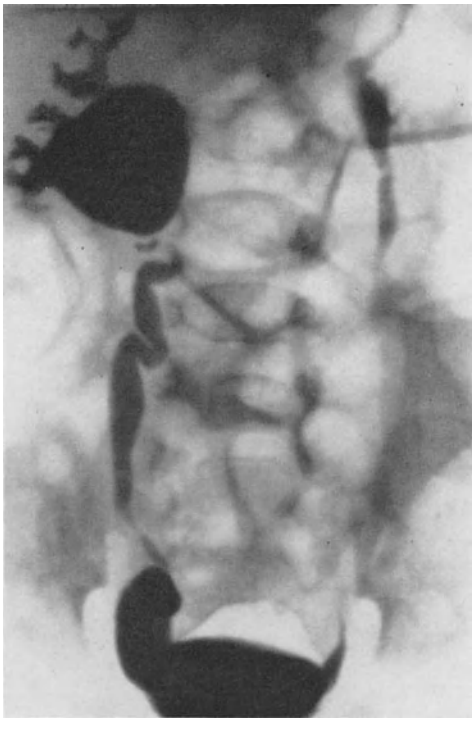

Fig. 52. Cystic dysplastic kidneys with reflux. Micturating cystogram in a uraemic neonate with sterile urine. Biopsy shows cystic dysplasia of the right kidney and no true pelvi-ureteric obstruction. The left kidney is very small and cystic

XVIII. Reflux and Ureteric Obstruction

Although at first sight reflux and uretero-vesical obstruction might seem to be the converse of one another there is, in fact, nothing incompatible about them, and on rare occasions there is obstruction to downflow but reflux up the ureter. It has already been seen that in the case of the paraureteric saccule either phenomenon may be seen and there is good evidence that in some both are present. Similarly on rare occasions in obstructive mega-ureter reflux can take place through the narrow lower segment and radiologically a small volume of reflux of opaque medium reaches the dilated segment where, since there is already a considerable mass of non-opacified urine it becomes diluted or shows as a fluid level. Gregoir and Debled (1969) found an increase in collagen in the terminal segment of the obstructive mega-ureter and if this rendered the intramural segment rigid reflux would naturally be expected. The treatment is, of course, excision of the narrow segment and re-implantation of the ureter by a reflux preventing technique.

K. Ectopic Ureter

D. Innes Williams

With 9 Figures

I. Ectopic Ureter with Duplication in the Female

The classical situation of the ectopic ureter causing incontinence in the girl is well recognised and adequately described (Schulman, 1972; Malek et al., 1972). The possible sites for the ectopic orifice are at the bladder neck, in the upper urethra, in the lower urethra, beside the external urinary meatus and in the vagina. Rare ectopic openings in the rectum are described (Uson and Schulman, 1972). In the upper urethra reflux is common, but incontinence does not necessarily occur. In the lower urethra reflux is not common but incontinence is the rule. In the mid-urethra reflux and incontinence are both possible, and to some extent the incontinence represents the return of urine which has temporarily distended the ureter during micturition. In some cases the upper end of the ureter is atretic and derived from a non-functioning renal element, while the lower end is dilated and may appear as a urethral diverticulum (Van Houtte, 1970). Ectopic ureteroceles are described separately in the next chapter.

The presenting symptom is ordinarily continual dribbling incontinence despite normal micturition, but urine may accumulate in a flaccid ectopic ureter so that the child remains dry when recumbent, and in some there is a late onset of urinary incontinence. If the urine is infected the complaint is often of discharge, usually attributed to the vagina rather than to the urethra. The high ectopic ureters which reflux but do not cause incontinence present as recurrent or persistent pyuria, and a few ureters opening at the high level are obstructed so that the signs are those of an abdominal mass due to hydronephrosis.

The diagnosis of low level ectopic ureter may occasionally be made from direct observation of the ectopic opening. More often inspection reveals the vulva to be wet, but the source of the urine is hard to detect. Intravenous injection of dye substances does not help since the renal element is unlikely to be capable of concentrating the dye. It is sometimes useful, however, to fill the bladder by catheter with a coloured fluid and then apply a pad to the vulva: if the pad rapidly becomes wet with clear fluid it is evident that the leak does not occur from the bladder.

Most diagnoses of ectopic ureters are made from intravenous urography, although it must be recognised that in some the renal element from which the ureter is derived is so small that it cannot be detected in this way, even though it is capable of producing sufficient urine to cause incontinence (Wiggishoff and Kiefer, 1966). With the use of very high doses of contrast medium and tomographic examination the majority of ureters can be opacified, but in some the diagnosis must still be made from the appearance of the lower pole of the kidney. The normal contralateral kidney may provide a contrast, but ectopic ureter is frequently bilateral or associated with some other form of contralateral dupli-

cation. The general features by which the lower pole may be recognised when the upper pole is non-opacified are as follows (Fig. 53–54, 65):

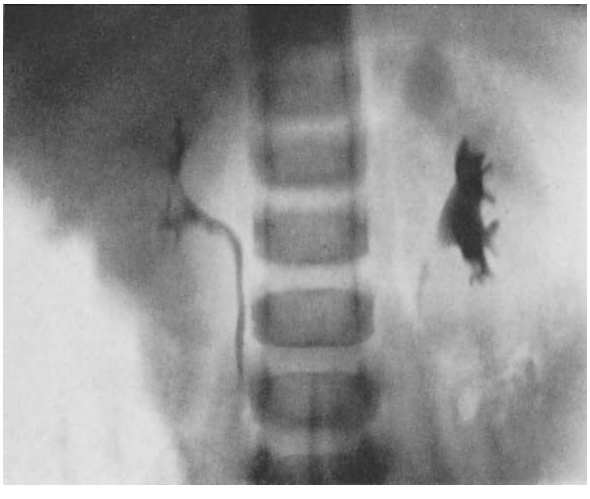

Fig. 53. Left ectopic ureter. Intravenous urogram (tomogram) in a girl with dribbling incontinence. Duplex left kidney with faintly opacified upper pole: the lower pelvi-caliceal system can be compared with the simplex right kidney

The calices are fewer in number than in the normal and the uppermost is further from the upper limit of the renal outline than the lowest is from the lower limit.

The calices of the kidney appear to be rotated downwards and outwards, the drooping flower appearance, though this may be mimicked by an upper pole tumour.

The upper calix is short, and although the cups of the calices may be directed upwards or medially they are close to the pelvis and have no long infundibulum. The whole pelvis may be mal-rotated.

The pelvis is displaced laterally away from the vertebral column and the ureter, instead of running vertically downwards, forms with the pelvis a gentle curve which gradually approaches the paravertebral region at the level of the 4th or 5th lumbar vertebra.

The ureter, being adherent to an unseen dilated ureter, is not straight but exhibits a series of scalloped curves.

These features are characteristic of a kidney bearing an ectopic ureter wherever that ureter opens and whether or not it is complicated by ectopic ureterocele. The site of the ectopic orifice may often be defined by a micturating cystogram because of reflux.

The treatment of ectopic ureter with duplication is almost always heminephrectomy and ureterectomy; since the lower end of the ureter is not infrequently dilated a complete excision down to the adventitia of the bladder should be undertaken. The terminal 3–4 cm of an ectopic ureter is hard to remove and total excision is not usually necessary. If it is to be accomplished access by incision of the trigone of the bladder may be more satisfactory than a purely extra-vesical

approach. Re-implantation of the ipsilateral lower pole ureter is then required. Moreover, since the unsuspected bilateral ectopic ureter is not at all uncommon it should be obligatory in all cases to expose the lower end of the contralateral ureter and exclude by careful inspection a possible duplication.

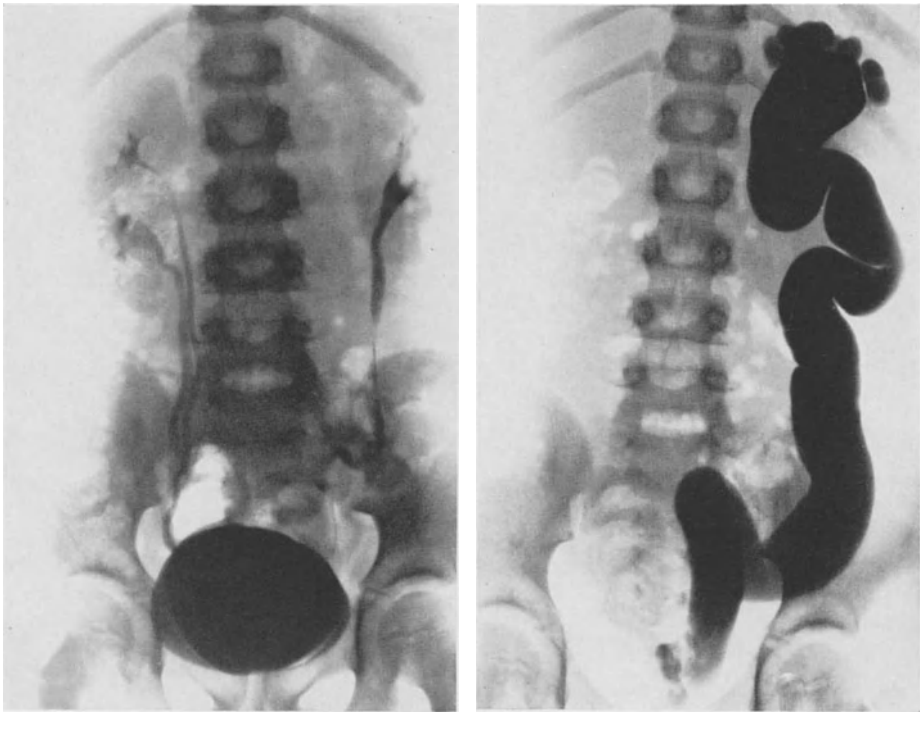

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Fig. 54a and b. Left ectopic ureter. a Intravenous urogram in a girl with dribbling incontinence. The right kidney is duplex but both elements are normal. On the left there is a duplex with a non-opacified upper element. The opacified renal pelvis is displaced outwards and possesses only a small number of calices. The ureter is looped around the non-opacified dilated ectopic ureter. b Retrograde ureterogram outlining the left ectopic ureter opening into the lower urethra

For the stump of a very low ectopic ureter, which is filling by reflux (Fig. 55) and therefore causing trouble after hemi-nephroureterectomy, a simple urethral meatotomy cutting back into the urethral stump will often relieve the symptoms, as in the operation of SPENCE for acquired urethral diverticulum in the female, but excision by a vaginal approach is simple.

II. Unilateral Single Ectopic Ureter in the Female

The single ectopic ureter is uncommon in girls and presents some diagnostic difficulties (JOHNSTON, 1969): the kidney from which it is derived is almost always

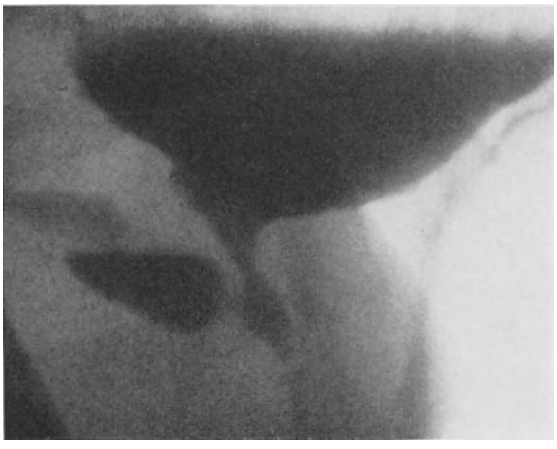


Fig. 55. Ectopic ureter stump. Cystogram in a girl previously treated by heminephro-ureterectomy for urethral ectopic ureter. The small stump has resulted in recurrent infection

Fig. 56. Unilateral single ectopic ureter. Cystogram in a girl with dribbling incontinence: an enormously dilated ureter is filled from the urethra. The corresponding renal element is anomalous

abnormal and frequently ectopic itself, and sometimes fused with its fellow (Fig. 56). It may be radiologically functionless and its presence is therefore difficult to determine; the problem arises of the girl with the typical history of ectopic ureter incontinence in whom there is no opacification on one side in the urogram, but in whom no ureteric orifice can be recognised on that side at clinical, endoscopic or urethrographic examination. Arteriography in these circumstances is seldom helpful since the kidney is, in any case, small and may well be misplaced with an unrecognisable vascular supply. In certain instances exploratory operation is the correct approach and the exploration should begin in the lower abdomen, directed first towards finding a ureter since the kidney itself may be remote from its usual situation. Unilateral single ectopic ureters are sometimes associated with a weakness of the bladder neck on the side of the lesion. This disorder is much more pronounced in bilateral single ectopic ureters, as discussed in a later section.

III. Ectopic Ureter in the Male

Except in the case of ectopic ureterocele, considered in the next chapter, an ectopic ureter in the male is much more likely to be a single ureter than associated with a duplex system. The more remote the ectopic orifice from the normal situation the more likely is the associated kidney to be dysplastic or ectopic. WILLIAMS and ROYLE (1969) discuss a series of cases in which a few high level ectopic ureters were associated with a duplication, and suffered from reflux and infection of the ectopic system. Rather more had ectopic ureters with a ureterocele. The remainder were single ectopic ureters opening into the urethra near the verumontanum or into the genital tract. In two instances there was an extravesical saccular dilatation of the terminal segment of an ectopic ureter ending in the urethra; this dilated segment resembled an ectopic ureterocele in many ways, except that it lay outside the bladder musculature, displacing and partially obstructing the bladder neck (Fig. 57, 58). The ureters involving the genital tract have been well reviewed by CENDRON and BONHOMME (1968), and earlier a collected series was published by LUCIUS (1963). The ureter may enter the seminal vesicle or the common ejaculatory duct, but it would probably be truer to regard the ureter and vas as joining to share a terminal common duct, as in embryonic life. This common duct may be relatively short and straight, but at other times it consists of a tortuous mass of tubules and cysts palpable on rectal examination (Fig. 58). The renal element in such cases is frequently aplastic and without function but reflux from the urethra into the vas produces epididymitis. In a child with this complaint the diagnosis of ectopic ureter is suspected when the urogram fails to opacify a kidney on one side, and it is often confirmed by a micturating cystogram which outlines the common duct and may opacify the vas. At times the urine within the vas is likely to cause it to dilate to form a tube closely similar to a ureter, and easily mistaken for it at the time of operation (Fig. 99). In one of the author's cases the testicle associated with such an anatomy exhibited a hamartomatous mass in the rete testis.

Treatment will consist of nephro-ureterectomy with excision of the common duct. It is essential that the vas is interrupted to prevent further attacks of epididymitis as a result of refluxed urine.

Fig. 57. Unilateral single ectopic ureter in the male. Micturating cystogram in a boy with recurrent urinary infection showing reflux into left ectopic ureter with grossly dilated terminal extravesical segment

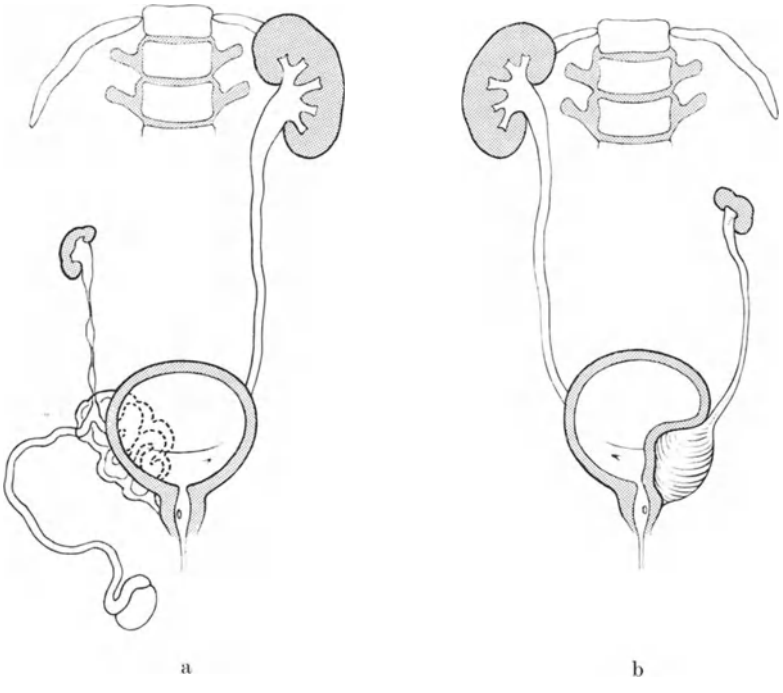


Fig. 58a and b. Diagrams to show the types of male ectopic ureters. a The ureter from a dysplastic kidney joins the vas in a tortuous tubular mass behind the bladder and urethra. b The ureter ends in a terminal dilated segment which displaces the bladder neck

IV. Bilateral Single Ectopic Ureters

In severe examples of this disorder not only does no ureter enter the bladder in a normal situation but the bladder neck itself is never properly formed (Fig. 59). This failure of development of the bladder neck can be explained embryologically, since ordinarily it is the section of the urogenital sinus between the orifices of the

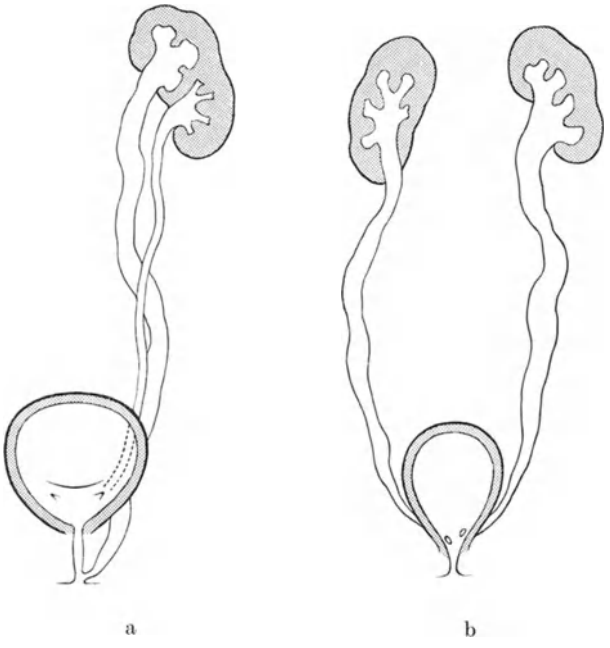


Fig. 59a and b. Diagram to show the form of the bladder neck in ectopic ureters in girls. a With duplication: the bladder neck is normal. b With bilateral single ectopic ureters: the bladder neck is absent

ureter and the Wolffian duct which develops the musculature of the bladder neck. If both ureters have remained in the position of the Wolffian duct orifice this section of the urogenital sinus is not represented and the appropriate muscle condensation does not occur (Fig. 60) (Cox and Hutch, 1966; Williams and Lightwood, 1972). Anatomically the ureters in the male open immediately above the verumontanum, or occasionally join the genital tract. In the commoner female cases they are characteristically just inside the external meatus. Milder anomalies will be found in which there is some length of female urethra, but there are also more severe ones in which the bladder is not completely formed so that the ureters open directly into the vagina (Palmer and Russ, 1970). The kidneys are grossly abnormal, either hydronephrotic or dysplastic; the ureters are dilated and the bladder of small capacity; the bladder neck is not perceptible as a ring and the complaint is of dribbling incontinence. In the male the urine is to some extent retained within the bladder because of the resistance of the distal urethra, but

the bladder neck is again absent and reflux into the ureters is common (Fig. 61).

The incontinence which occurs in bilateral single ectopic ureter has more in common with epispadias than with the forms of disease previously discussed in this chapter. The essential defect is the short urethra and incompetent bladder neck, while in addition the bladder capacity is likely to be reduced. Renal and ureteric anomalies are more common than in epispadias and complicate the treat-

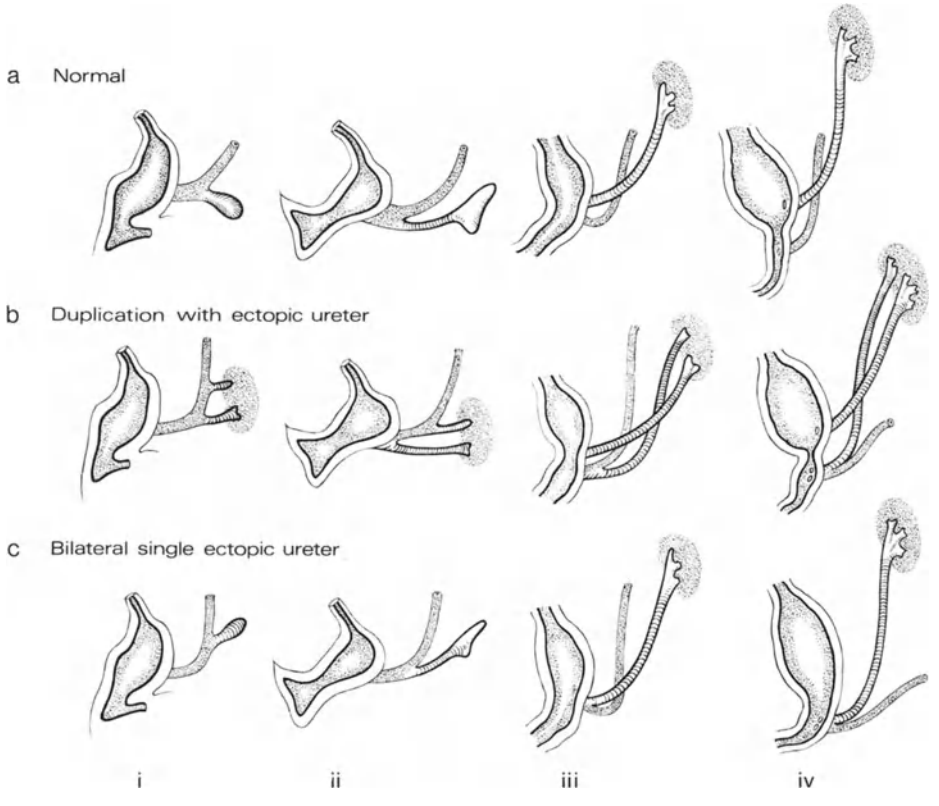


Fig. 60a–c. Diagram to show embryological development of the ureter and Wolffian duct. a Shows the normal development. i) The ureteric bud is seen arising from the elbow on the Wolffian duct a short distance from its entrance into the urogenital sinus. In ii) this terminal segment is being taken up in the wall of the urogenital sinus and in iii) it has disappeared, and at the same time the Wolffian duct is moving distally away from the ureteric orifice. In iv) the Wolffian duct and ureter have taken up their definitive position and in the gap between the two the bladder neck is formed. b Development of an ectopic ureter with ureteric duplication. i) shows the formation of accessory ureteric bud, cranial to the normal situation. In ii) we see the situation after the terminal segment of the Wolffian duct has been taken up into the wall of the urogenital sinus. iii), the Wolffian duct has now moved caudally, carrying with it the accessory ureteric bud; the normal ureter is opening separately. In iv) the definitive situation of a male ectopic ureter opening into the posterior urethra, with the bladder neck formed between this and the normally placed urethra. c Development in the bilateral single ectopic ureter. i) shows the formation of a single ureteric bud cranial to its normal situation. In ii) the terminal segment of the Wolffian duct has been taken up but the ureter still remains connected to the Wolffian duct because of its abnormally cranial situation. iii), the Wolfian duct has moved distally but the ureter still joins with it at its opening. iv), the definitive situation of a single ectopic ureter. There is no gap between the Wolffian duct orifice and the ureter and therefore no bladder neck is formed

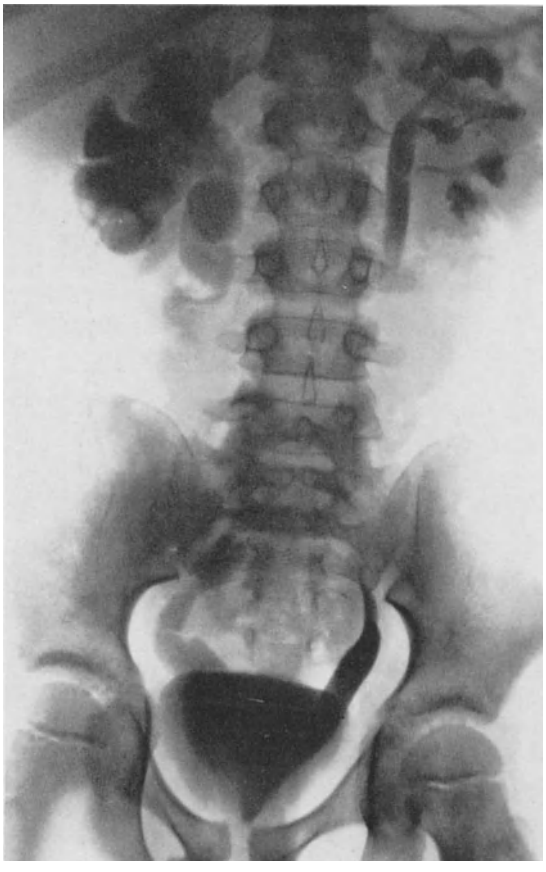


Fig. 61. Bilateral single ectopic ureter in the male. Intravenous urogram in a boy with dribbling incontinence. The kidneys are anomalous, the ureters dilated and open below the bladder neck

ment, so that in some girls urinary diversion is the only appropriate therapy. Reconstructive procedures may be attempted by re-implanting the ureters at a higher level and reconstructing the bladder neck in the manner of the Young-Dees operation. The results of this procedure have been satisfactory in some boys, but in very few girls. There are, of course, minor examples of the anomaly in which the two ectopic ureters open at the bladder neck, in which, therefore, some muscular activity in that region is preserved. These children have a better prognosis in regard to continence.

V. Ectopic Ureter with Triplication

A third ureter from one kidney is a very rare finding and is often associated with gross abnormalities. A partial triplication with an ectopic ureter was illustrated in the original volume of this series and the subject has recently been reviewed by Parker et al. (1970).

L. Ureteroceles

D. Innes Williams

With 18 Figures

I. Orthotopic Ureterocele

The terms "orthotopic" and "ectopic" here relate to the position of the orifice of the ureter upon which the ureterocele is formed. In the orthotopic variety the opening is well within the bladder, although lifted from its strictly normal position; in the ectopic variety it is at the bladder neck or in the urethra. In the case of the single orthotopic ureterocele the distinction is obvious enough and the anomaly familiar in adult practice, but where a double ureter is present there is often some confusion. The ureterocele is always formed upon the upper pole ureter and the lower pole ureter opens above it, as in the commoner ectopic cases, but the distinction between the two is important and it is not always recognised: several reports of good results following the conservative treatment of ectopic ureterocele give illustrations showing that the orthotopic variety was present, for which the prognosis is always better.

The single orthotopic ureterocele is a relatively uncommon cause of symptoms in childhood. The terminal cystic dilatation of the ureter lies entirely within the bladder cavity; it consists of an attenuated ureteric wall covered by vesical mucosa with adventitia and a few blood vessels intervening. There is a relative constriction as the ureter passes through the detrusor layer and above it a variable dilatation, greatest in the lower ureteric segment. The ureterocele fills and collapses according to the pressure produced by ureteric peristalsis and the pressure within the bladder. In some cases the obstructive element is minimal and treatment is not required; in others there is stasis leading to infection and often stone formation; in others again severe hydronephrosis. The cystoscopic appearance is well known: radiologically there is a terminal ureteric dilatation surrounded by a translucent halo within the bladder shadow, or if the renal function is poor and the ureter is not opacified, a complete spherical filling defect in the bladder.

Where treatment is required at all during childhood it should be operative. Endoscopic resection, so often appropriate for adults, is seldom sufficient since in the child the substitution of reflux for mild obstruction is disadvantageous. The recommended operation is excision of the ureterocele and re-implantation of the ureter. This is most easily performed through the bladder by a procedure akin to the Leadbetter-Politano method of reflux prevention. A circumferential incision is made through the mucosa of the bladder towards the base of the ureterocele; the plane between the vesical mucosa and the ureter is developed, and at the upper end the ureter can be isolated, mobilised and pulled up into the bladder (Hutch and Chisholm, 1966). The dilated segment of the ureter will then shell out leaving a bare area on the bladder base. The dilated segment is excised and the proximal cut end of the ureter advanced to be sutured at the lower end of this area; the vesical mucosa is closed over it to produce a valvular uretero-vesical junction.

Occasionally this operation must be modified to allow re-modelling of a greatly dilated ureter and the rare severe examples are best treated by nephro-ureterectomy.

In orthotopic ureterocele with double ureter the anatomy is essentially similar (Fig. 62). The terminal dilatation lies clear of the bladder neck and is entirely within the detrusor layer so that radiologically it shows as a spherical filling defect completely within the bladder shadow (Fig. 63). The lower pole ureteric orifice

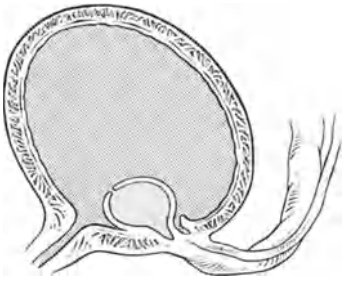


Fig. 62. Diagram to show the anatomy of an orthotopic ureterocele with ureteric duplication

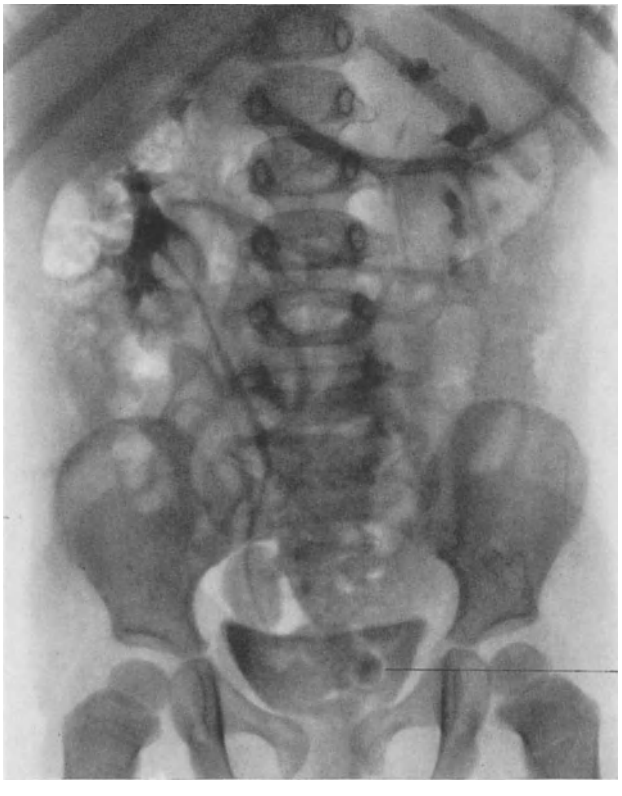


Fig. 63. Orthotopic ureterocele with duplication. Intravenous urogram in a girl with recurrent infection. Bilateral duplication, ureterocele on left upper pole ureter outlined within the bladder by translucent halo

may be drawn up on to the slopes of the ureterocele or it may be above it, where it is not infrequently involved in a para-ureteric saccule. The combination of saccule and ureterocele sometimes gives the impression that the ureterocele is capable of inversion to form the saccule, though this is an uncommon event. The lower pole ureter may be obstructed by the distortion of its lower end, but more usually it refluxes. Thus the upper pole of the kidney may show signs of obstruction due to ureterocele, the lower pole the signs of pyelonephritic contraction associated with reflux. It should be emphasised that in the orthotopic ureterocele with duplication the upper pole usually functions sufficiently well to produce good pyelographic opacification and even when damaged by obstruction and infection it is ordinarily capable of some recovery. This is the important distinction from the ectopic variety in which dysplasia and severe functional depression of the upper pole are the rule.

Operative treatment should therefore be conservative as in the single ureter cases: the ureterocele is excised, both ureters are pulled up into the bladder and together advanced medially and downward to provide a valvular submucosal segment for each. A saccule can be excised at the same time with repair of the large hiatus in the detrusor.

II. Ectopic Ureterocele

Ectopic ureterocele is one of the most important of the urinary tract anomalies requiring treatment in childhood, and it is surprising in view of the frequency with which it is encountered that there was so little reference to it in the literature before the monograph by Ericsson (1954). It can present in a wide variety of guises: the children often have recurrent or persistent urinary infection but in some the complaint is a large abdominal swelling, in some difficult micturition, in some acute retention, in some incontinence and in some girls a genital deformity. The standard anatomy of the ectopic ureterocele (Fig. 64) is well known and was fully described in the original volume, but improvements in the radiological diagnosis and better appreciation of the variations and complications of the anomaly demand a full discussion.

1. Sex and Side

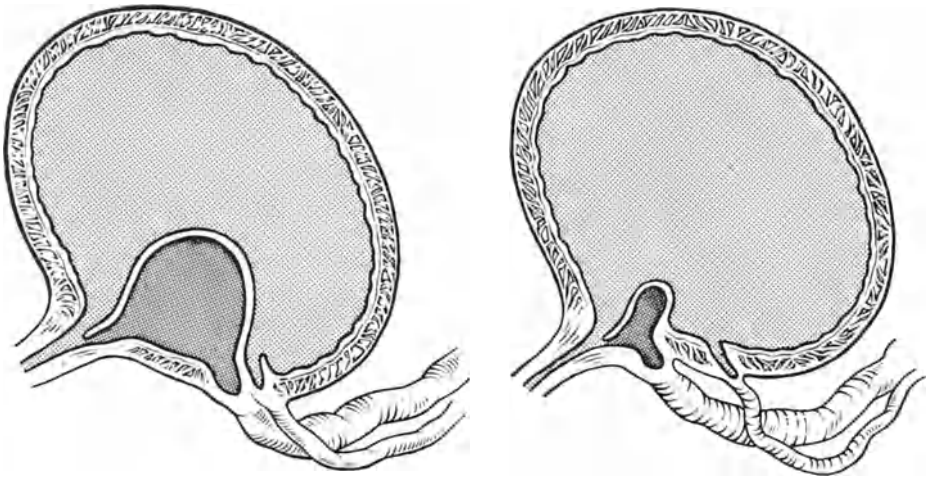
The disorder is commoner in girls in a ratio of 7 cases to one in the author's series. Either side may be affected and bilateral disease occurs in about 10 per cent. Contralateral duplication without ureterocele is also common, as is obstructive mega-ureter without duplication.

2. The Upper Urinary Tract

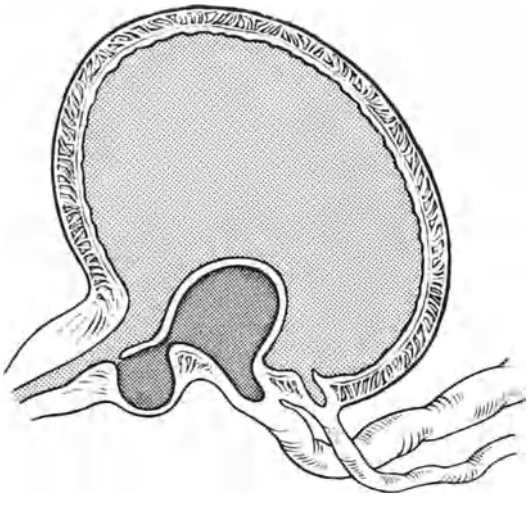
In the great majority of cases the ectopic ureter drains the upper pole of a duplex kidney. Occasionally, particularly in the male, the ectopic ureter is solitary but in either case the renal element which it drains is dysplastic; it is sometimes small and without function, sometimes severely hydronephrotic. Where there is a duplex system the upper pole of the duplex is always more severely damaged than the lower pole. The upper will occasionally concentrate the opaque medium sufficiently to define the calices, pelvis and ureter and the higher the dose of contrast medium and the more prolonged the examination the more likely it is to be seen.

Where no opacification of the upper pelvis occurs, however, the anatomical features of the lower pelvis and calices are usually diagnostic, as described in the previous chapter. Occasionally the upper pole ureter is so enormously dilated as to present a large palpable mass in the abdomen and radiologically it not only displaces the lower pole but impinges upon the bladder.

The lower pole of the kidney may be normal, but it is not infrequently pyelonephritic in association with reflux, or hydronephrotic because of obstruction and may be damaged to the point of non-function. The contralateral ureter may be



a Classical ectopic ureterocele. The classical form. b Ectopic ureterocele variant. Small variant.



c Ectopic ureterocele variant. Variant with retro-urethral sacculation.

Fig. 64a–c. Diagram to show anatomy of ectopic ureterocele: the classical form and variants. [Reproduced from Brit. J. Urol. **44**, 417–433 (1972), Fig. 5, p. 420]

similarly affected. These changes are usually the consequences of the ureterocele, but they may be due to intrinsic ureteric disorders.

3. Size and Position

The classical anatomy and variants are shown in Fig. 64. The ureterocele may be a simple spherical sac (Fig. 65), but it is sometimes a coiled dilated tube which can give it a loculated appearance in the cystogram, which might be mistaken for bilateral disease or even tumour. Cystographically the filling defect due to an ectopic ureterocele is always based on the bladder outline in any horizontal projection and never appears as does the orthotopic ureterocele as a complete circle within the bladder shadow. The size of the filling defect varies considerably, a few are so small that they produce only an inconspicuous crescentic bite out of the bladder neck outline (Fig. 66) and these are apt to be overlooked when attention is concentrated upon other pathology, particularly reflux into the ipsilateral lower pole renal pelvis. Occasionally the ectopic ureter exhibits not only the ureterocele

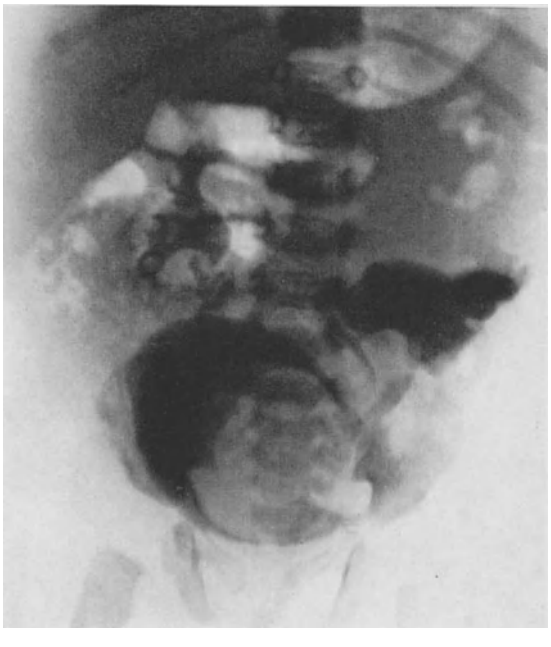


Fig. 65

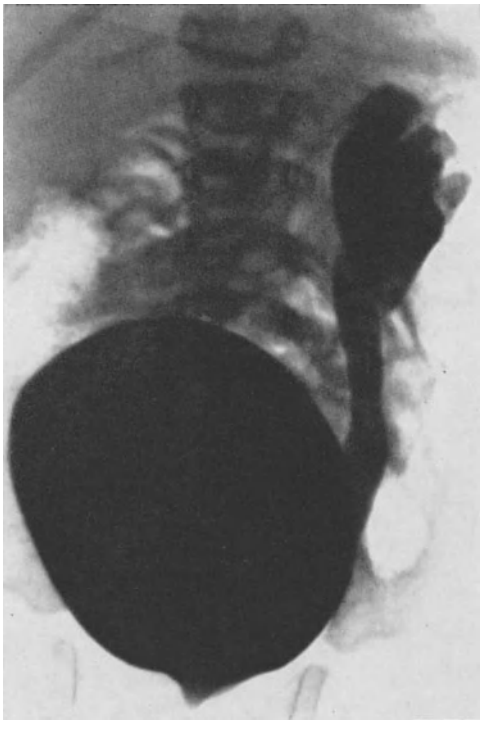
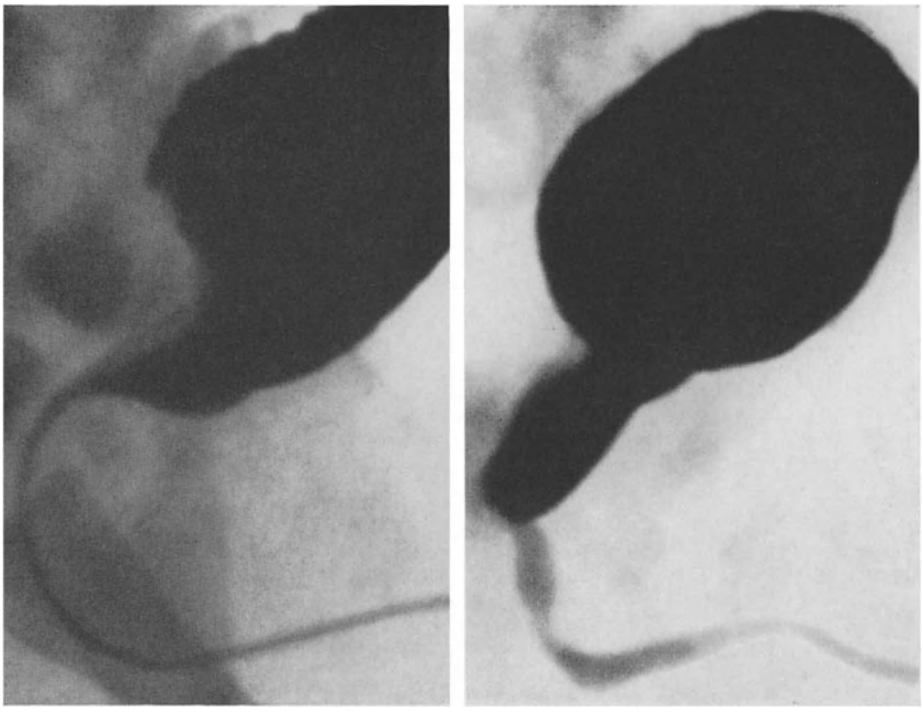


Fig. 66

Fig. 65. Ectopic ureterocele. Intravenous urogram in a girl with recurrent infection. Left duplex kidney with non-opacified upper pole, displaced lower pole. A large ureterocele filling defect in the bladder. [Reproduced from Brit. J. Urol. **44**, 417–433 (1972), Fig. 4, p. 419]

Fig. 66. Left ectopic ureterocele with lower pole reflux. Micturating cystogram in a girl with recurrent infection showing reflux into left lower pole ureter and deformity of bladder neck consequent upon small ectopic ureterocele

within the bladder but a second retro-urethral dilated sac stretching out and partially obstructing the supramontanal segment in the male (Fig. 67), or the entire urethra in the female. This type is described by STEPHENS (1971) as a caeco-ureterocele. This form of ureterocele is the only one in which reflux sometimes occurs into the intact ectopic ureter, a fact which makes its cystographic diagnosis easier. In other instances it must be surmised from the urethral deformity or the clinical appearance in the female of a pseudo-prolapse alongside the external urethral meatus.



a b

Fig. 67 a and b. Ectopic ureterocele in the male with retro-urethral dilated terminal segment. a Cystogram showing the filling defect of the ureterocele in the bladder. b Micturating film showing elongation of the supramontanal urethra. [Reproduced from Brit. J. Urol. **44**, 417–433 (1972), Fig. 8. p. 423]

4. Tension and Compressibility

The degree to which the ectopic ureterocele changes in size during the act of micturition varies greatly from one case to another depending upon its compressibility and this can be observed in good micturating cystograms with a diluted opaque medium, and lateral views. The tension within the ureterocele depends upon the severity of obstruction at the ureteric orifice: if the obstruction is virtually complete it is likely that the ureteric contents will be under high pressure whatever the function of the associated renal element. A few of the infantile cases have a completely sealed off orifice and contain sterile aqueous fluid much more

dilute than normal urine. In other cases tension will be increased during infection with obstructive oedema at the orifice. The tense ureterocele remains approximately the same size during micturition (Fig. 68) and the filling defect which it produces in the cystogram has a nearly circular outline. By contrast, where the ectopic orifice is wide and the contents of the ureter held at low pressure, the ureterocele is compressed during micturition and its contents empty back up into the ureter or down into the urethra (Fig. 69).

In the case of the tense ureterocele an ipsilateral lower pole ureter is drawn up on to its surface; this gives it a long submucous course which is pressed against the ureterocele during micturition and it is therefore valvular. It does not allow reflux

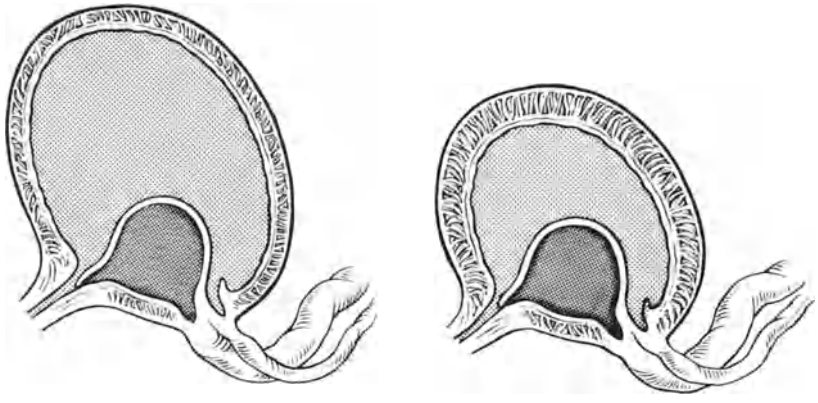


Fig. 68. Diagram of tense ureterocele. The ureteric orifice is narrow, the pressure within the ureterocele is high, so that it does not alter in size during micturition. The ipsilateral lower pole orifice is drawn up on to its surface; it remains in the same position with a long sub-mucous course during micturition and does not allow reflux, although it may be obstructed. [Reproduced from Brit. J. Urol. **44**, 417–433 (1972), Fig. 9, p. 424]

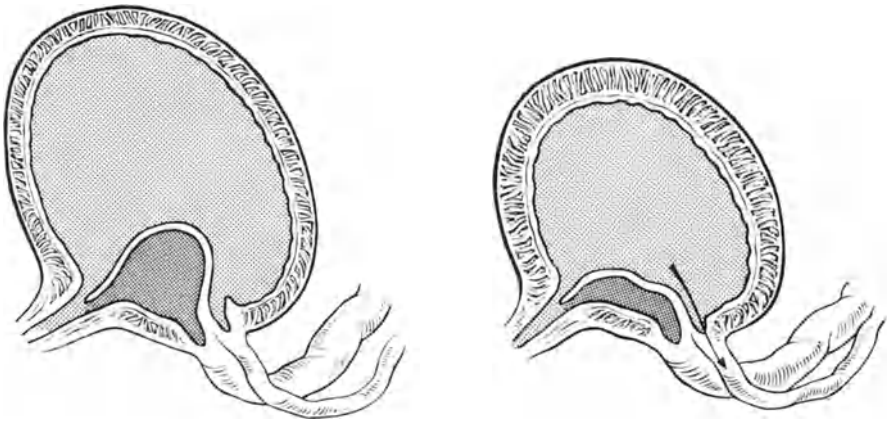
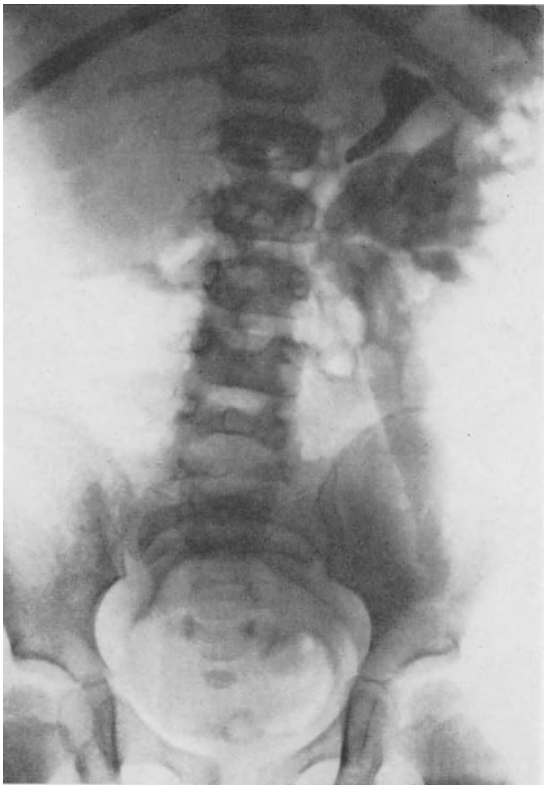
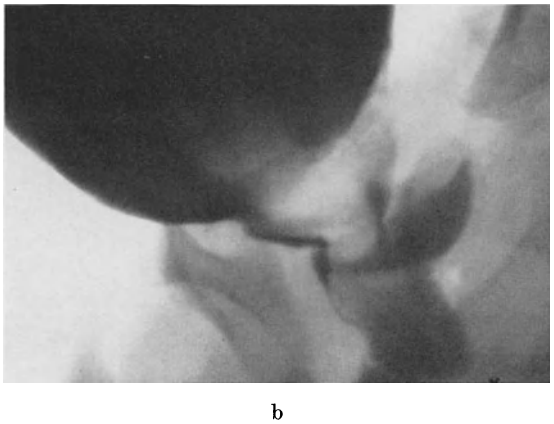


Fig. 69. Diagram of compressible ureterocele. The ureteric orifice is wide, or the ureter flaccid: the pressure within the ureterocele is low and it therefore collapses during micturition. The ipsilateral lower pole ureter is not supported and allows reflux. [Reproduced from Brit. J. Urol. **44**, 417–433 (1972), Fig. 11, p. 425]

and the lower renal pelvis may be normal or hydronephrotic (Fig. 70). With a compressible ureterocele during micturition the ipsilateral lower pole ureter is not stretched up, it has a lax support and no valvular action. Reflux is therefore likely (Fig. 71). If infection has been present, pyelonephritic scarring will then accompany reflux in the lower pole of the kidney. WILLIAMS, RAY and LILLEY (1972) have shown a statistical correlation between the compressibility of the ureterocele and the presence of reflux.

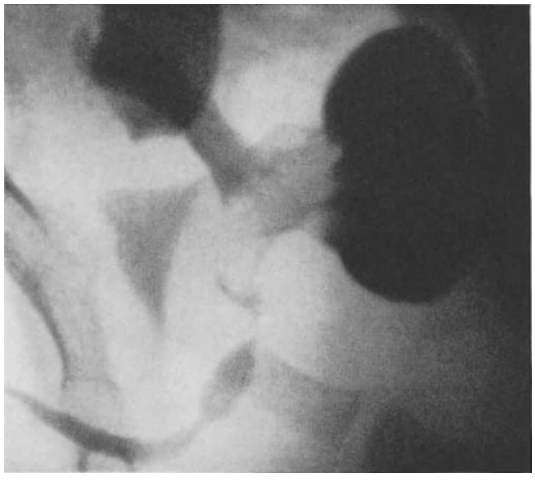


a



b

Fig. 70a and b. Tense ectopic ureterocele with urethral prolapse.
a intravenous urogram in a girl with persistent infection. Very poor function in the right duplex kidney, hydronephrosis in the left duplex kidney. Filling defect in the bladder due to large tense ureterocele on right upper pole ureter.
b Micturating cystogram: the filling defect of the ureterocele is unchanged in size but it is partly displaced downwards into the urethra. (Vagina also filled). [Reproduced from Brit. J. Urol. **44**, 417–433 (1972), Fig. 18, p. 431]



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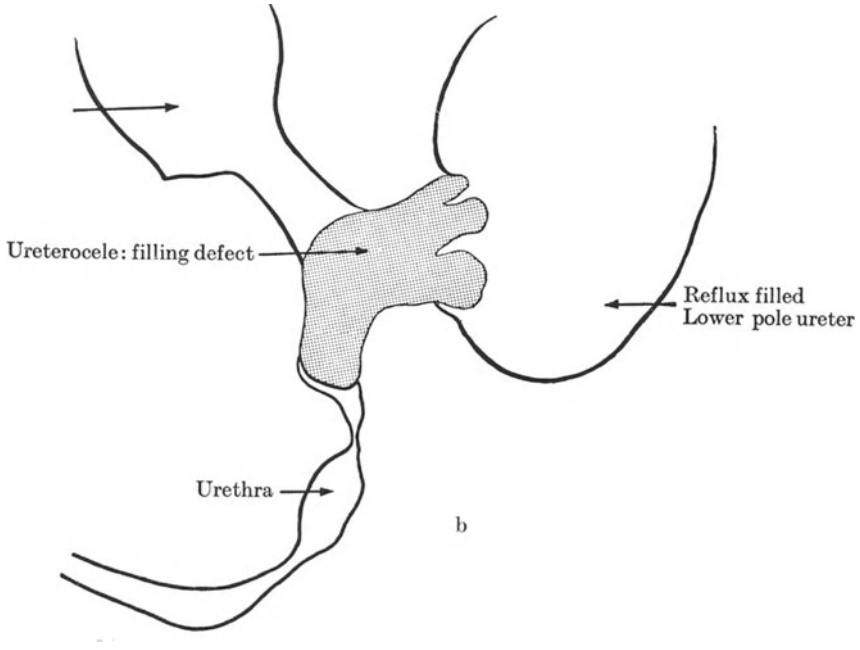


Fig. 71 a and b. Compressible ureterocele. a Micturating cystogram in a boy with persistent infection. b Explanatory diagram. The flaccid collapsed ureterocele is represented by the irregular filling defect at the base of the bladder. The opacity behind it is the ipsilateral lower pole ureter filled by reflux. [Reproduced from Brit. J. Urol. **44**, 417–433 (1972), Fig. 13, p. 426]

5. Detrusor Backing

In some cases the ectopic ureterocele, like the orthotopic one, is entirely within the bladder and has a normal sheet of detrusor muscle behind it. In others the detrusor coat is poor posteriorly and in a few it may even be absent (Fig. 72), this condition is defined as "poor backing" and there is, of course, a gradation between ectopic ureteroceles with good backing and those with poor backing. Indeed, there is further gradation to cases of ectopic ureter with a dilated segment lying entirely outside the detrusor coat. During micturition cystography those with poor backing may be demonstrably displaced outwards as shown by the position of the "circumferential sulcus". This term is applied to the gutter formed where the mucous membrane of the bladder is reflected on to the ureterocele (Fig. 73).

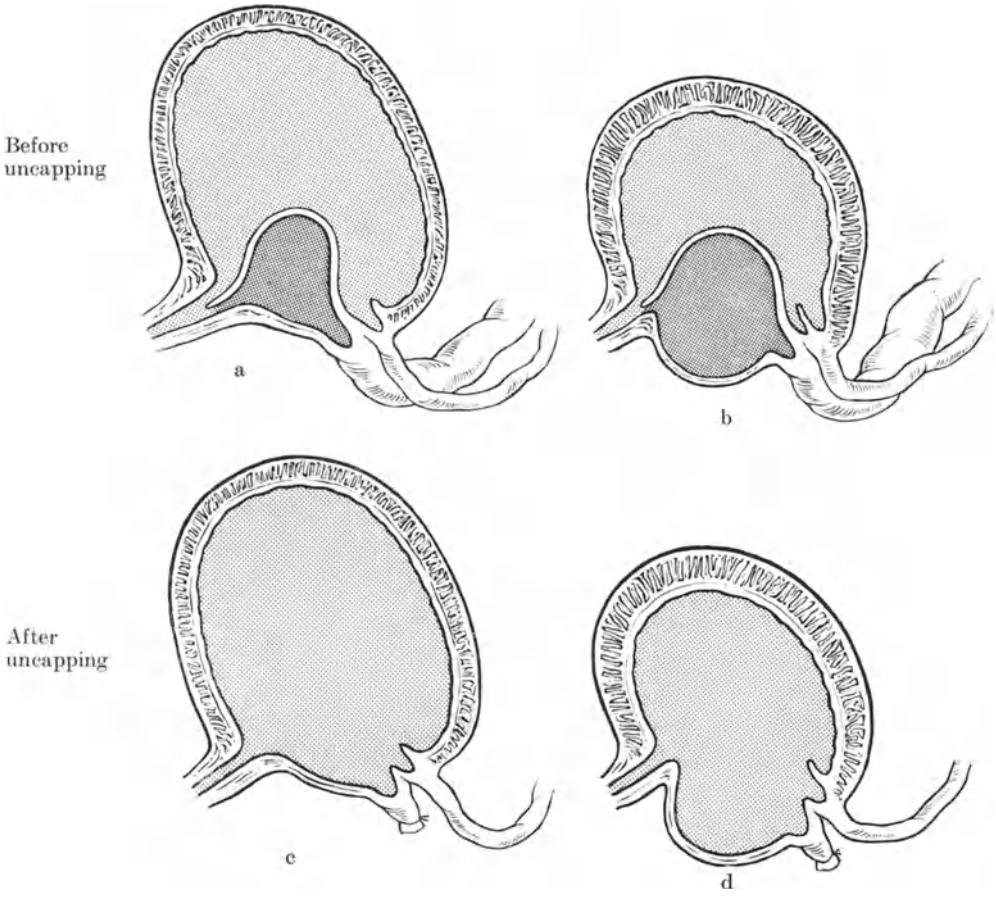


Fig. 72a–d. Diagram to show ureterocele with weak detrusor backing. a Bladder at rest. b During micturition. A tense ureterocele is displaced posteriorly to bulge out of the bladder wall. c After a simple uncapping operation with the bladder at rest. d The same during micturition: the bulging bladder wall throws up an obstructive distal lip. [Reproduced from Brit. J. Urol. **44**, 417–433 (1972), Fig. 15, p. 428]

As the bladder contracts the opaque medium in the fundus has a crenellated outline corresponding to the trabeculation of the bladder wall, but in the bladder base the ureterocele remains smooth with only a thin layer of opaque medium around it. This layer opacifying the circumferential sulcus may appear within the general outline of the bladder if the detrusor backing is good, or may be displaced widely outside the expected outline if the backing is poor (Fig. 74). The nature of the backing determines the choice of operation: the ureterocele with good backing may be uncapped within the bladder leaving a smooth wall which is well supported. Post-operatively cystograms will then show no deformity of the normal vesical outline. However, in the case of a ureterocele with poor backing simple uncapping will leave a weak area in the trigone forming a broad based bulge at rest but which blows out considerably on micturition throwing up a distal obstructive lip at the bladder neck or urethra. This lip cannot be permanently removed by endoscopic resection since the presence of the blow-out will cause the lip to reform. In these

cases complete excision of the entire circumference of the terminal ureter, together with adjacent bladder wall, and reconstruction of the detrusor coat is the proper treatment even though this is a much more considerable operation.

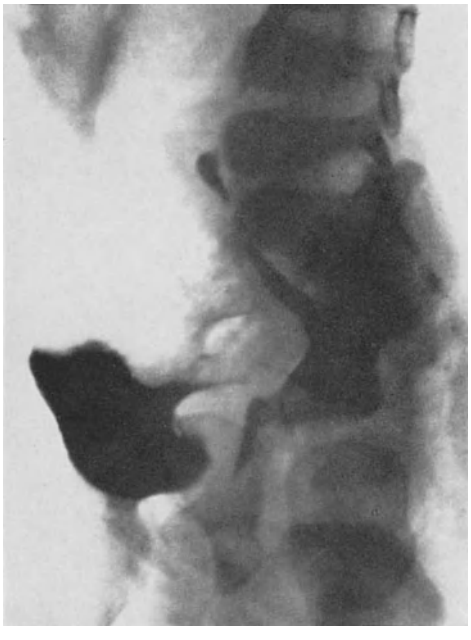


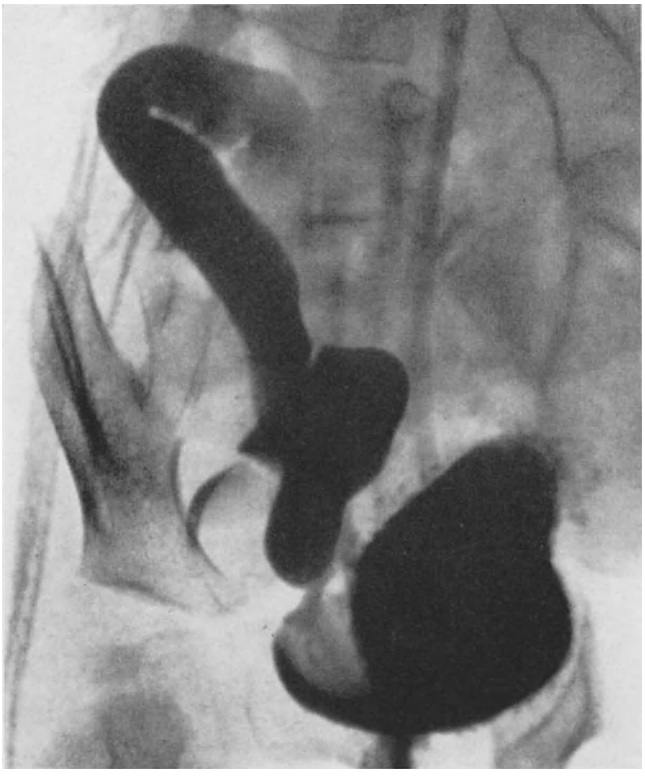
Fig. 73. Ectopic ureterocele showing circumferential sulcus. Lateral cystogram showing filling defect of ureterocele with a shelf of opaque medium above it. [Reproduced from Brit. J. Urol. **44**, 417–433 (1972), Fig. 6, p. 421]

6. Prolapsing Ureterocele

The majority of ectopic ureteroceles end at or slightly below the bladder neck and do not alter their position significantly during micturition, although they may be tense or compressible. Some, however, prolapse into the urethra either chronically or intermittently (Fig. 75). In girls the prolapsed portion will appear at the external urinary meatus and the diagnosis can be made clinically, but the cystogram may be misleading since the filling defect is not present in the bladder itself but in the urethra. In the male the ureterocele cannot prolapse beyond the membranous urethra, but a partial prolapse will produce a cone shaped dilatation of the posterior urethra which it is important to distinguish from obstruction due to stricture, particularly as in some cases where the opaque medium used for cystography is so dense that the filling defect of the ureterocele is not seen. Prolapse is naturally associated with obstruction, but if repeated prolapse occurs necrosis may supervene leading to spontaneous rupture.

7. Bladder Outflow Obstruction

The obstructive effect of a ureterocele varies from case to case and precise factors are not always apparent. A very large ureterocele may permit normal



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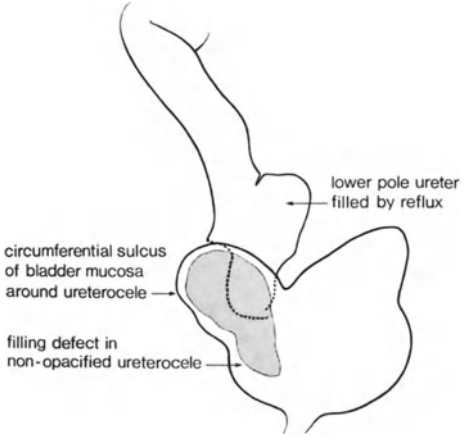

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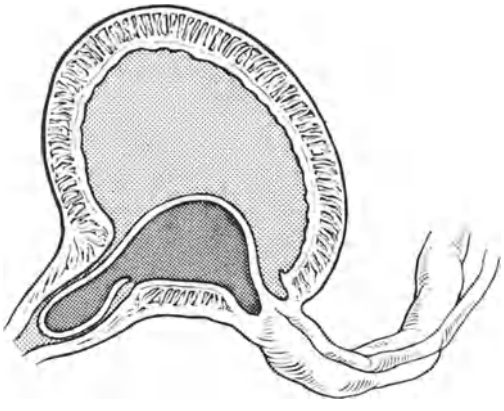
Fig. 74a and b. Ectopic ureterocele with poor detrusor backing. a Cystogram showing the contracted bladder with reflux into the right lower pole ureter. The filling defect of the ureterocele and the circumferential sulcus are displaced far out from the normal bladder outline. b Explanatory diagram. [Reproduced from Brit. J. Urol. **44**, 417–433 (1972), Fig. 17, p. 430]

bladder emptying while a small one may be obstructive. In girls ectopic ureterocele is the commonest congenital intrinsic defect producing severe obstruction in early infancy, but the degree of detrusor hypertrophy is greatest in the obstructed male cases (Fig. 76), particularly where prolapse occurs into the posterior urethra. In these cases not only the ectopic ureter is dilated but severe changes occur in the ipsilateral lower pole and in the contralateral ureter comparable to those seen in urethral valves and as likely to persist after the removal of the primary obstructive factor. Some of the most severe examples of upper tract dilatation are seen in children with ruptured ureteroceles. Presumably this dilatation has been established before the rupture occurred, though sometimes spontaneous rupture will leave an obstructive distal lip.



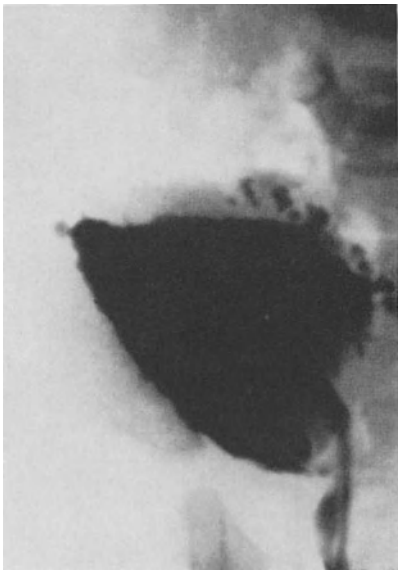


Fig. 75 Fig. 76

Fig. 75. Diagram to show prolapse of ectopic ureterocele. [Reproduced from Brit. J. Urol. **44**, 417–433 (1972), Fig. 18, p. 431)

Fig. 76. Ectopic ureterocele causing severe bladder outflow obstruction. Cystogram in a boy with urinary retention showing filling defect of ureterocele and extreme hypertrophy of bladder wall with sacculation

8. Ruptured Ureterocele

Rupture may follow simple instrumentation or may occur spontaneously, particularly in the prolapsed ureterocele. It is important to recognise the radiological appearance of the ruptured ureterocele: there is an irregular cavity lying just outside the outline of the bladder with a free edge forming an irregular filling defect within the bladder shadow. Characteristically on micturition reflux occurs both into the ectopic ureter and into the unsupported ureter of the ipsilateral lower pole (Fig. 77–79). Where the opening of the ectopic ureter is low down in the female urethra and rupture has occurred there may be a further complication due to the formation of a double channel, and consequently incontinence occurs as the urine

from the bladder can escape through the distal end of the ureter uncontrolled by bladder neck musculature. This can be demonstrated endoscopically or by very careful radiological technique. The septum between the urethra and the ureter is often paper thin and is therefore difficult to demonstrate. Recognition of the disorder is important, however, since it demands a radical removal of the ectopic ureter channel together with reconstruction of the posterior wall of the urethra.

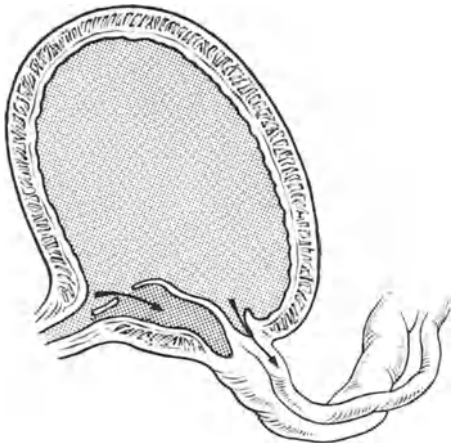


Fig. 77

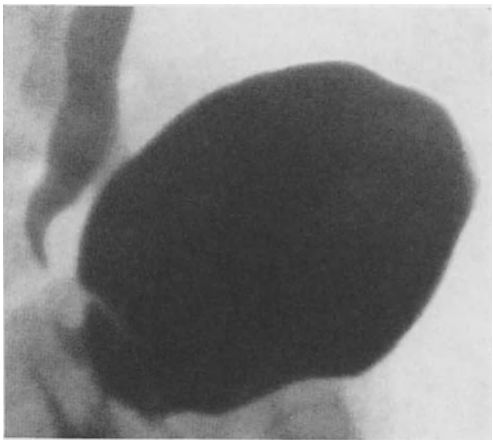


Fig. 78

Fig. 77. Diagram to show ruptured ectopic ureterocele with reflux into both upper and lower pole ureters. [Reproduced from Brit. J. Urol. **44**, 417–433 (1972), Fig. 21, p. 432]

Fig. 78. Ruptured ureterocele. Lateral cystogram in a girl with recurrent infection showing reflux and the filling defect of the free edge of the ruptured ureterocele in the base of the bladder. [Reproduced from Brit. J. Urol. **44**, 417–433 (1972), Fig. 22, p. 432]

9. Treatment

In general the treatment for ectopic ureterocele is heminephrectomy, ureterectomy, excision or uncapping of the ureterocele and often implanting of the ipsilateral lower pole ureter. Operative techniques have recently been discussed by Johnston and Johnson (1969); Hendren and Monfort (1971); Tanagho (1972); Malek et al. (1972). Upper pole heminephrectomy is a standard procedure which requires no special comment here, save to remark that where the upper pole ureter is grossly dilated the vessels to the lower pole are often severely stretched and very great care must be taken to preserve them, and subsequently to protect them from being pulled or distorted by performing a nephropexy. The older and widely practised method of ureterectomy, removing the ectopic ureter down to the point at which it enters the adventitia of the bladder with simple uncapping of the ureterocele within the bladder, can work well, particularly as already stated where the ureterocele is small, the backing firm and no reflux occurs into the lower pole ureter. With uncapping it is important to remove all the upstanding edge, particularly down in the posterior urethra, as otherwise it may form a valvular fold which can be more obstructive than the original condition. Uncapping may be

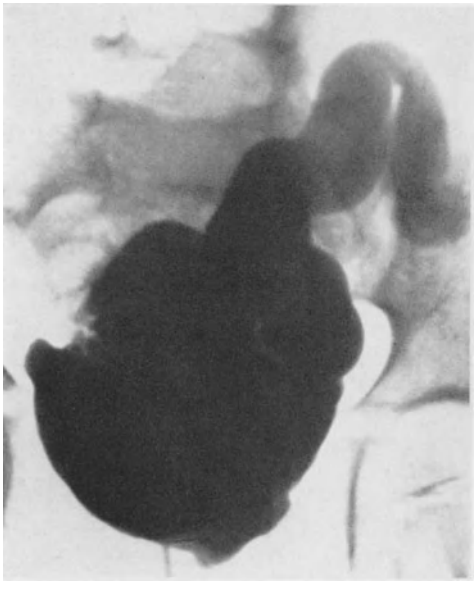


Fig. 79. Ruptured ectopic ureterocele. Cystogram in a boy with severe bilateral hydronephrosis showing reflux into the dilated left ureters and the irregular cavity outside the bladder outline characteristic of ruptured ectopic ureterocele. [Reproduced from. Brit. J. Urol. **44**, 417–433 (1972), Fig. 23, p. 433]

combined with an advancement type of re-implantation of the lower pole ureter if reflux is present, or if the lower ends of the two ureters are so closely bound together that complete excision of the ectopic one leaves the other non-viable at its extremity. However a complete excision of the ureterocele may be preferable in these circumstances and is essential if the detrusor backing is poor. This excision requires a complete extra-vesical mobilisation of both ureters and then an intravesical approach similar to, though more extensive than, that already described for orthotopic ureterocele. A circumferential incision through the vesical mucosa is made on the slopes of the ureterocele including within it the lower pole ureteric orifice. At the upper end the ureters are freed from the bladder muscle and drawn up into the bladder. The lower pole ureter is cut across at a suitable level for re-implantation, the ectopic ureter is dissected free down to its opening in the urethra. Sometimes this dissection is easy as in the orthotopic ureterocele, sometimes it is difficult at the lower end where the ureter becomes closely adherent to the prostatic tissue or to the vagina. Once the ectopic ureter has been removed the bladder wall is repaired, bringing together a muscle layer from either side to form a firm trigone. The mucosal cover is then completed with an advancement re-implantation of the lower pole ureter.

In some cases, particularly if the ureter opens very low down in the urethra as in the double channel type of incontinence, a purely intra-vesical approach to the distal extremity will not suffice and the plane behind the bladder must be fully opened up (Williams and Woodard, 1964). For this purpose the bladder should first be fully mobilised anteriorly and laterally so that it can be pulled up out of the pelvis; the plane between the bladder and vagina is then entered from above, through the peritoneum and in the mid-line. Development of this plane then pro-

ceeds downwards quite easily and firm upward retraction of the bladder exposes the posterior urethral wall with its included ectopic ureter. The ureter is excised completely and the urethra reconstructed around a catheter. There is no fear of producing permanent incontinence if the dissection is kept strictly to the posterior mid-line. This approach is easiest in the small child: adolescents and adults may be better tackled from below.

In the ordinary case of a fit child with a controlled infection the whole operative procedure can be undertaken in one session, often combined with re-implantation of the contralateral ureter. In some the procedure is simplified by the fact that the function of the lower pole of the kidney is so far depressed that complete nephro-ureterectomy is better, as well as easier, than hemi-nephrectomy. Nevertheless in the very young and the very sick some staging or preliminary drainage may be necessary, but satisfactory temporary drainage is not always easy to obtain without prejudicing the ultimate operation. For the pyonephrosis situation nephrostomies may be performed as an emergency measure, but it is vital that both poles of the kidney are drained and subsequent heminephrectomy will be rendered more difficult by the preliminary operation. A simple uncapping of the ureterocele in the bladder will, of course, relieve retention and will decompress the obstructed ipsilateral lower pole and contralateral ureters but will leave massive reflux into the ectopic ureter. A complete excision and reconstruction of the ureterocele area may be too much to perform in the severely infected infant, but it is usually feasible to supplement the uncapping by a low transection of the ectopic ureter, which can be mobilised and brought out in the flank as a temporary cutaneous ureterostomy. Even this will require catheter drainage and irrigation, however, for the dilated and dysplastic upper pole has no power to empty itself. Heminephrectomy and ureterectomy can then follow as soon as the child's condition permits and a follow-up study will show whether at a later stage complete excision of the posterior wall of the ureterocele together with re-implantation of the lower pole ureter is required.

M. Obstructive Uropathy: The Functional Disorder

D. Innes Williams and T. M. Barratt

With 5 Figures

I. Introduction

The need for elimination of obstruction in the urinary tract is so well accepted a principle of urology and surgical procedures for individual obstructions so familiar that it is a matter of surprise that the fundamental nature of the damage to the urinary tract and kidney consequent upon obstruction is not fully understood. Superficially it is abundantly clear that an obstructive lesion produces dilatation of the urinary tract above the obstruction, an increase of pressure within the kidney and an impairment of renal function which is, in the early stages, recoverable. Yet none of these features can be accepted without comment. The presence of dilatation does not necessarily indicate obstruction; the pressure within the apparently obstructed kidney is not always high; the pathology of temporary and permanent renal impairment is still a matter of investigation. Each of these aspects requires discussion from the clinical and experimental point of view, and this chapter is concerned with the upper tract disorder. The criteria for the diagnosis of bladder outflow obstruction are discussed in Chapter O.

II. Urinary Tract Dilatation

Dilatation of the ureter may be due to obstruction, maldevelopment, infection, polyuria or reflux, and more than one factor may be operative in any individual case. Urinary obstruction is unquestionably the most serious cause of dilatation, but the form which that dilatation takes depends upon the nature of the obstruction and the age of onset. Many infants are born with grossly dilated urinary tracts, particularly in the case of urethral valves or other major obstructions to bladder outflow, and it is apparent that the foetal urinary flow is sufficient to cause this dilatation when obstructed. There may, however, be other factors involved, as in the prune belly syndrome, where very gross dilatation appears to be at least partly due to a defect in the muscular wall of the ureters and bladder. The characteristic of the foetal dilatation is that the ureter is enormously widened and tortuous while the renal pelvis remains relatively small. The later in life that obstruction occurs, the less will be the consequent dilatation of the ureters, and this is doubtless related to the increase in the population of elastic and muscular fibres as recorded by Cussen (1967). In many of the milder congenital obstructions the dilatation is progressive, and it is not always clear whether this is due to increasing obstruction, to increasing urine flow or to other factors. In the urethral valve cases there may well be an acute dilatation occurring in the first week of life, perhaps due to the sudden increase of urine flow after birth. In the neuropathic

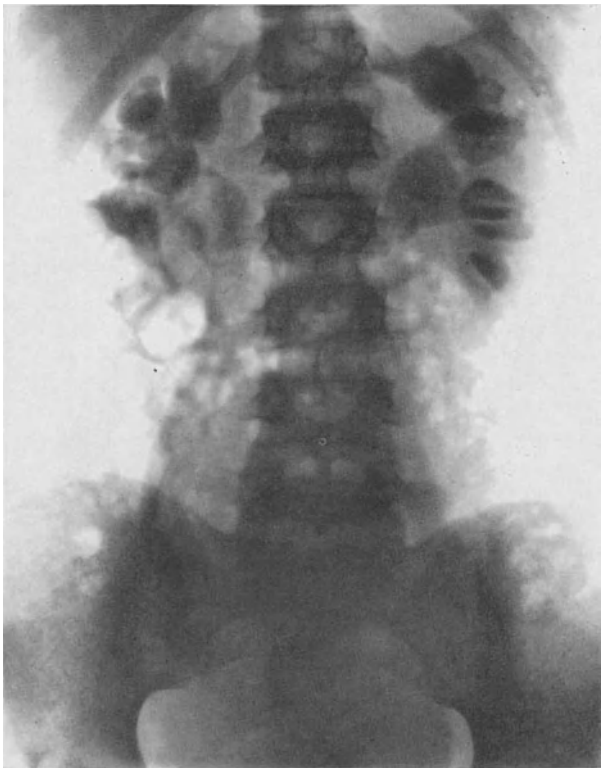


Fig. 80. Nephrogenic diabetes insipidus. Intravenous urogram in a boy with familial disease. Very considerable polyuria but no identifiable urinary obstruction

bladder very few children have gross dilatation at birth; it commonly develops during the first two years of life, partly on the basis of obstruction, partly perhaps associated with infection and reflux.

It has been demonstrated by TEAGUE and BOYARSKY (1968) that bacterial toxins are capable of paralysing ureteric muscle, and there is little doubt that the presence of infection within the urinary tract can contribute to ureteric dilatation. It is seldom possible to define a case in which infection alone is responsible for dilatation, though the moderate changes seen without reflux and without apparent obstruction in the chronically infected calculous disease of the renal pelvis might be an example (Fig. 176).

Increased urine flow is well known to be responsible for modest dilatation, a fact easily demonstrable in high dose pyelograms. It has often been observed that in states of obligatory polyuria ureteric dilatation is common, but the cause of the polyuria in such instances may well be due to the renal disease consequent upon urinary tract pathology. MANSON et al. (1970) investigated cases of pituitary and nephrogenic diabetes insipidus and found that the urinary tract was dilated in 8 out of 37 cases, but that in only one of the 8 could dilatation not be attributed to some cause other than polyuria. Nevertheless it is our impression that very severe polyuria can contribute to dilatation, particularly in early childhood (Fig. 80), and a "flow uropathy" has been described by TEN BENSEL and PETERS (1970) in

nephrogenic diabetes insipidus. Similar findings have occurred in juvenile nephronophthisis (GIBSON and ARNEIL, 1972) and Bartter's syndrome (CANNON et al., 1968). In a curious group of cases reviewed by ROSE et al. (1966) juvenile diabetes mellitus is associated with diabetes insipidus and optic atrophy. Some of these girls have exhibited a very severe dilatation of the entire urinary tract, perhaps due to the polyuria or perhaps to neuropathic dysfunction.

The dilatation associated with reflux is discussed in Chapter J. It is characteristically variable with changes in intravesical pressure, so that with the empty bladder the ureter appears flaccid and sometimes exhibits longitudinal striation; during bladder contraction it is wide, smooth and often actively contractile. That reflux from a normal bladder causes some dilatation can scarcely be doubted, but it will be seen that in sterile cases it is very seldom progressive.

It is clear, therefore, that radiological observation of upper tract dilatation cannot be taken as conclusive evidence of obstruction. Nevertheless, the indications for surgery, particularly in children with multiple anomalies, and in post-operative cases, depend very largely upon the presence or absence of an obstructive factor so that further investigations are often desirable.

III. Pressure Studies

Since the pioneer work of KIIL (1957) many investigators have followed ureteric and pelvic pressure recordings in various circumstances. The experimental work on dogs by BÄCKLUND and REUTERSKIOLD (1969) and by STRUTHERS (1969) may be cited as examples. The intra-ureteric pressure depends both upon the renal secretory pressure and upon the ureteric muscular activity. When the ureter is acutely obstructed the basal pressure rises, the contractions are more frequent, but the wave amplitude rises only slightly until with complete ureteric distension a high basal pressure is no longer interrupted by any contraction waves. Similar, although much less severe changes, may be seen in the intact ureter by inducing a diuresis or by raising the bladder pressure. In the chronically obstructed ureter, which is dilated with hypertrophied muscle, the resting basal pressure may be normal or only a little above it: diuresis induces a considerable rise and contraction waves soon disappear, but electromyographic recording confirms the visual observation that muscular contractions are still occurring, though they fail to raise the intra-ureteric pressure.

In the clinical situation KIIL (1951) found that the pressure in many hydronephroses did not exceed normal levels, but STRUTHERS (1969) and others have demonstrated that this observation is partly the result of pre-operative dehydration and of the anti-diuretic effect of anaesthesia. With forced diuresis pressure rises may be observed in the hydronephrotic kidney. The changes are most easily demonstrable by infusing fluids at relatively high rates, e.g. 10 ml/minute (WHITAKER, 1973), either through a percutaneous nephrostomy needle or at open operation. The ability of the normal ureter to transport this flow is easily contrasted with the inability, with consequent rise in pressure, of the obstructed one. WHITAKER has used this method to differentiate dilated obstructive from dilated non-obstructive ureters, particularly in post-operative cases when dilatation persists after removal of urethral obstruction or after reimplantation of the ureter. As pointed out in Chapter N, some mega-ureters appear to be progressive, producing renal changes, others stable with well cupped calices. BÄCKLUND and REUTERSKIOLD (1969b) investigating wide non-refluxing ureters found many in which there

was no obstruction, as evidenced by pressure rises on perfusion. They comment that despite their large width the ureters retain a capacity for contraction, but that since the lumen is not completely obliterated the peristalsis is not bolus-propelling as in the normal ureter, but allows regurgitation of urine into the upper ureter. The deficiency in bolus-propelling ability could be compensated by the renal secretory pressure if the kidney were adequate, so that a normal urine flow might be maintained. They conclude that the decision as to whether a ureter should be re-implanted must be taken on the basis of obstruction as demonstrated by pressure changes. However, it is also clear that re-modelling of such a dilated contracting ureter may enable the contractions to become more effective, so that even in the non-obstructed situation surgery may be justifiable. It has also become clear from many studies that the intravesical pressure must be taken into account in the wide non-obstructed ureters, and further research into this aspect is required.

It may be concluded from the pressure investigations that in chronic obstruction intrapelvic and intra-ureteric pressures are raised, although perhaps only intermittently and during periods of high urine flow; further that ureteric dilatation does not necessarily indicate increased ureteric pressure and that in some clinical situations pressure measurements may be an important factor in deciding upon the need for surgery.

IV. Renal Morphology

Matz, Craven and Hodson (1969) have reported changes in the pig's kidney following complete experimental obstruction of the ureter. Changes in the renal substance are primarily due to the direct pressure effect on and within the papillae. There is extensive tubular rupture, disintegration and atrophy. Initial cortical changes are secondary in the papillae and consist predominantly of tubular atrophy. Compression of the pelvic renal vein branches may be a contributory factor to further tubular damage, but there is no evidence of a major ischaemic effect; when the ureteric obstruction is relieved and a period allowed for repair, the kidney is contracted with some surface scarring but without evidence of chronic pyelonephritis, and histological appearances show reconstruction of the cortex with disappearance of some nephrons and minimal fibrosis. Hodson (1967) correlates these experimental findings with clinical and radiological observations, showing that during acute ureteric obstruction there is a progressive loss of renal parenchyma, most clearly demonstrated by the contraction of the kidney after the obstruction has been relieved. However, the process of tubular destruction and disappearance has progressed steadily during the period of obstruction. These radiological findings are illustrated in Fig. 81.

In most childhood obstructions the lesion is congenital and of longstanding, so that the kidney is enlarged and hydronephrotic with thinning of the renal parenchyma and flattening of the papillae, but continuing tubular loss presumably occurs with episodes of high pressure obstruction. A further factor has to be taken into consideration in disorders commencing during foetal development: Bernstein (1968) and later Beck (1971) have demonstrated experimentally that obstruction at this stage can result in renal dysplasia (Chapter F), and this pathological change will lead to further impairment of renal function. An interesting model for studying this relationship was observed by Lozzio (1964) in a mutant strain of Gunn rats: these animals developed congenital mid-ureteric strictures on a genetic basis, the renal lesion varying between simple hydronephrosis and cystic dysplasia.

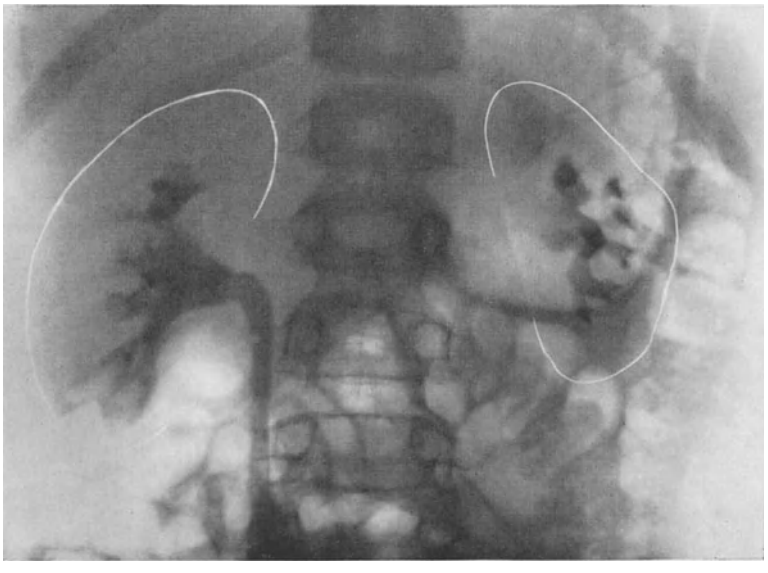


Fig. 81 a

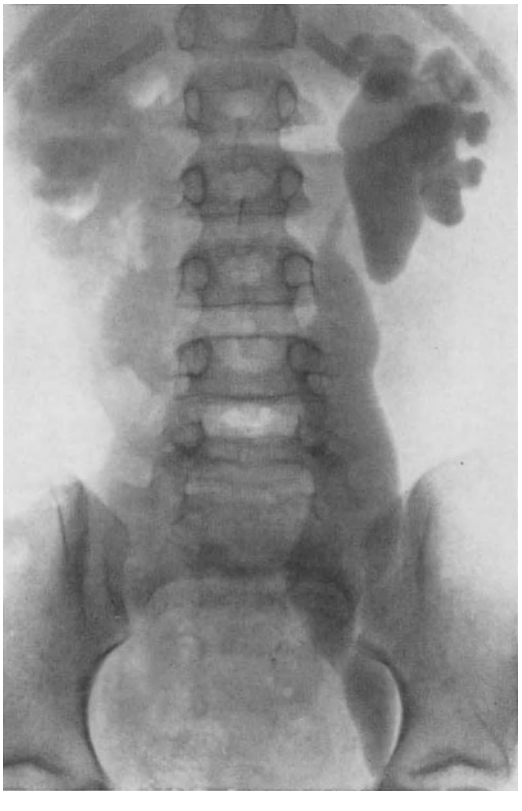


Fig. 81 b

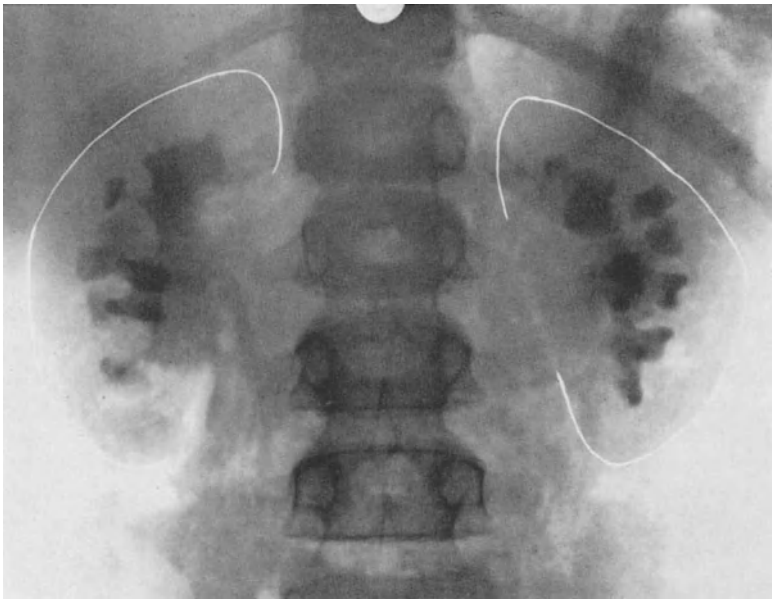


Fig. 81 c

Fig. 81 a–c. Obstructive renal atrophy. Serial urograms in a boy referred for ureteric obstruction complicating reflux preventing re-implantation of the ureters. a Original pre-operative urograms showing a normal right kidney, small and slightly pyelonephritic left. b Post-operative urograms showing enormous bilateral hydronephrosis and ureteric dilatation. c Intravenous urograms following revision operation showing post-obstructive atrophy, most marked on the previously normal right kidney

V. Renal Function

1. Experimental Observations

In rats, micropuncture studies show that applied ureteric pressure has no effect on the pressure in the proximal tubules until it exceeds the resting tubular pressure of 13 mm Hg (17 cm H_2O); further increments then result in an equivalent rise of both proximal tubular and peritubular capillary pressure (Gottschalk and Mylle, 1956). Clearly, as the tubular pressure rises, so the glomerular filtration pressure gradient, and thus the filtration rate, falls. Renal blood flow is, however, well preserved even with ureteric pressure increments of up to 70 mm Hg (Kiil and Aukland, 1961; Murphy and Scott, 1966), but falls with complete ureteric obstruction (Vaughan et al., 1970).

Kiil and Aukland (1961) observed that increased ureteric pressure imposed upon one kidney of a dog during water diuresis resulted in diminished flow rate and sodium concentration with increased osmolality and creatinine concentration of the urine of the experimental kidney relative to that of the control kidney. These findings point to an increased water re-absorption in the proximal tubule, distal tubule or both; the diminished sodium concentration supports a predominantly proximal effect. These findings in the acutely obstructed kidney were con-

firmed by SUKI et al. (1966) who pointed out the similarity of the functional disturbance to that of renal artery stenosis: in both, the fractional excretion of filtered water, V/GFR (V = urine flow rate; GFR = glomerular filtration rate), during hypotonic volume expansion is reduced on the affected side. V/GFR under these circumstances is determined by the fractional proximal reabsorption of filtered sodium, and the data are taken to imply nephron under-perfusion, that is, a reduction in GFR per nephron, resulting in a distortion of glomerulo-tubular balance such that the fraction of filtered sodium reabsorbed by the proximal tubule is increased (FULOP and BRAZEAU, 1970). This functional disturbance is responsible for the prolonged dense nephrogram characteristic of acute obstruction.

Immediately after complete unilateral ureteric obstruction intrapelvic pressure is high, approaching arterial blood pressure, but it rapidly falls and within one week is nearly back to pre-obstruction levels. Initially, recovery of renal function after relief of obstruction is rapid and fairly complete, but even after only one week of obstruction recovery is perceptibly lower and less complete (KERR, 1956). Incomplete chronic unilateral ureteric obstruction results in a different pattern of response to hypotonic volume expansion from that observed in the acutely obstructed kidney (SUKI et al., 1966): V/GFR is increased on the affected side in a manner characteristic of a kidney which has undergone nephron destruction with resultant over-perfusion (i.e. increased GFR per nephron) of the remaining nephrons.

In summary, the experimental evidence suggests that acute obstructive nephropathy is a reversible situation, characterised by decreased GFR per nephron, but that as obstruction persists there is nephron destruction, overperfusion of remaining nephrons and renal changes that are less readily reversible. It might seem that children with congenital obstructive uropathy should invariably behave as in the chronically obstructed model of SUKI et al. (1966), but in all such cases episodes of high pressure occur and these cases behave as if they were subject to acute obstruction. It may be that the relevant distinction in SUKI's experiments is not the duration of obstruction but the level of intrapelvic pressure.

2. Clinical Observations

a) Technical Considerations

There are certain restrictions on the assessment of function of the obstructed kidney in a clinical setting: the large volume of residual urine precludes accurate timed urine collections, particularly over short periods, and the classical clearance techniques of renal physiology are not applicable. Passage of catheters above the level of obstruction does not overcome the problem, for the kidneys will then no longer be obstructed. Furthermore, if any function of the kidney is acutely stressed, the large residual volume may damp the renal response, and it is important to demonstrate that the relevant urinary parameter has reached a plateau before it can be concluded that the urine passed externally is representative of that secreted by the kidney. This restriction applies particularly to tests conducted at low urine flow rates, such as water deprivation, and for this reason the ability of the obstructed kidney to concentrate the urine is virtually unmeasurable. In addition to these problems, the sick infant tolerates investigational procedures poorly. Repeated venepuctures, for example, are unacceptable and all laboratory techniques must be miniaturised for capillary blood sampling. Under the circumstances it is hardly surprising that data on renal function on infants with obstructive

nephropathy are limited (McCrory, 1971), and it is in this context that the development of techniques which permit the assessment of renal function without timed urine collection (see p. 10) is so promising.

b) Abnormalities of Function

The principal aspects of renal function which may be abnormal in obstructive nephropathy are:

1. Glomerular filtration rate.
2. Sodium conservation.
3. Hydrogen ion excretion.
4. Urine concentration.
5. Urine dilution.

It is of interest that the major functions of the distal nephron are all involved. The inability to conserve sodium may be exaggerated after relief of obstruction and is considered below. Hydrogen ion secretion is faulty: Berlyne (1961) has documented failure of acidification of the urine following ammonium chloride administration in six or seven patients with chronic hydronephrosis.

Perhaps the most striking effect of urinary obstruction is upon the urinary concentrating mechanism (Ericsson et al., 1955). In view of the anatomical disruption of the papillae, the counter-current system could hardly be expected to function normally. Obligatory hyposthenuria is common (Winberg, 1959; Earley, 1956) and may precipitate the infant into negative water balance, as discussed on p. 5. The clinical picture may then mimic nephrogenic diabetes insipidus. This defect may diminish after the obstruction is relieved (Dorhout-Mees, 1960; Berlyne, 1961).

c) Prediction of Recovery

A few children with obstructive uropathy have a restricted ability to dilute the urine in response to an oral water load (Barratt and Chantler, 1970). Although perhaps of limited clinical significance, this observation is of interest in relation to the experimental data described above. In this investigation V/GFR was estimated from plasma: urine creatinine (P_c/U_c) concentration ratio using the creatinine clearance ($U_c V/P_c$) as an estimate of GFR:

$$\text{V/GFR} = V/(U_c V/P_c) = P_c/U_c$$

It was found that those children who resembled Suki's acutely obstructed model, that is who had a restricted ability to lower the plasma: urine creatinine concentration ratio during water diuresis, had the greatest percentage rise in GFR in the first week after relief of obstruction. This data gives some hope that it may be possible to identify the functionally acute and reversible obstruction from physiological data alone.

d) Post-Operative Natruresis

Following the relief of obstruction there may be an exaggerated urinary loss of sodium. This phenomenon is rather unpredictable and may achieve massive proportions (Bricker et al., 1957; Chisholm, 1970). Osmotic diuresis due to the excretion of retained urea may play a role (Maher et al., 1963), but seems inadequate to account for the more dramatic examples. Experimental data suggest that there is impaired proximal tubular sodium reabsorption with inability to sustain a normal tubular fluid: plasma sodium concentration ratio (Bercovitch et al., 1971). The natruresis appears to be more marked in those children in whom relief

of obstruction subsequently results in a greater increase of GFR (GHAZALI and BARRATT, 1973). Whatever the mechanism it is important to be aware of the possibility that such a natruresis may occur, for, if not replaced, saline depletion may lead to further deterioration of renal function. The tendency of the obstructed kidney to lose both salt and water means that the customary practice of restricting their intake after surgical operations should not be applied indiscriminately to the child with obstructive nephropathy.

VI. Radiological Studies: The Nephrogram

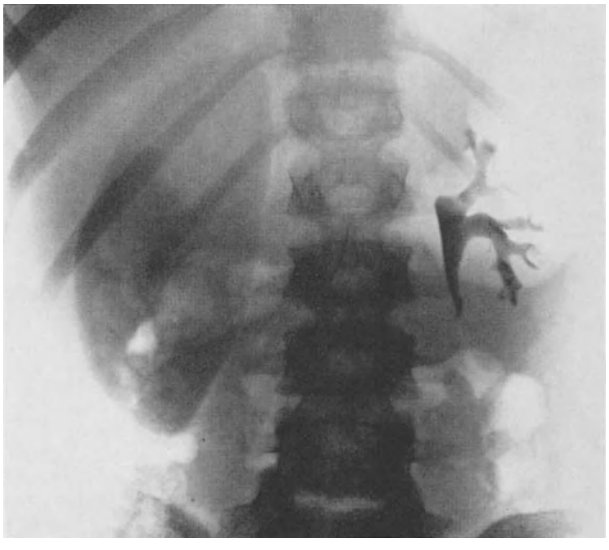
In recent years the importance of the nephrographic phase during intravenous urography has received increasing attention. The opacification in the nephrogram is caused by opaque medium within the lumen of the renal tubule: its density will depend primarily upon the concentration of the medium in the plasma, and therefore in the glomerular filtrate, and secondly upon the amount of water reabsorbed as the filtrate passes down the tubule. Obviously the size of the kidney and the number of functioning nephrons will also have an influence on the pictures obtained. The normal nephrogram is maximal immediately at the end of an acute intravenous injection of contrast medium, when the plasma concentration is highest. The larger the dose the longer will the nephrogram last: it disappears as the pyelogram begins to show. There is a variety of conditions, well reviewed by KELSEY-FRY and CATTELL (1972), in which persistent nephrograms are observed. The presence of a persistent nephrogram is not in itself diagnostic of obstruction for an immediate or faint persistent nephrogram is commonly seen in uraemic cases with chronic glomerular disease. An immediate dense and persistent nephrogram may be seen in acute tubular necrosis, and perhaps too in acute suppurative pyelonephritis. The nephrogram which is delayed in appearance, but then becomes increasingly dense over a period of hours, is the characteristic pattern of obstructive uropathy, and where this pattern is associated with early non-opacified areas due to dilated calices obstruction may safely be diagnosed. It appears that in this type of acute obstruction glomerular filtration occurs with continuing reabsorption of water from the filtrate. Dilatation of the tubules and stasis within them are additional factors in contributing to the dense nephrogram. These changes are seen in children of all ages with acute obstructive episodes in the urinary tract (Fig. 82), and since they indicate a high glomerular filtration rate with active reabsorption of water from the tubules they are associated with a potentially recoverable situation.

A special type of nephrogram is seen in some acutely obstructed hydronephrotic kidneys: it is the "shell nephrogram" in which the calices are outlined by a thin rim of opacification, perhaps presenting a soap-bubble appearance (Fig. 83). Later in the investigation the urine contained in the calices will be opacified. The shell nephrogram appears to be due to retention of the opaque medium in the collecting tubules which, because the calix is so tensely dilated, have come to lie tangential to the calix rather than perpendicular to it. In our experience this type of nephrogram has also indicated a potentially recoverable situation.

VII. Isotope Studies

Radioactive renography can give important evidence as to the presence of obstruction, but in cases with dilated urinary tracts the results need to be inter-

preted with caution. By contrast with the opaque substances used in radiology which are largely excreted by glomerular filtration, the I 131 Hippuran commonly used in isotope renography is actively secreted by the tubules so that a different function of the kidney is emphasised in this investigation.



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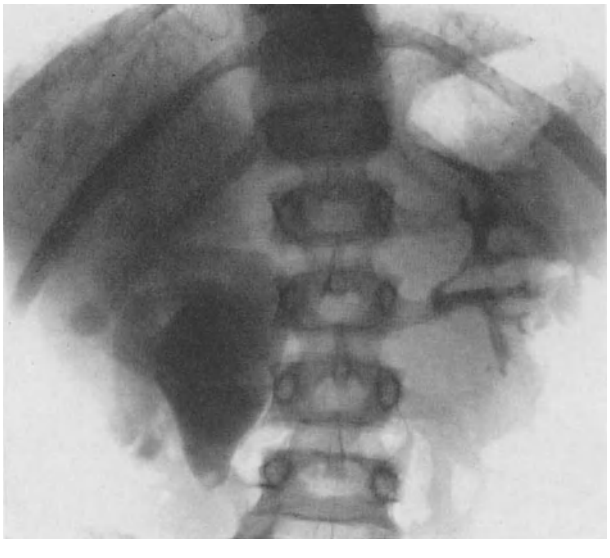
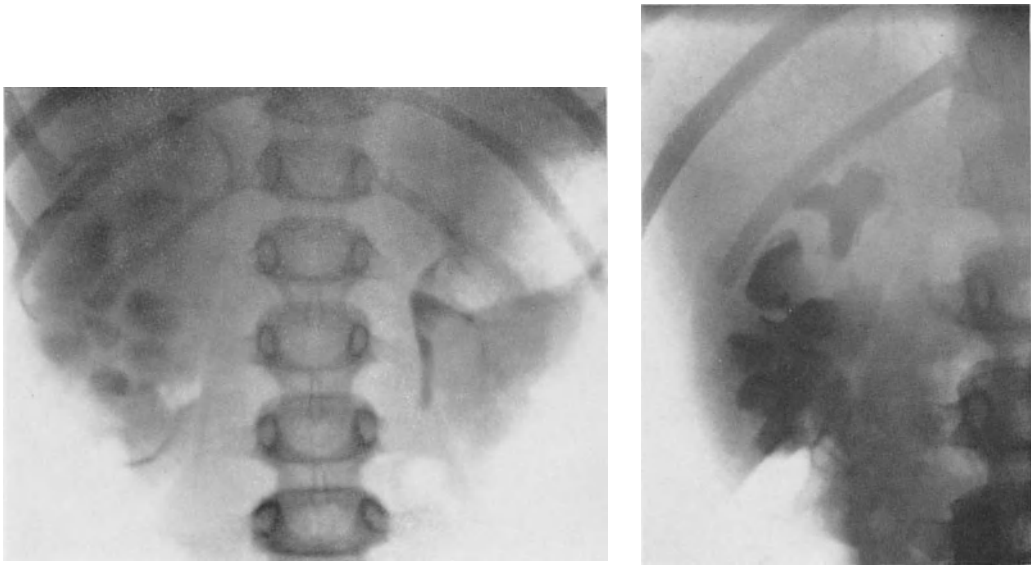


b

Fig. 82a and b. Obstructive nephrogram. Intravenous urograms in a child with hydronephrosis due to pelvi-ureteric obstruction. a 5 minute intravenous urogram showing nephrogram with filling defects due to dilated calices. b 45 minute urogram showing the dilatation of the renal pelvis



a b

Fig. 83a and b. Shell nephrogram (crescent sign). Intravenous pyelogram in a boy with ureteric obstruction consequent upon ureterosigmoidostomy. a Urogram showing multiple crescent signs due to opacification of collecting tubules lying tangentially around dilated calices. b Intravenous urogram after operative correction showing persistent opacification of collecting tubule area

The renographic changes in obstruction have been well analysed by WAX (1968). The immediate result of acute obstruction leaves the first (vascular) and second (secretory) phases of the renogram unaffected, but in the third (excretory) phase the curve continues to rise, reaching a high level and persisting for a long period. The implication is that the renal blood flow, cellular uptake and secretion continue normally at this stage in the obstructive process. With a chronic obstruction and deteriorating function there is a progressive flattening out of the second phase of the renogram with a persistent plateau in the third (Fig. 84). WAX suggests that once the second phase has been totally abolished recovery of renal function is impossible.

It is sometimes suggested that radioactive renography will detect early obstruction in the ureter before any hold-up is shown pyelographically, but this may well be due to the dehydration customary in the radiological investigation as compared with the normal urinary output during renography. In hydronephrosis and in the dilated ureter, where there is difficulty in deciding whether obstruction is present or absent, renography is not helpful since the analysis of the third phase will not differentiate between obstruction and stasis due to peristaltic failure, though perhaps both in pyelography and renography the use of intravenous frusemide to demonstrate a washout effect may give a partial answer to this question. Gamma camera scan has a potential for resolving the isotope in the renal parenchyma from that in the pelvis, and therefore permits a quantitative analysis of the radio-isotopic equivalent of the dense prolonged nephrogram characteristic of obstructive uropathy (HOLROYD and JONES, 1969), and there is little doubt that in future camera scans will provide more useful information.

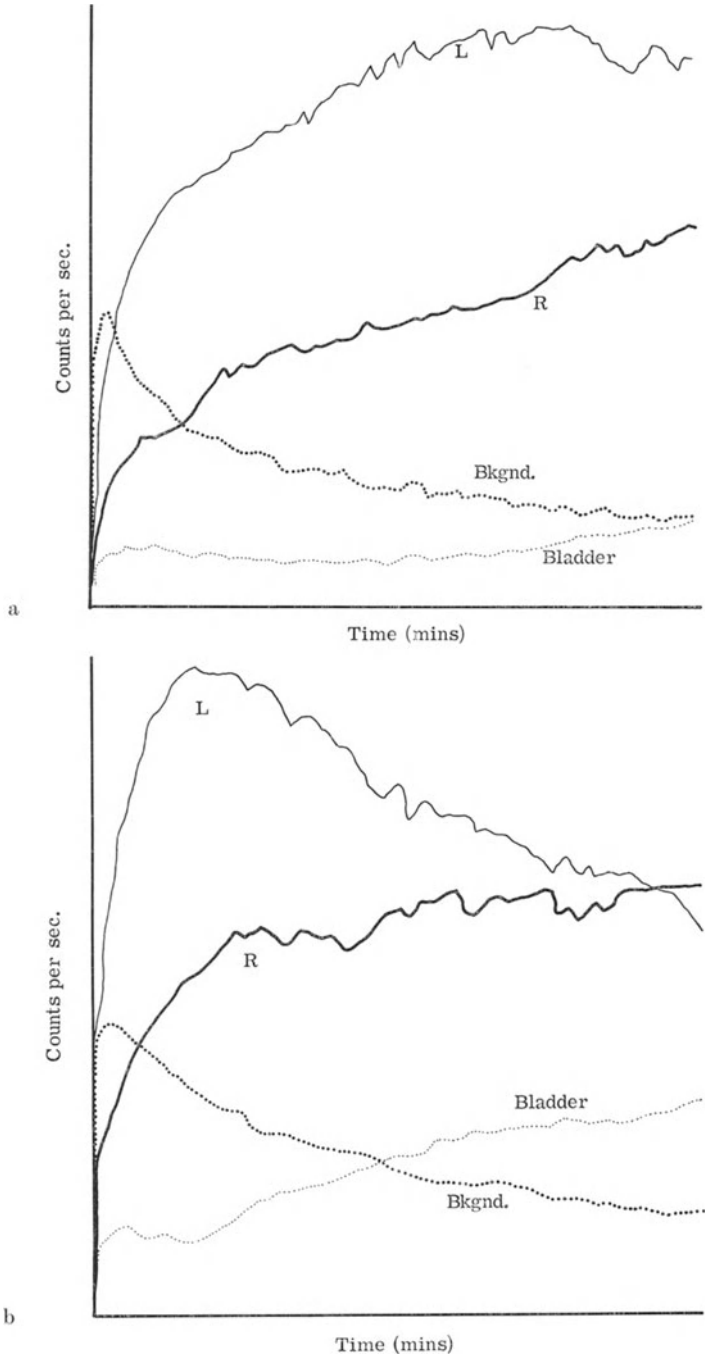


Fig. 84a and b. Isotope renogram in urinary obstruction. A boy with urethral valves and persistent upper urinary tract dilatation after restoration of bladder function. a First study showing persistent and rising third phase, but also some flattening of the second phase on the right side. b Following reconstruction of the lower end of the ureter; the left tracing now approaches normal but the right side, with flattened second phase, remains in the obstructive pattern

VIII. Conclusion

It is possible to recognise two types of urinary obstruction whose polar characteristics are given in Table 7. They are labelled acute and chronic, although it must be admitted that it is not clear whether the duration of obstruction is, in fact, the principle determinant of the physiological characteristic. In an acute obstruction the intrapelvic pressure is high; renal blood flow and glomerular filtration continue, but there is avid proximal reabsorption of filtrate so that the secretory phase of the renogram persists, the nephrogram is dense and there is a limitation of the ability of the kidney to dilute the urine; the glomerular filtration rate rises after relief of obstruction, often accompanied by post-operative natriuresis. On the other hand in the chronically obstructed kidney the intrapelvic pressure may be only raised under diuretic conditions, there is a reduction of renal blood flow with a poor secretory phase in the renogram and an inconspicuous nephrogram. Sodium reabsorption in the proximal tubule is diminished, as in other forms of chronic renal failure. These kidneys do not improve after relief of obstruction.

Table 7. Characteristics of obstructive uropathy

	"Acute"	"Chronic"
Intrapelvic Pressure	High	Normal but high during diuresis
Prolonged dense nephrogram	Yes	No
Fractional reabsorption of filtered sodium by proximal tubule.	Increased	Decreased
I 131 Hippuran uptake in second phase of renogram.	Yes	No
Improvement in function after relief of obstruction	Yes	No
Post-operative natriuresis	Yes	No

N. Obstructive Uropathy: The Upper Tract

D. Innes Williams

With 23 Figures

I. Hydrocalicosis

In the child, as in the adult, isolated obstruction to the infundibulum of a calix with consequent proximal dilatation is uncommon and needs to be carefully distinguished from multiple caliceal dilatations due to ureteric obstruction and from clubbing of the calix due to pyelonephritis or medullary necrosis. In the adult tuberculosis is also misleading, but this is unlikely to be observed in the child. Three forms of caliceal dilatation may be recognised:

1. Hydrocalicosis Due to Vascular Obstruction

Dilatation of the upper calix with some narrowing of the upper infundibulum is not uncommon, particularly on the right side (Fig. 85), and Fraley (1966 and 1969) has described a syndrome in which this radiological appearance is associated with renal pain. He finds the infundibulum compressed by the near presence of a leash of vessels and has subsequently reported that a "dismembered infundibulopyelostomy" in which the obstructed calix is transplanted to a separate opening into the renal pelvis, escaping pressure from the vessels, can relieve this pain. However, Rusiewicz and Reilly (1968), reviewing 2000 intravenous pyelograms, found mild upper pole caliceal dilatation due to partial infundibular obstruction in 52, but very little correlation between the child's symptoms and the radiological appearance. Undoubtedly it is easy to overdiagnose this condition, but Johnston and Sandomirsky (1972) have supported Fraley's claim in finding three examples of persistent renal pain with upper caliceal dilatation and clear-cut vascular compression which was relieved by operation. The subsequent pyelographic appearances, however, were very little different from the initial ones.

2. Hydrocalicosis Due to Infundibular Stenosis

In rare cases isolated dilatation of one or more calices is associated with a long stenotic segment in the infundibulum. In these examples the intravenous pyelograms will show the dilated calix (Figs. 86, 87) which fails, however, to fill on retrograde pyelography. At exploration it is found that although there may be vessels in the neighbourhood of the obstructed infundibulum their mobilisation makes no difference to the obstruction, which is clearly intrinsic. In the author's cases this form of hydrocalicosis has sometimes been associated with a dysplastic kidney and with recurrent infection or renal pain. Without infection, however, it is only very slowly progressive and in the absence of symptoms it is doubtful whether any sort of operative interference is justifiable. If operation is undertaken

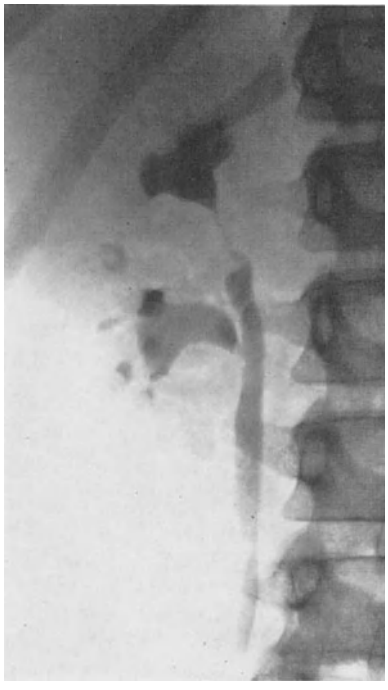


Fig. 85

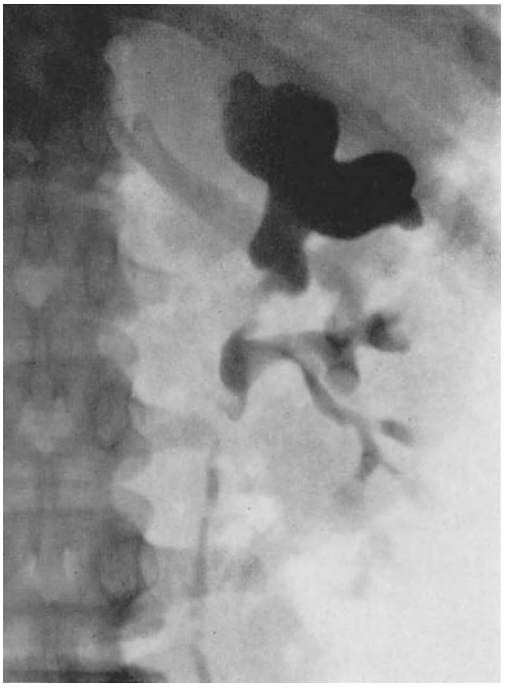


Fig. 86

Fig. 85. Vascular obstruction to the upper calix. Intravenous pyelogram showing very slight obstruction to the upper infundibulum resulting from overlying vessels. No treatment is required

Fig. 86. Hydrocalicosis due to infundibular stenosis. Intravenous pyelogram showing obstruction to the upper infundibulum, having the appearance of a vascular lesion but found at exploration to be due to intrinsic stenosis

it is a simple matter to remove the obstructed segment by partial nephrectomy, but reconstructive surgery is not particularly successful. The method employed by the author has been an intubated infundibulotomy, splitting down the stenosed infundibulum and allowing it to heal around an indwelling splinting tube. In the follow-up of these cases urinary infection has been eliminated, but the pyelographic appearances are not significantly changed. In a sub-group are examples with extra-renal calices: the kidneys are usually mal-rotated and otherwise anomalous, the renal pelvis somewhat dilated, but the calices arise well clear of the renal parenchyma and one or more of them may be long and narrow.

3. Megacalicosis

PUIGVERT (1962) has described a syndrome of generalised caliceal distension and malformation accompanied by thinning of the renal medulla, but without cortical changes or function alteration of the kidney. He regards the disorder as due to hypoplasia of the renal medulla of congenital origin; in later life it may be

complicated by infection or stone, but in childhood there are very few symptoms. It is important to distinguish this disease (Fig. 88) from obstructive disease, as clearly pyeloplasty will be of no value.

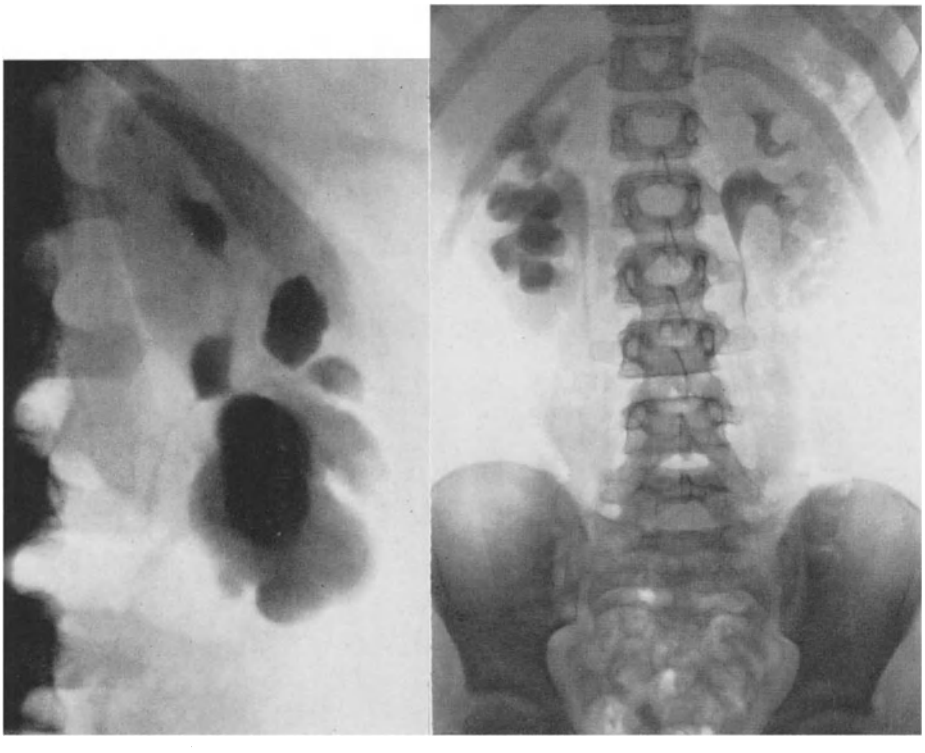


Fig. 87 Fig. 88

Fig. 87. Hydrocalicosis due to infundibular stenosis. Intravenous pyelogram in a girl suffering from recurrent urinary infection showing severely distended lower calices, but also a moderate infundibular stenosis of the upper calices. Partial nephrectomy performed

Fig. 88. Megacalicosis. Intravenous pyelogram showing dilatation of all calices in an otherwise unobstructed kidney of normal size and not complicated by infection. No treatment required

4. Caliceal Diverticulum

A cystic space is present in the renal parenchyma which communicates by a narrow channel with a normal calix. When such a diverticulum enlarges considerably it may be difficult to distinguish from a hydrocalicosis. Small diverticula are usually symptomless and found accidentally at pyelography, but a few are associated with pain, infection or stone formation and if treatment is required a partial nephrectomy or wedge resection of the area of kidney, including the diverticulum, should be undertaken (Devine et al., 1969; Williams et al., 1969).

II. Hydronephrosis Due to Pelvi-Ureteric Obstruction

The classical form of hydronephrosis due to pelvi-ureteric obstruction is a common disorder of childhood: in general it is well recognised and adequately treated. A number of reviews of the subject have been published in recent years, e.g. KELLALIS et al. (1971), USON et al. (1968). The precise cause of obstruction is still a matter of debate. NIXON (1953) found aberrant vessels as at least a contributory cause in 25 out of 78 cases. Adhesions binding the upper ureter to the pelvis have been regarded as responsible for ureteric obstruction by many observers, and JOHNSTON (1969), measuring the intrapelvic pressure has found that freeing these adhesions alone can allow decompression. Nevertheless, a narrow stretch of the upper ureter remains and if at operation lysis of adhesions is the only procedure undertaken the kinks and adhesions recur. MURNAGHAN (1959) claims that there is an interruption of the circular element of the musculature in all cases as a primary lesion, while NOTLEY (1968), on the basis of electron microscopy studies, believes that there is an excess of collagen in a thin muscle layer at this point. Very rarely a true obstructive mucosal valve may be discovered on section of an obstructed renal pelvis.

The symptomatology and diagnosis of the classical case require little comment: treatment by pyeloplasty is ordinarily successful in children and only a small proportion require primary nephrectomy. The author's preference is for a dismembered pyeloplasty of the Hynes-Anderson type with the addition of a nephrostomy drainage with ureteric splinting for one week. Certain special forms of hydronephrosis in childhood are, however, worthy of further comment.

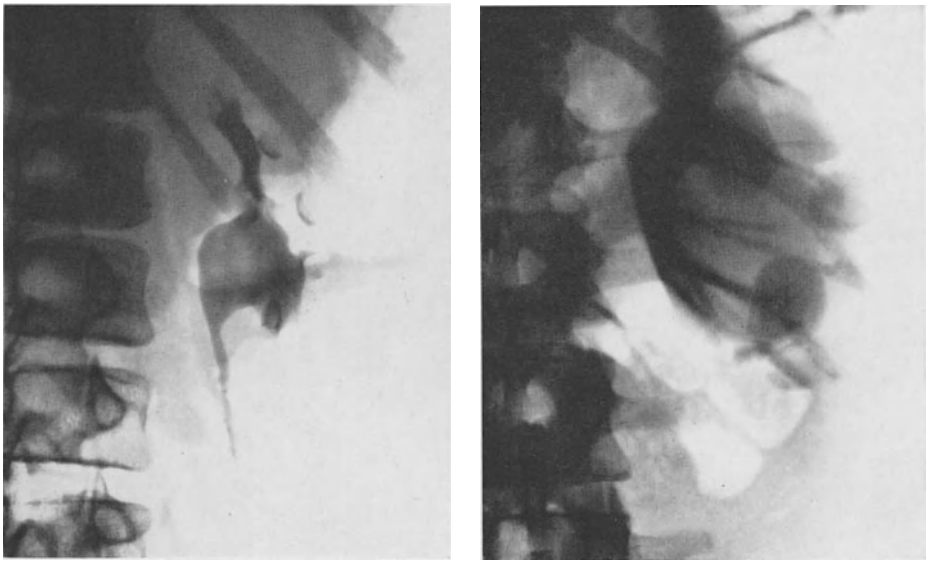
1. Intermittent Hydronephrosis

In some children the intravenous urogram between attacks of pain may be entirely normal (Fig. 89), but there is often some suggestion of a hold-up with at least a sharp cut-off at or slightly below the pelvi-ureteric junction. In any child with a history of severe attacks of loin pain and vomiting this possibility should be borne in mind and investigated by high dose pyelography with diuresis, which will cause distension of the renal pelvis. At operation on intermittent hydronephrosis the renal pelvis is usually collapsed when first exposed, but the point of obstruction is readily demonstrable by inflating the pelvis by injection of saline. Pyeloplasty gives exceptionally good results.

2. Hydronephrosis in Neonates

In cases presenting during the first three months of life a characteristic form is that of an enormously ballooned extrarenal pelvis (Fig. 90) with a cap of relatively good renal parenchyma pushed far laterally. The calices are moderately dilated only and function is often surprisingly good, although the pyelograms are not clear because of the enormous volume of non-opacified urine in the renal pelvis. In such cases a palpable kidney is the usual mode of presentation and bilaterality is more common in infancy than in later childhood. Pyeloplasty is successful in preserving renal function in these cases, though the appearance of the kidney scarcely ever returns to normal (WILLIAMS and KARLAFTIS, 1966). In another neonatal type of hydronephrosis the renal pelvis is relatively small, but there is below it three or four centimetres of ureter which is extremely narrow and exhibits multiple kinks of mucosa and muscularis within the adventitia. This type of disease is often seen

with urinary infection. It may be difficult to secure a satisfactory pyeloplasty because of the length of the narrow segment, but it is essential to anastomose the renal pelvis to the wider ureter lower down in the lumbar region. Hydronephrosis with cystic dysplasia of the kidney may be seen in the neonate (Fig. 91), often in cases where the contralateral kidney is multicystic. Prognosis in such cases is poor since renal function is considerably impaired.



a b

Fig. 89a and b. Intermittent hydronephrosis. a Intravenous pyelogram between attacks of pain. b Intravenous pyelogram during episodes of pain

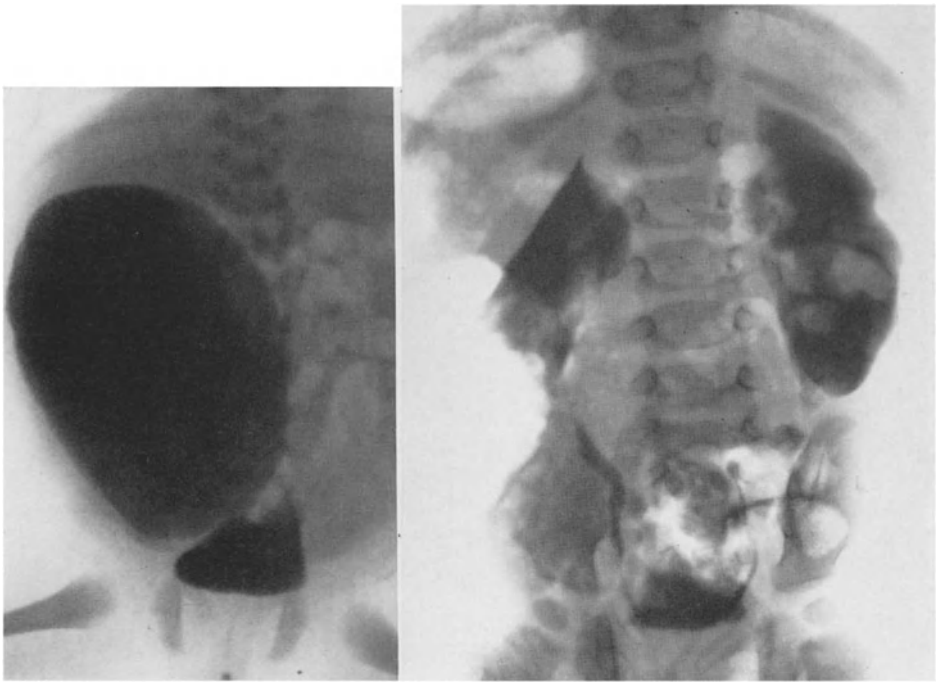
3. Hydronephrosis in Mal-Rotated Kidneys

The renal pelvis of a mal-rotated or fused kidney ordinarily arises from a broad base and the ureter takes off from the top of a dome-like cavity. The shape of the renal pelvis makes for ineffective emptying contractions and the high insertion of the ureter is apt to cause a degree of pelvi-ureteric obstruction. There may be in addition compression by vessels. It is important to recognise the presence of a malrotation in hydronephrosis since the intravenous pyelogram often gives an exaggerated impression of obstruction because of the size and broad base of the renal pelvis (Fig. 92). Moreover, in mal-rotated or fused kidneys the results of pyeloplasty are less satisfactory than in the normally rotated organ.

4. Hydronephrosis in the Duplex Kidney

In the usual form of ureteric duplication a true pelvi-ureteric junction is present only in the lower pole: in the upper the ureter breaks up into calices without first expanding to form a pelvis. Pelvi-ureteric obstruction is therefore almost confined to the lower pole and there presents no unusual features; the diagnostic problem

may arise when the obstruction is severe and the lower pole non-opacified in the pyelograms, leaving the distorted upper pole in a form which may suggest renal tumour (Fig. 93). Rarely, the upper pelvis is formed and may show signs of dilatation; very rarely the lower pole is a minute dysplastic appendage on an otherwise normal kidney with pelvic hydronephrosis.



a b

Fig. 90a and b. Neonatal hydronephrosis. a Micturating cystogram showing reflux into one side with grossly dilated renal pelvis. The opposite side was similarly affected but did not reflux. Pyeloplasty performed. b Intravenous pyelogram a year later showing good function but still grossly distorted renal pelves

5. Hydronephrosis with Low Pelvi-Ureteric Obstruction

The renal pelvis is at times elongated, so that the pelvi-ureteric junction lies near the level of the iliac vessels: hydronephrosis developing in this type of kidney may mimic mid-ureteric obstruction, but the results of a simple dismembered pyeloplasty can be very satisfactory (Fig. 94).

6. Hydronephrosis Due to Ureteric Polyps

A rare but consistent variety of hydronephrosis in childhood results from obstruction to the upper ureter by polyps. They arise 1–2 cm below the pelvi-ureteric junction and consist of finger-like projections about 1 mm across and 10–15 mm long. They are covered by transitional epithelium over a nondescript central

stroma. They are of uncertain origin, not neoplastic and not obviously inflammatory (WILLIAMS and NEIDERHAUSEN, 1963). The symptoms are those of simple hydronephrosis and haematuria is no more common than in the uncomplicated case. Radiologically the site of obstruction may be recognisably a little below the pelviureteric junction (Fig. 95), and in a few instances a filling defect may be discernible. At operation they can be suspected from the absence of usual kinking and from thickening of the ureter below the pelvis. Excision of the polyp bearing area with modified pyeloplasty gives good results.

III. Mid-Ureteric Obstructions

1. Functional Obstructions

In many pyelograms the lumbar segment of the ureter, particularly on the right, appears to be dilated down to a point somewhere near the brim of the pelvis. Cine studies will show that there is no true obstruction here, rather that there is in effect a reservoir in the lumbar region which empties intermittently. True func-

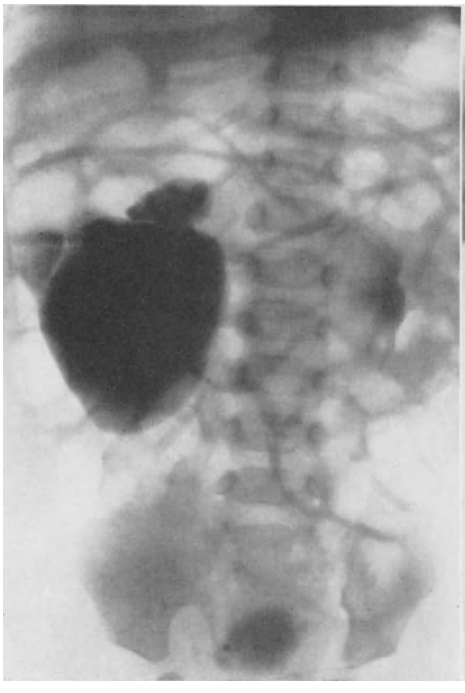


Fig. 91

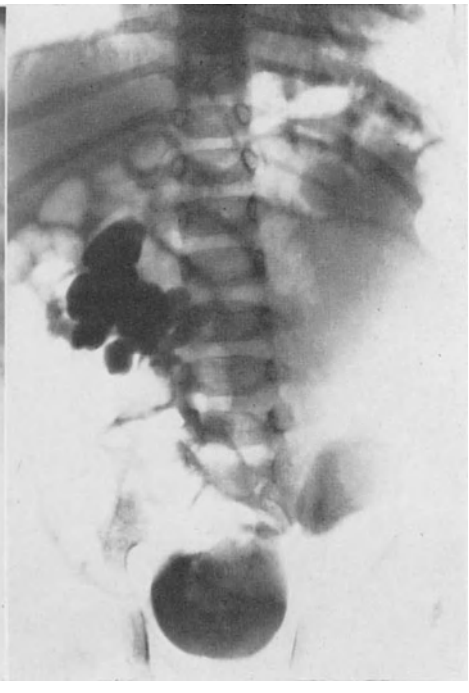


Fig. 92

Fig. 91. Hydronephrosis with renal dysplasia. Retrograde pyelogram showing large vertically disposed renal pelvis with calices directed upwards. At exploration a small cystic kidney was found with flaccid atonic renal pelvis

Fig. 92. Hydronephrosis in horseshoe kidney. Infant presenting with abdominal mass. Intravenous pyelogram shows malrotated hydronephrotic right kidney, very little opacification on the left

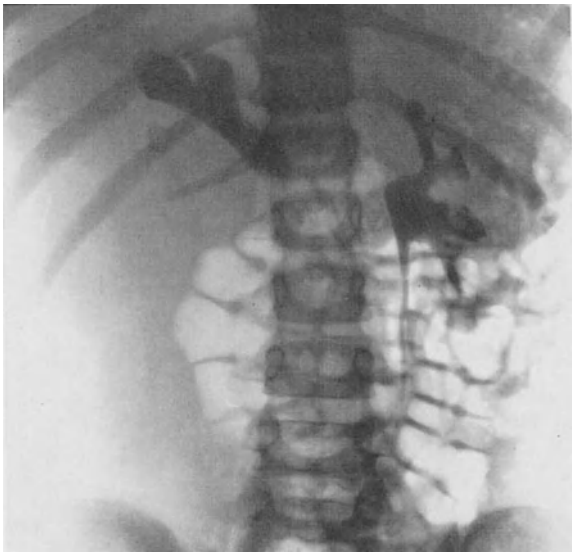
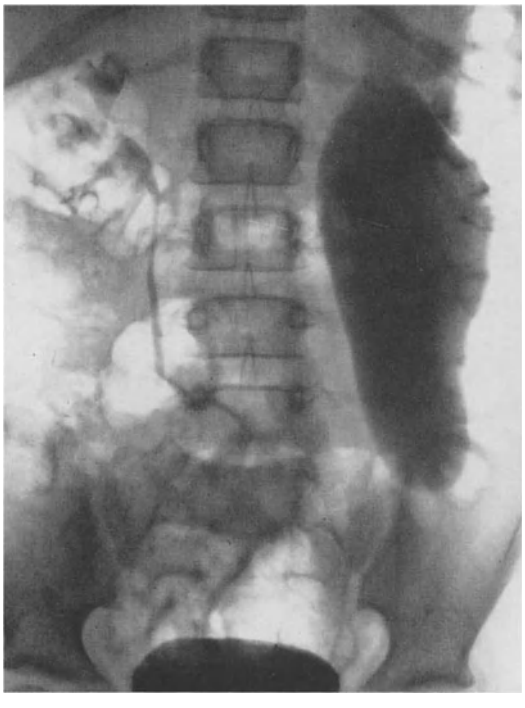


Fig. 93. Hydronephrosis in duplex kidney. Boy presenting with a large abdominal mass. Intravenous pyelogram shows opacification of the upper calices only, which are displaced and distorted by an enormously enlarged and non-opacified hydronephrosis in the lower half of a duplex



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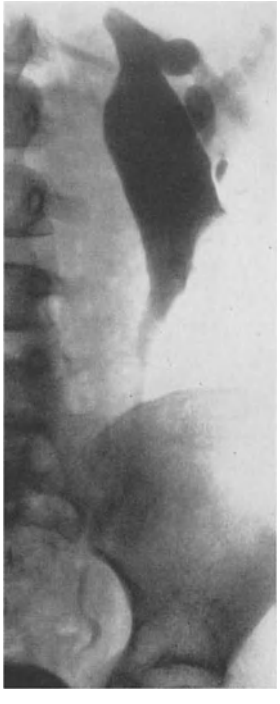

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Fig. 94a and b. Hydronephrosis with low pelvi-ureteric junction. Girl with recurrent urinary infection. a Intravenous pyelogram showing hydronephrosis with low elongated renal pelvis. b Intravenous pyelogram showing post-operative state

tional obstruction in any way comparable to that seen in the upper or lower end of the ureter is very rare indeed, if the cases of low pelvi-ureteric junction with obstruction are excluded.

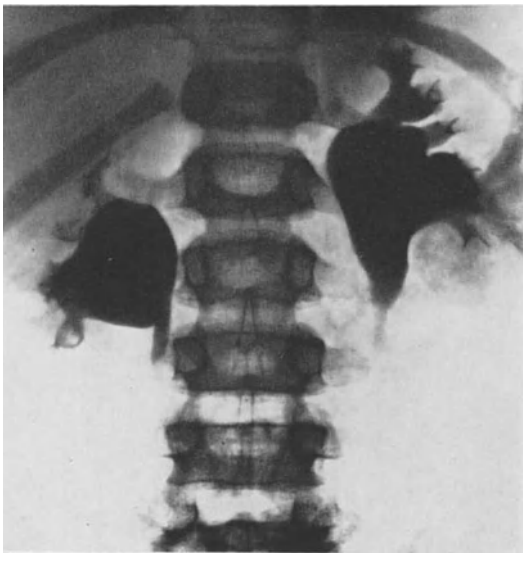


Fig. 95. Hydronephrosis due to ureteric polyps. Boy presenting with left loin pain. Intravenous pyelogram shows mild hydronephrosis only with obstruction a little below the pelvi-ureteric junction on each side

2. Peristaltic Disorders in the Bifid Ureter

Ureters which bifurcate in the mid-ureteric region are not infrequently complicated by unco-ordinated peristalsis. KAPLAN and ELKIN (1968) have shown that reverse filling of one limb from another during the course of a cine pyelogram is a usual observation, and they found slight dilatation in 42 per cent of such cases. Occasionally a child has renal pain in association with such a disorder, although there are no true obstructive changes in the calices of either half of the kidney. Some authors have advised operation for this type of case (LENAGHAN, 1962; TRESIDDER et al., 1970), usually with the intention of converting a bifid ureter into the bifid pelvis which, because of the different functional properties of the pelvis, would not be painful. In the present author's experience this type of operation is seldom required since serious pain which can be attributed with certainty to the kidney in bifid ureter is rare, nevertheless operation can be effective (Fig. 96). Somewhat similar considerations apply to examples of blind bifurcation of the ureter, which may be distended during peristalsis of the normal ureter.

3. Congenital Stricture: Atretic Segment

This type of obstruction is most often encountered in cases with contralateral multicystic kidney associated on that side with a long atretic segment of ureter.

On the functioning but obstructed side a short (1–2 cm) length of the ureter, often in the lower lumbar region, is extremely narrow and thin-walled. The proximal ureter is dilated, often with a kinked pelvi-ureteric junction and tense hydronephrosis. Occasionally a second narrow segment is present in the lower ureter, which is easily overlooked since the segment between the two strictures is of normal calibre and not dilated.

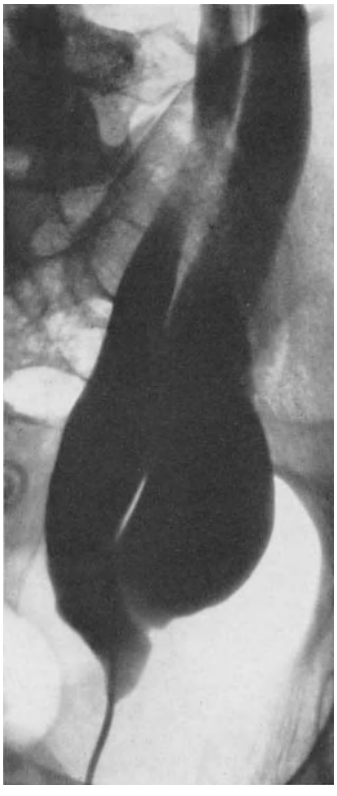
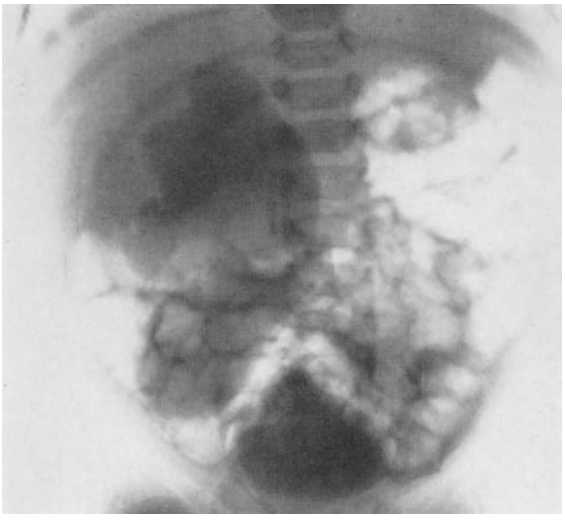


Fig. 96. Peristaltic disorder in bifid ureter. Girl with recurrent urinary infection. Intravenous pyelogram shows gross dilatation of both limbs of a bifid ureter with normal calibre common stem. Exploration and pressure studies confirmed the absence of any obstruction in the lower segment. Treated by excision of the common stem and re-implantation of both branches directly into the bladder

Infants with this disorder present with infection or signs of renal failure: with multicystic and hydronephrotic kidneys both being palpable. Intravenous pyelograms demonstrate the hydronephrosis and usually the dilated upper ureter (Fig. 97), with a functionless contralateral kidney. On cystography there may be reflux into the normal calibre lower ureter on both sides. Operative treatment consists of excision of the strictured area with re-modelling of the dilated segment and re-anastomosis using a long oblique suture line. Recovery of renal function

may be satisfactory, but hydronephrosis is often too far advanced for restitution of a normal anatomy and there may be dysplastic changes in the kidney with a poor prognosis.



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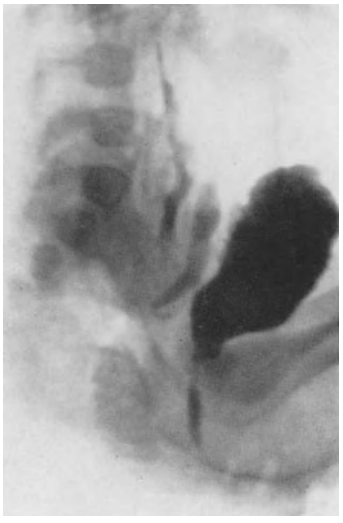

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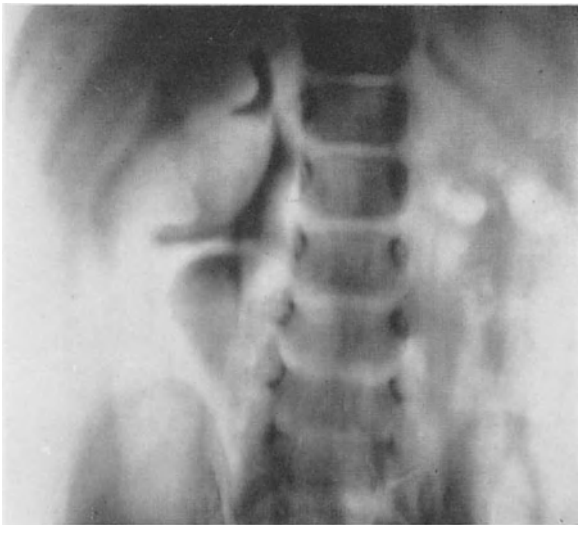


c

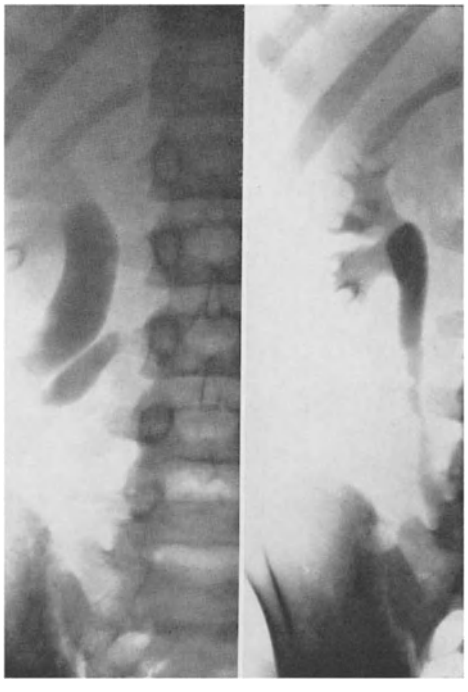
Fig. 97a–c. Mid-ureteric stricture due to atretic segment. Infant female presenting in uraemia with palpable multicystic kidney on the left side, hydronephrosis on the right. a Intravenous pyelogram shows no opacification on the left, but gross hydronephrosis on the right with dilatation of the ureter extending down to the mid-ureteric segment. b Micturating cystogram showing bilateral reflux: on the left side, the ureter reaches the multicystic kidney; on the right, it ends abruptly at the atretic mid-ureteric segment. Multicystic kidney excised, atretic segment of right ureter excised with ureteric re-anastomosis. c Intravenous pyelogram after recovery of renal function. Some residual dilatation of the upper ureter

4. Retrocaval Ureter

The anatomy of the retrocaval ureter is well known and has been reviewed on many occasions (CONSIDINE, 1966). It is a rare anomaly, however, and often diagnosed in later life. The right ureter has a dilated segment below the renal pelvis which then loops upwards, passing behind the vena cava, to emerge between the aorta and cava to resume its normal course. The obstruction is seldom acute, and in very early childhood hydronephrosis may not be sufficiently severe to suggest the diagnosis. Progress is towards increasing dilatation with renal pain and often a complicating infection. The characteristic radiological picture is shown in Fig. 98. The diagnosis is usually made from this alone, though confirmation may be obtained by catheterising the cava at the time of pyelography. Medial displacement of the ureter is not at all uncommon and it should not suggest the retrocaval situation without the typical loop.

Since the anomaly arises by abnormal development of the vena cava it is not primarily a urological disorder, but secondary changes appear to take place in the ureteric wall after some years and the best results are obtained by excising the segment of ureter which lies behind the cava and anastomosing the dilated upper part, often after re-modelling, to the lower normal ureter.

The anomaly is ordinarily confined to the right side, but a double vena cava may rarely be found and thus the left ureter may be involved. In one of the



a b

Fig. 98a and b. Retrocaval ureter. Boy presenting with recurrent urinary infection. a Intravenous pyelogram showing the characteristic deformity of retrocaval ureter. b Post-operative state

author's cases the left ureter exhibited a mid-ureteric stricture, although there was no vascular compression and the vena cava was single.

5. Retro-Iliac Ureter

One or both ureters may at times pass behind the iliac arteries and be obstructed at this point. This very rare anomaly has been reviewed by HANNA (1972), illustrating one of the author's cases in which multiple anomalies of the urinary tract were also present (Fig. 99).

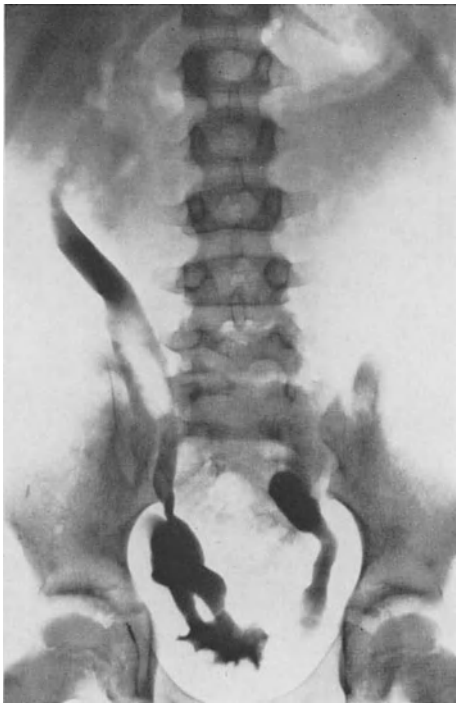


Fig. 99. Retro-iliac ureters. Micturating cystogram showing reflux into grossly dilated ureters on both sides. The dilatation is, however, greater above the iliac vessels. There is also reflux into a grossly dilated vas deferens leading over to the right spermatic cord

6. Ureteric Polyps and Tumours

The finger-like polyps just below the pelvi-ureteric junction have been described above. Other polyps are exceptionally rare in children, but a fibrous, myomatous or angiomatous polyp may arise in the lower ureter and prolapse intermittently through the ureteric orifice. The obstructive element in these cases is small and the usual presentation is haematuria. The diagnosis may be made cystoscopically or pyelographically. Simple excision of the polyp through a ureterostomy will suffice. Ureteric polyps have been reported in association with the Peutz-Jeghers syndrome, where there is multiple polyposis in the intestine.

7. Extrinsic Obstructions

Retroperitoneal fibrosis in the form seen in adults is not on record in childhood, but can occur from other causes (Fig. 100) and involvement in the retroperitoneal inflammatory process seen in chronic granulomatous disease can produce a somewhat similar picture. Retroperitoneal tumours can obstruct and displace the ureters (Fig. 101), particularly neuroblastomata and ganglio-neuromata arising from the sympathetic chain. Lymphosarcoma in the small intestine with mesenteric nodes can also produce ureteric obstruction.

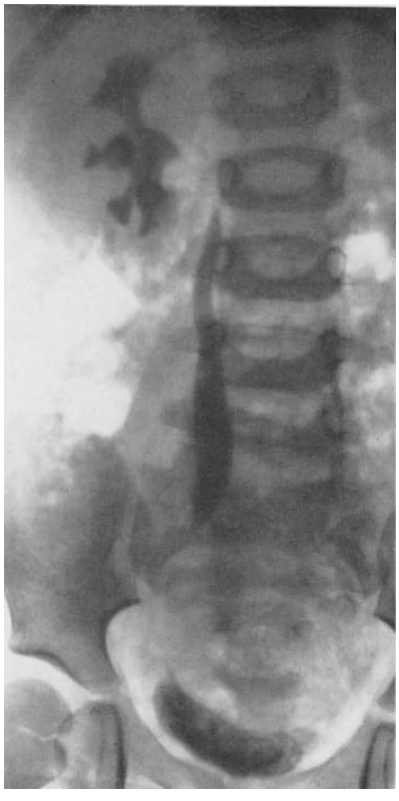


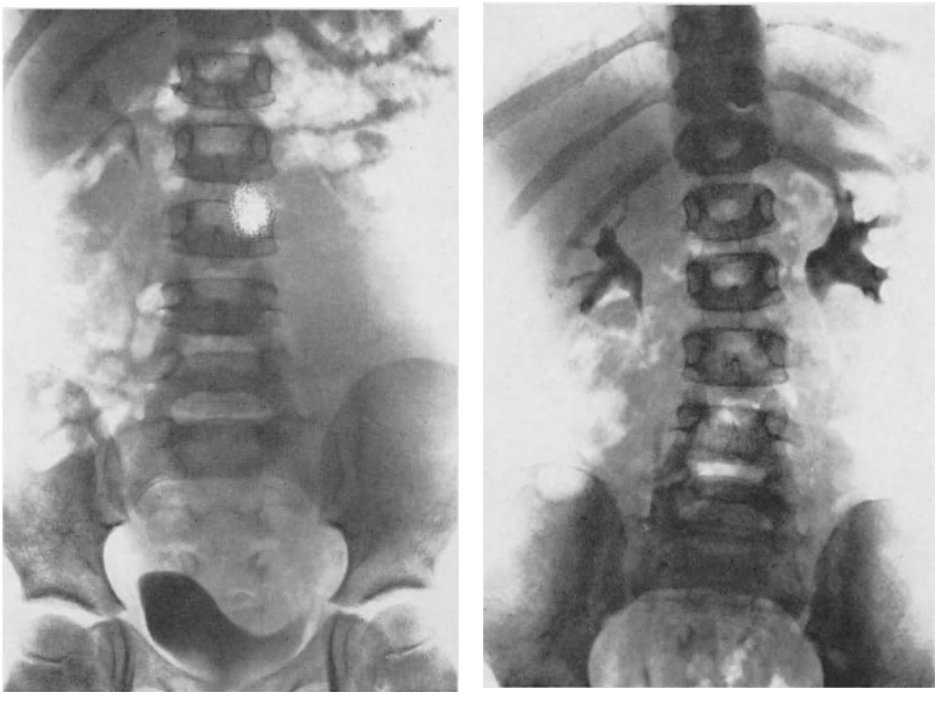
Fig. 100. Extrinsic ureteric obstruction. Intravenous pyelogram in a girl with recurrent urinary infection; found to have mid-segment ureteric obstruction; proved at operation to be due to localised retroperitoneal fibrosis associated with chronically obstructed and inflamed appendix

IV. Lower Ureteric Obstructions

Although acquired causes of lower ureteric obstruction, such as tuberculosis, bilharziasis (Fig. 102) and stricture following the passage of stone, are well known in childhood congenital obstructions are much more important. The classical ex-

ample of this disease is the primary obstructive mega-ureter, but other obstructive lesions are ureterocele, ureteric ectopia and, more importantly, the para-ureteric saccule. It is not clear why a saccule herniating through the ureteric hiatus in the detrusor is usually associated with reflux, but on occasions with a non-refluxing obstruction. In the latter case it is usual to find that the terminal segment of the ureter is almost devoid of musculature and is closely bound within the adventitia surrounding the saccule, a condition analogous to that found in obstructive mega-ureter. It is even not impossible for a lower ureter to allow reflux and yet to offer some obstruction to the downward passage of urine.

Primary obstructive mega-ureter is usually regarded as a disease analogous to pelvi-ureteric obstruction; there is dilatation and hypertrophy of the greater part of the ureter but a short terminal segment of normal calibre which will not allow reflux. Various views have been expressed in regard to the pathology of the narrow segment; the theory that there was a lack of ganglion cells was disposed of by Leibowitz and Bodian (1963) and it has been subsequently confirmed by Notley (1972) that ganglion cells are not normally found within the ureter. Murnaghan (1959) found an excess of circular fibres in proportion to the longitudinal muscle in this area and postulated functional obstruction for this reason. Gregoir and Debled (1969) find an excess of fibrous tissue and Notley (1972) emphasises the



a b

Fig. 101 a and b. Retroperitoneal lymphangioma. Boy presenting with left sided pain and mass. a Intravenous pyelogram pre-operatively showing a normal right kidney, a poorly functioning hydronephrosis on the left. b Intravenous pyelogram after partial excision of lymphangiomatous tissue on the posterior abdominal wall obstructing the ureter

role of collagen amongst the muscle fibres in the functionally obstructive segment. STEPHENS (1963) believes that there is commonly a fibrous stricture and that the ureteric lumen is actually narrowed in most cases. In the author's experience, however, the ureteric orifice is usually easily catheterisable and there is very little evidence of the rigidity of tissues normally associated with stricture formation.

Obstructive mega-ureter is a disease of early life: there is a heavy male predominance (FLATMARK et al., 1970) and the left ureter is more likely to be involved than the right (JOHNSTON, 1967). Sterile cases present with episodes of pain, usually located in the iliac fossa area, but severe recurrent infection is the most common mode of presentation. In the infant group bilateral disease is common and many such cases present with renal failure, some having in addition to the obstructive disorder dysplastic changes in the kidney.

The degree of obstruction varies greatly from case to case, as can be observed clinically and radiologically. In some mild examples the calices and upper part of the ureter appear to be entirely normal; the pelvic segment is dilated and at this level the peristaltic waves no longer obliterate the lumen. The terminal segment appears to be of normal calibre but of doubtful peristaltic activity. In such cases there may be a brief episode of haematuria or infection which draws attention to the condition, but otherwise no symptoms and very little evidence of progression of the disease. Some authors regard the dilated segment as the pathological one in these cases and BÄCKLUND and REUTERSKIOLD (1969) demonstrate that there is very little rise in pressure during perfusion of the ureter at high rates. WILLIAMS

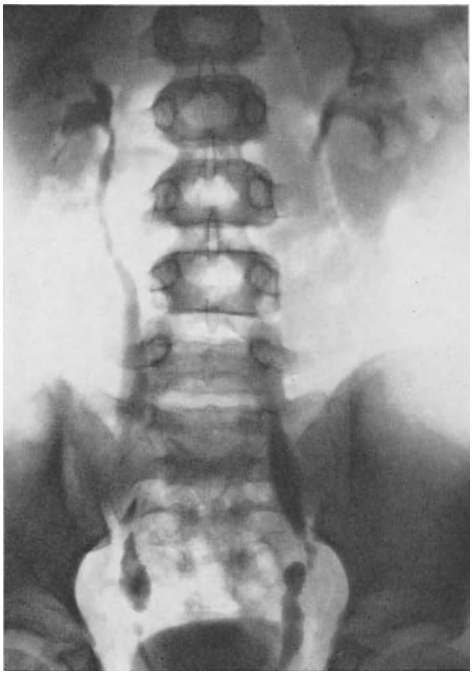
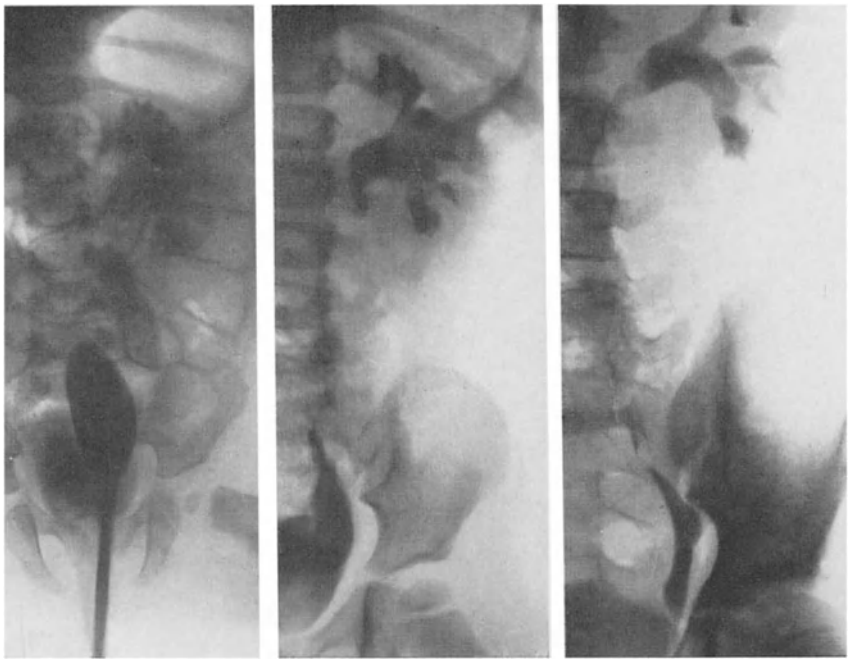


Fig. 102. Bilharzial obstruction to the lower ureter. Intravenous pyelogram in a child with haematuria showing irregular infiltration and obstruction to the lower ends of both ureters

and HULME MOIR (1970) followed 18 such mild examples treated by conservative regime; in some there was a definite improvement in the degree of dilatation and only 3 showed a deterioration (Fig. 103).

By contrast, in other children there is a hydronephrosis with tensely dilated calices and rapidly progressive dilatation of the ureter down to the narrow segment, which in these examples is often kinked upon itself (Fig. 104). Perfusion studies in these can show almost no flow and a very rapid rise in pressure once the system has completely filled. Active peristaltic waves are seen in the early stages of such cases, though they do not obliterate the lumen of the ureter. At a later stage muscular activity fails and there is irreversible renal damage. In a few infants an enormous ureter and ballooned renal pelvis are associated with relatively well preserved renal parenchyma (Fig. 105) and a good response to conservative surgery. In a number, a secondary kinking at the pelvi-ureteric junction produces some local obstruction.

Diagnosis ordinarily presents no difficulty if high dose pyelograms are employed, which outline the obstructive ureter down to the narrow segment. Cystograms show no reflux, or only the escape of a very small amount of opaque medium through the narrow segment where it is immediately diluted by the non-opacified urine lying in the dilated segment. Bladder emptying is complete and cystoscopically the ureteric orifice appears normal, or sometimes elevated on a



a b c

Fig. 103 a–c. Mild obstructive mega-ureter. Boy treated in infancy for urinary infection by chemotherapy. No surgery. a Retrograde pyelogram at the time of first investigation. b Intravenous pyelogram three years later. c Intravenous pyelogram eleven years later. No surgical treatment employed. The boy remains free of symptoms

slight nipple. Obstruction due to accompanying ureteric saccule can, of course, be recognised cystographically and cystoscopically.

In determining the plan of treatment first consideration should be given to the evidence of obstruction. As already emphasised, many mild cases do not deteriorate and do not require treatment of any sort. If, therefore, the renal function is normal, the calices well cupped and the urine sterile, the case should simply be observed. In the majority, however, where infection and pain occur and there is clear evidence of obstruction re-implantation of the ureter is the routine treatment and can ordinarily be very successful (Fig. 106). A unilateral gross dilatation of the ureter with destruction of the kidney, particularly if complicated by infection and stone formation, requires nephro-ureterectomy. In bilateral cases with severe upper tract damage the possible alternatives are immediate re-modelling and reconstruction of the ureters; a period of temporary urinary diversion by nephrostomy or ureterostomy or; permanent cutaneous diversion.

The method of re-implantation has been described by many authors and with the addition of the excision of the narrow segment all methods used for reflux pre-

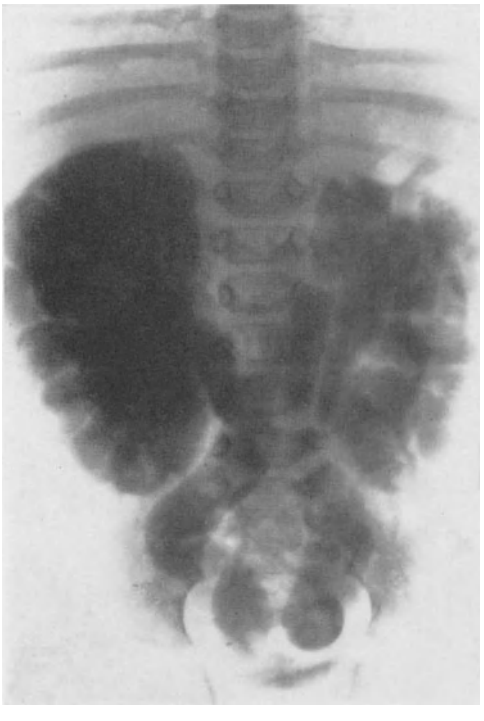


Fig 104

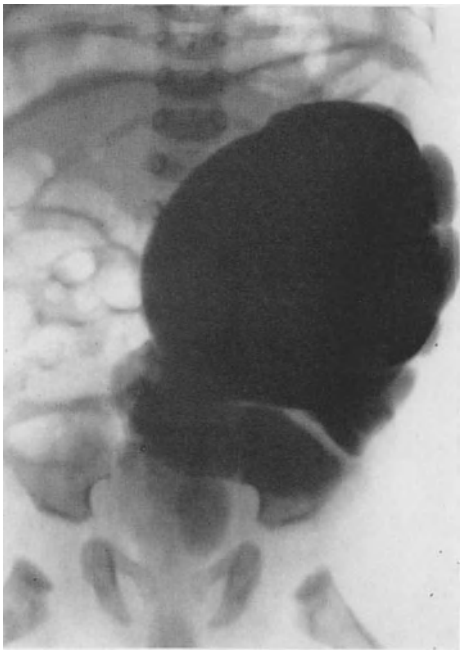
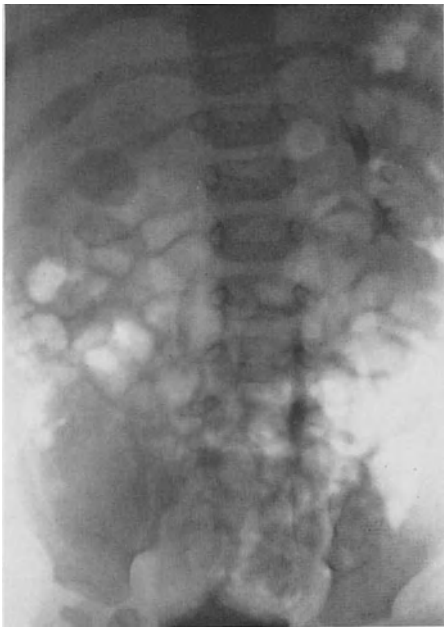


Fig. 105

Fig. 104. Bilateral mega-ureter. Infant boy presenting with severe urinary infection. Intravenous pyelogram showing gross bilateral hydronephrosis and hydro-ureter with tense dilatation of the lower ends of both ureters deforming the bladder outline

Fig. 105. Mega-ureter in a neonate. Infant presenting with large abdominal mass at birth. Antegrade pyelogram performed by direct needle puncture of the hydronephrotic sac outlines the enormously dilated renal pelvis and obstructive mega-ureter



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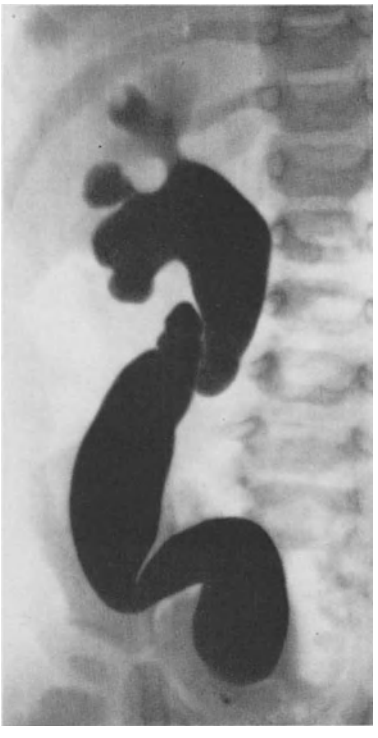

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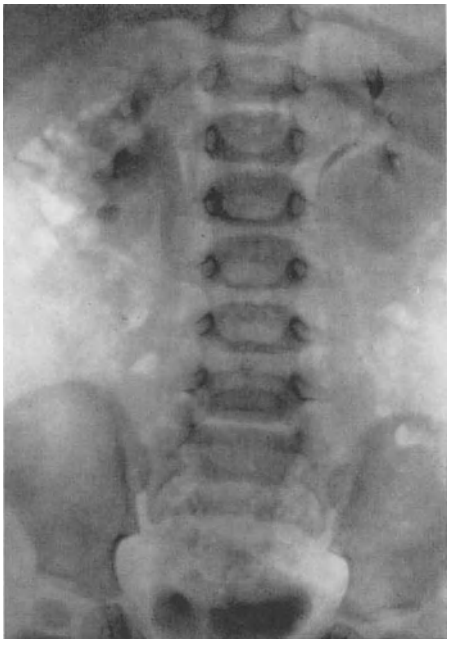
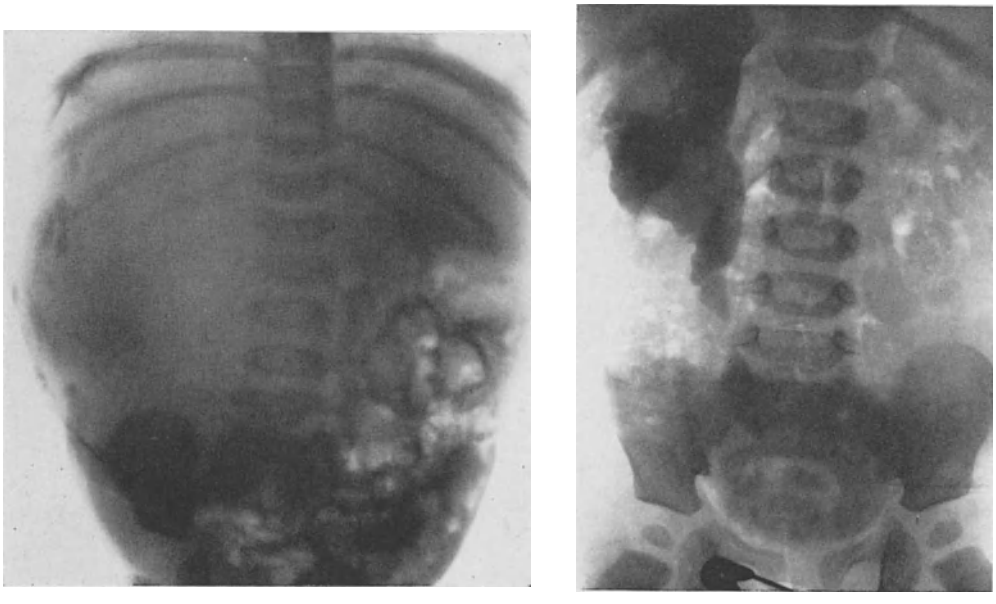


c

Fig. 106 a–c. Mega-ureter. Boy presenting with recurrent urinary infection. a Intravenous pyelogram pre-operatively showing a normal left kidney and a grossly hydronephrotic right. b Antegrade pyelogram outlining the tensely obstructed megaureter but relatively well preserved kidney. c Post-operative intravenous pyelogram showing recovery after reimplantation of ureter

vention may be appropriate. Some re-modelling of the lower end of the ureter is usually necessary to secure reflux prevention. JOHNSTON (1967) advises re-modelling only up to the pelvic brim. BISCHOFF (1961) has advocated a very much more extensive re-modelling in order to bring the ureter down to a normal calibre over a considerable length, and recently HENDREN (1969) has been an advocate of this form of treatment, often undertaken in two stages. It has, however, been the experience of many that once the obstruction is removed and the lower end remodelled the upper ureter and renal pelvis will show a satisfactory spontaneous improvement. A second operation is, however, required if there is any suggestion of pelvi-ureteric obstruction (Fig. 107). All series contain some disappointments, however; in a number there will be persistent obstructive dilatation and in others reflux. In JOHNSTON's (1967) series, 8 out of 33 cases were essentially unaltered by surgery, and in the group reported by WILLIAMS and HULME MOIR (1970) only 31 out of 45 ureters were considerably improved. The bad results may represent technical failures or errors in selection, but it must be recognised that while spectacular results can often be achieved in the more acute forms of obstruction the chronically and severely dilated ureter presents great problems in reconstruction, and that extensive operations can be followed by disastrous scarring.

In an attempt to obtain muscular contractions in a previously atonic ureter HIRSCHBORN (1964) employed an operation wrapping the ileum, denuded of its mucosa, around the ureter. POLITANO et al. (1972) has reported on some successful results in such cases, but more appear to be failures.



a b

Fig. 107 a and b. Mega-ureter in an infant presenting with a large abdominal mass and raised blood urea. a Intravenous pyelogram shows no function on the left side; on the right there is a very large soft tissue swelling with some opacification of flattened calices far out in the loin. Reduction pyeloplasty performed as well as re-implantation of the lower end of the ureter b Intravenous pyelogram a year later showing return of good function but distorted pelvi-ureteric system

O. Obstructive Uropathy: The Bladder

D. Innes Williams

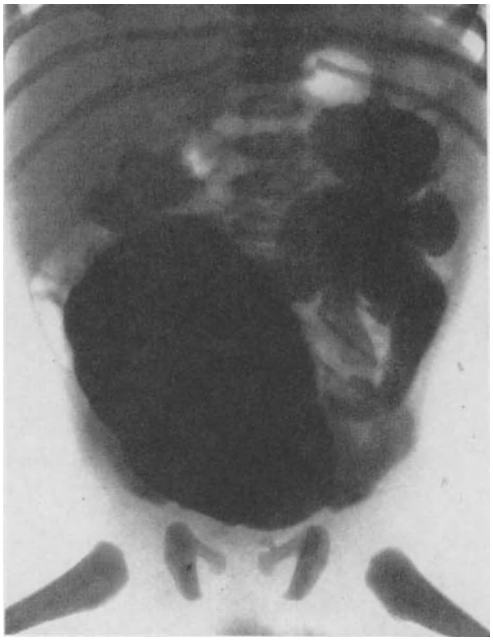
With 14 Figures

I. Introduction

Any discussion of the vesical element in urinary obstruction must necessarily centre around the problem of bladder neck obstruction and the changing attitudes to this disease. The classical description of Marion (1940) referred to a disorder closely akin to prostatism in which a hypertrophied internal sphincter alone appeared to be the cause of obstruction which could be relieved by its resection. Since cases were seen in young adults with a long history of difficult micturition a congenital cause was postulated by many (e. g. Badenoch, 1949), but the diagnosis was made seldom and only in adults with clearly recognisable obstructive signs. In subsequent years, however, many urologists came to believe that a large proportion of children of both sexes suffering from recurrent urinary infection and reflux had a bladder neck obstruction as their primary disorder, so that very many operations or endoscopic revisions were performed. The literature of the 1950's and 1960's, which has been well summarised by Young (1972), contains many papers reporting good short term results of operations in numerous children, but the diagnostic criteria in most were unreliable and little permanent value can be gained by a study of these statistics. Later, the disappointing long term results, the better understanding of reflux and the failure to establish any histological basis for bladder neck obstruction threw considerable doubt on the validity of this diagnosis. The development of accurate hydrodynamic methods, especially those reported by Nunn (1965), Zatz (1965) and Whitaker et al. (1969) demonstrated that in the simple recurrent infection and reflux cases there was no evidence of bladder neck obstruction, and Smith (1969), in a wide ranging review, found no justification for this diagnosis in children, though he believed the possibility of distal urethral obstruction in girls remained. Currently the consensus of opinion regards bladder neck obstruction as a disease which does not occur in the female child and only exceptionally rarely in the pre-pubertal male. It is therefore important to discuss first bladder disorders which might be confused with, but which are now recognised as other than, bladder neck obstruction.

1. Urethral Obstruction

Congenital lesions, particularly valves in the urethra, are the most important causes of obstruction in the male, though the diagnosis has often been missed because inadequate micturating cystograms have been performed, failing to demonstrate the valves in the absence of bladder contraction or omitting examination of the anterior urethra. Urethral strictures are missed because in children they are soft and easily dilated by instrumentation before cystography.



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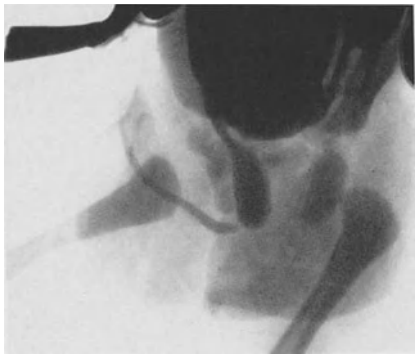

b

Fig. 108a and b. Large refluxing bladder in urethral valvular obstruction. a and b Cystograms in a newborn infant with retention and urinary infection

The congenital urethral lesions demonstrate the varying reaction of the bladder to obstruction: hypertrophy of the detrusor is present in all, but some develop a massive trabeculation and sacculation with a relatively small capacity (Fig. 124), others are atonic with a large bladder volume (Fig. 108). Diverticula, if present, are multiple, frequently involving the ureteric hiatus. Reflux is present in under half the cases (p. 131). The internal sphincter participates in the detrusor hypertrophy so that the bladder neck is prominent in proportion to the degree of trabeculation, though it is never tightly closed. A secondary bladder neck obstruction has often been postulated, but never satisfactorily established, and as the dilatation of the posterior urethra advances the bladder neck widens out and even disappears.

2. Occult Neuropathic Bladder

Many cases of spinal dysraphism without meningocele are referred for urological opinion as examples of bladder neck obstruction, but radiological investigation of the vertebral column and myelography will easily establish the neuropathic cause (Fig. 109). There are, however, children of both sexes who have severe obstructive signs with many of the characteristics of neuropathic bladder, but in whom no spinal cord disorder can be identified. The diagnosis is discussed in Chapter R. Dribbling incontinence is present from an early stage, even when the vesical residue is small, and it is often accompanied by obstinate constipation or faecal soiling. Infection is a common complication and later there may be a rapid deterioration with the accumulation of a large vesical residue and overflow incontinence. Reflux, hydronephrosis and renal failure follow. On radiological examination (Fig. 110) the bladder neck area is hypertrophied but not tightly closed, the

posterior urethra is dilated down to the membranous area. Cystometrograms show features of neurogenic disorder with exaggerated Bethanecol response. Bladder neck resection is not helpful; external sphincterotomy may reduce the residue, but most cases come to urinary diversion.

3. Incomplete Prune Belly Syndrome

Classical cases of absent abdominal muscles are easily recognised, but examples of incomplete syndromes where the urinary tract anomaly is unaccompanied by abdominal wall defects are encountered from time to time. The characteristic finding is an anomalous development of the entire urinary tract: dysmorphic kidneys, incongruously dilated ureters, large capacity bladder and dilated posterior urethra (Fig. 144). The topic is fully discussed in Chapter Q.

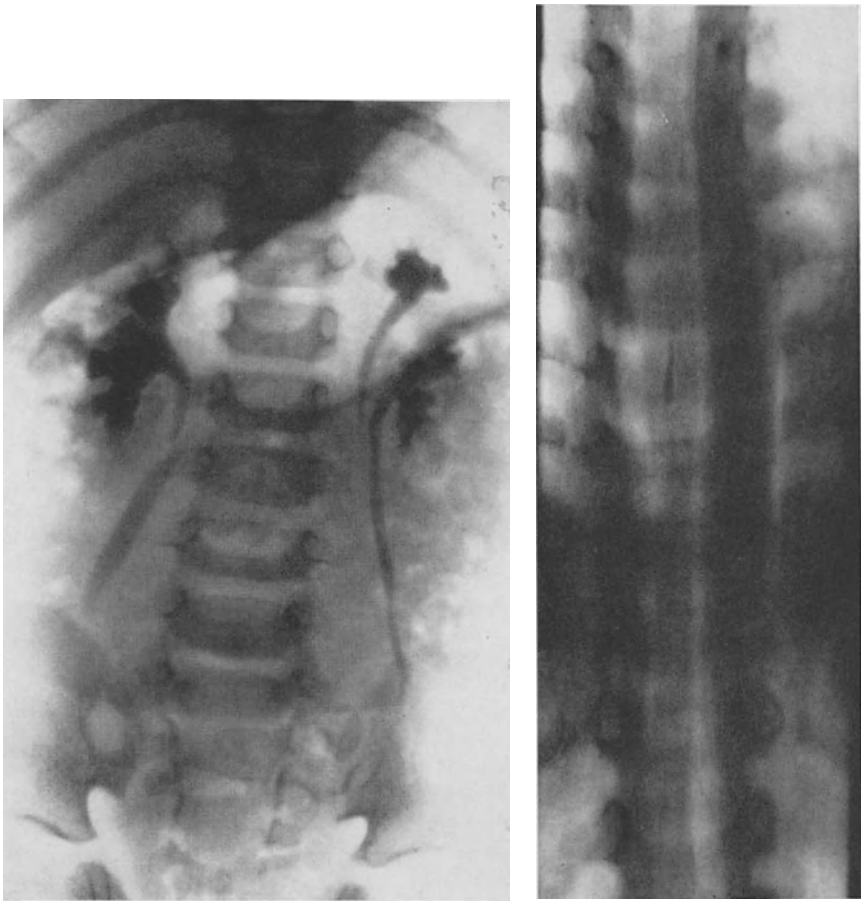

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Fig. 109a and b. Neuropathic bladder with easily overlooked vertebral deformity. a Intravenous urogram showing urinary obstruction and some widening of the spinal canal in the sacral area. Myelogram showing diastematomyelia in the thoracic region

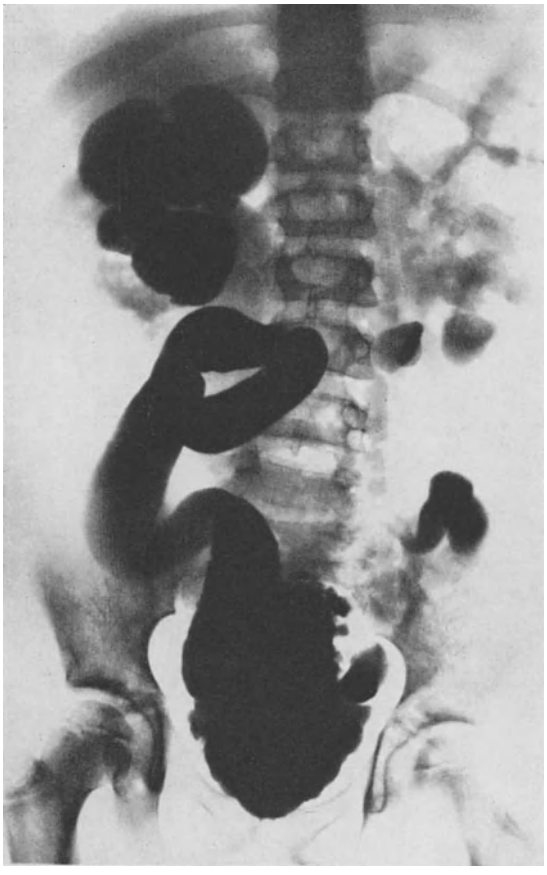

Fig. 110. Occult neuropathic bladder. A boy of 10 years with lifelong incontinence of urine, and formerly of faeces, with rapid deterioration of renal function. Cystogram showing grossly trabeculated bladder. No obstructive lesion could be identified, the bladder neck was relaxed. No neurological signs could be elicited, but there was a positive Bethanechol sensitivity test. Urinary diversion required

4. Mega-Ureter-Megacystis Syndrome

A large capacity, smooth-walled bladder with a wide trigone and dilated ureteric orifices, free reflux and grossly dilated ureters are characteristics of this disorder (Fig. 111) Williams (1954), Paquin et al. (1960). In the absence of acute infection or post-instrumental trauma, micturition is effective in emptying the bladder completely, though because of massive reflux rapid refilling occurs. This absence of true residual urine contrasts with the inability of the obstructed bladder to empty, though the distinction of the megacystis case from simple reflux is not so clear. Most of the symptoms of these cases are relieved by reflux prevention, but in the severe examples the large capacity bladder remains and micturition cannot be initiated with small bladder volumes. No pathological explanation for this disorder has been established. Liebowitz and Bodian (1963) demonstrated that

the ganglion cell population of the bladder wall was normal. YOUNG (1972) postulates a smooth muscle dysplasia.

5. Atonic Bladder

The category of atonic bladder is an imprecise and unsatisfactory one: the obstructed bladder may be of very large capacity and relatively atonic. Rarely, however, a child is encountered with a very large flaccid bladder which empties incompletely and largely by abdominal compression through an apparently normal urethra, but without reflux and with a well preserved upper urinary tract (Fig. 112). The cause of the disorder is obscure and insufficient cases have been followed to allow an assessment of prognosis. There is certainly a liability to infection which can be difficult to eradicate, but in the author's experience a prolonged period of drainage and bladder neck revision has resulted in better emptying. The "lazy bladder syndrome" as a cause of incontinence is discussed on p. 240. Cases so described appear to be less serious and have possibly a psychological explanation.

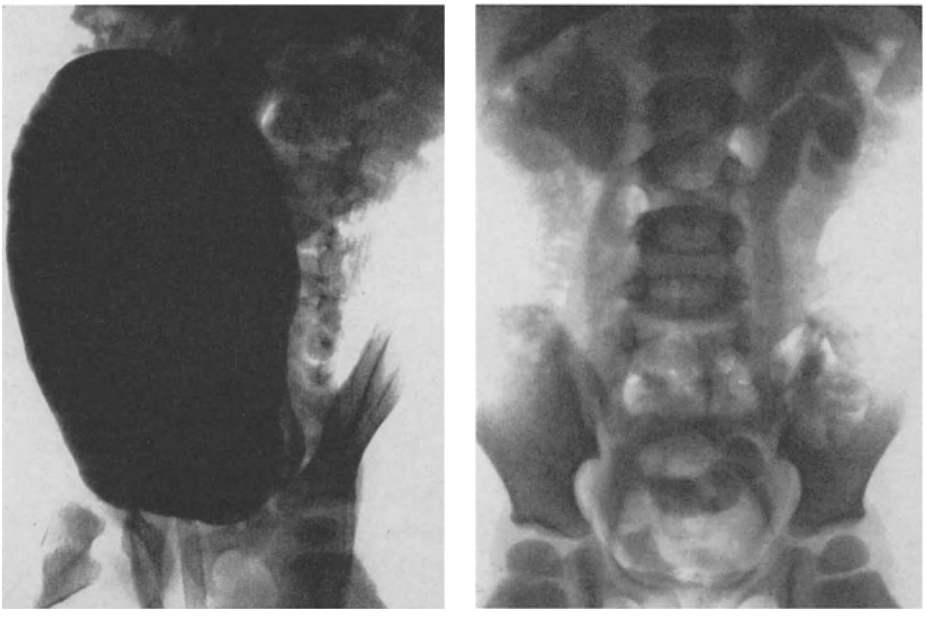

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Fig. 111a and b. Mega-ureter-megacystis. a Cystogram in a uraemic infant with urinary infection, showing very large capacity bladder and free reflux. Cystoscopy demonstrated wide trigone with laterally displaced and dilated ureteric orifices. b Intravenous pyelogram after temporary ureterostomy and later re-modelling and re-implantation of ureters

6. Polyuric Bladder

The bladder may enlarge in response to need and cases of diabetes insipidus have large capacity bladders: the enlargement is relatively modest in cases of

pituitary origin, but as CARTER and GOODMAN (1963) have shown, in cases of congenital nephrogenic diabetes insipidus it can be considerable and accompanied by hydronephrosis (Fig. 80).

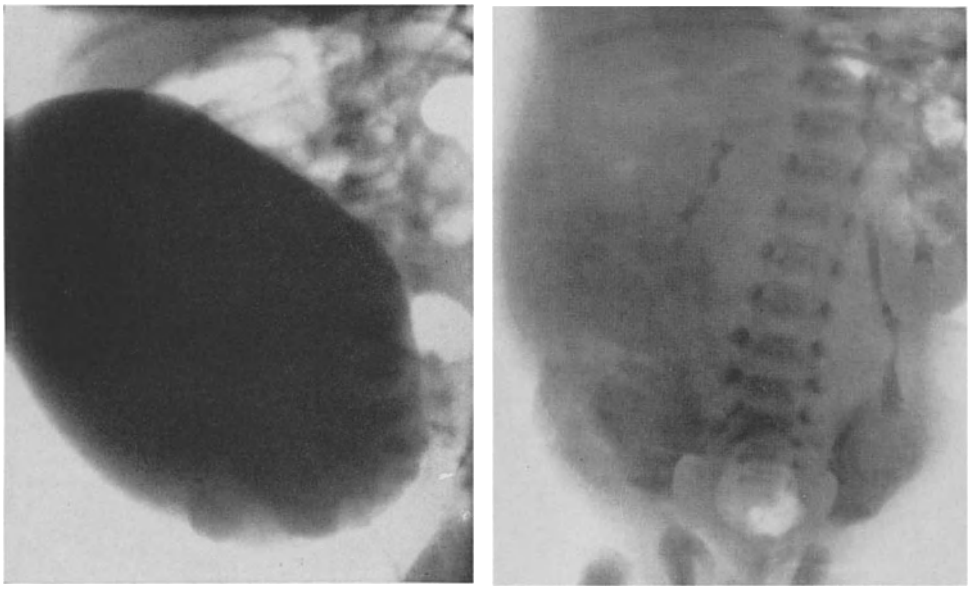

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Fig. 112a and b. Atonic bladder. Newborn infant with abdominal swelling but normal renal function and sterile urine. No neurological signs. a Cystogram showing enormous bladder capacity but no reflux. b Intravenous urogram showing very slight upper tract dilatation only. Good progress without operative interference at first; later plication of bladder required

II. Bladder Neck Obstruction

Having set out the conditions which are not examples of this disease, it remains to enquire if there are any children in whom the diagnosis of bladder neck obstruction can properly be made. In adults the disorder is encountered with some regularity and the efficacy of bladder neck resection seems to confirm the correctness of the diagnosis; it might therefore be anticipated that a few cases would be seen during childhood. It would be reasonable to search for such cases amongst boys with enuresis accompanied by bladder trabeculation and residue, or those with vesical diverticula, with reflux or with chronic retention. The minor degrees of the disorder might be diagnosed by hydrodynamic studies, which have been shown by TURNER-WARWICK et al. (1973) to be reliable indicators in adults, but as discussed in Chapter R the diagnosis of bladder neck obstruction in enuretics has been difficult to establish by similar methods (GIERUP and ERICSSON, 1971) and bladder neck resection has given disappointing results. It cannot be safely denied that this form of obstruction causes enuresis, but it would probably be wiser to confine treatment to medical methods.

Children with diverticula, as described in the next section, fall into two categories, those who have one or two relatively large diverticula with an otherwise normal bladder and those with multiple diverticula accompanied by generalised detrusor hypertrophy (Fig. 115). In the latter cases it is certainly justifiable to consider the diagnosis of bladder neck obstruction. In reflux cases there is no doubt that a few children without evident urethral obstruction have trabeculated bladders, though whereas in 1965 the present author (WILLIAMS and ECKSTEIN, 1965) reported that bladder neck revision was performed in 27 per cent of operations for reflux prevention, in common with most urologists this figure has dropped progressively over the years without any ill consequences. WOODROW and MARSHALL (1971) continue, however, to regard the procedure as of value. There remain the cases of chronic retention without diverticulum, but these must be extremely rare and on a retrospective view, and taking into consideration the alternatives set out in the previous section and adding the criterion that improvement must follow bladder neck resection, the author was only able to find 4 boys and one girl (Fig. 113) in his practice to whom the diagnosis of bladder neck obstruction might properly be applied. Similar views are expressed by CENDRON and LEPINARD (1972).

The more satisfactory method of diagnosis by pathological examination has not so far been achieved. The earlier reports of submucous fibrosis at the bladder neck in obstructed cases have not been confirmed; most investigators find only muscle tissue in resected specimens. BODIAN (1957) described a condition of fibroelastosis of the urethral wall which he believed responsible for Marion's disease, though in fact the changes which he demonstrated occurred in the lower part of

Fig. 113. Bladder neck obstruction in a girl presenting with retention and uraemia. No neurological signs. Cystogram shows trabeculated bladder with a narrow bladder neck and a normal distal urethra. Reflux on the left side only. Normal bladder function with complete continence restored by bladder neck Y–V plasty with reimplantation of left ureter

the posterior urethra extending down into the bulb and there was no satisfactory correlation with obstruction at the bladder neck. YOUNG (1972) mentions 8 cases (4 male and 4 female) in whom dense fibro-elastosis of the bladder neck was the principal histological finding, and it is clear that further studies of this type are required. TURNER-WARWICK et al. (1973) believe that bladder neck obstruction is due primarily to 'dyssynergia': inco-ordination between detrusor contraction and sphincter relaxation, and that the bladder neck hypertrophy usually observed is secondary to the generalised detrusor hypertrophy. No specific local pathology is therefore to be expected.

III. Bladder Neck Resection

Operative or endoscopic revision of the bladder neck, which is specific for bladder neck obstruction, may also be performed for neuropathic or atonic bladder, or to relieve the pressure on the upper tract in severe reflux cases. The classical procedure of posterior wedge excision seems logical in cases where there is a distinct and firm bar posteriorly, and a similar procedure may be performed endoscopically. The anterior vesico-urethroplasty (YOUNG and NEIBEL, 1958) has often been preferred in childhood and eliminates the rare but tiresome complication of vesico-vaginal fistula which can follow posterior excision whether open or endoscopic. Any type of revision may at times be followed by incontinence of the stress type, particularly in boys, even though the original procedure does not appear to have been extensive. Incontinence following the anterior plastic operation is easy to correct by reconstituting the original bladder neck, but posterior or circumferential excision with loss of tissue presents a much more difficult problem: even a rare case of this type is enough to discourage the urologist from undertaking bladder neck revision on anything but the most unassailable indications. Retrograde ejaculation, and thus sterility, is a possible complication of all forms of bladder neck revision. OCHSNER et al. (1970) found it in 33 per cent of 21 adults with a long follow-up after childhood operation; this risk, which does not appear to be preventable by modifications of technique, emphasises the need for conservative management of suspected bladder neck obstruction unless the symptoms are severe.

IV. Vesical Diverticula

The frequent use of the micturating cystogram has made it evident that there is no clear-cut distinction between a saccule and a diverticulum, though it is useful to have some criterion for deciding whether a stable condition is present or whether progress is to be expected and surgical excision therefore preferred. Both saccule and diverticulum are essentially herniations of bladder mucosa through a weak point in the detrusor layer, most often at the ureteric hiatus. Neither is truly congenital, except insofar as the detrusor weakness is a defect in development, and both vary in size with contraction and relaxation of the bladder. In general the saccule is smaller and ordinarily remains within the intact adventitia of the bladder; at rest there may be no herniation at all, so that the saccule is not visible cystoscopically except on overfilling. The diverticulum is larger; it may appear enormous during micturition since the tissues in childhood are extremely elastic, and it never empties completely; it remains as a well defined cavity at least 2–3 cm across when the bladder is relaxed. It is evident cystoscopically as a

black hole. On this definition a saccule does not require excision except insofar as it interferes with the lower end of the ureter, whereas a diverticulum will almost certainly enlarge and cause some symptoms at some stage: it is better removed.

In the obstructed bladder multiple saccules are common, but large diverticula rare (Fig. 114). In the absence of obstruction solitary or bilateral symmetrical diverticula are seen, which STEPHENS (1963) finds to be due to a localised muscular defect. In both types of diverticula boys are affected very much more often than girls, and in a series reviewed by the present author there was only one girl amongst 49 cases. In 23 of the children there was no evidence of outflow obstruction; in 8 there was a definite urethral lesion causing obstruction and in the remaining 18 generalised detrusor hypertrophy with an apparently normal urethra led to the diagnosis of bladder neck obstruction (Fig. 115). All neuropathic bladders were excluded from this series. CENDRON and ALAIN (1972) find that most diverticula in childhood are not associated with bladder outflow obstruction.

A simple solitary diverticulum may be present for years without causing symptoms, but most ultimately become infected: the symptoms are then severe and often accompanied by haematuria. A large low placed diverticulum occurring in the infant male may be the cause rather than the result of retention of urine: as shown in Fig. 116 the sac enlarges downwards into the pelvis as it fills. During bladder contraction it stretches the urethra and compresses it, so that ultimately urine flows more easily into the diverticulum than down the urethra.

A saccule or diverticulum at the ureteric hiatus has certain special features (Fig. 117), not only is it intimately connected with the terminal ureter but it lies within the adventitial layer of Waldeyer's sheath. Outward displacement of the ureter with herniation of the saccule destroys the valvular effect of the intra-

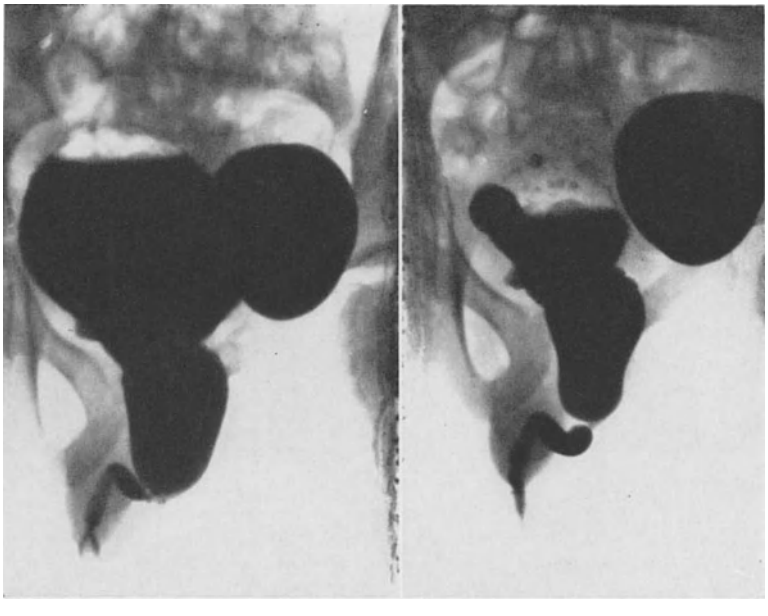

Fig. 114. Vesical diverticulum with urethral valve. Cystogram in a boy with urinary infection and bilateral hydronephrosis showing large left vesical diverticulum. Urethral valvular obstruction but no reflux

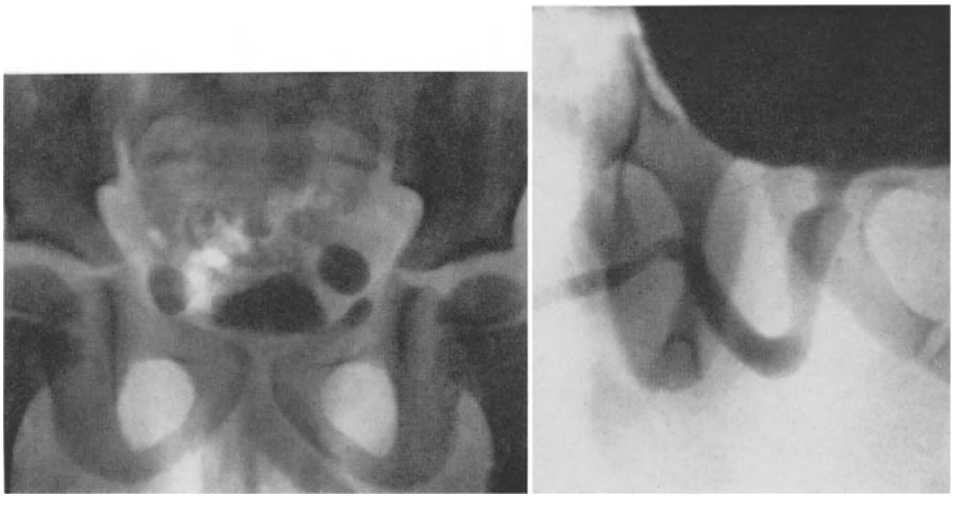

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Fig. 115. Multiple diverticula with possible bladder neck obstruction. Boy with haematuria. Cystogram showing multiple diverticula, a somewhat narrow bladder neck but a normal urethra

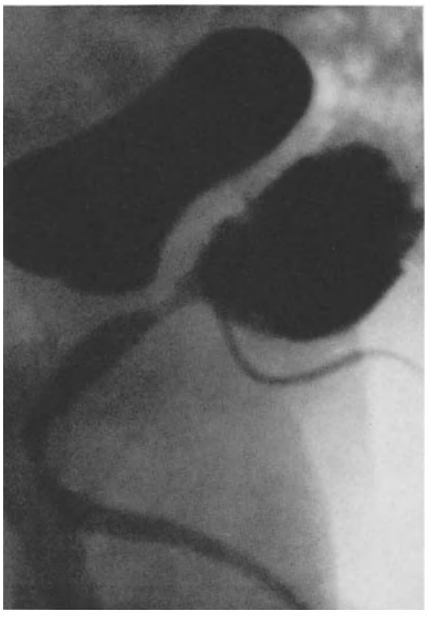

Fig. 116

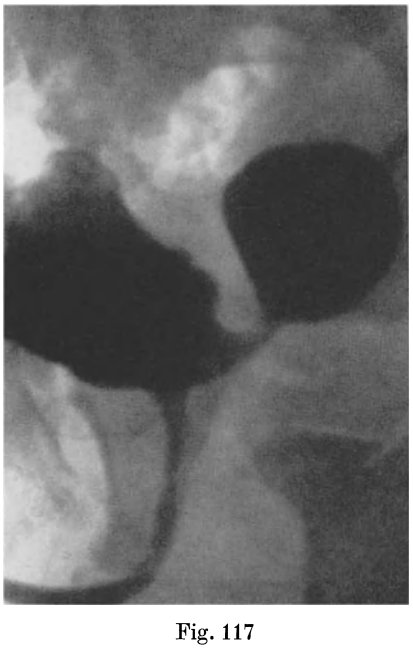

Fig. 117

Fig. 116. Solitary vesical diverticulum compressing urethra. Male infant presenting with retention of urine. Cystogram performed through low suprapubic cystostomy showing a trabeculated bladder, enormous posterior diverticulum impinging upon the upper urethra. No intrinsic urethral abnormality

Fig. 117. Para-ureteric diverticulum. Boy presenting with recurrent urinary infection but no difficulty in micturition. Cystogram showing normal bladder and bladder outflow, large para-ureteric diverticulum. No reflux

mural ureter and facilitates reflux (Fig. 118), but ureteric obstruction is also common, perhaps as a result of lack of muscle tissue in the common wall of ureter and saccule, perhaps because of compression.

Diverticula in children are usually easily excised since they present before inflammatory adhesions have rendered their dissection difficult. The large solitary diverticula are best excised from outside the bladder, the para-ureteric saccules and diverticula most easily from within. In the latter case it will, of course, be necessary to re-implant the ureter after reconstitution of the detrusor layer.

Certain conditions in children must be distinguished from true diverticula. In males under the age of six months there may be bladder pouches placed antero-laterally in relation to the inguinal ring: these have been named "bladder ears" by ALLEN and CONDON (1961), though this term is also applied to lateral pouches in the flaccid female bladder. The pouch related to the inguinal ring will be distinguished by its position and the absence of any neck to the sac; it will disappear spontaneously with time (Fig. 119). Another condition called by STEPHENS (1963) "the wide mouthed diverticulum" is a saucer-shaped depression postero-lateral to the ureteric orifices, occurring particularly in girls with large atonic bladders (Fig. 120). The depressed area is covered by a thin layer of muscle and bulges

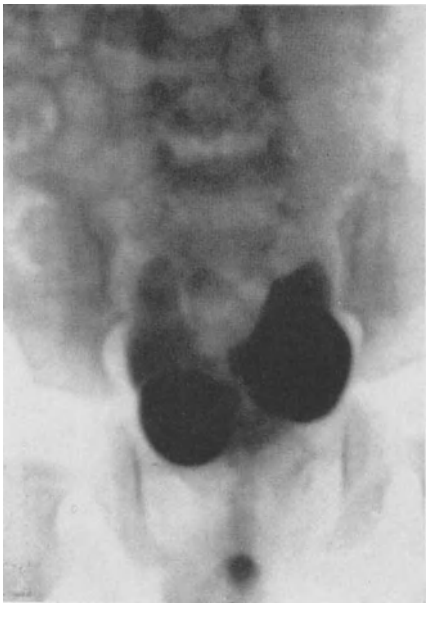

Fig. 118

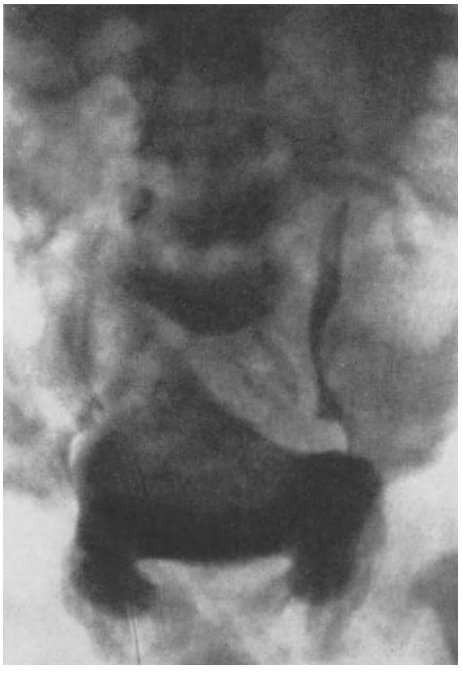

Fig. 119

Fig. 118. Para-ureteric diverticula with obstruction and reflux. 1 year old boy presenting with renal failure. Micturating cystogram shows complete bladder emptying but large bilateral para-ureteric diverticula with slight reflux into the lower ends of enormously dilated ureters. Pressure measurements confirmed obstruction to downflow of urine

Fig. 119. Transitory pseudo-diverticula in a male infant. Cystogram showing pouches related to inguinal canal which disappeared spontaneously after a year

during micturition. It does not remain full when the bladder is empty, however, and its role in perpetuating infection is somewhat doubtful. It can, if necessary, be treated by plication of the muscle layer. Finally, in association with multiple abnormalities, the bladder may be loculated, wide pouches being covered by normal or even thickened layer of muscle. True duplications of the bladder occur from time to time, sometimes with obstruction to one side, but sometimes with normal function of both elements (Fig. 121).

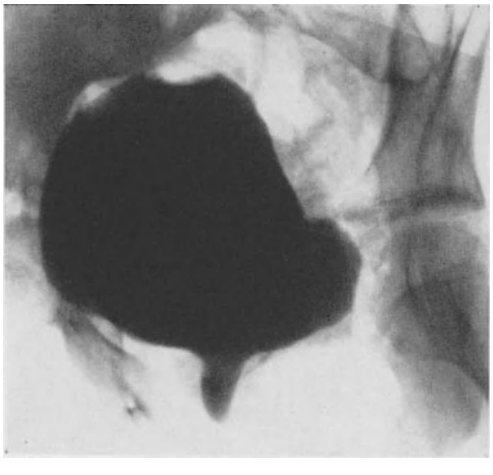

Fig. 120

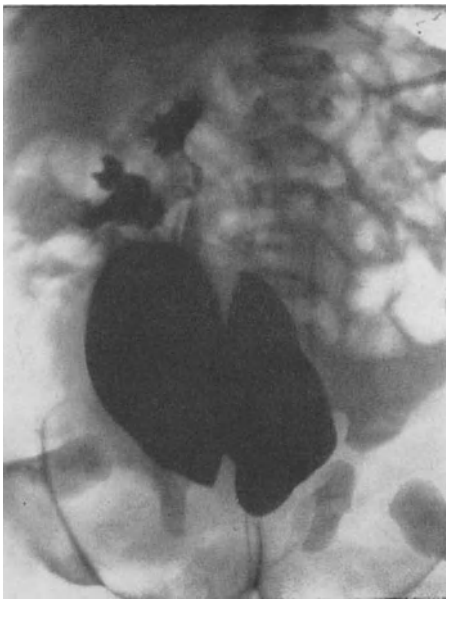

Fig. 121

Fig. 120. "Wide mouthed diverticulum". Cystogram in a girl with recurrent urinary infection showing out-pouching of the bladder on the left side but no reflux

Fig. 121. Double bladder. Cystogram showing two unconnected bladders with complete urethrae

P. Obstructive Uropathy: The Urethra

D. Innes Williams

With 19 Figures

I. Introduction

The causes of urethral obstruction in the child are very numerous, and in this chapter posterior urethral valves are selected as the main topic of discussion being the most common severe congenital lesion. Other intrinsic disorders of the male urethra are summarised at the end of the chapter together with some rare conditions of the female urethra. Reference should also be made to the chapter on ectopic ureteroceles as a cause of obstruction in both sexes, and to the section on lower urinary tract tumours which may well be obstructive.

II. Pathology of Urethral Valves

The classical description of the pathological anatomy as given by Young et al. (1919) has dominated all further discussion of this subject, though it has gradually become clear that his Type I is the only important variety encountered. Young's Type II, in which apparently obstructing folds run upwards from the verumontanum towards the bladder neck, appears to be something of a misconception since these ridges are, in fact, a secondary consequence of the excavation of the posterior urethra resulting from distal obstruction and the ridges themselves cannot be obstructive. Nevertheless, the usual diagram of Young's Type I does give a somewhat erroneous impression since it emphasises two folds springing from the lower end of the verumontanum and passing outwards to the lateral wall of the urethra, whereas in fact these two folds unite with one another anteriorly. The valve would be better described as a flap of mucosa on the anterior wall leaving a small slit for the urethral opening posteriorly below the verumontanum. (Fig. 122). This view of the anatomy is clearly shown by lateral urethrograms during micturition (Fig. 123), whereas the endoscopic view inevitably emphasises the lateral elements rather than the more important anterior element which is difficult to visualise. The practice of exposing the valves in post mortem specimens by opening the urethra through an anterior longitudinal incision has also led to an exaggerated impression of the lateral elements in the valve, Robertson and Hayes (1969), by unroofing the urethra, have demonstrated the almost diaphragmatic nature of the valve, and it is clear that Young's Type III was, to some extent, a recognition of this anatomy.

The degree of obstruction produced by the valve is variable, but there is also a range of variation in the secondary changes in the urinary tract above the valve. In some the urethra is very grossly dilated leaving the bladder neck relatively narrow, in others the bladder neck itself almost disappears due to dilatation. The hypertrophy of the trigone which accompanies the obstruction sometimes results

in elongation of the intramural ureter and therefore in very effective reflux prevention, so that high pressures can be reached in the bladder and in the ureters without reflux. At other times the ureteric orifice is involved in a para-ureteric saccule, and in these circumstances the ureter may reflux or may be obstructed. At times a relatively mild urethral obstruction is accompanied by saccule formation with severe ureteric obstruction so that the complication can be rather more serious than the primary lesion. The ureters are always dilated in any case presenting in infancy, but the degree of dilatation, the degree of tortuosity and the sclerosis of the ureteric wall vary very considerably even at birth before any possible infection has occurred. The prognosis of urethral valve cases depends as much upon the state of the ureters as upon the state of the bladder. Renal damage may be due to hydronephrosis or pyelonephritis, but also to the cystic dysplasia of a kidney which has been mentioned in Chapter F as a complication of obstruction, usually with reflux (Fig. 26). The overall incidence of dysplasia is probably not very high, its importance having been exaggerated by the fact that it is most likely to be seen in autopsy cases and nephrectomy specimens where a functionless kidney has been removed.

III. Presentation

Severe cases of obstruction present in infancy, mild ones often in later childhood. In the series reported by WILLIAMS et al. (1973) half were under the age of a year and one third under three months when they reached hospital. In the infants the signs were usually those of renal failure with vomiting, dehydration and failure to thrive, or perhaps a bowel disturbance. These were found to have a raised blood

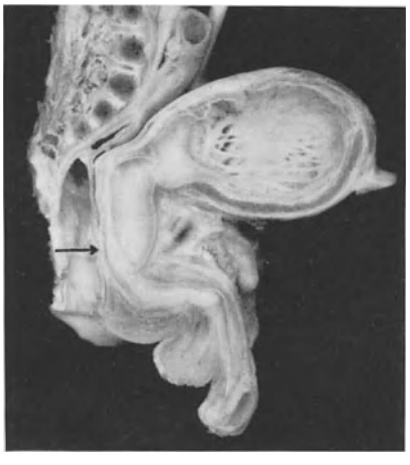

Fig. 122

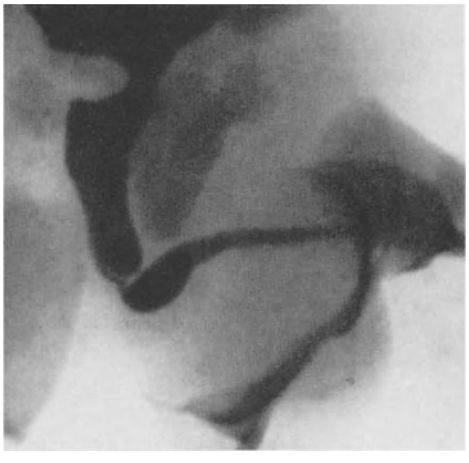

Fig. 123

Fig. 122. Posterior urethral valves. Post mortem specimen of a neonate dying on admission to hospital. The saggital section shows the obstructive anterior part of the urethral valvular fold

Fig. 123. Posterior urethral valves. Infant with chronic retention. Micturating cystogram shows dilated posterior urethra and obstructive valve arising from the anterior urethral wall

urea, but in the majority of such children it was the palpation of a distended bladder which led to further investigation. Acute retention in the sense that no urine can be passed at all is very uncommon, but some infants present during the first days of life with an extremely tense bladder and evidence of acute obstruction in the upper tract, whereas others have a lax, distended, and easily overflowing bladder. Nevertheless, in some examples the bladder appears to be able to compensate for urethral obstruction by massive hypertrophy; it empties with a reasonably good stream but produces severe upper urinary tract dilatation, and paradoxically therefore these cases with little micturition disturbance may have very advanced renal damage (Fig. 124). Renal rather than vesical enlargement is characteristic of some of these cases. Palpable kidneys are found with infection and oliguria where there is often massive oedema of the renal parenchyma and incipient abscess formation. A cystic swelling in the kidney is also seen from time to time: in one case WILLIAMS and MINNINBERG (1968) interpreted the cyst as hydrocalicosis, but in others it has appeared to be a simple cyst which, when uncapped, has left a relatively healthy kidney.

Some children with urethral obstruction present with abdominal enlargement due to intestinal distension rather than a full bladder. Not infrequently such children have had a barium enema investigation for suspected intestinal disorder before the urinary obstruction is suspected. In these cases there appears to be oedema of the posterior abdominal wall around infected dilated ureters, causing a

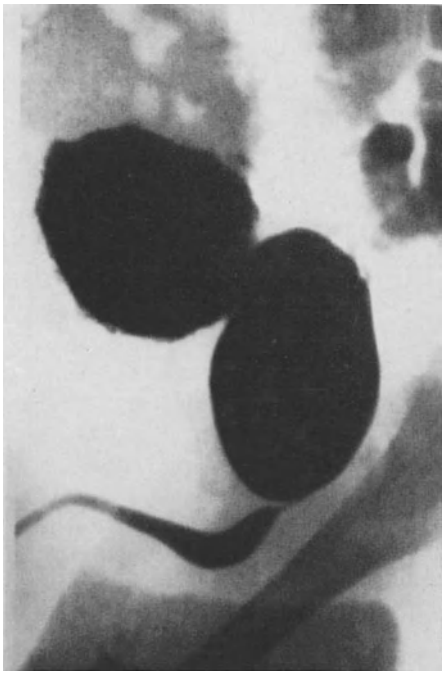

Fig. 124. Posterior urethral valves. Infant presenting with enlarged abdomen due to intestinal distension, raised blood urea and severe renal failure. Micturating cystogram shows partially contracting bladder with enormous dilatation of the posterior urethra above a valvular obstruction

secondary ileus. On very rare occasions the distension can be due to urinary ascites, a rare complication occurring in neonates with obstruction at any level in the urinary tract, or even with neuropathic bladder (HOWAT, 1971). It may result from a small perforation in the bladder (LEONIDAS et al., 1970) or from a leak through the renal substance, usually starting as a perinephric extravasation and later bursting through into the peritoneum. The rapid accumulation of urine in the peritoneum is accompanied by a low output from the bladder and a rapidly rising blood urea with wild electrolyte disturbances; although only occurring in severe disorders it can be controlled by upper tract drainage, or even by urethral catheterisation, and no specific repair is required.

In older children urinary incontinence is one of the common modes of presentation: it is seldom a purely nocturnal enuresis but usually a daytime incontinence with poor stream and progressive deterioration.

As in all forms of severe urinary obstruction a few children are first investigated for retardation of growth and have no specific complaints.

IV. Diagnosis

The diagnosis is reached in almost all cases by intravenous urography and micturition cysto-urethrography. The latter should be performed without anaesthetic wherever possible, and where voluntary micturition is impossible a fine urethral catheter is passed and the bladder filled until contractions occur. In the majority there is no doubt about the presence of an obstructive valve (Fig. 125), but

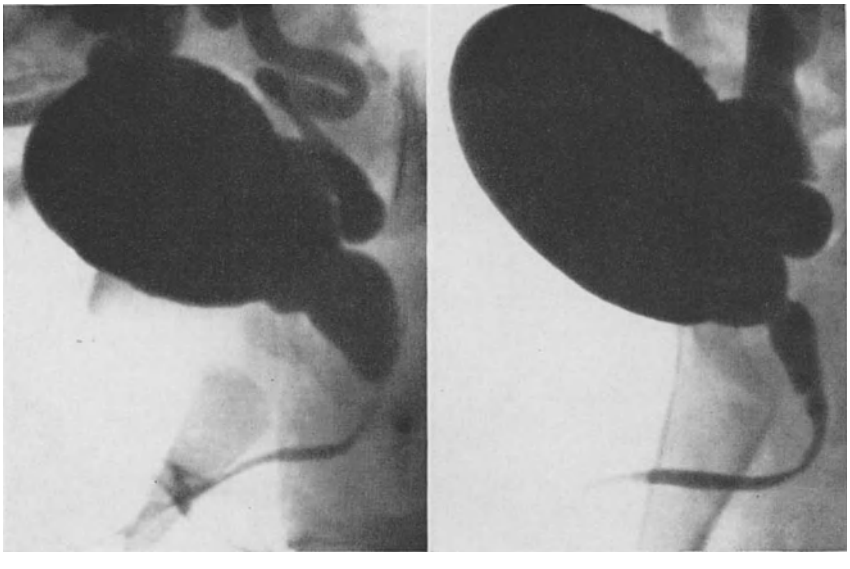

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Fig. 125a and b. Posterior urethral valves. Infant with recurrent infection. Micturating cystograms a before, b after valve ablation, showing the change of urethral outline. Vesico-ureteric reflux persists after operation

occasionally in the older enuretic child with a normal intravenous pyelogram there is some uncertainty as to whether folds of mucosa, often crossing the urethra transversely, are obstructive or not. Conscious voiding cine studies are of great value in this decision since the hold-up is then evident from the temporary dilatation above the fold. Measurements of voiding flow rate and pressure studies may also be helpful. In the differential radiological diagnosis other forms of urethral obstruction should be borne in mind as well as the bladder disorders discussed in the previous chapter.

V. The Infant Emergency

The most serious cases of urethral valvular obstruction present in early infancy, and it is in these that there can be a significant mortality. Even in the neonatal period, however, there is a considerable variation in the severity and the reversibility of renal damage. Urine formation starts somewhere about the third month of foetal life and in many instances urethral valvular obstruction has caused gross upper tract changes before birth, but it is probable that the rate of urine flow rises very considerably in the few days immediately after birth and a lesser degree of obstruction may be rendered more acute at this time. Some babies have, therefore, a very tense bladder with acute hydronephrosis, shown radiologically as a nephrogram, which is relatively reversible; others have chronic changes for which very long term measures must be planned. On admission an infant with evidence of bladder outflow obstruction should have as a matter of urgency a very full investigation from the clinical, biochemical and radiological standpoints. The programme of medical management, emergency drainage and definitive surgery, must be carefully integrated, since the chances of survival from any operation are greatly enhanced if the biochemical state is first corrected. The co-operation of a paediatric nephrologist is therefore essential to the proper management of these cases.

If the child's condition on admission is good, hydration adequate and the blood urea less than 150 mg/100 ml, then short term catheter drainage and early operative resection of valves may be planned. If the baby's condition is poor, management must depend upon his reaction to emergency corrective measures and an estimation of the capacity for improvement under long term medical treatment. A dehydrated baby with acidosis but sterile urine can be treated by catheterisation, re-hydration and correction of electrolyte balance while surgery is postponed for a few days. If, however, the blood urea is high despite adequate hydration and a low protein milk diet, then it is certain that severe renal damage is present and that upper urinary tract drainage over a long period is likely to be required. A child whose condition does not improve on emergency catheterisation, or who actually deteriorates following this method of drainage, will certainly require temporary nephrostomies. A child in very poor general condition who is already over-hydrated or has a severe electrolyte disturbance but sterile urine can be treated by urethral catheterisation and peritoneal dialysis. In any case, the presence of a urinary infection must favour early operative intervention; urethral catheterisation is adequate as a short term measure, but bilateral nephrostomy provides the best emergency drainage of the upper urinary tract.

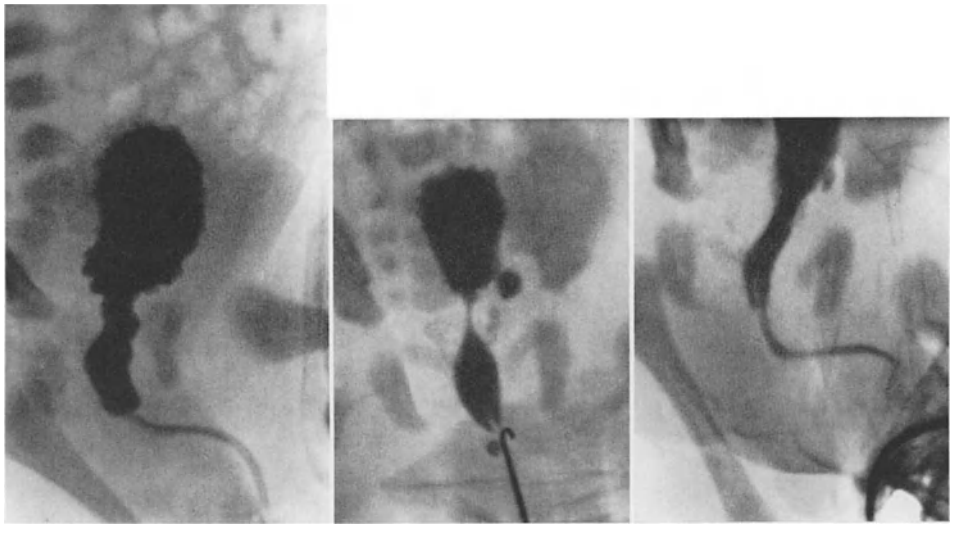
Urethral catheterisation in male infants has at times been the cause of many complications, but the routine use of an 8 F polythene feeding tube, or a similar catheter, does enable this form of drainage to be used for a number of days without

trouble. Drainage by a large suprapubic tube has also been responsible for infection, contracted bladder and persistent upper tract dilatation, but as an emergency measure suprapubic puncture with the introduction of a small plastic tube has enabled bladder drainage to be maintained for two or three days without difficulty. Bilateral nephrostomy is a simple and efficient method of securing upper tract drainage in infants. It has at times been employed as a long term drainage, but tubes are apt to become displaced or obstructed and infection can be maintained by the presence of a foreign body in the renal pelvis. Cutaneous ureterostomy by the loop method is discussed later. It has been advocated as an emergency operation in infants with urethral valves, but it is only appropriate where the changes are of a chronic nature, and as already stated some of the neonates have an acute condition which is reversible by simpler measures. It is therefore to be emphasised that the first decision in the infant emergency must be whether to proceed immediately to valve ablation or to institute long term upper tract drainage.

VI. Operation for Urethral Valve Ablation

Endoscopic resection of the valvular tissue has been the method most often employed for destroying the valve, and with the development of better infant endoscopes this operation becomes progressively easier. Open operative approach by the suprapubic route is now seldom used, but JOHNSTON (1966) has advocated perineal urethrostomy with the introduction of an otoscope through which the valves can be visualised directly and destroyed with a small diathermy hook. Non-operative methods have been used by some; for instance, CENDRON et al. (1969) advocate long term urethral catheterisation lasting some weeks and relying on the pressure from the urethral catheter to wear away the obstructing valvular tissue. This can at times be successful, but risks the consequences of infection and of damage to the penile urethra, and must in any case sometimes be followed by operative measures. The danger of removing too much tissue by the resectoscope loop has led some surgeons to prefer a simple diathermy electrode, introduced through a urethroscope (CORNIL et al., 1971), and HENDREN (1971) uses a slender electrode made from the stilette of a ureteric catheter to catch the valve and destroy it. All endoscopic methods with instruments at present available encounter some difficulty in regard to the calibre of the penile urethra in the neonatal case, and although the use of a perineal urethrostomy can allow the introduction of large instruments it increases the danger of infection. The present author (WILLIAMS et al., 1973) has recently introduced a purely radiological method of introducing a hook electrode which can engage in the anterior flap of the valve, drawing it down and cutting it through with the diathermy current (Fig. 126).

Some degree of stress incontinence is observed after any method of destruction of urethral valves in the infant, but clearly this danger is greatest if the muscular integrity of the urethra is also damaged by deep resection or if there is an associated resection of the prominent bladder neck lip. Many endoscopists have been so impressed by the appearance of the bladder neck that they have believed that some obstruction must be present at that level, but it has been clearly demonstrated (WHITAKER et al., 1971) that bladder neck resection increases the risk of incontinence. Urinary control improves with time and growth, particularly at puberty, but it may also be greatly assisted by the use of imipramine, indicating that there is an element of bladder dysfunction as well as a simple sphincter weakness.



a b c

Fig. 126a–c. Posterior urethral valves. Treatment by diathermy hook electrode introduced under radiological control. a Preliminary micturating cystogram showing hypertrophied bladder, dilated posterior urethra and valvular obstruction. b Hook in place engaged on the anterior aspect of the urethral valve. c Cystogram immediately after diathermy destruction of valve showing the absence of urethral obstruction

VII. Post-Operative Management

In the simple uncomplicated case where ablation of valves has been performed and the catheter left in situ for four or five days micturition may be resumed without difficulty, but post-operative infections are common and severe biochemical disturbances have occurred in some infants. Where there has been a very acute obstruction, often evidenced by a nephrogram in the pre-operative intravenous urograms, there has been a tendency to post-operative diuresis with sodium loss, but these children have ultimately a good prognosis (Fig. 127). Other infants have less acute obstruction but less easily reversible changes in the upper urinary tract, and longer lasting disturbance of renal function. Sometimes careful management by long term antibiotics, parenteral fluid or tube feeding and a low protein diet serves to control these disorders, but persistent infection or failure of improvement of renal function after operation is usually evidence of the need for further surgery to the upper urinary tract. The efficacy of valve resection is easily checked by repeat micturating cystogram, which will also give evidence as to the presence or absence of reflux and of any acquired urethral abnormality, such as stricture following long term catheterisation or frequent instrumentation.

VIII. Persistent Upper Tract Disturbance

All the infants, and a substantial proportion of the older children, have a dilated upper urinary tract on presentation. The mild acute cases may return to

normal after simple valve resection, but the majority have some degree of persistent dilatation, even though renal function has improved. The factors preventing complete recovery need to be analysed in some detail.

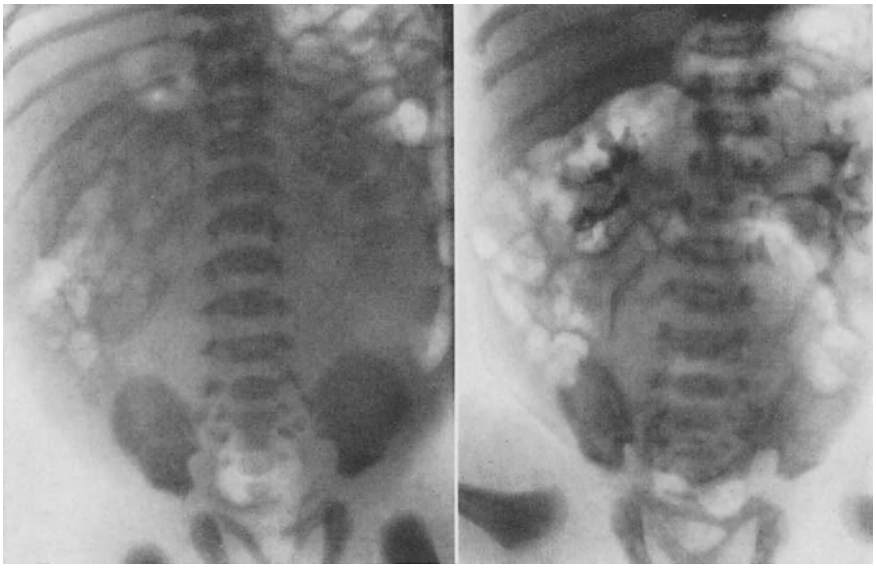


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Fig. 127a and b. Posterior urethral valves, neonate presenting with acute bladder distension. a Intravenous urogram on admission. Poor visualisation of kidneys but nephrogram shadow on the right, vague hydronephrosis on the left. b Intravenous urogram three days after valve ablation, rapid return towards normal anatomy

1. The Functionless Kidney

Asymmetrical upper tract damage is a feature of many valve cases. Quite frequently one kidney is virtually without function at birth, or at least by the time the child presents for treatment, sometimes in association with unilateral reflux with more severe damage to the refluxing kidney. It is evident that such a functionless kidney is of no value to the child and should be removed. Complete absence of function is hard to prove, however, unless upper tract diversion has been established, since radiologically it is obscured by reflux. It is important to bear in mind the possibility that a refluxing kidney is functionless since great benefit will follow nephro-ureterectomy while nothing but harm will come from attempts to reconstruct the ureter. In the series reported by WILLIAMS et al. (1973), of 172 boys 24 ultimately had a nephrectomy. Dysplastic changes were frequently found amongst the functionless kidneys.

2. Reflux

In the series referred to, reflux was present in 44 per cent of boys at presentation, 16 per cent bilateral, 28 per cent unilateral. It ceased spontaneously after

valve ablation in approximately one third of these cases, and the review did not show that reflux was such a serious complication as might have been anticipated; the difference between children with and without reflux was not so remarkable. The mortality was, in fact, lower in the refluxing group, but the pre-operative infection rate was somewhat higher and the nephrectomy rate was also higher. This review suggests reflux alone is not an indication for immediate ureteric surgery in valve cases and that an opportunity for spontaneous recovery should be allowed where upper tract dilatation is not too enormous. Where reflux is accompanied by persistent urinary infection and deteriorating renal function a reconstructive operation or a diversionary procedure will be required.

3. Uretero-Vesical Obstruction

If, following the restoration of efficient bladder emptying, a non-refluxing ureter remains considerably dilated the cause may lie in a failure of the ureteric peristaltic function, the presence of obstruction at the uretero-vesical junction or, possibly, in "bladder hypertension", seen where a massively hypertrophied bladder, although capable of emptying efficiently, retains ordinary volumes of urine at extraordinarily high pressures. Some degree of peristaltic failure is common to all grossly dilated ureters, since although they still possess active musculature the

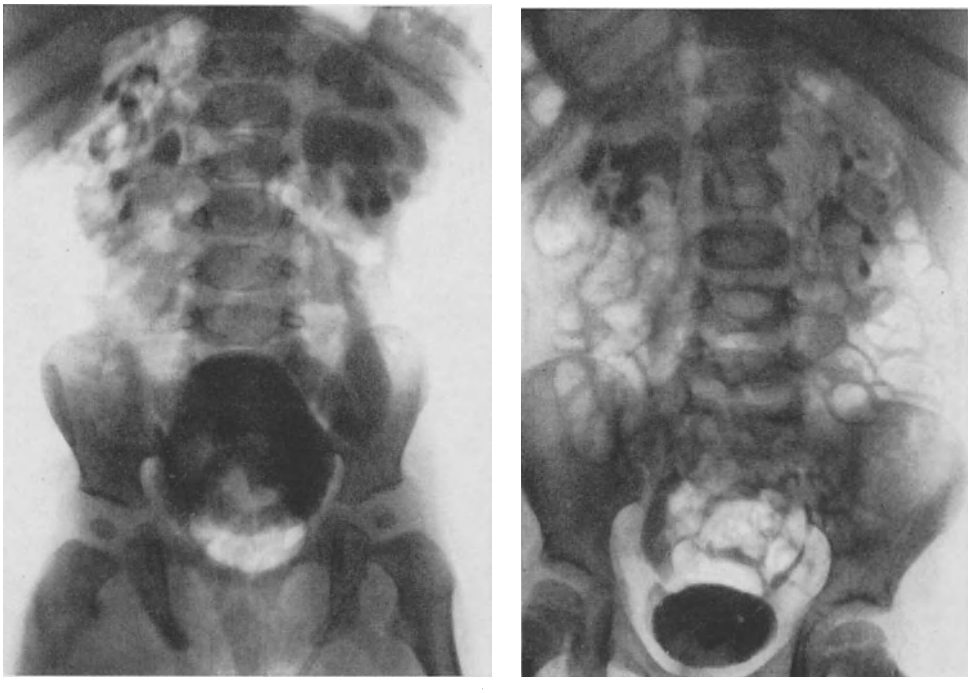

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Fig. 128a and b. Posterior urethral valves (post-op.). a Intravenous urogram showing dilatation of ureters and calices persisting despite normal bladder function. b Intravenous urogram two years later showing substantial recovery of caliceal pattern and improvement of ureteric dilatation

propulsive contractions no longer obliterate the lumen and therefore fail to propel the urine forward. The slightest increase of resistance at the uretero-vesical junction is therefore effective in maintaining stasis in the ureter. In most such instances some amelioration over the years may be anticipated (Fig. 128), and a child whose renal function is improving and whose urine remains sterile should not be subjected to ureteric surgery solely on account of the appearance of tortuous dilated ureters. Pressure flow measurements in the upper urinary tract by the method described by WHITAKER (1973) will show that in these cases of dilatation flows of at least 10 ml per minute may be maintained without significant pressure rise.

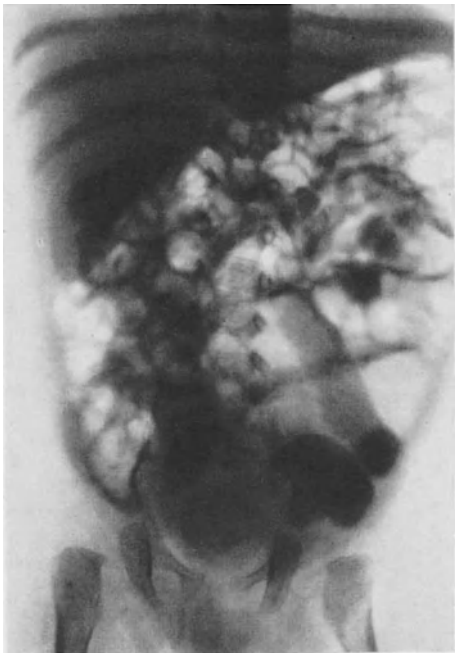
A uretero-vesical obstruction secondary to any form of bladder outflow obstruction could be due to elongation of the intramural ureter with pressure from the surrounding hypertrophied detrusor, or to the involvement of the ureter in a para-ureteric saccule. In the author's experience a saccule has usually been found in most of the clear-cut cases of obstruction in which perhaps there has been deterioration of the upper tract after correction of the bladder function (Fig. 129). The lower end of the ureter in these examples is closely bound to the saccule, sharing a common adventitia and often lacking any substantial muscle coat. It is not clear why some such ureters reflux without obstruction and some are obstructed without reflux, but it does appear that in a few reflux can be accompanied by obstruction to the downward passage of urine. All forms of uretero-vesical obstruction will be associated with high pressure in the ureter on perfusion or during diuresis; such high pressures result in persistent or increasing dilatation of the renal calices and are an indication for early operative interference, whether by drainage or by reconstruction of the terminal ureter.

By contrast Fig. 130 illustrates a case of a dilated ureter in which there was no rise of pressure when perfused at 10 ml/min. and in which re-implantation would have been of no avail. However, this type of ureter is extremely susceptible to slight rises in bladder pressure: being atonic and unable to raise its intraluminal pressure in the lower ureteric segment. Urine cannot easily be forced into the full bladder, and even in the absence of reflux a small rise in intravesical pressure produces an immediate damming back and a rise in pressure in the renal pelvis.

IX. Cutaneous Ureterostomy and Vesicostomy

Free drainage on to the skin surface enables the renal function to recover to the maximum and allows easy control of urinary infection. A number of papers have attested the value of this procedure in uraemic infants (e.g. LEAPE and HOLDER, 1970, and FEIN et al., 1969). Cutaneous ureterostomy, usually performed by the loop procedure, has therefore an important place in the management of the infant with urethral valves, particularly when a urinary infection is present. As performed by JOHNSTON (1963), the method consists of mobilising a high loop of ureter, bringing it up to the skin and reconstituting a skin bridge beneath it; the ureter is then opened laterally and allowed to drain freely. It is important that a high loop should be chosen so that there are no kinks or obstruction above it, but it must not be too tight. Such a loop cannot easily stenose its opening and is therefore very suitable for long term drainage; it does, however, require an operation to close it with excision of the exteriorised loop and end to end anastomosis of the ureter. In the operation described by PERLMUTTER and TANK (1968) the ureter is brought to the surface and incised laterally. The ureteric opening is then stitched to the skin incision without any bridge behind it to keep it in place. This type of

stoma can stenose, but it is easily replaced without excision of any length of the ureter. Similarly, a cutaneous pyelostomy may be undertaken (IMMERGUT et al., 1969) in any grossly dilated renal pelvis which may, in the infant, be rotated outwards, opened longitudinally and stitched to the skin.



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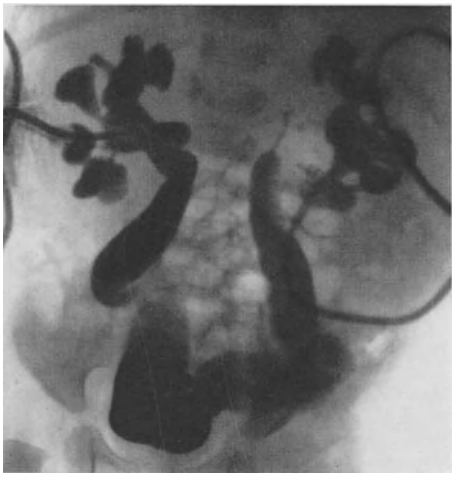

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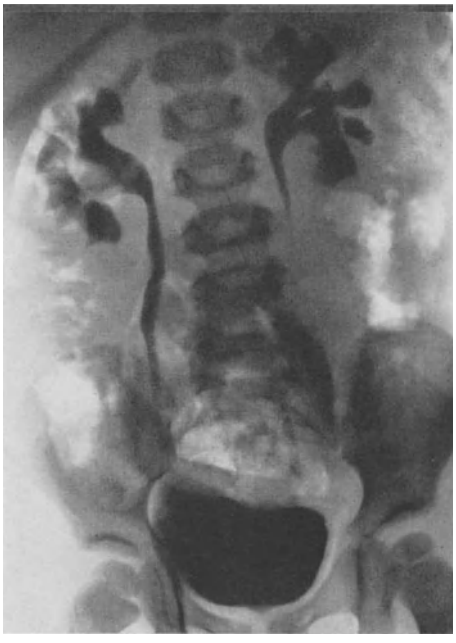

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Fig. 129a–c. Persistent ureteric obstruction due to saccule involvement following successful ablation of valves. a Intravenous urogram three months after valve resection. b Descending ureterogram after nephrostomy drainage. c Intravenous urogram six months after re-modelling and re-implantation of ureters

The institution of cutaneous ureterostomy drainage has often a dramatic effect in improving the general condition of the infant and allowing normal renal growth during the first year of life, but it leaves considerable problems in reconstruction, and not infrequently reconstitution of the urinary tract proves impossible, so that the infant is left with the need for permanent diversion by ileal loop. The defunctioned bladder may become contracted: in a series analysed by LOME et al. (1972) 6 out of 21 suffered this change, mostly those with considerable inflammation of the bladder wall. Such contraction may be reversible if the urine is again allowed to flow in, but it may leave a condition of "bladder hypertension" and cause upper tract damage. If the ureter allowed reflux before ureterostomy it is likely to continue to reflux, and some sort of preventative procedure is required if restoration of continuity is going to be re-established. The Gregoir operation (see p. 172) is most suitable in these cases since it does not involve interruption of the ureteric blood supply, which may already have been jeopardised by the

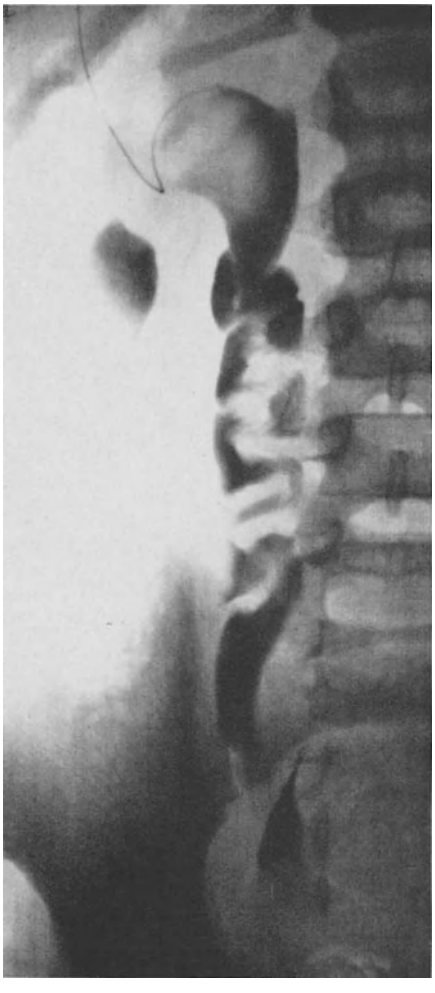


Fig. 130. Posterior urethral valves. Persistent ureteric dilatation. Antegrade pyelogram outlining a hydronephrotic kidney. Grossly tortuous and dilated ureter but no pressure rise on perfusion and free flow of opaque medium into the bladder

cutaneous ureterostomy. Because of the need to do a reflux preventing procedure at the time of reconstruction the present author employed a terminal ureterostomy as initial diversion in a number of cases, the ureter being divided at the bladder level and brought down directly on to the surface. This did not give such satisfactory drainage as the loop ureterostomies because of the tortuous dilated ureter above the opening and because the terminal stoma is more apt to stenose than the loop. LOME and WILLIAMS, (1972) analysed the results of restoration of continuity in cutaneous ureterostomy and found that in general the loop could be most easily closed. With a view to obtaining the benefits of free drainage by cutaneous ureterostomy without completely defunctioning the bladder the Y type of ureterostomy was suggested by SOBER (1971). In this procedure the ureter is cut across sufficiently far below the pelvi-ureteric junction to enable the proximal end to be brought out as a terminal cutaneous ureterostomy, while the distal end is anastomosed to the renal pelvis. The urine has therefore the possibility of flowing directly out on to the surface or down into the bladder, and at a subsequent operation closure is very easily effected by excision of the cutaneous limb of the Y. In the author's experience this has been most satisfactory in older children with considerably dilated ureters, but less effective in the uraemic neonatal case where the upper part of the ureter is often not grossly dilated but extremely tortuous, and the terminal stoma formed there is apt to retract and stenose.

In infants with a considerable bladder capacity a temporary vesicostomy is simple and may give adequate drainage, though the problem of tortuous and possibly obstructed ureters remains.

X. Re-Modelling and Re-Implantation of the Ureters

In recent years HENDREN (1970) has been a particular advocate of immediate reconstruction of the upper urinary tract in valve cases, and reference should be made to his work for full details of the procedure employed. The method has considerable attractions in the avoidance of any long term drainage system and in the relative immunity from infection which should be obtained by an efficiently emptying urinary tract. It can be performed with advantage in the older children without advanced renal failure and in whom infection has already been controlled, but in the author's opinion the risks in the neonatal case are very great and the theoretical advantage of immunity from infection not always obtained. Published results in this respect are often misleading since good results are more apt to be reported than bad, and in a great many centres it has been found that the re-implantation of severely dilated ureters into the grossly hypertrophied and sacculated bladder carries a high risk of secondary obstruction or persistent reflux. From the preceding discussion it will be clear that many urethral valve cases at all ages can be treated adequately by valve resection alone, with or without preliminary nephrostomy drainage. The indications for surgery on the ureter should therefore be either demonstrable uretero-vesical obstruction or persistent reflux with dilatation of the ureter and ineradicable infection: the choice in surgical intervention lies between cutaneous ureterostomy with later reconstruction as already described, which is certainly a safer method for those urologists without considerable experience of infants, and immediate re-modelling and re-implantation as described by HENDREN (1970).

XI. The Results of Treatment

Some mortality is almost inevitable in any large series of urethral cases due to the severity of the renal damage before birth. In the series reported by WILLIAMS et al. (1973) 28 out of 172 children had died: it was clear that the mortality was almost confined to those presenting under the age of three months and to the earlier years of the series. The causes of death are sometimes difficult to identify, but there is no doubt that uncorrected biochemical imbalance has resulted in death from surgical procedures and that infective complications have tipped the balance against an infant with already gross abnormalities of the upper urinary tract. In the author's clinic the mortality has fallen sharply within recent years because paediatricians have referred cases at an earlier stage, medical management of the biochemical disturbance has been more effectively performed and antibiotic control of the infection has been more efficient. The survival of the neonatal emergency case will, however, leave a number of children with severely impaired renal function who will almost certainly come to a renal substitution programme in later childhood or adolescence.

XII. Other Urethral Anomalies

A wide variety of urethral lesions may at times be responsible for obstructive uropathy; meatal stenosis and acquired urethral stricture (DEVEREUX and WILLIAMS, 1972) are well known and require no further comment. The solitary urethral polyp arising from the region of the verumontanum (see p. 316) but freely mobile from the bladder neck to the bulb of the urethra, is an occasional cause of urinary obstruction. Urethral duplications and diverticula are sometimes associated with an obstruction, and since the classification of these disorders has become clearer as a result of radiological studies in the last few years their pathological anatomy is briefly outlined here. The obstructions which they cause are seldom so severe as those due to posterior urethral valves, but the management of the retention of urine which they cause and the persistent ureteric dilatation which complicates their treatment should follow the lines already described.

1. Posterior Urethral Diverticula

In the presence of urethral valves or of neuropathic bladder dilatation of the prostatic ducts may give the appearance of multiple small diverticula of the posterior urethra, but other epithelial lined cavities communicating with the posterior urethra arise from developmental abnormalities.

a) Cystic Dilatation of the Prostatic Utricle

This abnormality is very rare in male children with otherwise normal genitalia, but it can occur and form a reservoir for infection, a site of stone formation or an obstruction to the posterior urethra (NEUSTEIN and SCHUTTE, 1968). Two cases have occurred in the author's practice, one of whom was noted to pass pus from the urethral meatus whenever his bowels were opened: a mass was found lying behind the prostate which could be emptied by pressure. The cystogram outlined the dilated cavity (Fig. 131); excision of the "diverticulum" was satisfactorily accomplished through a laparotomy approach.

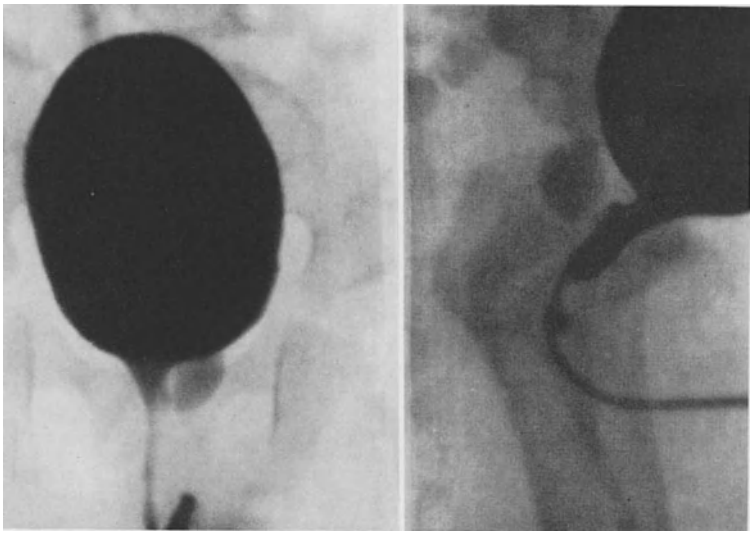


Fig. 131. Cystic dilatation of the prostatic utricle. Infant with discharge of pus from the urethra during defaecation. Micturating cystogram showing filling of dilated prostatic utricle. No urethral obstruction. Satisfactory recovery after excision

A tubular utricular diverticulum is often seen in association with the prune belly syndrome, it does not seem in these circumstances to cause any particular symptoms and does not require treatment. Similar considerations apply to the slight dilatation which can be found in some boys with hypospadias. A closed Mullerian duct cyst has been described in adults as a cause of retention of urine, but such cases do not appear to have been reported in the child.

b) The Vagina in Male Intersex

Occasional cases with apparently normal external genitalia are found to have well differentiated Mullerian structures, often revealed at the time of operation for inguinal hernia. A capacious vagina more often occurs in the male intersex child with equivocal genitalia, particularly in the mosaic group; a vagina of this type is seldom a cause of symptoms, however, unless there is a concomitant urethral stricture, often caused by hypospadias repair. In these circumstances it will fill with infected urine, cause epididymitis, or develop into a considerable pelvic mass which impairs bladder emptying. The diagnosis can be made on urethroscopy or urethrography. Hysterectomy and excision of at least the upper part of the vagina is then required together with the correction of the urethral stricture.

c) Ectopic Ureter

A ureter entering the posterior urethra or genital tract in the male may exhibit a considerable saccular dilatation at its lower end, comparable in size with ectopic ureterocele but based extra-vesically. Distension of this cavity stretches the posterior urethra and may cause retention. In other cases there is free reflux from the urethra and a chronic urinary infection. On excretory urography it is rare to find any evidence of opacification on the side of the lesion since this type

of ectopic ureter is often single and associated with a small dysplastic kidney. On cysto-urethrography the cavity may be filled (as in Fig. 57) or the displacement due to the extra-vesical mass may be seen. The ectopic orifice should be found on urethroscopy and the treatment is total excision of the dysplastic kidney and ureter.

d) Rectal Stump

In cases of imperforate anus with a recto-urethral fistula which have been treated by reconstructive operations, a stump of bowel may be left to form a diverticulum of the urethra (WILLIAMS and GRANT, 1969). This usually opens immediately below the verumontanum, though there are a few cases of congenital anobulbar fistula where the stump is much lower down. Small stumps retain some secretion but seldom give rise to symptoms. Where, however, an unabsorbable type of suture has been used to close off the bowel a stone may form in the stump which results in persistence of pyuria and haematuria. The diagnosis will be suspected from the history and may be confirmed by urethrography (CURRARINO, 1969). Stone containing stumps must be excised.

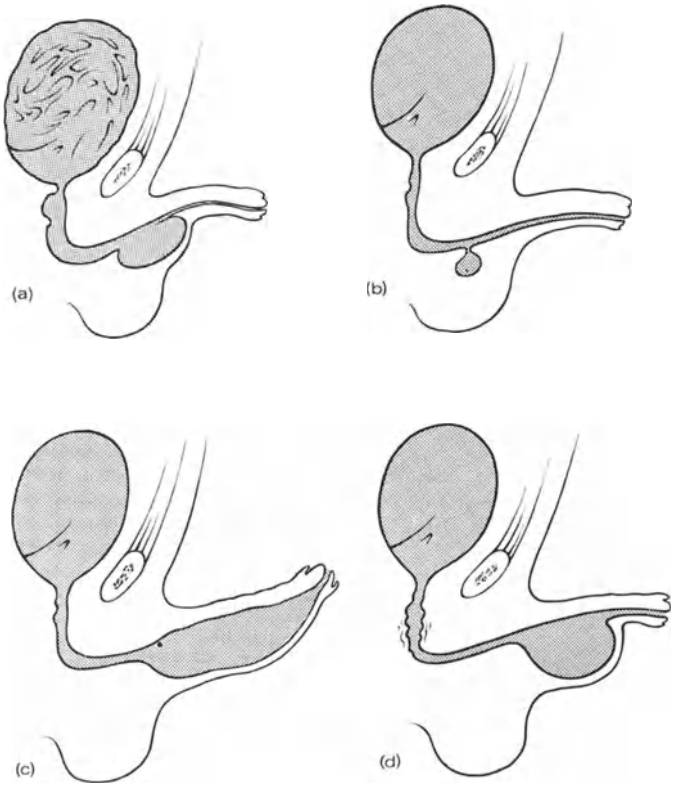


Fig. 132a–d. Diagrams to show types of anterior urethral diverticula presenting in childhood. a Wide mouthed diverticulum with valvular distal lip. b Narrow necked diverticulum with no urethral obstruction. c Megalo-urethra. Wide dilatation of the penile urethra with deficiency of the corpus spongiosum. No urethral obstruction. d Acquired traumatic diverticulum, often due to pressure of indwelling catheter used in treatment of posterior urethral rupture

2. Anterior Urethral Diverticula

a) Wide Mouthed Diverticula

An elongated defect in the ventral wall of the urethra results in a wide mouthed diverticulum which has, characteristically, a valvular distal lip but a rather insignificant proximal margin (Fig. 132) (WILLIAMS and RETIK, 1969). The obstruction may at times be severe so that many cases present in early infancy, but less serious obstructions may not cause symptoms until later childhood or may on occasions be found incidentally during investigation for other disorders. The lesion commonly described as "anterior urethral valve" appears to be in this group and represents the mildest form of diverticulum (RUDHE and ERICSSON, 1970).

The symptoms and signs of urinary obstruction are likely to bring the child for treatment, but some have in addition a palpable swelling in the scrotal area, enlarging during micturition, and a continual dribbling incontinence due to subsequent emptying. A micturition or expression cystogram will show some dilatation of the posterior urethra and of the bulb, but the diverticulum itself is distinct, though shallow and wide mouthed (Fig. 133, 134). The obstructive distal lip is clearly shown up during micturition. At times there is a posteriorly directed channel opening from the diverticulum and suggesting a partial urethral duplication or a dilated duct to Cowper's gland. Cysts of this duct are, on occasions, sufficiently distended to cause urethral obstruction (COOK and SHAW, 1971).

Anterior urethral diverticulum causing severe obstruction in infancy is best treated by laying the urethra open on to the skin, as in urethroplasty for stricture. At the time of subsequent closure the obstructive distal lip may be removed and the excess urethral mucosa excised. A one-stage correction may be possible,

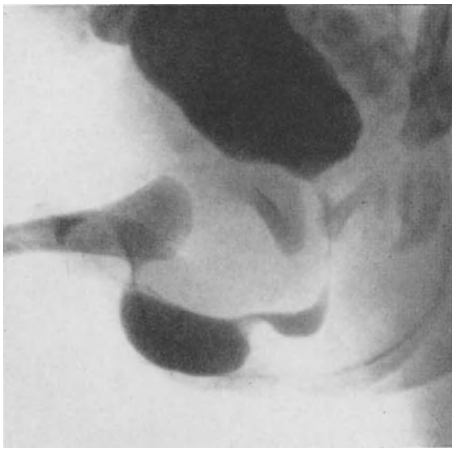


Fig. 133

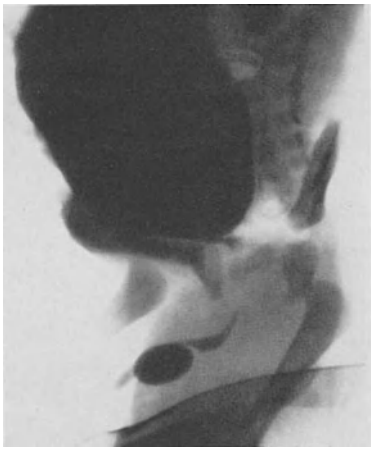


Fig. 134

Fig. 133. Anterior urethral diverticulum. Micturating cystogram in an infant with severe bilateral hydronephrosis. A very large saccular swelling is present with obstructive distal lip. The penile urethra is very narrow

Fig. 134. Anterior urethral diverticulum. Micturating cystogram in a uraemic neonate, clearly defined saccular diverticulum in the anterior urethra with distal obstruction

however, (BREUZIÈRE and DEMONT, 1971) and the minor cases in older children may be treated by simple trans-urethral resection of the distal lip.

b) Narrow Necked Diverticula

A narrow necked diverticulum occurs in the perineal area, it is a spherical cavity communicating with the bulb of the urethra through a narrow neck (Fig. 132). There is seldom any obstructive element here, but stasis within the diverticulum predisposes to infection and stone formation. The symptoms are those of local pain and dysuria and the diagnosis is made by urethrography (Fig. 135). Simple excision will suffice in treatment.

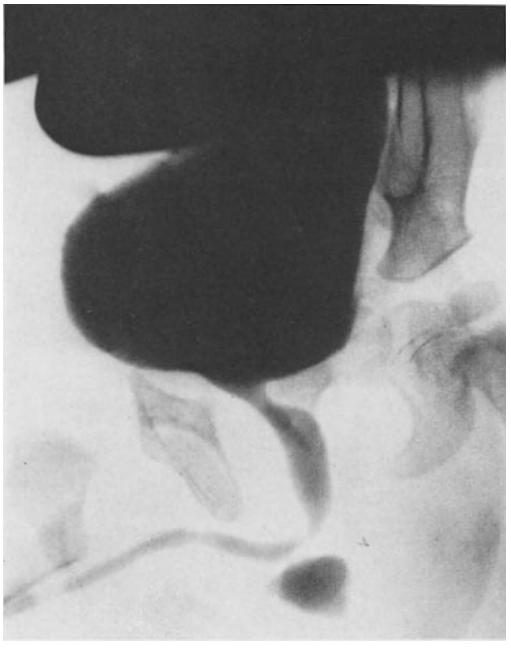


Fig. 135. Anterior urethral diverticulum. Micturating cystogram in a boy with recurrent infection. A narrow necked diverticulum is present without urethral obstruction

c) Traumatic Diverticula

An indwelling catheter, particularly when traction is applied to it in the treatment of rupture of the posterior urethra, damages the ventral wall of the anterior urethra in the region of the peno-scrotal junction (Fig. 132); this may result, during the acute phase, in peri-urethral abscess, or more chronically in a wide mouthed diverticulum with, on occasions, a fistula or distal stricture. The diverticulum causes incontinence and infection; it may be visible on simple inspection and readily emptied on palpation. The diagnosis is confirmed by urethrography and treatment by excision is effective.

d) Megalo-Urethra

A large saccular dilatation involves the anterior urethra distal to the peno-scrotal junction, though the meatus and glans are not seriously affected (Fig. 132) (JOHNSTON and COIMBRA, 1970). The condition gives rise to enlargement of the penis with elongation of the corpora cavernosa and upward tilting of the glans on top of the enormous saccular swelling. The condition is easily recognisable clinically, although urethrograms could be mistaken for the wide mouthed diverticulum (Fig. 145). This abnormality may be seen in the prune belly syndrome and also in cases with normal abdominal muscles but with the total urinary tract "dysplasia" commonly associated with their absence. Correction of the distal urethra may be undertaken by simple excision and reduction of the urethral lumen, but the possibility of more extensive disorders of the urinary tract should be borne in mind.

In rare cases, defined by STEPHENS (1963) as the fusiform variety, the corpora cavernosa are also deficient, the penis is enormous and flabby and incapable of reconstruction to a normal appearance.

3. Urethral Duplications

Partial duplication is not uncommon in cases of hypospadias; the accessory channel opens distally and lies dorsal to the normal urethra, extending for a number of centimetres proximally. It causes very few symptoms but occasionally becomes infected, producing a purulent discharge. More often it is the cause of difficulty in instrumentation, the catheter entering the blind channel instead of the normal one.

A partial duplication in which two channels descend from the bladder but unite in the peno-scrotal region is observed on rare occasions (Fig. 136); it may be suspected that an obstruction occurs at the point of union of the two channels, but in the case illustrated in Fig. 137 it will be seen that both are obstructed in the membranous area, while the point of union causes no hold-up.

A complete double urethra is a rare anomaly; 4 of the author's cases were reported with a review of the literature by CASSELMAN and WILLIAMS (1966): 3 further examples have been seen since that time and others have been recorded by TRIPATHI and DICK (1969). The accessory channel normally lies on the dorsum of the penis, opening on the glans at the coronal sulcus, on the shaft or at the base (Fig. 136). Proximally the urethra passes behind the symphysis and joins the bladder anterior to the normal bladder neck. In one example a minute track passed upwards, not entering the bladder at all, but ultimately being connected to the umbilicus alongside the normal urachus. Some children have incontinence, some a double stream, some no symptoms at all. The diagnosis can be made by inspection and urethrography. Excision of the distal part of the urethra is simple and may suffice; if the channel is wide a retropubic approach will also be required to excise the proximal segment.

In a further form of double urethra, originally described by WILLIAMS (1968) one channel is normally placed in the urethra, the other opens at or immediately outside the anus (Fig. 136, 138). The normally placed urethra is extremely narrow and although in infancy some urine may be passed through it, it later becomes completely occluded, particularly if attempts have been made at instrumentation. The greater part of the urine is passed from the posterior channel, which is ordinarily wide and well formed with normal continence so that there may be very little handicap (SELVAGGI and GOODWIN, 1972). There are, however, a few ex-

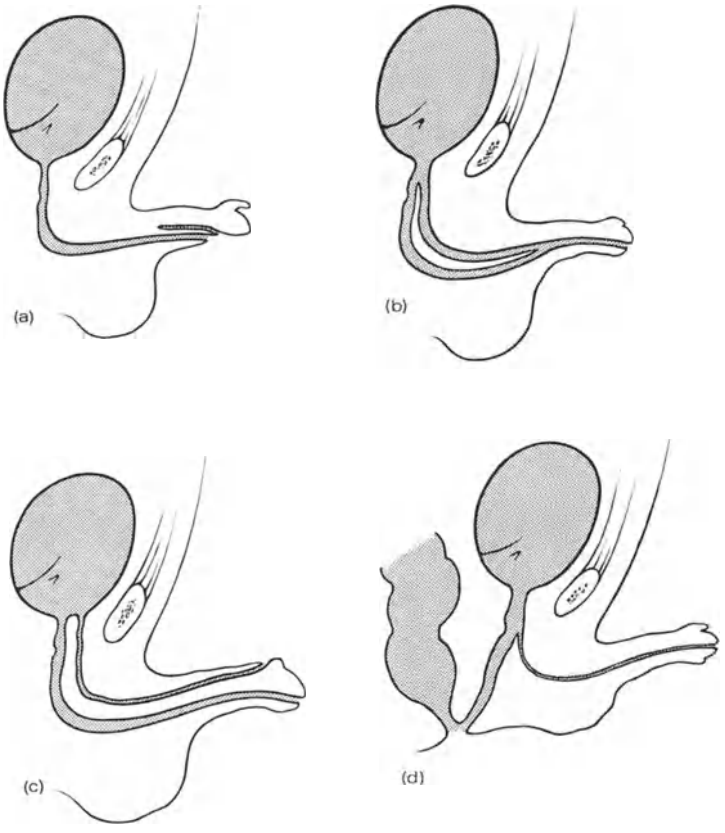


Fig. 136a–d. Diagrams to show the types of urethral duplications presenting in childhood. a Partial duplication with hypospadias. A blind channel lies dorsal to the complete urethra but very close to it. b Partial duplication with union of the two channels at the peno-scrotal junction. c Complete urethral duplication with two functioning channels. d Complete urethral duplication with atresia of the normally placed urethra and a wide channel to the ectopic urethra opening at the anal verge

amples in which it might seem proper to regard the posterior channel as a fistula rather than as a second urethra and these are associated with severe upper tract changes resulting from obstruction. Some children with this disorder have been born with a covered anus, but this is easily opened up and the condition should not be confused with the recto-urethral fistula found in the typical imperforate anus case. Attempts to dilate the normally placed urethra are useless, and a complete urethroplasty must be undertaken, reconstructing a channel from the posteriorly placed urethra. If this opens into the anus it will be necessary as a preliminary to transplant it into the anterior part of the perineum, and this operation should be preceded by a defunctioning colostomy to allow good healing. At a second stage a buried strip of skin from the perineal opening up along the ventral surface of the penis will produce a complete channel. Fortunately in many of these cases the scrotum is flat or bifid, so that there is no great excess of skin in this area.

4. Urethral Atresia in the Female

There are a number of rare anomalies involving the female urethra, some of which can be obstructive. Typical examples are depicted diagrammatically in Fig. 139. The simplest form of imperforate anus with recto-vestibular fistula is not associated with urethral obstruction and this is included to differentiate it from the cloacal anomaly found in Fig. 139 c. In this disorder there is only a single opening on the perineum which does not have the appearance of a urethra or a vagina; it is, in fact, a short and often obstructed cloacal channel into the upper end of which open the urethra, the vagina which is often bifid and distended, and the rectum, with or without a stenotic junction. Children with this anomaly are usually treated at birth for the imperforate anus by colostomy, but the obstruction of the cloacal channel results in severe hydrocolpos and sometimes in retention of urine. They must be treated by enlargement of the cloacal channel. Some of them are fortunate in having an adequately formed bladder neck and urethra so that they attain continence, in others the bladder base is absent or the bladder itself is incompletely formed so that no continence is possible and urinary diversion is required.

In the anomalies with a normal anus, Fig. 139 b shows the disorder known as female hypospadias in which the opening of the urethra is placed on the anterior vaginal wall. In this situation it is ordinarily stenosed and this may be a cause of obstructive signs in the upper tract. The position of the meatus may also lead to the accumulation of urine in the distended vagina producing a reservoir of local sepsis easily mistaken for a true urinary tract infection. In Fig. 139 d there is a urogenital sinus in which the bladder opens widely into a vagina, often bifid in its

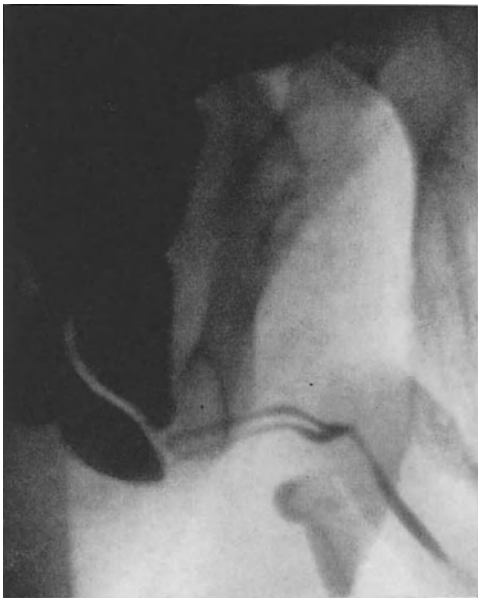
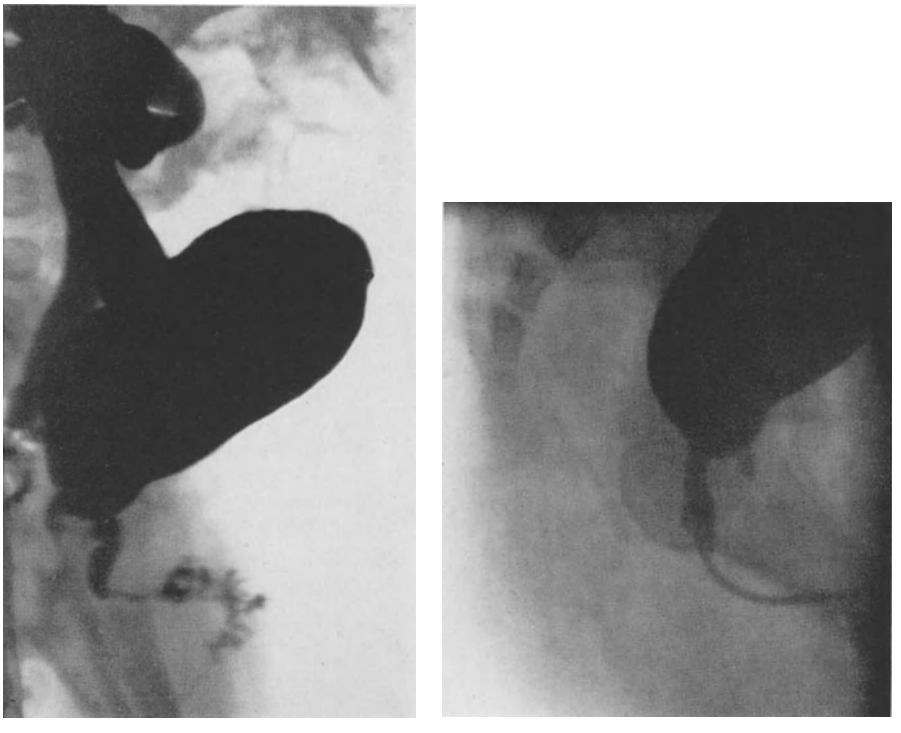


Fig. 137. Urethral obstruction with partial duplication of the urethra. Micturating cystogram in a boy with a solitary right kidney and deteriorating hydronephrosis. There is a valvular type of obstruction involving both posterior urethral channels, the point of union of the two urethrae is not obstructed

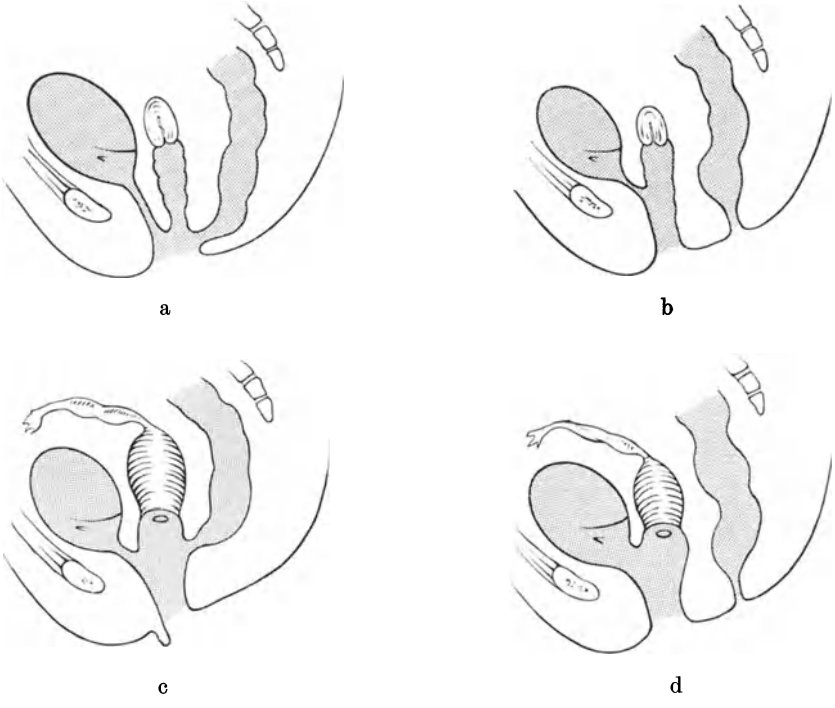


a b

Fig. 138a and b. Double urethra with atresia of a normal channel. a Micturating cystogram showing stenosis and extravasation from the penile urethra. The posterior urethral channel is poorly defined but opens at the anal verge. b Cystogram in the same child with catheter placed in the posterior channel. The anterior channel is only partially filled

upper part. These cases are hopelessly incontinent and not infrequently associated with upper urinary tract anomalies. A few may be reconstructed by building up the posterior wall of the bladder, but most will come to diversion.

Fig. 140 shows diagrammatically a rare type of female intersex in which a 46XX infant with normal ovaries, Fallopian tubes and uterus, has complete fusion of the labial folds, producing a small flabby penis-like structure and a tight obstruction to the urethral and vaginal outlets. There is usually a communication between the urethra and the vagina so that a trabeculated bladder with some upper tract dilatation is associated with a huge urinary hydrocolpos. The child presents soon after birth with a large swelling in the lower abdomen, which may be either bladder or vagina distended with urine. On palpation the "penis" is found to be a flabby organ consisting of folds of skin with no palpable corpora cavernosa (Fig. 140). The scrotum is absent and no testicles are felt. The urethra is too small to accept any catheter, but cysto-urethrograms may be obtained by suprapubic puncture and will reveal the diagnosis. The emergency treatment required is excision of the pseudo-penis with opening up of the urethra and vaginal orifices: this will allow immediate decompression, but it is likely that re-stenosis will occur and require a plastic enlargement of the introitus, turning in a flap of labial skin to secure permanent free drainage.



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c d

Fig. 139a–d. Diagrams to show urethral anomalies in the female. a Imperforate anus with recto-vestibular fistula. A normal urethra. b Female hypospadias. A short narrow urethra opens into the vagina well above the normal position. The rectum is normal. c Cloaca. The bladder, genital tract and rectum all empty into a single common channel which is stenosed and causes urinary and genital tract obstruction. d Urogenital sinus with normal rectum. The bladder neck area is completely deficient and there is no urinary control

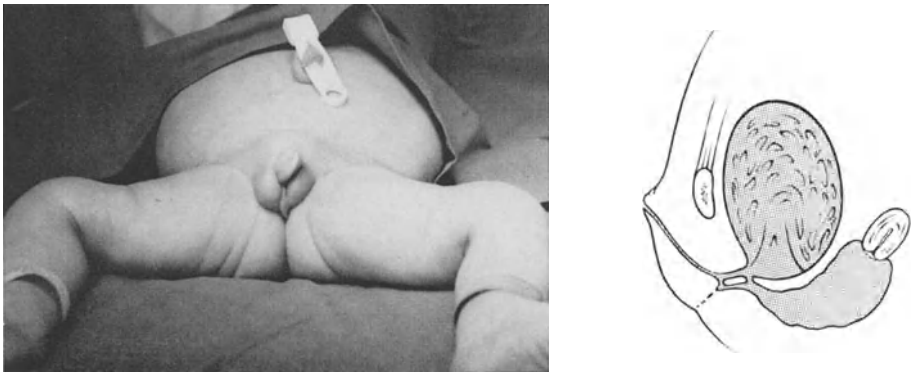

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Fig. 140a and b. Female intersex with pseudo-penis and vulval obstruction. a Clinical appearance of a neonate with enormously distended bladder and vagina. The pseudo-penis consists only of folds of skin and no corpora cavernosa are palpable. The apparent scrotal swellings are empty. b Diagrammatic anatomy showing trabeculated bladder, hydrocolpos and atretic urethral channel

Q. The Prune Belly Syndrome

D. Innes Williams

With 7 Figures

I. Introduction

Agenesis of the abdominal musculature, urinary tract abnormalities and undescended testicles form a well known clinical complex often known as the prune belly syndrome (Fig. 141) of which many features have become better defined in recent years. The disease is undoubtedly rare, and most reported series are small; the present author's total experience is of 34 cases. In its classical form the disorder is confined to the male, and although female examples of absent abdominal muscles have been reported they have not, in general, been associated with the classical anomaly of the urinary tract. A familial incidence is distinctly rare, but Harley et al. (1972) have reported two siblings with a mosaic chromosomal pattern. Burkholder and Williams (1967) found no chromosomal abnormalities in their cases.

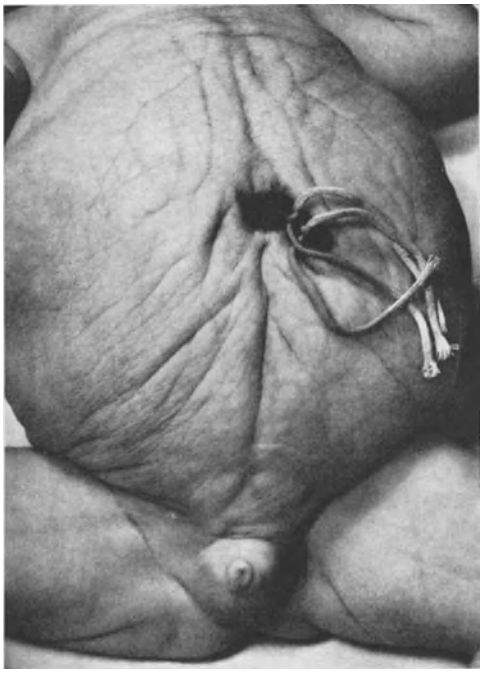
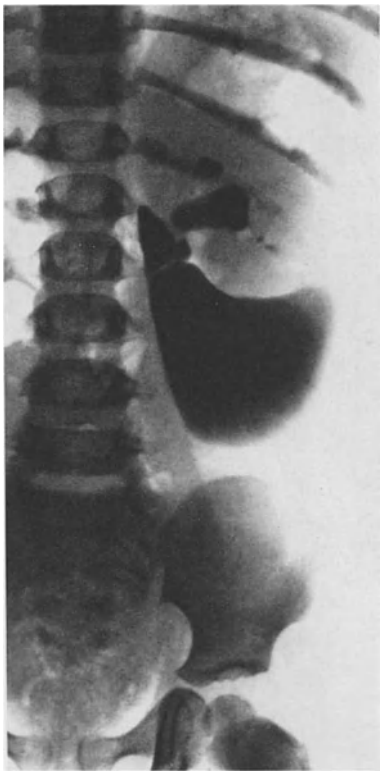


Fig. 141. Prune belly syndrome. The appearance of the abdominal wall in the newborn infant

II. Urinary Tract Pathology

The striking feature of the prune belly syndrome is that there appears to be an anomalous development of the entire genito-urinary system. It is impossible to localise a particular lesion which has caused the other changes, a fact which has considerable bearing on the possibilities of surgical treatment. The kidneys are frequently dysmorphic (Fig. 142) with clubbed, irregular and sometimes isolated calices. Histologically they may also be dysplastic: a few of them have the extreme form of dysplasia, the multicystic kidney without function, and others are minute, better described as aplastic. Hydronephrosis is common in all functioning kidneys, but is seldom so considerable as might be expected from the dimensions of the ureter. The ureters have a characteristic appearance of dilatation, elongation and tortuosity in the presence of a relatively well preserved kidney which may immediately suggest the diagnosis. Irregular and saccular dilatations also occur. Dilatation of the ureters is present in the newborn child in many examples



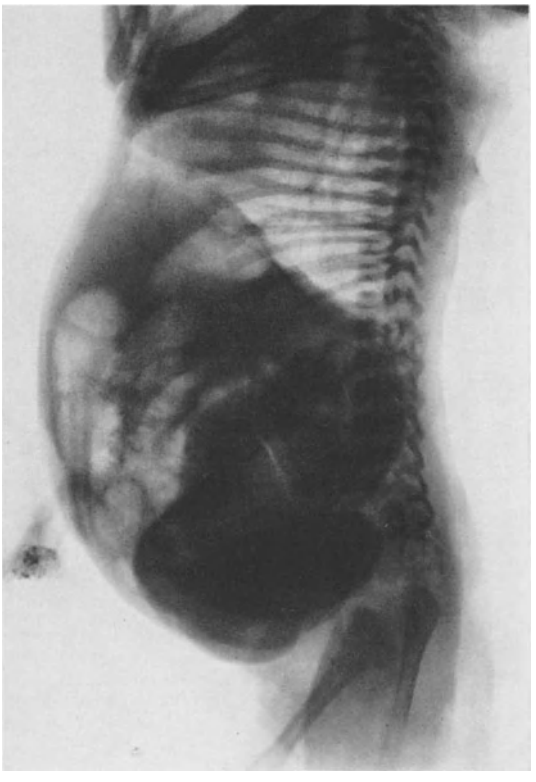


Fig. 142

Fig. 143

Fig. 142. Prune belly syndrome. Boy with mild symptoms of urinary infection only. Intravenous urogram shows a solitary left kidney with good thickness of parenchyma but irregular "dysmorphic" calices and incongruous dilatation of the ureter

Fig. 143. Prune belly syndrome. Neonate with complete urethral obstruction. Antegrade pyelogram demonstrating grossly dilated ureters

(Fig. 143) and may at times be progressive. Histological examination has revealed chronic inflammatory changes, and according to NUNN and STEPHENS (1961) some defect of muscle development. In general the propulsive power of the ureters as seen in cine radiology is poor, but not always absent and may be perhaps to some extent recoverable after a period of drainage and elimination of infection.

The bladder is usually large, smooth and non-trabeculated. Its capacity is enormous, but is associated in the early stages with complete emptying on micturition, though this ability may be lost later in childhood. Apical diverticulum and attachment of the bladder to the umbilicus are frequently seen. Reflux occurs in about two thirds of cases: it may be massive, flooding the whole upper tract, or slight with a little opaque medium flowing back into a ureter already distended by non-opacified urine. In micturating cystograms the bladder neck is shown to be open and there is a tapering dilatation of the urethra, narrowing to a point just below the verumontanum (Fig. 144). Obstructive valves are not seen in the classical case. A tubular diverticulum of the posterior urethra is common, presumably due to enlargement of the utricle. In one special group of children, the stillborn cases, complete atresia of the membranous urethra occurs. In the anterior urethra an enlarged penis with absence of the corpus spongiosum and megalo-urethra (Fig. 145) occurs in a proportion. Radiological findings are reviewed by CREMIN (1971) and by GROSSMAN et al. (1970).

Fig. 144. Prune belly syndrome. An infant with enormous abdominal distension and severe urinary infection. Cystogram showing huge bladder with apical fixation to the umbilicus bulging through the lower abdominal wall. The posterior urethra is dilated but tapers down to a point near the membranous urethra; there is reflux into grossly dilated ureters. No urethral obstruction was found

III. The Abdominal Muscles and Other Anomalies

The key feature of the condition is complete absence of muscle from the lower mid-line part of the abdominal wall. The extent of the defect is variable and may be more on one side than the other, but the upper rectus muscles and the most lateral part of the oblique muscles are present in almost all cases. The absence of

muscle produces the characteristic wizened prune appearance in newborn infants, but as the subcutaneous fat increases the wrinkles are flattened out and the weight of the abdominal contents produces a pot belly rather than a prune belly. The flaccid atrophic muscles seen in chronic abdominal distension associated with other forms of urinary obstruction may be deceiving at superficial examination, but with care the distinction between them and the true prune belly is evident. Paralysed muscles, exomphalos and the huge ventral hernia seen in the split symphysis variants (p. 277) have nothing in common with true agenesis.

Bilateral cryptorchidism is a consistent feature of this syndrome in its fully fledged form, both testes being high on the posterior abdominal wall.

In the gastro-intestinal tract a universal mesentery with mal-rotation is a common finding and of importance to the surgeon contemplating ileal loop diversion of urine. Imperforate anus may be found with complete membranous urethral obstruction. Oligohydramnios consequent upon this obstruction can produce pressure on the limbs causing talipes, congenital dislocation of the hip and other deformities, even at times the Potter facies.

IV. Clinical Presentation

In ideal circumstances the absence of abdominal muscles would always be recognised by the paediatrician at the postnatal examination and a full assessment of the urinary tract undertaken as a routine. However, not all children with this abnormality present urgent symptoms or are in any need of urgent treatment and many of them are not recognised until some months or years have elapsed. Three types of presentation may be recognised.

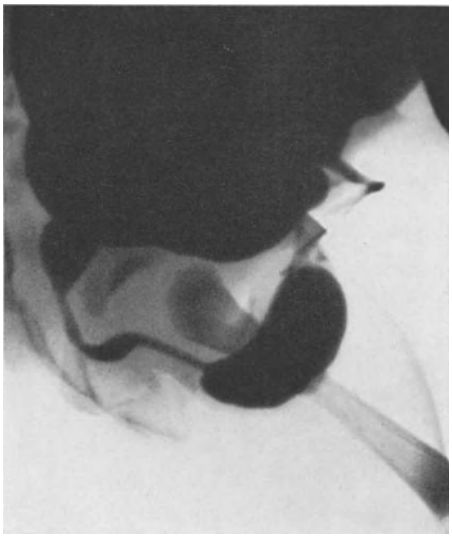


Fig. 145. Prune belly syndrome. Infant with megalopenis. Cysto-urethrogram shows tapering dilatation of the posterior urethra and enormous saccular dilatation of the anterior urethra: megalo-urethra. There is no meatal stenosis, the terminal urethra being of normal calibre

1. Complete Urethral Obstruction: Neonatal Presentation

Where the urethra is completely obstructed at the membranous level and no urine can be passed at all the infant will exhibit the pressure deformities consequent upon oligohydramnios, and may die from pulmonary hypoplasia. The bladder and urethra are often palpable and enormously dilated, but the kidneys are small and cystic. These children have no chance of survival, though they may be kept alive for some days and their kidneys will, if drained, produce a little dilute urine. Other system abnormalities, such as rectal atresia, are common, and it is clear that treatment should not be attempted in this group.

2. Infant Emergencies

Where the urethra is not completely obstructed and urine is passed from the bladder the child is unlikely to have pressure deformities or pulmonary hypoplasia, but in many cases the urinary tract changes are still very severe and produce an emergency situation within the first few weeks of life. The infants are apparently able to void urine from the bladder, and often do so with apparent ease, but they have a rapidly rising blood urea with a failure to thrive and enormous abdominal distension, or an even more acute presentation with urinary infection and septicaemia. An enormous bladder with free reflux into hugely dilated ureters is the rule

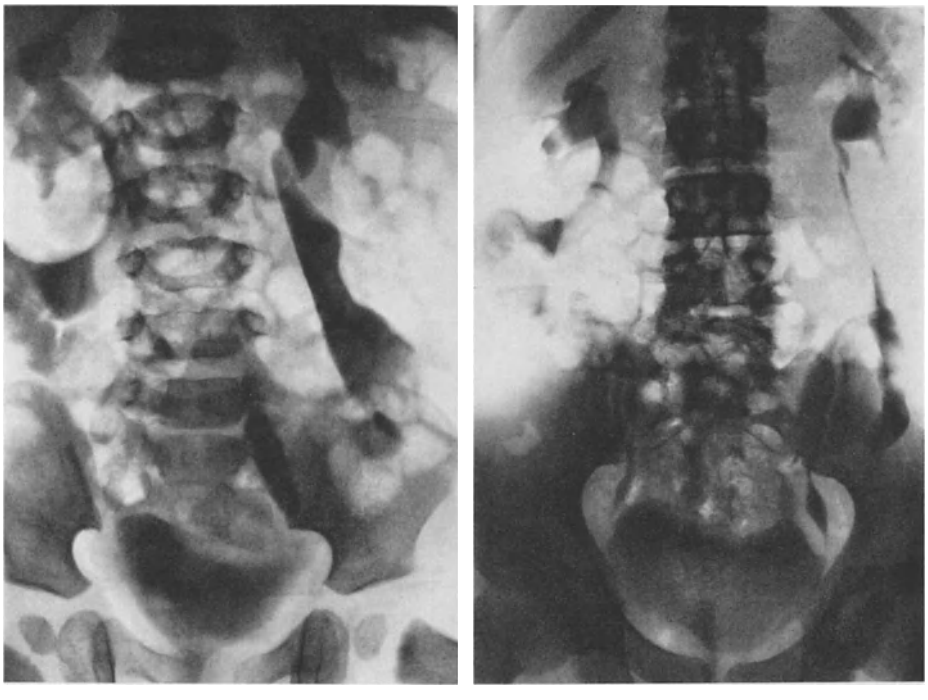


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Fig. 146a and b. Prune belly syndrome. Boy with no significant urinary symptoms. a Intravenous urogram at 1 year of age. b Intravenous urogram at 17 years of age

in these cases. Renal dysplasia is to be expected and in many one kidney will be functionless.

The diagnosis in these cases is never in doubt, and the emergency treatment required is the correction of the biochemical abnormalities and, if necessary, the administration of antibiotics as in the uraemic infants with urethral valves. Only a few of the prune belly infants have acute retention, however, and if the urine is sterile on admission there should be no haste to pass any sort of urethral instrument, since the chief danger to life will be infection. Many of these infants will require cutaneous ureterostomy diversion as a life saving procedure as soon as the biochemical imbalance is corrected and the antibiotic has had time to take effect. A high loop ureterostomy or a cutaneous pyelostomy should be performed, since the very tortuous ureters drain badly even when brought directly to the surface. Recovery of function is unlikely in these ureters and therefore it is almost certain that a permanent diversion will be required later in life. If both kidneys are functioning this may be best by means of an ileal loop diversion with the loop draining directly from the renal pelves.

A few infants run into an emergency situation on account of pulmonary complications. The absence of abdominal muscles makes coughing difficult and if chest infection is present it is not easily eliminated.

3. Late Presentations

Many children with the prune belly syndrome maintain surprisingly good renal function over many years in spite of the bizarre radiological appearance of their urinary tract. It will often be noted, however, that the renal parenchyma is thick and well preserved in spite of the enormous dilatation of the ureters. Three of the cases in the author's series now aged 17, 16 and 12, have maintained apparently good health with no progression of urinary tract disorder (Fig. 146), and two of them have had episodes of urinary infection but have thrown it off readily without apparent damage. The possibility of infection following instrumentation should, however, contra-indicate the routine use of cystography in the prune belly cases.

Other children, although they maintain a stable situation for some years, later develop severe complications from infection or an insidious deterioration in renal function associated with increasing dilatation. This latter group require more careful investigation to determine the possible role of surgery in the prevention or reversal of these changes. Most urologists, e.g. McGovern and Marshall (1959), Lattimer (1958), Wiltschke (1969), have assumed that bladder outflow obstruction is the usual cause of this deterioration and have undertaken surgical procedures to overcome such obstruction, often trans-urethral resection of the bladder neck. In the author's experience, however, the bladder neck in these cases is very seldom narrowed and an obstruction, if present at all, is in the lower part of the posterior urethra where there may be evidence of constriction by a musculofibrous ring. Resection of tissue at this level or urethrotomy with the Otis urethrotome can improve bladder emptying, but sometimes at the expense of stress incontinence of urine. The risk of incontinence may be justified by the degree of upper tract dilatation, but bladder emptying may also be improved by plication procedures to reduce the enormous capacity of the bladder. Three cases have been successfully treated by the author in this way.

The dilated and often refluxing ureter may also be incriminated as the cause of persistent infection and progressive pyelonephritis. Extensive re-modelling and

re-implantation of the ureter might appear to be the answer and have been successfully accomplished by HENDREN (1972). Nevertheless, in the aperistaltic ureter common in this condition the operation is hazardous and a fatal result has at times complicated this type of reconstructive surgery. If it is to be attempted at all it should be done in stages with temporary diversion by nephrostomy or pyelostomy to prevent further damage to the kidney during the postoperative phase. It is clear from the conservatively managed group that reflux is present in a number without entailing any rapidly progressive disease; reflux alone is not an indication for surgery. Pyeloplasty or upper end re-modelling of the ureter is required in a few and in some chronically infected cases renal calculi occur and require removal. For the unilateral non-functioning kidney nephro-ureterectomy is, of course, a valuable operation. In the late presentation, as in the infant emergency, permanent skin diversion of urine is the only hope for some children and usually takes the form of a high ileal loop. The absence of abdominal muscles and laxity of the skin causes surprisingly little difficulty in the fitting of stick-on ileostomy bags and diversion should not be ruled out for this reason.

Surgery for the abdominal wall is only seldom required, since with the passage of years the wrinkled appearance disappears and the laxity of the abdomen is readily controlled by belts. In a few infants, however, the abdominal wall is not only lax but redundant, and partial excision with plication may be performed with advantage. In spite of the apparently poor material for suture, the abdominal

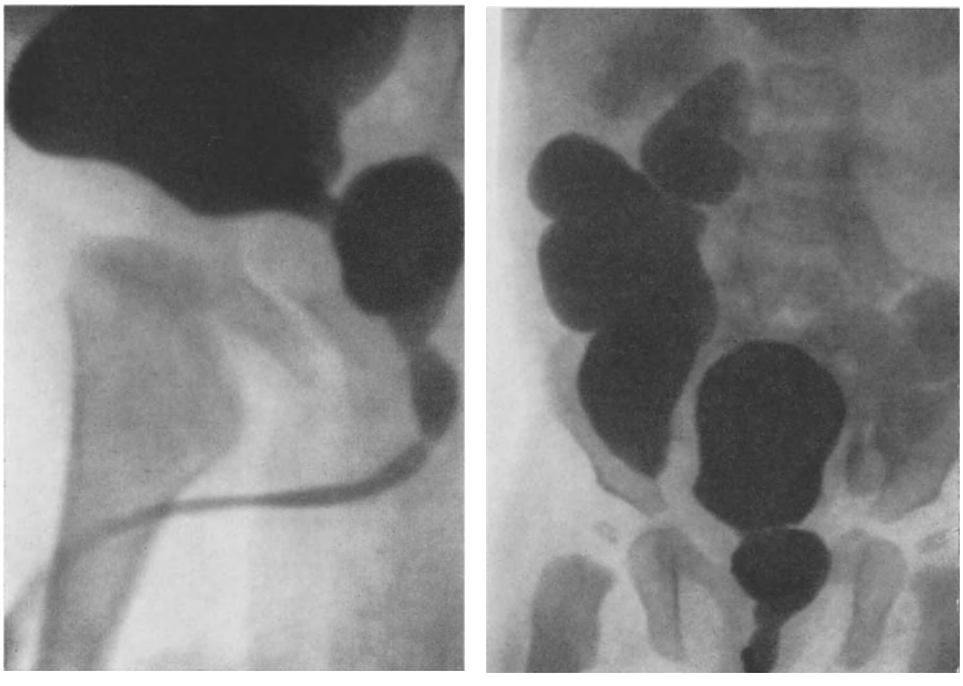

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Fig. 147a and b. Incomplete prune belly syndrome. Boy with normal abdominal muscles but dysplastic kidneys and multiple urinary tract anomalies. Micturating cystogram shows reflux into the right kidney and a dilatation of the posterior urethra, without identifiable obstruction

wounds heal without difficulty or delay. Reconstruction of the abdominal wall has also been advocated to improve respiratory function and to facilitate urination and defaecation, though this effect remains in doubt.

Orchidopexy is an operation of extreme difficulty in these cases: it has been accomplished as a two-stage procedure on occasions and Johnston notes that in some of his cases the artery to the vas was adequate so that section of the testicular vessels allowed free mobilisation of the testicles and then satisfactory emplacement in the scrotum. Alternatively it may be considered wise to leave the testicles in situ on the posterior abdominal wall and to insert prostheses into the scrotum.

V. Incomplete Syndromes

It has already been noted that in some cases the abdominal muscles are absent on only one side. There are, however, also some infants with lax abdominal walls, often with some wrinkling of the skin, yet without any definite areas of absent musculature, in whom the urinary tract anomaly follows the pattern already described. There are others again in which the abdominal wall is normal but the bladder dysfunctional. Undescended testicles are common in this group. It therefore appears likely that there are examples of incomplete syndromes in which the visceral manifestations of the disease are present, but the parietal absent. A group of such cases has been described by Williams and Taylor (1969), and also by King (1969). The characteristic features have been a large bladder, an open bladder neck, tapering dilatation of the posterior urethra without a clear point of obstruction, and an irregularly dilated upper urinary tract often with renal dysplasia (Fig. 147). These children have to be distinguished from those with simple mega-ureter-megacystis syndrome and those with neuropathic bladders or congenital obstructions. In them it will be impossible to find one primary lesion, and an appreciation of the extent of the disorder will demand caution on the part of the urologist attempting corrective surgery.

R. Urinary Incontinence

D. Innes Williams

With 4 Figures

I. Introduction

Urinary incontinence is one of the commonest complaints for which children are brought to the urologist, and during the past years methods of investigation have developed in many ways. Clearly, however, the great majority of incontinent children will be "simple enuretics" and it is a matter of concern that unnecessary investigations should be avoided in these, while at the same time ensuring that those with serious and remediable disease should not be overlooked. The literature of enuresis contains records of a great many investigations, some wide ranging studies aimed at discovering the cause of enuresis as a whole; others more restricted, aimed at separating off from the morass of enuresis specific causes of urinary incontinence. The general studies have covered most aspects of the child's physiological and psychological existence and have often reported positive results without contributing very much to our understanding of the condition or its treatment, as, for instance, the report by Campbell and Young (1966) who found electro-encephalographic disturbance in 42 per cent of enuretic children during sleep. The specifically urological investigations have been endoscopic, radiological and urodynamic: enuresis has been ascribed to inflammatory changes in the urethral mucosa, to ill-defined obstructions and folds in the urethra seen on micturating cystograms and to a variety of abnormalities in the response of the bladder muscle to distension. The endoscopic and radiological investigations have undoubtedly revealed causes of incontinence other than simple enuresis, but have failed to solve the problem of the chronic but uncomplicated bedwetter. The urodynamic investigations may still hold some promise, but their usefulness is limited by the difficulty of applying them to the young child. The simple filling cystometrogram has been used for the investigation of enuresis for many years, though in children under the age of 5 it is difficult to obtain sufficient co-operation. In an enuretic suffering from diurnal frequency and urgency the cystometrogram will show frequent uninhibited contractions and a small functional capacity, but unfortunately this does not tell us whether we are dealing with an emotionally disturbed child, a neurogenic disorder or an obstructive uropathy. Simple flow studies will confirm the presence of a urinary obstruction where this is already evident from radiological examination, but the normal range of variation is so great, particularly with small bladder volumes, that borderline cases are hard to categorise. Concomitant estimations of voiding pressure and of urine flow with radiological studies, such as have been reported in the investigation of adult incontinence by Turner-Warwick et al. (1973), are very hard to apply to the children and Gierup and Ericsson (1971) have concluded that as much useful information can be obtained from simple micturition flow studies. The urethral pressure profile, as described by Brown and Wickham (1969), or the urethral resistance studies undertaken by Tanagho et al. (1969), can tell us something

about the activity of the sphincter muscles in organic incontinence, but have not proved helpful in the elucidation of the enuretic problem.

Often the most important investigation is the careful history. Parents are frequently bad historians and it requires persistence to find out the true facts of the child's incontinence. It must, however, be established whether the wetting is a continuous dribble, whether it is with urgency or stress, whether micturition is normal, frequent or difficult, whether the bowel habit is in any way unusual and whether there is any disturbance of general health. A family history is of vital importance in giving a lead in the diagnosis of enuresis. Physical examination is often unproductive, but a careful inspection of the genitalia to detect any anomaly of the urethral meatus is important. A neurological examination and careful palpation of the spine should be routine. The urine must be microscoped and cultured. Often at the end of such simple investigation the clinician will have a clear idea as to whether the child fits into the category of simple enuresis or whether further investigation is justifiable. In the latter case pyelography and cystography will be routine, and in a few cases urodynamic investigations are helpful. It should then be possible to place the child in some diagnostic and prognostic category, perhaps with a urinary obstruction or sphincter weakness problem, perhaps with a neuropathic bladder or local neuromuscular imbalance, perhaps with a clear anatomical abnormality, but in many cases will be within the diagnostically unsatisfactory category of simple enuresis. This chapter aims at brief comment upon the causes of urinary incontinence in children as they are seen by the urologist rather than by the paediatrician or psychiatrist.

II. Enuresis

Enuresis is a generally accepted but ill-defined concept, most often regarded as a failure of maturation of the neuromuscular function which controls the bladder unaccompanied by any detectable physical abnormality. The disorder is extraordinarily common, thus MILLER et al. (1960), report that 8.9 per cent of children at the age of 5 years were wet at night on at least some occasions. A very large number of general reviews of this topic have been published and a detailed discussion would be out of place in this volume; it should be emphasised, however, that while nocturnal enuresis without significant day symptoms is the commonly recognised form of the disorder and the one in which organic changes in the urinary tract are least likely to be found many children have accompanying frequency and urgency by day, or in the younger age groups, urgency and incontinence by day, yet share the absence of physical abnormality and the good prognosis recognised for simple enuresis. A family history is very common in enuresis, though few author's have recorded as high an incidence as BREGER (1963), who found one parent involved in 47 per cent of cases. Although psychological disturbance may undoubtedly lead to incontinence, statistically the disturbed child does not figure largely in the total problem of enuresis. WERRY and COHRSSEN (1965) found little benefit from psychiatric treatment as opposed to no treatment at all, and MOWRER (1938) found training methods more effective than psychotherapy. The trend towards spontaneous recovery is well known. BARBOUR et al. (1963) found in a follow-up study that after 5 years 75 per cent of children were cured, but this cure rate did not appear to be related to any particular form of treatment.

The general management of enuretics, their treatment by daytime training, by alarm systems at night and by general disciplinary measures, have been ex-

haustively discussed in the literature. On the drug side it must be remarked that imipramine (Tofranil) has been shown to have a remarkably beneficial effect in controlled trials (Poussaint and Ditman, 1965; Diokno et al., 1971; Woodhead et al., 1967; Steinicke, 1971.)

III. Small Capacity Bladder

Many enuretics, in addition to nocturnal incontinence, suffer day frequency and urgency and such children have cystometrograms with frequent uninhibited contractions at low volumes and a small functional capacity. Most of the adolescents and young adults with persistent symptoms fall into this group. Esperanca and Gerrard (1969) have emphasised the importance of the small bladder in the enuretic situation, but suggest no cause for this complaint. Treatment of this group by anticholinergic or ganglion blocking drugs is sometimes helpful and it is the author's practice to use Cetiprin in doses of 100–200 mg three times a day. The majority have a prospect of obtaining a larger functional capacity by medication and training (Troup and Hodgson, 1971), but for extreme cases with persistence of severe symptoms into adult life Hickinbottom (1971) has advised colocystoplasty, and though this seems an extreme measure, it can be justified in rare instances.

IV. The Lazy Bladder Syndrome

By contrast with the last group, incontinence is occasionally found in association with large capacity bladders with infrequent voiding despite the absence of any demonstrable outflow obstruction (de Luca et al., 1962). Most authors suspect that a psychological cause may be at work in such cases. Children may, however, be trained to empty their bladders completely at regular intervals, sometimes with the help of drugs such as Carbachol, and will then usually recover continence.

V. Giggle Incontinence

Incontinence during giggling appears to be a disorder of cerebral control of micturition, though there may be at times some local bladder abnormality. Characteristically only girls are involved and the complaint is troublesome only during later childhood and adolescence. Micturition is normal and the child is dry at night, but when overcome by a fit of the giggles a complete act of micturition occurs. In a few cases there is some relationship to a stress type of incontinence in which only part of the bladder content is lost during straining: there does not appear to be any medical or surgical measure which effectively controls giggle incontinence, but the prognosis is ultimately good, due in general to a change in attitude towards humorous situations which no longer seem quite so convulsing.

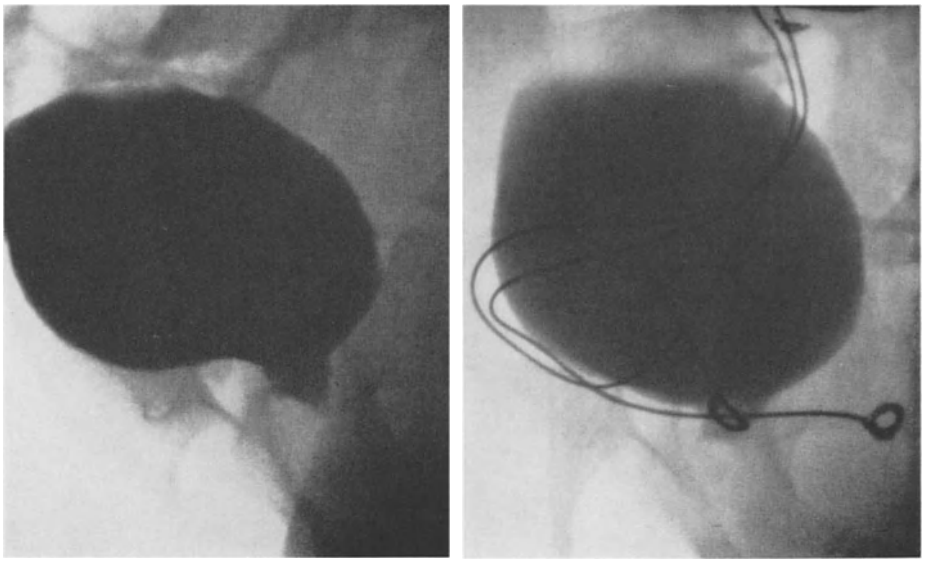
VI. Wide Bladder Neck Anomaly

The concept of incontinence due to a congenitally wide bladder neck is one which has been proposed and denied many times over the years. Bruns (1970) and

LINDNER (1969) have been particularly critical of this diagnosis, but STANTON and WILLIAMS (1973) have produced some evidence to suggest that it should be considered as a specific disorder The complaint is of diurnal continence primarily, sometimes accompanied by night wetting: in girls a stress type of incontinence is characteristic though this is rather rare in other disorders. It is recognised radiologically by a widening of the bladder neck which is open at rest so that when the child is in the standing position the posterior urethra is full (Fig. 148). At the end of micturition there is an incomplete milk-back of the opaque medium into the bladder. Cystoscopically the bladder neck is open and on pressure profile investigations a low peak is found (Fig. 149). The cystometrogram is normal, there are no neurological signs and no distal urethral stenosis. Judged on these strict criteria the wide bladder neck anomaly is distinctly rare and should not be confused with the common "spinning-top" appearance of the female urethra. It has been a feature of girls more often than boys, though in the latter a widening of the anterior as well as the posterior urethra has been present (Fig. 150). Some of these cases have responded to conservative treatment and growth, and it is clear there is some tendency to improvement towards puberty. Others have been successfully treated by surgical procedures to support the bladder neck and urethra.

VII. Behaviour Disorders and Incontinence

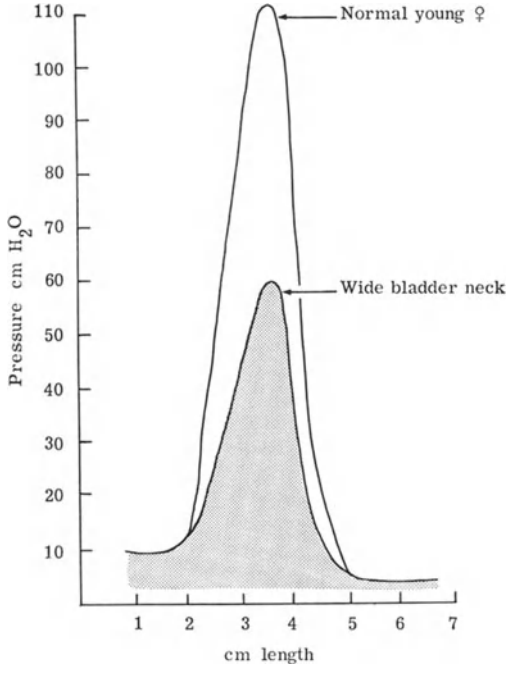
Psychological factors are clearly of some importance in many enuretics, but as already remarked it cannot be statistically demonstrated that psychotherapy is more effective than simple training. In some children, however, incontinence



a b

Fig. 148a and b. Wide bladder neck anomaly. Girl with diurnal stress incontinence. a Cystogram in erect position with bladder at rest; the posterior urethra is filled. b Cystogram in the same girl after insertion of electronic pelvic floor stimulator to show position of electrodes

accompanies a definite behaviour disorder for which psychiatric advice is most necessary. The urologist should be on the look out for evidence of general emotional disturbance when taking the history of an incontinent child, and clearly a late onset of enuresis associated with some disturbing event will be suggestive, as are other behaviour disorders, such as stealing, temper tantrums or running away from school. Encopresis very commonly accompanies enuresis in a child with psychological problems and, in the absence of clear-cut neurological signs, faecal



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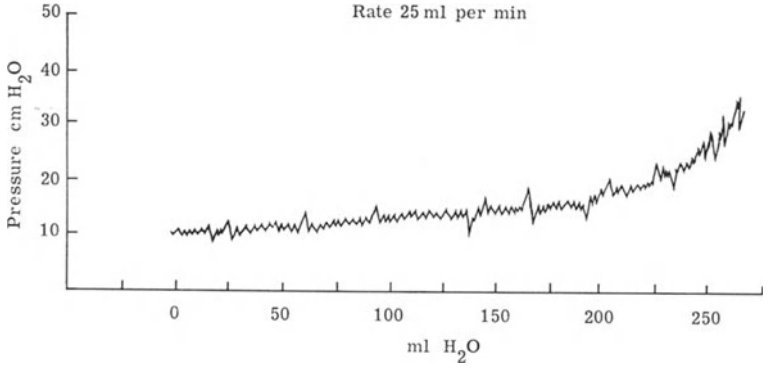


b

Fig. 149a and b. Wide bladder neck anomaly. a Urethral pressure profile. b Cystometrogram (normal)

soiling in an enuretic should indicate the need for psychiatric treatment. The incontinence itself may be of various types, most often daytime frequency and urgency accompanying nocturnal enuresis. As would be expected the findings on urological investigation are ordinarily negative. Nevertheless a spastic type of bladder with a small capacity and some evidence of trabeculation may well be found; HINMAN and BAUMANN (1972) believe that a ureteric dilatation may also result from this voiding dysfunction.

VIII. Infection and Incontinence

Urinary infection is a common cause of incontinence, and when its signs are predominantly those of fever, pain and dysuria wetting is easily recognised as a part of the inflammatory process. However, it is not infrequent for girls to be brought up for investigation of an onset type of incontinence, usually with day frequency as well as nocturnal wetting without any constitutional signs of infection. The first investigations will, of course, demonstrate that the urine contains pus and is infected on culture and the routine investigations of such problems will then proceed, revealing, perhaps other abnormalities such as obstruction or reflux. Many of these girls cease to wet as soon as the urine is rendered sterile, but it is not uncommon for the bladder to remain in an irritable state for some months after prolonged infection and in these cases the incontinence is slow to clear.

IX. Obstruction and Incontinence

Severe cases of urinary obstruction are associated with a dribbling overflow type of incontinence; the less severe have nocturnal incontinence only but also slow micturition with a poor stream during the day. The nature of this disorder

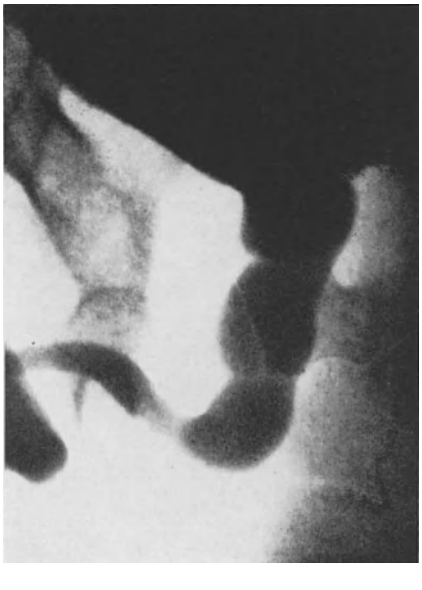


Fig. 150. Wide bladder neck and urethra in a boy with diurnal incontinence

will be evident from the history and physical examination and later investigations will determine the site of obstruction. The difficulty arises with the least severe cases where the symptoms are chiefly of frequency and urgency by day with wetting by night, where the upper urinary tract is normal and residual urine absent or small. It is well recognised in adult disease that early obstruction with hypertrophy of the bladder may cause frequency and urgency before any significant volume of residual urine is present, and BATES et al. (1971) have demonstrated on pressure flow studies that high pressure bladder contractions with relatively slow voiding are characteristic of this condition. Such studies in children have not given clear-cut results: many such investigations have been aimed at defining the presence of bladder neck obstruction or distal urethral obstruction in girls and are referred to in the appropriate sections of this volume. GIERUP and ERICSSON (1971) found that the well recognised causes of obstruction, such as urethral valves, gave clear-cut changes in pressure flow measurements but that in borderline cases results were rather equivocal. It may be that in future better methods of estimating pressure and flow in children will be established, but the need to obtain co-operation from a small and frightened child will remain a problem.

In suspect cases it is clearly necessary to search clinically, radiologically and endoscopically for a possible site of obstruction, and occasionally in boys the presence of urethral meatal stenosis provides a simple answer to the diagnostic question. Radiologically the classical urethral valve cases and other obstructive lesions, such as polyps, anterior urethral diverticula and stricture, are readily diagnosed, but other urethrographic findings are less definite and demand cine studies to help in the identification of an obstructive lesion. In enuretics, as in normal boys, it is not uncommon to see a transverse linear filling defect in the posterior urethra a little below the verumontanum with no change in urethral calibre above and below this line. This finding is not diagnostic of obstructive valves and endoscopic treatment of the folds, although it may like other forms of instrumentation cause some temporary improvement in the simple enuretic, does not lead to permanent cure. In girls the observation of a relatively narrow area at the membranous urethra is common, but as discussed in Chapter I it is difficult to find any satisfactory correlation between radiological findings and calibration by instruments. In the author's experience urethral dilatation in girls has been disappointing as a cure for incontinence.

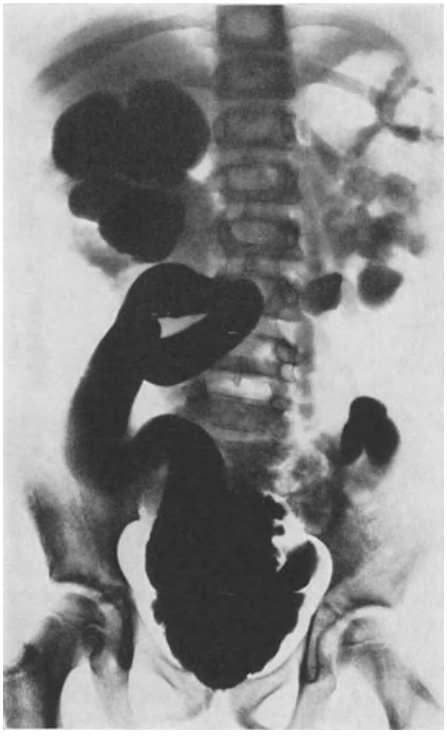
Bladder neck obstruction was at one time diagnosed as a cause of enuresis in many boys with slightly trabeculated bladders and a frequency and urgency type of incontinence (GRIEVE, 1967; MITCHELL, 1963), and since this diagnosis can be substantiated in some young adults it is not at all unlikely that early cases may present in childhood. Nevertheless the results of bladder neck resection for enuresis have been disappointing, as shown in the extensive series published from Bristol (BARBOUR et al., 1963) where the cure rate in children diagnosed as having obstruction and treated by resection was no better than the general cure rate for all forms of enuresis treated by simple management and medication.

X. Neuropathy and Incontinence

Incontinence is an expected feature of the neuropathies associated with myelomeningocele, and these are discussed in Chapter S. There are, however, many children who present because of incontinence who may be suspected of having a neurological problem without spina bifida cystica. DORFMAN et al.

(1969) refer to a group of subclinical neurogenic bladders; MARTIN et al. (1971) refer to occult neurological bladder". KAMHI et al. (1971) to "isolated neurogenic dysfunction". Since the identification of a neurogenic origin to incontinence is of great importance in treatment and prognosis every effort should be made to define this group.

Investigations must be concentrated on the bladder itself, the neurological signs, the vertebral column and the spinal cord. Neuropathic bladder is most often suggested by the complaint of severe daytime frequency and urge incontinence together with a trabeculated, and possibly sacculated bladder with a small residual urine. There are a few instances in which a large residue builds up with upper tract dilatation and the sudden change from the mild to the serious condition is very suggestive of a neurological lesion. Only a few cases have the typical expressible bladder seen in myelomeningocele but many have dribbling incontinence between urgent acts of micturition. Radiologically the bladder is hypertrophied and irregular (Fig. 151), the bladder neck open at rest, the urethra narrowing down in the region of the external sphincter with, in the male, some filling of the prostatic ducts. On cine studies the act of micturition is often hard to initiate and is incomplete. Cystometrograms often show frequent uninhibited contractions, but in some cases a large insensitive bladder is found. The urecholine sensitivity test devised by LAPIDES et al. (1962) is a refinement of the cystometrogram which can give additional evidence. It depends upon an exaggerated sensitivity of the denervated bladder to urecholine, as shown by a pressure rise following subcut-



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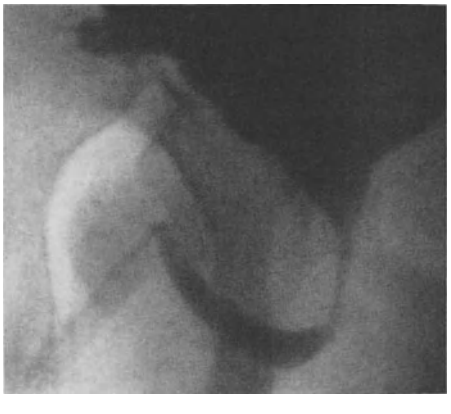

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Fig. 151 a and b. Occult neuropathic bladder. A boy with lifelong incontinence of urine and faeces, recent deterioration, no clinical neurological signs, a positive urecholine sensitivity test. a Filling cystogram showing massively sacculated bladder and free bilateral reflux into grossly dilated ureters. b Micturating cystogram showing wide open bladder neck

aneous injection of the drug (Bethanecol). This has been reported as the diagnostic feature of the isolated neurogenic dysfunction by MELZER (1972).

The neurological examination should test carefully the perineal sensation, the tone of the anal sphincter, the presence or absence of a bulbo-cavernosus reflex, the knee and ankle jerks and plantar responses. DORFMAN (1969) has emphasised the value of anal sphincter electromyography, and it is clear that if a neurological lesion of the pelvic floor musculature can be established then incontinence is likely to be of similar origin. In the author's experience the EMG tests give little more information than simpler clinical examination. Sacral nerve stimulation by direct introduction of stimulating electrodes into the sacral roots after spinal anaesthetic has been reported as a diagnostic test by MARKLAND et al. (1971) though this has not been employed in children.

Examination of the back for hairy patches, lipomata and coccygeal sinuses should be routine, and the sacrum should be carefully palpated with a finger in the rectum since it is extraordinarily easy to overlook a sacral anomaly on superficial examination. X-Rays of the spine may show a spina bifida occulta, although the mere absence of fusion of the laminae in the lower lumbar and upper sacral region is common and this alone should not be taken as evidence of a neurological disorder. More important is a localised widening of the spinal canal as measured by the distance between the pedicles: there may also be a bony spicule associated with diastematomyelia, or major deformities of the vertebral bodies. If there is a suggestion of a neurological disorder or any abnormal signs in simple X-rays of the spine air myelography should be undertaken to demonstrate the level of the conus and its mobility as well as to identify other lesions in the theca, such as dermoid cysts or lipomata. These investigations will establish in some children the presence of spinal dysraphism as a cause for neuropathic bladder and incontinence, and in those the first consideration must go to possible treatment of the spinal cord lesion. A neurosurgical opinion must be sought as to the possible value of laminectomy with freeing of the tethering bands fixing the conus, or the removal of cysts or lipomata. It must be remarked, however, that judged by the cure of incontinence alone these laminectomy procedures are disappointing, although they may be essential to prevent progressive damage to the innervation of the lower limbs. In some spinal anomalies, such as sacral agenesis, a neuropathic bladder is present without any local tethering of the cord and in these a laminectomy is not advised.

There will remain a group in which the behaviour of the bladder strongly suggests a neuropathy, yet in which no other evidence of a neurological lesion can be found, and in these the treatment must be confined to the bladder condition alone. Such treatment may follow the lines suggested for myelomeningocele, but this occult neurological group contains a high proportion of cases in which conservative treatment is more appropriate. At times the spastic bladder can be controlled by large doses of probanthine or Cetiprin; in other examples bladder emptying may be facilitated by the use of carbachol or by surgical section of the external sphincter using the Otis urethrotome. Most of these cases, where infection can be controlled and the upper tract is normal, should be treated conservatively rather than by early diversion of urine, and a number will improve in later childhood and adolescence. In others infection and increasing dilatation will demand diversion.

XI. Post-Traumatic and Iatrogenic Incontinence

Post-traumatic incontinence is most often seen in children who have had a rupture of the posterior urethra, following fracture of the pelvis. Subsequent elimination of the stricture by urethroplasty may well be successful, but leaves them with some diurnal and nocturnal incontinence. Before urethroplasty most of these children have had a widely relaxed bladder neck, forced open by the bladder pressure above stricture, and after the operation the bladder neck may take months or years to regain its control: some must wait until puberty. In a proportion the whole posterior urethra remains rigid and the sphincter area has been destroyed to such an extent that incontinence is permanent.

Iatrogenic injury results from surgical revision of the bladder neck or resection of urethral valves. Massive bladder neck revisions were a feature of the era in which the diagnosis of bladder neck obstruction was commonly made and a number of these children, more particularly the boys, remained incontinent afterwards. Where the revision had been by means of anterior Y–V plasty correction is relatively simple: the Young-Dees operation is ordinarily successful. Where a large wedge of tissue has been removed from the posterior vesical lip repair is less satisfactory though it may proceed on the same principle. In the urethral valve group incontinence may be expected to improve at puberty, but although the symptom is frequently one of stress incontinence by day there is often a surprisingly satisfactory response to the use of imipramine. Injury to the pelvic nerves at the time of operation for imperforate anus with recto-urethral fistula is another cause of incontinence, but the external sphincter is usually still capable of contraction and there may be slow improvement with years of training. In general a conservative management is desirable for such cases.

XII. Epispadias and Incontinence

Provided a simple inspection of the external genitalia is made the diagnosis of epispadias will not be overlooked as a cause of urinary incontinence, but it may be noted here that between a quarter and a third of male epispadiacs achieve continence spontaneously and that it is rash to embark on very early surgery to the bladder neck region before the degree of the disability is evident. The incontinence is often total, but may be of the simple stress type. Most girls are incontinent, but again some are able to remain dry while lying down. As noted in Chapter T the bladder capacity plays an important part in the recoverability in these cases which cannot be considered simply as a defect of the sphincteric mechanism. Similar considerations apply to girls with absent urethra or urogenital sinus.

XIII. Ectopic Ureter and Incontinence

The ectopic ureter is well known to produce a characteristic form of incontinence: a continuous dribble of a small quantity of urine despite normal acts of micturition at normal intervals. There are, however, possible variants in that a few children are dry at night if the ectopic ureter is large enough to form a reservoir in the supine position, and a few cases can, in fact, contract the vaginal or pelvic floor musculature sufficiently to retain urine in the vagina for short periods so that they are not continously wet. A few may complain of a late onset of

incontinence due to a breakdown in control following infection. On examination the vulva is almost always wet, though the actual opening is difficult to find. The diagnostic problem is discussed in Chapter K. Bilateral single ectopic ureters form an interesting variant: in girls the two ureters open very low in the urethra, the bladder is never adequately filled and they suffer total incontinence from birth despite an apparently normal external meatus and absence of neurological signs. In boys the bladder neck is inadequately formed and they have dribbling incontinence despite normal micturition.

XIV. Implanted Electronic Stimulators

Although the use of an implanted stimulator to initiate bladder contraction has scarcely passed the experimental stage, the use of an implanted stimulator in the pelvic floor to restrain the passage of urine in incontinent patients has been reported by a number of workers and has roused considerable interest. There have, in general, been very many more failures than successes and, as shown in the next chapter, pelvic floor stimulators in the congenital neuropathic bladders are very seldom effective. There are, however, as already seen in this chapter, a number of causes of incontinence which might be susceptible to this form of control. The whole topic has been recently reviewed by EDWARDS and MALVERN (1972) and HARRISON (1971) has reported the use of stimulators in children.

In the author's unit, implanted stimulators have been used in 18 children, 3 of these had the wide bladder neck anomaly, 3 had epispadias, 5 were incontinent after resection of urethral valves and 2 after bladder neck revision. One was a case of incomplete prune belly syndrome treated by urethrotomy. One followed rupture of the posterior urethra with repair of stricture, and there were 3 neurological cases, 1 following operation for imperforate anus. The criteria employed in selection were: a child of 6 or more years of age, an adequate bladder capacity shown on cystometrogram, absence of reflux, positive response to perineal stimulation and an intelligent child with co-operative parents. The electrodes were first implanted perineally, but subsequently the retropubic route was chosen because of breakdown of the perineal wound and exposure of the wires. Satisfactory control was obtained in 5 patients and 8 more were considerably improved, but the results were often vitiated by breakdown of the wound or of the apparatus, necessitating its removal. It is concluded that this method should be reserved for a very small minority of cases in whom all other methods of control of incontinence have failed.

S. Neuropathic Bladder

H. B. Eckstein

With 10 Figures

I. Introduction

With the increased survival of children born with myelomeningocele (spina bifida cystica) the importance of the neuropathic bladder and its management in childhood has increased enormously during the past decade. It is likely that in the United Kingdom alone no less than 2000 new patients with congenital neuropathic bladder are born annually and at least half of these will survive. At the outset it is important to appreciate that most children with a congenital neuropathic bladder will have associated lesions and abnormalities in other parts of the body which require treatment, and the surgeon responsible for the management of the neuropathic bladder is well advised to consult his colleagues in other specialities, especially his orthopaedic colleagues, before any major decision is taken relating to the management of a particular patient's bladder and urinary tract.

The physiology of micturition and the pathological processes which can interfere with normal micturition were summarised by us in detail (Eckstein, 1969) and will not be discussed further. Pellman (1965) suggests that a partial loss of bladder innervation is more likely to produce upper urinary tract damage than a total denervation of the bladder. This has also been our experience.

II. Classification

Various classifications of the neuropathic bladder resulting from congenital causes have been suggested by Nash (1957), Roberts (1962), and Smith (1965). The details of such classifications vary, but in general there appear to be two main types. In the first, the bladder is thin walled, flaccid and free from trabeculation and the urethral resistance is low. In such cases the upper tract is usually well preserved. In the second type, the bladder hypertrophied, heavily trabeculated and of small capacity. The urethral resistance is high and upper tract dilatation and recurrent infection are common. However, such a classification cannot be adhered to rigidly and a thin flabby bladder can become a small contracted bladder as the result of chronic infection (Johnston, 1968). A thick-walled bladder may, in the absence of active detrusor function and of chronic infection become stretched and thin walled as the result of increased outflow resistance.

It should be noted that associated abnormalities of the upper urinary tract which are not the direct result of the neuropathic bladder (especially malposition and malrotation of the kidneys) are more frequently seen in children with congenital neuropathic bladder than in controls (Wilcock and Emery, 1970; Pompino et al., 1971).

III. Causes of Neuropathic Bladder

1. Spina Bifida Occulta

It is now generally accepted that spina bifida occulta, the bony abnormality alone, is not necessarily associated with a neuropathic bladder. Failure of fusion of the arches of one or more vertebrae is common and probably occurs in fifty per cent of the population. In the absence of other abnormalities of the spine or spinal cord isolated spina bifida occulta does not cause any neurological deficit. If spina bifida occulta is associated with other lesions it should be classified as spinal dysraphism.

2. Spinal Dysraphism

In this condition there is a congenital anomaly of the spinal cord. It may become involved for instance, by the typical bony spur seen in diastematomyelia. There may or may not be a tuft of hair in the skin overlying the vertebral column over the bony abnormality. Tethering of the conus medullaris by an abnormally thick filum terminale will produce similar neurological lesions and in the above-mentioned conditions neurosurgical intervention to relieve traction on the spinal cord and the nerve roots may cure the urological symptoms and should, in any event, prevent further neurological deterioration. Sacral lipomata with extension into the spinal canal come into this group of abnormalities. In these conditions, there are always abnormal physical signs in the extremities and patchy anaesthesia of the legs or an isolated foot drop which may be progressive. Symptoms and signs of neuropathic bladder do not usually develop until the growth of the child reaches a certain point when the upward movement of the conus medullaris results in traction from the bony spike or tethering bands and incontinence typically develops at some stage during the growth period. Neuro-radiological facilities, especially myelography are vital to the correct diagnosis.

3. Sacral Agenesis

A partial absence of one or more of the sacral segments is not uncommon. It appears that the absence of the lowermost two segments will produce no symptoms but the absence of three or more sacral segments is likely to result in a neuropathic bladder with signs evident from early infancy. Williams and Nixon (1957) reported the first series of such patients and Koontz and Prout (1968) presented a further eight cases. Sigel (1971) has summarised the published cases of sacral agenesis and has shown that this abnormality is not uncommon. Absence of the lumbar vertebrae as well as the sacrum is rare but presents essentially the same urological problem as total sacral agenesis (Eckstein and Sipahi, 1958).

4. Myelomeningocele

Undoubtedly the increased survival rate of infants born with myelomeningocele in the past decade has become the most important cause of the neuropathic bladder in childhood. The drop in the mortality of this particular congenital abnormality was demonstrated by Eckstein and Macnab (1966) and the urological consequences following the policy of early closure of the spinal defect and the treatment of hydrocephalus by ventriculo-atrial drainage using a shunt have been

demonstrated by VAN DER FELTZ and FELDERHOF (1966), and BACKER et al., (1965). In clinical practice, children with myelomeningocele will make up the large majority of patients with a congenital neuropathic bladder.

5. Spinal Cord Tumours

Tumours of the spinal cord are rare in childhood but extra-dural metastases which can cause cord compression and a neuropathic bladder are not infrequently seen in children suffering from a neuroblastoma. This type of cord compression should be suspected in a child who has had normal micturition initially, but develops a neuropathic bladder after a few years in the absence of cutaneous abnormalities over the vertebral column. Plain radiographs of the spine often show expansion of the neural canal and myelography is invaluable in establishing an accurate diagnosis.

6. Osteomyelitis of the Vertebral Bodies

Osteomyelitis of the vertebral bodies is uncommon but can result in extra-dural abcesses which can cause cord compression and thus a neuropathic bladder. There is usually a previous history of infection, generalised illness and pyrexia and nerve root pain. Radiological signs of bone destruction in the vertebra may not be present at the time the neuropathic bladder develops but will appear soon afterwards.

7. Traumatic Paraplegia

In contrast to the problem of the adult with a neuropathic bladder, injury to the vertebral column, and damage to the spinal cord in childhood is extremely rare (RANZOWSKY, 1972). The management of the traumatic cord injury in childhood is essentially the same as in adults. Extensive fractures of the pelvis are sometimes associated with significant bladder denervation.

8. Infections

While a neuropathic bladder occasionally follows an episode of measles encephalitis or an attack of acute poliomyelitis, both these diseases can now be prevented by prophylactic immunisation and both diseases have become extremely rare. Bladder dysfunction in encephalitis and poliomyelitis is in any event unusual.

9. Transverse Myelitis

Transverse myelitis is usually the result of a virus infection in childhood and may produce a temporary neuropathic bladder. The prognosis as far as bladder function is concerned is usually good but temporary bladder drainage may be required.

10. Operative Trauma

Trauma to the nerve supply of the bladder or its sphincters may occur during surgical procedures to correct ano-rectal agenesis or Hirschsprung's Disease.

Meticulous dissection close to the bowel wall helps to avoid such trauma and the operations devised by REHBEIN, DUHAMEL and SUAVE have been designed to reduce such possible nerve damage. Likewise, the removal of a sacro-coccygeal tumour in the neonatal period or in infancy may result in a neuropathic bladder.

11. Subclinical Neuropathic Bladder

This will be disscused on p. 245.

IV. Complications of Neuropathic Bladder

Because of the inadequate emptying either spontaneously or by expression of the neuropathic bladder, urinary stasis results and urinary tract infection is common. Pyelonephritic scarring is often seen especially if vesico-ureteric reflux accompanies the neuropathic bladder. Reflux increases with age and is unusual in the new-born but may be present in 50 per cent of these patients by the age of ten years (ERICSSON et al., 1971). Anaemia is a common finding in those children with recurrent or chronic urinary infection and may have to be corrected before any operative procedures are undertaken. Detrusor dysfunction or detrusor hypertrophy may lead to a uretero-vesical obstruction resulting in progressive upper tract urinary dilatation. In contrast to adult patients with paraplegia and neuropathic bladder, stone formation in the urinary tract is distinctly uncommon and in the writer's experience occurs in only 1 or 2 per cent of these patients. No adequate explanation for this low incidence has been put forward. LORBER and LYONS (1970) have shown an alarmingly high incidence of hypertension in children suffering from congenital neuropathic bladder and as these patients become older renal failure or progressive hypertension may become important causes of death in this group of patients.

V. Investigations of Neuropathic Bladder

Numerous investigations are available in relation to the neuropathic bladder. Some of these are of vital clinical importance to the individual patient while others are more of a scientific interest.

1. Urinalysis

Most of the complications in relation to the neuropathic bladder are the result of recurrent or persistent urinary tract infection. Regular and repeated urinalysis is therefore essential. Urine specimens are usually easily obtainable as the majority of neuropathic bladders are more or less expressible and a clean specimen can therefore be collected with relative ease. In the presence of proven infection a suitable antibiotic can be chosen as a means of treatment. There is some evidence that in children with a sacculated bladder without any vesico-ureteric reflux or upper tract dilatation the urinary tract infection may be localised to the bladder only and is therefore of less serious clinical significance than an infection which involves the kidneys themselves. In clinical practice, urinalysis should be performed at least monthly and a suitable antibiotic treatment should be instituted as a result of

this investigation. Persistent infection is suggestive of either upper tract dilatation or a large volume of residual urine.

2. Excretory Urography

This is undoubtedly the most valuable single investigation as it demonstrates any anatomical changes in the upper tract and at the same time yields an indication of renal function. In clinical practice excretory urography should be performed within a few weeks of birth on those children with congenital neuropathic bladder and should be repeated at least every second year and ideally every year. We have been impressed by the number of infants, especially with sacral lesions, who have developed dramatic and rapid upper tract dilatation over the course of a few months when the original excretory urogram taken at a few weeks of life was completely normal (Fig. 152–153). The problem of exposure to radiation must be considered in this group of children and the films taken should be reduced to a minimum. On the other hand, the majority of this particular group of male patients at least, are likely to be impotent and almost certainly sterile and the radiation hazard is therefore less serious than in normal children.

3. Cystography

This gives a more accurate picture of the bladder anatomy and bladder function but requires urethral catheterisation. Alternatively the bladder can be filled by supra-pubic puncture but extravasation of medium or even of infected urine is a potential hazard. Cystography as a routine measure has been recommended by Nergardh et al. (1971), Ericsson et al. (1971), and Chapman et al. (1969). Cooper (1967) has shown that there is a significant incidence of urinary tract infection following cystography and this investigation should probably not be used routinely. Thomas and Hopkins (1971) have also shown a relatively high infection rate following cystography. Graf et al. (1964) have demonstrated the relationship between the excretion urogram and the micturating or expression cystogram. The cystogram will however localise the site of obstruction (if any) and usually shows urethral narrowing at the level of the external sphincter.

4. Pressure Studies

Intra-vesical pressure studies have been performed by a number of authors (Cooper, 1968; Fry et al., 1966). It appears however, that such pressure studies, although scientifically interesting are of little help with the individual patient and we have found that pressure tracings may change considerably from one year to the next in the same patient. Pressure profile measurements of the urethra may help to localise the site of outflow obstruction.

5. Electromyography

Electromyography of the anal sphincter and pelvic floor may be helpful to determine the degree of innervation (Stark, 1969) but it is time-consuming and liable to technical errors.

6. Isotope Renography

Isotope renography has been recommended by Ross (1965) and by CUDMORE and ZACHARY (1970). The investigation is simple if the necessary equipment is available. Isotope renography will demonstrate differential renal function and entails less irradiation than intravenous pyelography. Isotope studies can also be used to determine the presence or absence of vesico-ureteric reflux but their application is somewhat limited by the cost of the necessary equipment.

7. Cystoscopy

Cystoscopy in this group of patients is of little practical help, especially if adequate radiological facilities are available. Cystoscopy will confirm the presence of trabeculation and the presence of a funnel shaped bladder neck; both these findings are usually apparent on the cystogram. Because of trabeculation and sacculation of the bladder, retrograde catheterisation of the ureters (if needed) may be technically difficult.

VI. Treatment of the Neuropathic Bladder

No general regime can be laid down for the management of the neuropathic bladder. The treatment in each individual patient must take account not only of the neuropathic bladder itself and its effects on the upper urinary tract, but must also take into consideration the other handicaps of the patient, his mental development, his home conditions and the attitude of his parents. On the other hand the fundamental principle of management is the reduction of residual urine to a minimum, the prevention of renal damage and the prevention or treatment of secondary urinary infection. The various forms of treatment available for the neuropathic bladder in children are summarised below.

1. Bladder Expression

Expression of the bladder is a feasible form of management provided the bladder is of a reasonable capacity, the urethral resistence is low enough to make expression possible and there is no upper tract dilatation. The child has to be co-operative and the parents moderately helpful. A small number of paediatric patients can be kept socially dry by regular (three hourly) bladder expression. Bladder expression has been advocated by MIYAZAKI (1972) but PEKAROVIC et al. (1970) suggest that bladder expression should not be performed in the presence of vesico-ureteric reflux, especially when associated with urinary tract infection. Bladder training usually associated with bladder expression has been claimed as a successful means of management by AUDIC (1970) and ERICSSON (1972) but in our experience bladder expression and bladder training have been relatively disappointing.

2. Drug Treatment

The management of the neuropathic bladder by the use of drugs has received considerable attention in relation to adult traumatic paraplegia (KOHLER and MORALES, 1968; PEDERSEN and GRYNDERUP, 1966). However in clinical practice, drug therapy of the neuropathic bladder in childhood appears to have been generally unsuccessful.

3. Catheter Drainage

Catheter drainage whether by intermittent catheterisation or prolonged catheterisation has been recommended by SOKELAND et al. (1967), OTT and ROSSIER (1972), and MADERSBACHER (1972). In the paediatric age group, prolonged catheterisation is not recommended. Such treatment may well lead to urethral strictures and in any event will produce urinary tract infection. Catheterisation as a means of definitive treatment of the neuropathic bladder is to be condemned but on the other hand there is a definite place for urethral catheterisation in children with a neuropathic bladder undergoing hip surgery. Catheterisation will reduce contamination of the plaster of paris cast and subsequent wound infection and is a justifiable procedure to cover a period of immobilisation in a plaster spica, especially in girls. Prolonged urethral catheterisation other than to cover an orthopaedic intervention is not recommended as a form of treatment of the neuropathic bladder in childhood. Boys in this situation can usually be managed with Paul's tubing fixed to the penis.

4. Urethral Plication

Plication of the urethra to increase outflow resistance was suggested by NASH (1957) but as this procedure does not improve detrusor function or indeed bladder sensation, its use must be very limited.

5. Pudendal Neurectomy

In children with outflow obstruction at the level of the external sphincter (the usual site of outflow obstruction in the neuropathic bladder) neurectomy of one or both pudendal nerves has been recommended by SMART (1965) and STARK (1969). The operative procedure is technically difficult in small boys and technical failures are likely to be due to incomplete nerve resection. In any event, pudendal neurectomy will add the certainty of impotence to the patient's many other disabilities and this procedure is not widely practised.

6. Bladder Neck Resection

Widening of the Bladder neck is recommended by JAKOBSON et al. (1966) and by GIBBON et al. (1965) using a resectoscope. However, in the majority of neuropathic bladders, the bladder neck is wide open and the indications for bladder neck resection must be limited. JEEJEEBHOY (1962) has described a trans-vesical method of bladder neck resection in this condition but this procedure has received little support from other authors.

7. Resection of the External Sphincter

In the large majority of patients with obstructive uropathy resulting from a neuropathic bladder, the site of obstruction is at the level of the external sphincter. External sphincterotomy would therefore seem a reasonable procedure to reduce outflow resistance and this has been described by HASLOWE et al. (1965), JAKOBSON

et al. (1966), Regemorter (1966), Ross et al. (1967), and Currie (1970). Johnston (1968) recommends the use of an aural speculum instead of a resectoscope for this procedure. Forceful dilatation of the sphincter is an alternative method. A perineal urethrostomy may be required for any of these procedures in male infants. In female patients requiring destruction of the external sphincter because of upper tract dilatation secondary to the neuropathic bladder, an extensive resection which may lead to a vesico-vaginal fistula is fully justifiable as this will provide free drainage of urine and the child will be incontinent in any event. The improvement that may follow such a trans-urethral resection is shown in Figs. 152 and 153.

8. Continence Restoring Procedures

Surgical procedures to restore urinary continence usually by increasing the outflow resistance are generally unsuccessful. The writer has attempted a number of muscle sling procedures coupled with tightening of the bladder neck and while urinary continence has improved in a few patients, the improvement of continence has invariably been accompanied by progressive upper tract dilatation (Figs. 154 and 155). Like plication of the urethra, such procedures are rather irrational as they do not take into account the basic pathology.

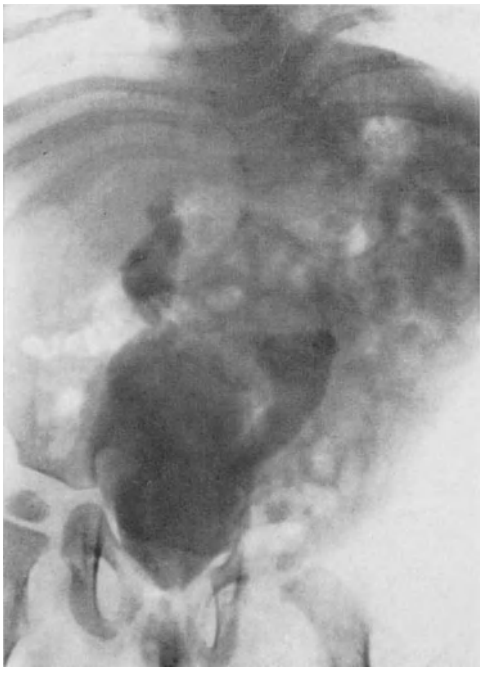


Fig. 152

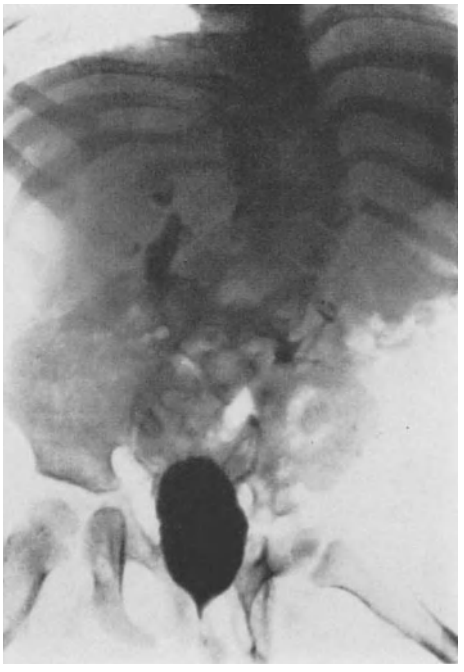


Fig. 153

Fig. 152. Excretory urogram in a 3 month old female. Note marked bilateral upper tract dilatation

Fig. 153. Same infant, 4 months after transurethral resection of external sphincter

9. Intestinal Cystoplasties

Intestinal cystoplasties in the management of the neuropathic bladder have been described by HRADEC (1964), BITKER (1966), and GRASSET (1967) but these procedures, likewise, are not based on sound fundamental pathological or physiological principles and have not been widely accepted.

10. Electrical Stimulation of the Bladder and its Sphincters

Electrical stimulation of the bladder muscle on the one hand or the sphincter mechanism on the other, has attracted considerable interest in the past decade. Experimental studies, usually on cats and dogs, have been reported by BRADLEY et al., (1963), SCHAMAUN and KANTROWITZ (1963), HALD and ROSSEL (1965), GRABER and RUTISHAUSER (1965), SCOTT et al. (1965), DE JONGE (1966), GRABER et al. (1966), and KANTROWITZ and HALD (1966). In animal experiments, especially in the dog it appears quite feasible to stimulate the detrusor muscle to produce satisfactory contraction of the bladder with effective micturition. It appears however, that this procedure is not applicable to the human (ELLIS et al., 1964; STENBERG et al., 1967; SUSSET and BOCTOR, 1968). Stimulation of the sphincter mechanism to prevent involuntary micturition so that micturition can take place when the electrical impulses are stopped appears to be more applicable

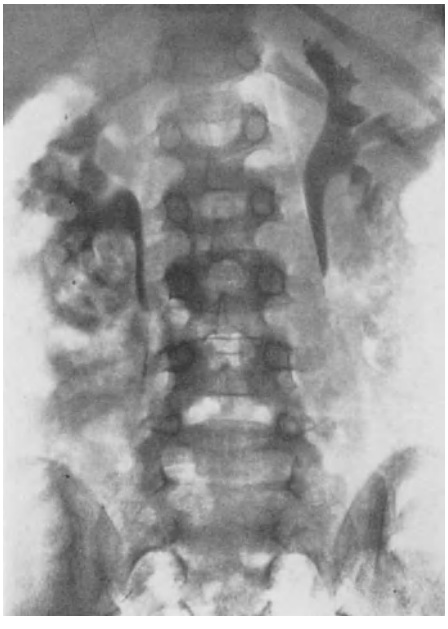


Fig. 154

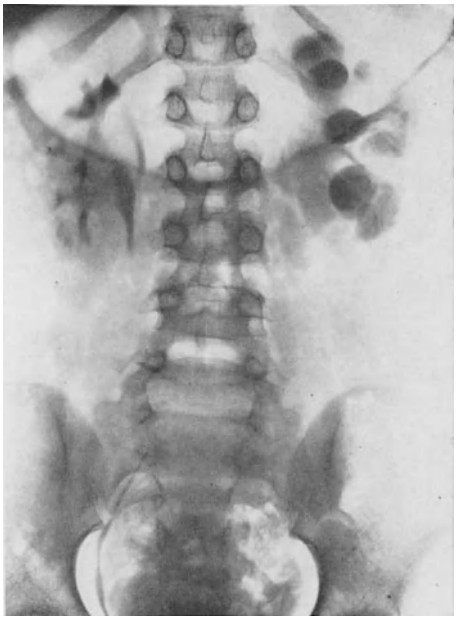


Fig. 155

Fig. 154. Excretory urogram, ten year old girl with neuropathic bladder and total incontinence

Fig. 155. Same patient one year following bladder neck tightening and muscle sling procedure. Satisfactory result in relation to continence but has now developed upper tract dilatation

to the human. CALDWELL et al. (1969) have reported a number of successes, including children with congenital spinal palsy, using an implantable stimulator. The complication rate especially from fractures of the electric wires inside the body is high and revision procedures are not infrequently required. HOPKINSON (1972) has devised an anal plug with circular electrodes which will produce a similar effect to the implanted stimulator and which does not require any operative procedure. This rectal plug undoubtedly works in selected cases and the writer has had one dramatic success as far as continence is concerned but yet again severe upper tract dilatation and urinary tract infection was the price the patient had to pay for his artificial continence (Figs. 156 and 157). KATONA et al. (1959) have reported successes following the use of a square wave current intra-vesical stimulation but their apparently highly successful results have as yet be to confirmed by other workers. The whole question of electrical stimulation of the bladder or the sphincters has been well summarised by BRADLEY et al. (1971). While there is little doubt that electrical stimulation has a definite role in the management of the neuropathic bladder, the success rates in the congenital types of neuropathic bladder in children is alarmingly low (MAYER, 1970).

11. Reflux Prevention

The surgical correction of vesico-ureteric reflux using one of the standard reflux preventing procedures has little place in the management of the neuropathic

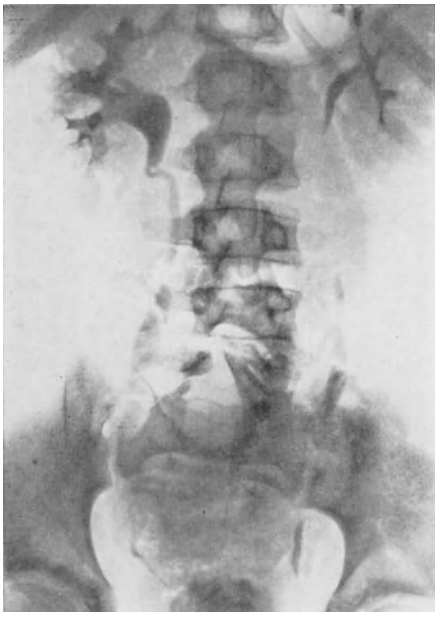


Fig. 156

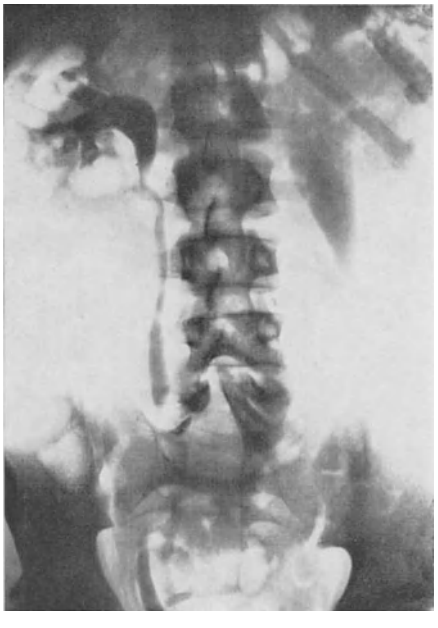


Fig. 157

Fig. 156. Excretory urogram in twelve year old boy with incontinence. Essentially normal upper tracts

Fig. 157. Same patient six months later after successful treatment with anal plug pacemaker. Continence was achieved but at the price of upper tract damage

bladder and such operations tend to be unsuccessful in this group of patients. Reflux in the presence of a "high pressure" bladder is best treated by reducing the outflow resistance.

12. Appliances

Penile urinals have a very definite place in the management of the neuropathic bladder in boys. In the majority of patients a satisfactory appliance can be fitted by the age of four or five years depending on the size of the penis. The collecting bags, as in the appliances used following urinary diversion (ECKSTEIN, 1967), should be of a disposable type as rubber bags cannot be satisfactorily cleaned or sterilised (Fig. 158). Penile clamps should not be used in this condition as these are certain to cause ulceration of the penis and may result in a urethral fistula as the penile skin is anaesthetic. No satisfactory appliance to control incontinence has been designed for the use in girls with an anaesthetic perineum.

13. Urinary Diversion

Urinary diversion may be indicated either for progressive upper tract dilatation in either sex, or for incontinence in girls. Diversion procedures such as uretero-sigmoid anastomosis have no place in the management of the neuropathic bladder as in these patients the anal canal is invariably denervated and patulous.

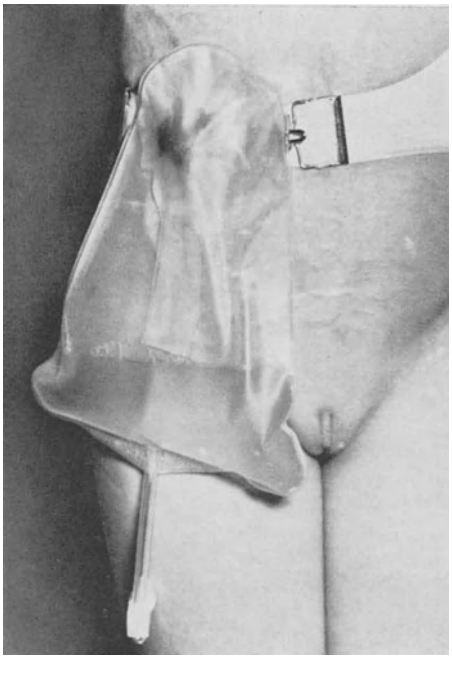


Fig. 158. Plastic disposable urinary collecting bag to be used with either diversion stoma or penile appliance. Note non-return flap valve, which prevents leakage following accidental detachment

a) Vesicostomy

Vesicostomy has been advocated by LAPIDES et al. (1960), and by BELL et al. (1968). The procedure is technically simple but stenosis at the stoma is common and the fitting of appliances may be difficult. The operation has not been universally accepted. GORDON and SCOTT (1968) have described an inguinal cystostomy.

b) Cutaneous Ureterostomy

Cutaneous ureterostomy is the operation of choice if one or both ureters are grossly dilated. The operation is simple and avoids intra-peritoneal manipulation, (ECKSTEIN, 1963), Numerous patients with cutaneous ureterostomy have been reported by LISTER et al. (1968), SHAFIK (1968), and WILLIAMS and RABINOVITCH (1968). The "Y" ureterostomy in patients with one grossly dilated ureter and one normal or only slightly dilated ureter was suggested by MADDEN et al. (1967) and this procedure has been employed by us on numerous occasions (ECKSTEIN and KAPILA, 1970), with success (Figs. 159 and 160). Cutaneous ureterostomy avoids intestinal surgery, it can be performed without opening the peritoneal cavity, and on the whole, provides satisfactory urinary drainage. Stoma complications are, however, commonly seen and in our experience ureterostomy stomata have to be converted to some kind of intestinal stoma sooner or later in approximately fifty per cent of patients undergoing cutaneous ureterostomy. The introduction of a "V" shaped flap of skin into the ureterostomy stoma has reduced the incidence of stomal strictures (SMITH, 1964).

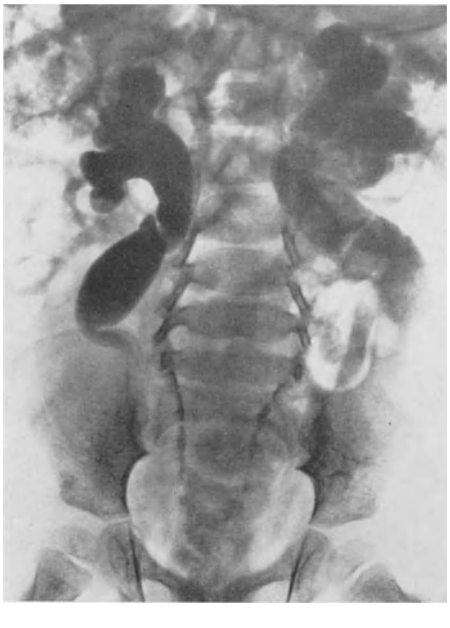


Fig. 159

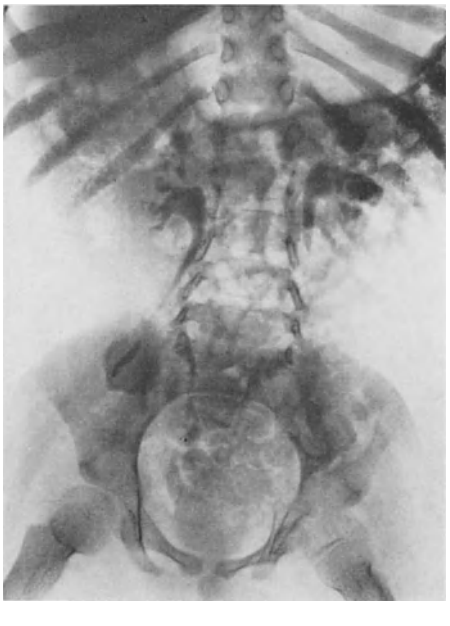


Fig. 160

Fig. 159. Excretory urogram in a six year old patient with marked upper tract dilatation

Fig. 160. Same patient one year following cutaneous ureterostomy. Note marked regression of upper tract dilatation

c) Ileal Conduit

Ileal conduit urinary diversion as described by BRICKER (1952) has become the most commonly practised diversion procedure for the neuropathic bladder. SMITH (1972) has advocated ileal conduit diversion for all patients over the age of two years but this approach appears to be much too radical. At this age, he must have diverted a number of patients who would have become continent in due course, or those who could alternately be managed by bladder expression. On the other hand, it seems unnecessary to perform a urinary tract diversion in boys in the absence of upper tract dilatation or serious urinary tract infection as penile appliances are generally acceptable. RICKHAM (1964) advocates a short transperitoneal conduit while we feel (ECKSTEIN and BOYD, 1969) that an extra-peritoneal conduit has a lower complication rate. The number of ileal conduits performed in recent years has increased steadily (ECKSTEIN, 1965). Such ileal conduits in this group of patients have been advocated by NASH (1956), STRAFFON (1963), NASH (1965), RETIK et al. (1967), ROSS (1967), COOK et al. (1968), MURPHY and SCHOENBERG (1968), PUIGVERT (1968), RAY and DOMENICO (1972), TARABULCY et al. (1972). BENTLEY (1968) suggested a conduit between the bladder and the skin which is a simple surgical procedure but tends to leave a large reservoir of residual urine and in our experience this operative procedure has not been successful. PEKAROVIC et al. (1968) have studied the intra-luminal pressures in conduits which were placed trans-peritoneally and extra-peritoneally and suggest that on pressure studies alone, a trans-peritoneal conduit is preferable. SCHMITT et al. (1971) have combined the management of urinary and faecal incontinence with a urinary ileostomy and a faecal colostomy, but this combined approach has re-

Fig. 161. Excretory urogram in a girl five years after ileal conduit diversion. Note excellent state of the upper tracts, although the ileal conduit is longer than it need be

ceived little support elsewhere. Ileal conduit urinary diversion appears to be a generally satisfactory method of managing incontinence especially in the female (Fig. 161). It is important to use as short a segment of ileum as possible and the anastomosis between the ureters and the ileum should be made with a single layer of interrupted catgut sutures and no reflux preventing procedure should be attempted. In the writer's experience, uretero-ileal obstruction is extremely unusual.

d) Colonic Conduit

The colon rather than the ileum as a conduit has been preferred by a number of authors (BREUZIÈRE and VIGNE, 1967; MOGG, 1968; HOHENFELLNER and WOLFF, 1970). Because of the thicker muscular coat of the colon as compared with the ileum, an anti-reflux procedure can be performed at the uretero-intestinal anastomosis but it would seem that the preference of ileum or colon is a question of personal choice.

In the occasional patient with severe kypho-scoliosis it may be important to place the stoma in the right or the left iliac fossa because of the deformity of the vertebral column. In clinical practice, a left sided stoma is much more easily made using a colonic conduit while a right sided stoma is much more easily made using an ileal conduit.

VII. Defunctioned Neuropathic Bladder

Problems associated with a defunctioned bladder following urinary tract diversion were first mentioned by NASH (1956). KICKHAM and KEEGAN (1963) and KEMP (1966) have also described such cases. RAY et al. (1971) reported five patients with "pyocystis" treated by various methods. In our experience (ECKSTEIN and MOHINDRA, 1970) approximately 20 per cent of children who have undergone urinary tract diversion to the skin will develop a significant bladder discharge. This discharge is almost always purulent and in the absence of mucous glands in the bladder must be regarded as a transudate secondary to infection within the bladder. Such discharge occurs more frequently in girls than in boys but it may lead on to epididymitis in the male. We were unable to correlate the incidence of such discharge with age, the length of the urethra or the time following diversion but those children who had had recurrent urinary tract infection before diversion were more liable to develop such bladder discharge than children without previous infection. This discharge may be managed satisfactorily by a series of bladder washouts with a mild antiseptic solution, such as HIBITANE or NOXYFLEX but in the event of failure a cystectomy is fully justifiable and is a relatively simple surgical procedure. Cystectomy at the time of the original urinary diversion is not advocated as this undoubtedly would increase the operative risk and make the operation of urinary diversion more final and definitive. If, however, the bladder is grossly sacculated, immediate cystectomy is sometimes justifiable. SPENCE and ALLEN (1971) have advocated a "vaginal vesicostomy" which is technically simple and provides excellent bladder drainage. Five successful cases have been reported as an alternative to cystectomy.

VIII. Neuropathic Anal Canal

Surprisingly little has been written about the neuropathic anal canal which is invariably associated with the neuropathic bladder since the nerve supply to the bladder and the anal canal are similar. CUENDET (1969) has discussed the theoretical implications of anal canal paralysis. We (SCOBIE et al., 1970) have found that although the anal canal is almost always affected by the neurological deficit and the anus is almost always patulous, clinical anal incontinence is not as common as might be expected. The majority of patients with congenital spinal palsy can be trained to have one or two regular bowel actions a day by the use of a carefully adjusted diet coupled with the administration of carefully selected laxatives. The regular use of suppositories may help to develop a regular bowel habit. In general, children with a neuropathic bladder will also have a neuropathic bowel but the management of faecal soiling and incontinence can almost always be controlled by good training by the parents or the medical attendants. Rarely, a gracilis sling operation is justifiable; in those few patients who have normal innervation of the legs such an operation will increase the resistance to faecal outflow and may produce some form of artificial faecal continence.

IX. Sexual Function Associated with the Neuropathic Bladder

Since the innervation of the genitalia is essentially the same as the innervation of the bladder and its sphincters, the sexual function in patients with a neuropathic bladder is inevitably abnormal. There is almost always a complete anaesthesia of the external genitalia and orgasm by direct stimulation is not possible. On the other hand, orgasm resulting from emotional stimuli may be possible. Females with a neuropathic bladder can have intercourse and can conceive and pregnancy will continue normally. Spontaneous delivery or delivery by caesarian section are possible and a number of female myelomeningocele patients with and without urinary diversion have given birth to normal infants. Spontaneous delivery may be totally painless and the commencement of labour may be difficult to assess.

The majority of males with a neuropathic bladder are likely to be impotent although spontaneous erections can occur. However, because of the open bladder neck, such males are unlikely to be fertile even if they are potent.

X. A Practical Guide to the Management of the Congenital Neuropathic Bladder

This final section summarises the various points made in this chapter and is intended as a practical guide to the management of the congenital neuropathic bladder especially in relation to children with myelomeningocele.

An intravenous excretory urogram should be performed as soon as the back incision has healed and certainly during the infant's first admission to hospital. The urogram should be repeated every two years but sooner if there is a suggestion of upper tract dilatation or if there is persistent or recurrent urinary tract infection.

Urinalysis should be performed at monthly intervals and on the whole, urinary tract infection should be treated with suitable antibiotics. The use of sulphonamides, FURADANTIN, NEGRAM (Nalidixic Acid) and SEPTRIN is preferred to the broad spectrum antibiotics which may cause side effects. If antibiotic therapy is necessary this should be continued for at least one month but on the other hand prophylactic antibiotic treatment is not advocated.

Once the back incision after closure of the myelo-meningocele has soundly healed, bladder expression should be performed at regular intervals to reduce the volume of residual urine.

At the age of four to five years, a proper assessment should be made of bladder function. In the majority of patients a simple clinical assessment will provide sufficient information to decide whether or not there is any chance of a particular patient becoming continent of urine. A suggestion that there is a sensation of bladder filling, or intermittent micturition with definite periods of dryness are strongly suggestive that normal micturition may develop and in these particular children the management should be as conservative as possible. It is at this stage that cystography, cystoscopy and bladder pressure measurements may be helpful in deciding upon a line of action to be taken in the individual patient.

Males with incontinence by the age of five years can almost always be fitted with a suitable penile appliance connected to a bag and can be made socially continent by this method. There is no point whatever in performing a urinary diversion in a male child in the absence of urinary tract complications.

The female child who is obviously going to be incontinent of urine by the age of four or five years should have a urinary diversion performed as no suitable appliance is available. It would appear at this stage that an ileal conduit is the operation of choice. Such a diversion should preferably be performed before the child reaches school age which at present is five years in the United Kingdom.

In the presence of urinary tract dilatation in infancy, resection of the external sphincter is advocated in either sex, but the improvement of such dilatation must be checked by repeat intravenous urograms. In female infants who do not rapidly improve following a trans-urethral resection of the external sphincter, an early urinary diversion by cutaneous ureterostomy or ileal conduit is quite justifiable. In those male infants whose upper urinary tracts do not improve following removal of the outflow obstruction a urinary diversion is also indicated. It should be remembered that the thick walled trabeculated bladder may produce an obstruction at the uretero-vesical junction so that trans-urethral resection of the external sphincter or even the bladder neck will produce no improvement and in this situation a urinary diversion is indicated even in the male. It is of note that in the writer's experience of urinary tract diversion in 150 patients in the years 1961 to 1971 there were 123 females but only 27 males who required urinary tract diversion. Even after a urinary diversion intravenous urograms are indicated at two yearly intervals to check the condition of the upper urinary tract.

The presence of infected urine collected from an ileal conduit in an otherwise healthy child with no clinical symptoms should not be treated routinely with antibiotics but in the presence of clinical urinary infection (loin pain, pyrexia, generalised malaise, etc.) antibiotic therapy according to sensitivity tests should be instituted. The writer's results of urinary tract diversion in 150 children with congenital neuropathic bladder are summarised in Table 8. Approximately half of these patients have been followed up for a period of five years or more and it would appear that renal function is considerably improved in the majority of patients following urinary tract diversion.

Table 8. Congenital neuropathic bladder: ureteric dilatation pre- and post-diversion

Pre-operative I.V.P.	Post-operative I.V.P.					
	Same	Better	Worse	Too soon	Not done	Total
Normal	19	—	3	4	5	31
Mild Dilatation	11	11	1	3	1	27
Moderate Dilatation	2	19	2	6	4	33
Gross Dilatation	7	39	4	5	4	59
Total	39	69	10	18	14	150

T. Epispadias and Exstrophy

D. Innes Williams

With 9 Figures

I. Introduction

Exstrophy of the bladder is the commonest member of a group of anomalies of varying severity in which there is a failure of symphysis of the pubic bones, a defect of the abdominal wall, a deficiency of the ventral aspect of the genito-urinary tract and sometimes anomalies of the lower bowel. Cloacal exstrophy is the most severe of these, penile epispadias the least, but there are many variants in the combination of musculo-skeletal with visceral defects. Marshall and Muecke (1970) have given a well documented account of the whole range and their paper should be consulted for references to the literature before 1962. Muecke (1964) has also made an outstanding contribution to the embryology: working on earlier observations of anomalous embryos with grossly hypertrophied cloacal membranes he has suggested that such a lesion might block the invasion of the membrane by the lateral mesoderm, which would then be diverted caudally leaving the cloacal membrane continuous up to the umbilical stalk and forming the genital tubercle caudal to it as in the classical anatomy of exstrophy. He has then gone on to show experimentally in the chick embryos that the insertion of a small foreign body in the cloacal area could form such a block and produce an exstrophy-like deformity. The corollary of his theory is that all the normal tissues are present, though misplaced and under-developed, and that it should therefore be possible to achieve a surgical reconstruction of a functioning bladder. It must be conceded, however, that the displacement and under development is often so serious as to render reconstruction impossible.

II. Cloacal Exstrophy

In this rare but well documented anomaly (Syn. Vesico-intestinal fissure) the exstrophied bladder presents as two separate areas on the lower abdominal wall with an area of exstrophic bowel between them. The bowel represents the caecal region and has two or more openings on it (Fig. 162). The upper opening is of the small intestine and this often prolapses for a distance of 10–30 cm. Lower down is an opening into the large intestine which is short and ends blindly with an imperforate anus. A colonic duplication is not uncommon and one or two appendices may be present: the phallus is bifid or duplicated, the genital passages of either sex are anomalous and the gender is often difficult to determine. Concomitant anomalies occur elsewhere, sometimes a severe meningomyelocele.

The condition of these infants is often critical and sometimes the presence of multiple anomalies makes it unwise to attempt any sort of corrective treatment:

the loss of small intestine contents leads to mal-absorption problems and electrolyte disturbances which preclude long survival. In less serious cases treatment is possible and life may be preserved, a number of successful cases are on record (Soper and Kilger, 1964; Fonkalsrud and Linde, 1970; Tank and Lindenauer, 1970; Boix-Ochoa, 1970). The best that can be achieved is, of course, a colostomy and an ileal loop ureterostomy and even then the shortness of the intestine may cause nutritional problems. Operations must be undertaken only after careful preparation and must be staged. The most urgent requirement in most cases is the reduction of the ileal prolapse and closure of the exstrophic bowel with the formation of a terminal colostomy. The exstrophic bladder area should be left alone or simply brought together in the mid-line in order to close the abdomen, urinary diversion can then be postponed for years.

III. Vesical Exstrophy

The classical anatomy of vesical exstrophy (Syn. ectopia vesicae) is well known (Fig. 163) and the literature is largely concerned with the problem of urinary incontinence and the merits or otherwise of diversion or reconstruction as a method

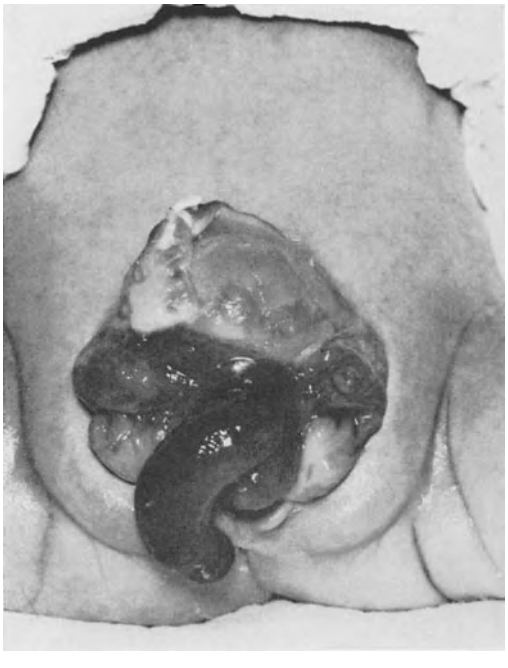


Fig. 162

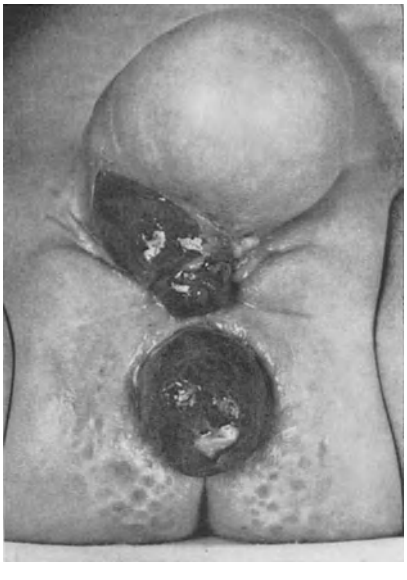


Fig. 163

Fig. 162. Cloacal exstrophy. The genitalia of a newborn male infant with cloacal exstrophy. The prolapsed small intestine forms a phallic protrusion from the central intestinal area, the areas of bladder mucosa may be seen on either side

Fig. 163. Vesical exstrophy in an infant with large umbilical hernia and rectal prolapse. The bladder area is too small to allow any possibility of reconstruction

of treatment of this disability. In addition to the urinary tract disorder there are, however, important defects in the musculo-skeletal system, in the ano-rectal region and in the genital tract: almost all of these will require surgical correction whether the treatment for the urinary incontinence is diversion or functional reconstruction. There is some danger that their importance will be overlooked because of the emphasis on the urinary disorder.

1. The Musculo-Skeletal Anomaly

The split symphysis pubis with outward rotation of each os innominatum is obvious, but the disability it causes is minimal. After a short period the gait becomes normal and no orthopaedic procedure is required for this. As a consequence of the anomaly, however, there is a defect in the abdominal wall between the lower ends of the rectus muscles and if in later life a large hernia is to be avoided this defect must be closed. In cases of primary urinary diversion it is usually a simple matter to strip off the mucosa from the exposed bladder to the trigonal area, to plicate the bladder muscle and then cover this with a skin flap. The bladder muscle itself will then prevent herniation. Where, however, the bladder is reconstructed or has been totally excised other measures are required. A pelvic osteotomy by an incision in the iliac bone lateral to the sacro-iliac joint allows the pelvic ring to be closed anteriorly and thus brings together the lower attachment of the rectus muscles. This operation is efficient in securing a good abdominal wall since it allows the midline closure of the rectus sheath and skin. There is, however, a strong tendency towards re-separation of the pubic bones and no satisfactory means of maintaining the correction has been devised. The use of compressing plaster casts or the insertion of steel wire sutures into the bone may maintain the ring for a period but in the course of years separation occurs; any unabsorbable suture material cuts out and is apt to involve the bladder.

The mid-line abdominal wall defect may be filled without bone operation by rotating rectus sheath flaps inwards, either from their medial attachments or from their inferior ones, though either system is apt to leave a little weakness in the region of the inguinal canal. Concomitant umbilical and inguinal herniae are very common in exstrophy, both can be treated by routine operation which must often preceed any other surgical treatment.

2. The Ano-Rectal Defect

The perineum is shortened and the anus displaced anteriorly in a large proportion of cases. In some there is in addition congenital anal stenosis which responds to simple dilatation, in others there is a serious defect of the pelvic floor and a tendency to rectal prolapse; this is commonest in infancy and in untreated children, probably accentuated by the presence of the painful inflamed bladder. The prolapse is usually easily reduced and may be controlled by simple measures such as the insertion of an encircling subcutaneous catgut stitch around the anus. Occasionally very major degrees of prolapse are found, even requiring recto-sigmoidectomy or internal fixation of the bowel. In all cases considered for diversion it is important to make an assessment of the degree of anal continence, and this is usually hard to complete before the age of three years.

3. The Male Genital Defect

The testicles often appear to be undescended because of their position outside the separated pubic bones, but in fact permanent undescent is uncommon and the testicles themselves are normal in the great majority of cases. Vasa deferentia run a normal course to the ejaculatory ducts and in the absence of surgical interference with the verumontanum normal ejaculation will occur after puberty. HANNA and WILLIAMS, 1972 have shown that semen is likely to be normal where no surgical procedure has been undertaken in the urethral area, but that if a urethral stricture is caused, or if direct damage done to the verumontanum itself, azoospermia is likely.

The penis is relatively short and in early childhood may appear to be entirely inadequate. However, although there are a few cases of genuine micropenis, in most, pubertal growth will be sufficient to produce a short but serviceable organ with which it is possible to achieve normal intercourse if this is not prevented by severe upward chordee. The wide separation of the crura of the corpora cavernosa produces a short penis but the chordee is due to the shortness of the urethral strip and to tethering of the corpora upwards and outwards to the region of the pubic tubercles by tissue analagous to the suspensory ligament. Chordee correction must therefore be undertaken at some stage: if reconstruction of the bladder is to be attempted it is preferable to correct the curvature first, but the operative success is greater if the child is much older and in cases of urinary diversion correction should be postponed for some years. The object of the operation is lengthening of the urethral strip and freeing of the upward tethering and is analagous to chordee correction in hypospadias so that a number of routine operations may be adapted for the purpose. A simple V-shaped incision, apex upwards, can be sewn as a Y bringing preputial skin round, or the Byars or Nesbit operation can be adapted. Where the preputial skin is almost lacking the shaft of the penis can be buried beneath the anterior scrotal skin, bringing the glans out through a buttonhole opening. Subsequently the shaft can be freed and clothed in scrotal skin. The technique of bringing the urethra between the corpora and creating a hypospadias has allowed good chordee correction but has been followed by stricturing at the muco-cutaneous junction. After any of these chordee correction procedures a second stage to form a tubular urethra is necessary.

KELLEY and ERAKLIS (1971) have devised a technique for lengthening in a patient with a very short penis who has had a urinary diversion. The nerve supply and blood supply to the corpora in Alcock's canal are isolated and the bone on which the crura are based is cut away from the pubic ramus, the whole penis is then displaced forwards and implanted on the anterior part of the pubic bone. The shaft is then covered by a skin graft. This operation is clearly not without risks and should only be undertaken by those with considerable experience in the field and on patients whose incapacity is already proved.

4. The Female Genital Defect

The uterus, tubes and ovaries are normal: the vagina is ordinarily rather short and directed forwards at its lower end. Sometimes there is vaginal stenosis which must be treated by episiotomy to make intercourse possible. Uterine prolapse may occur in adolescence because of the short vagina, but it is more common after pregnancy when the pelvic floor musculature is relaxed. Some form of uterine suspension can be performed with ease once the bladder has been removed and the urine diverted.

5. The Urinary Tract Defect

Apart from the obvious mid-line defect it is clear that the bladder is often very small having a potential capacity varying from nil to something a little less than normal. The muscular layer is usually thin, in parts defective and in parts fibrous. There is little evidence of development of specifically bladder neck musculature. The mucosa is, on occasions, smooth and healthy, but frequently polypoid and metaplastic. At the apex squamous metaplasia is common, at the base glandular metaplasia with polyp formation is apt to occur. Sometimes exuberant folds of mucosa grow from a very small muscular base and render inversion of the bladder impossible. These changes may be found at birth, but may progress due to exposure and lack of cleanliness. Adenocarcinoma of the exposed bladder has been recorded on many occasions. The malignancy is relatively low-grade, but presumably the carcinomatous tendency is an inherent property of abnormal epithelium. RUDIN et al. (1972) have shown that the changes of proliferative cystitis persist after closing the bladder and the risk of malignant change is often cited as a reason against undertaking functional reconstruction. There is only one recorded case of carcinoma (ENGEL and WILKINSON, 1970), and this occurred in a man whose bladder was not closed until the age of 29 years. Undoubtedly the risk is a good reason for regular supervision of the functioning bladder and for cystectomy if reconstruction fails.

The ureters make a wide lateral sweep in the lower part of their course and enter the bladder at a right angle so that they are extremely liable to reflux after reconstruction. Slight dilatation of the terminal 2–3 cm. of ureter is not unusual. Severe dilatation only occurs in cases on the borderline between exstrophy and epispadias where the bladder prolapses through a relatively small gap in the abdominal wall and therefore compresses the terminal segment of the ureter.

6. Functional Reconstruction

Although functional reconstruction seems the logical treatment and is certainly the one desired by most parents of the children with exstrophy, many urologists are opposed to it on the grounds that the success rate is small, that the children are subjected to multiple procedures and that the complications are by no means negligible with serious urinary infections, pyelonephritis and stone. It is clear that no operation on the exstrophied bladder can produce normality. The sphincteric system is incomplete: reconstitution can only produce a urethral tube with some elastic resistance and minimal active contraction. If both the detrusor and the sphincteric systems are defective there is no hope of control and great danger of obstruction. Operations which aim to enlarge the bladder capacity by intestinoplasty at the same time as reconstructing the bladder outflow are almost entirely unsuccessful (CUKIER and OTT, 1971).

The proponents of reconstruction point out, however, that some reconstructive procedure is required in all cases and that where the bladder is large and supple the child should be given the chance of possessing a normally functioning organ. The complications may be avoided by careful management and since multiple procedures are admittedly undesirable, attempts at reconstruction should be abandoned after a second operation has failed. Some selection of cases is clearly important and the present author finds that only 50 or 60 per cent of cases referred are sufficiently encouraging to justify attempts at reconstruction. A bladder which is very small, polypoid or incapable of inversion should not be reconstituted, while concomitant abnormalities such as myelomeningocele are obviously

strong contra-indications. Girls have a better chance of success than boys, particularly if in the latter the penis is very small. There has been a trend towards closing the bladder at a very early age and ANSELL particularly advocates closure within a day or two of birth. At this stage the tissues are more easily moulded and the pelvic ring may be closed by simple pressure and the insertion of unabsorbable sutures. Others have found that operation in later childhood is more likely to succeed, but because of progressive changes in the mucosa and the discomfort suffered by the child with an exposed bladder delay must not be too great. CENDRON (1971), and FISHER and RETIK (1969) have advocated turning the bladder in during the first year of life but postponing any attempt to form a bladder neck until later in childhood. This allows an opportunity for bladder expansion and at the later procedure reflux prevention can be undertaken much more easily than at the initial procedure. SMITH and LATTIMER (1966) believe that in some cases it is desirable to close the bladder but not attempt to get control since it is the tight closure of the bladder neck which risks upper tract complications. The author's practice has been to close the bladder during the first year of life but to tighten the bladder neck only if the bladder is of large capacity and the muscularis well formed.

As a preliminary to reconstruction, chordee correction in the male has already been mentioned. Pelvic osteotomy with closure of the symphysis may be performed together with bladder closure or a few days before. Pelvic osteotomy has been part of the author's routine for many years and has greatly facilitated reconstruction of the abdominal wall, but ultimately X-rays have shown that the pubic bones have split apart and the follow-up shows that pelvic osteotomy has been of no assistance in obtaining urinary control. The procedure is no longer advocated as a routine in functional reconstruction.

The technique of bladder closure is a relatively simple one: it involves an incision around the mucosal bladder and urethral area, the mobilisation of the muscle layer from the rectus sheath, the opening up of the retropubic space and the stripping from the inferior aspect of the pubic bone of the strong fibro-muscular bar which runs into the bladder base. The bladder neck is narrowed by a modification of the Young-Dees procedure and the bladder is closed. The urethra may be tubed at this stage or at a later one. At some stage reflux prevention is likely to be required, if the bladder is very large it may be undertaken at the same time as reconstruction, if not it may be postponed until a second operation. The abdominal wall closure has already been discussed, and post-operatively it must be protected by maintaining the legs in an adducted position. Following operation, if performed in the first year of life, there will clearly be a long period before it is possible to say whether continence is going to be achieved, but during this period follow-up for possible urinary infection or upper tract dilatation is essential (Fig. 164). Some children will require long term chemotherapy. If the urine remains sterile several years may be allowed to elapse in the hope of progress towards urinary control, and those who attain continence by day but remain wet at night have ultimately a good prognosis. Many, however, have continual incontinence and at the age of five or six years a further procedure should be contemplated with a view to tightening of the bladder neck. If, however, infections are present, if the bladder capacity remains small or if there is any sign of upper tract obstruction then diversion should be undertaken at an early stage. In the author's experience greater care in the operation and in the follow-up procedures has resulted in a greater proportion of successful cases. Thus, WILLIAMS and SAVAGE (1966) reviewed 80 cases of exstrophy treated between 1952 and 1963 of which 51 were reconstructed. The late follow-up showed acceptable continence in 5 of these cases

only, though this continence has been maintained over the years. A high proportion of the failures have had diversion because of recurrent infection and stone as well as incontinence. A second series has been reviewed by WILLIAMS and KEETON of 36 cases seen between 1963 and 1969: 19 were reconstructed and acceptable continence was attained in 6. The complications in this series were very much less. Recent reviews in the literature give somewhat similar results. Thus EZELL and CARLSSON (1970) had 19 patients of whom 9 were reconstructed and 2 were continent. FISHER and RETIK (1969) had 38 cases and reviewed 26 of them, of which 9 were continent. MARSHALL and MUECKE (1970) reviewed 20 reconstructions of whom 4 had good control and 4 fair. CENDRON (1971) obtained successful continence in 6 out of 12 children, though reflux was present in 3 (Fig. 164).

7. Urinary Diversion

Urinary diversion is likely to be the ultimate procedure required in the majority of cases of exstrophy of the bladder and for many it should be the first. The method of diversion, therefore, requires some discussion. Uretero-sigmoidostomy has in recent years returned to favour after a period in which its disadvantages were emphasized and in which the better preservation of renal function by ileocutaneous diversion was thought to over-ride the disability involved in the permanent use of an appliance. The recognition that no form of diversion is ideal and that the psychological development of the adolescent and young adults must be balanced against the possible renal damage has, however, resulted in a return to the use of the intact bowel to maintain continence. This policy has always been strongly supported by SPENCE (1966), and also by WILLIAMS, BURKHOLDER and GOODWIN (1969) who have recently reviewed their long term experience with uretero-sigmoidostomy. It is essential to success in this method that the ureters are not seriously dilated and that the uretero-intestinal anastomosis obviates both obstruction and reflux. This end can be achieved in several ways, as reviewed by BAKKER and CORNIL (1972). The simplest is undoubtedly the use of a long submucous tunnel ending in a direct mucosa to mucosa suture line. The direct implantation of the isolated trigone of the bladder into the sigmoid colon as originally proposed by MAYDL has been advocated by GREGOIR (1967), who believes that in these circumstances reflux prevention is usually obtainable. SINGER (1966) has employed an operation of closure of the extrophied bladder and direct anastomosis of the posterior wall to the rectum: this again aims at protection of the upper urinary tract by the uretero-vesical junction but stenosis of the anastomosis is common and stone formation in the bladder is a likely complication. The use of an isolated bowel segment, anastomosed at one end to the isolated trigone and at the other to the sigmoid, has been used and HAYS, POWELL and STRAUSS (1969) recently reviewed their long term results with this method: 6 out of 18 had excellent results but the complexity of the surgery does involve more complications than a straightforward uretero-sigmoidostomy.

The rectal bladder with defunctioning colostomy which allows a sterile reservoir for urine has not been used very extensively in exstrophy patients and is not, in general, acceptable to parents, but some attention has been given to operations constructing an isolated rectal bladder with the proximal cut end of the colon pulled through the anal sphincter to give faecal continence. The various methods employed are reviewed by DUHAMEL (1971), who introduces his own modification based on previous work in the treatment of Hirschsprung's disease. The ureters are implanted into the recto-sigmoid region leaving sufficient capacity in the sigmoid for an adequate reservoir. The proximal colon is then brought po-

a

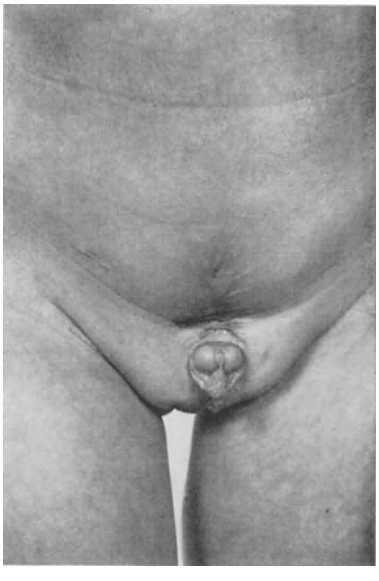
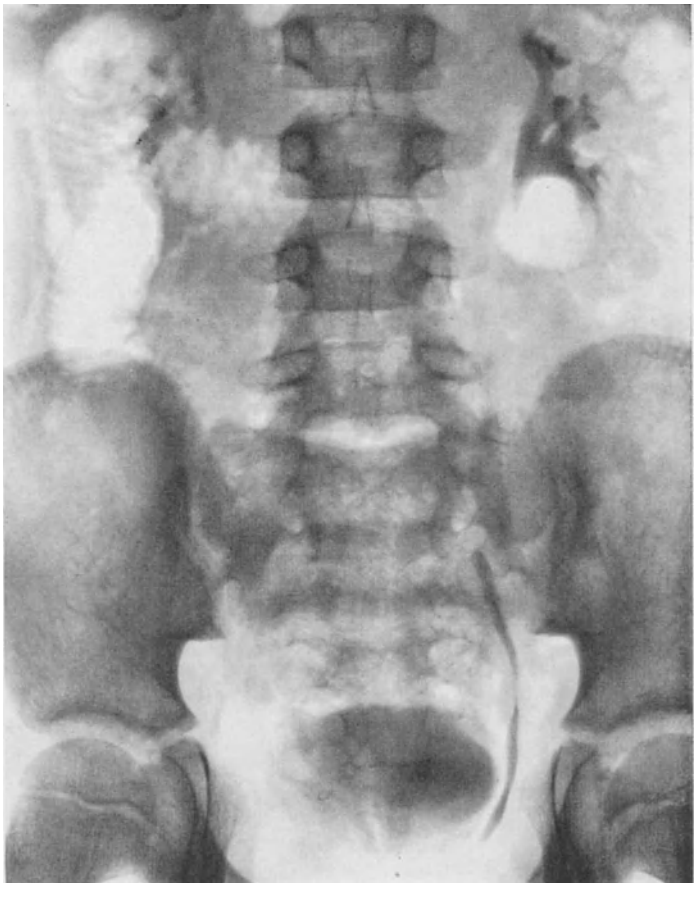


Fig. 164a and b. Vesical exstrophy. Functional reconstruction with satisfactory continence.
a Clinical appearance. b Intravenous urogram

b



steriorly behind the rectum and working from below a submucous rectal plane is opened up so that the terminal colon is brought down within the rectal sheath. This close approximation of the two segments of bowel can activate faecal continence, but unfortunately mixing of urine and faeces is very common as the septum between the two retracts and once this mixing has occurred there is little advantage over direct uretero-sigmoidostomy. In general these methods have lost favour after the initial enthusiasm of the surgeons who have tried them (FLOCKS, 1967).

All forms of uretero-sigmoidostomy require a careful follow-up, both to correct the hyperchloraemic acidosis which results from differential electrolyte absorption in some patients and to allow early recognition of complicating pyelonephritis or obstruction. Parents of children with this type of diversion should always be warned that a revision to a skin diversion may be required if the pyelograms show signs of renal damage. The usual revision is to an ileal loop type of diversion but if the problem is simply infection a proximal colostomy, isolating a rectal bladder, will do as well.

All forms of diversion into the intact rectum naturally demand that the anal sphincter is adequate to control the urine. In some exstrophy cases the pelvic floor is very weak and uretero-sigmoidostomy only results in an incontinence of both urine and faeces. It is therefore vital to make some assessment of the function of anal sphincter before embarking on this form of diversion and this assessment is often unsatisfactory before the age of two and a half or three years. In general a simple filling of the rectum with saline and testing the child's capacity to hold it will suffice and complex pressure measurements are not usually required.

In all cases where the anal sphincter is deficient, where the ureter is dilated or where uretero-sigmoidostomy has been followed by complications, an ileal loop ureterostomy with diversion to the surface is required: this operation is a standard one which does not require further comment here.

IV. Female Epispadias

In the girl the external deformity of epispadias (Syn. Sub-symphyseal exstrophy) is small: a wide transverse slitlike urethra, and a clitoris separated into two distinct bodies by a flattened area of thin skin. This external deformity can be corrected by a simple surgical procedure if it is thought desirable. The disability is the urinary incontinence which is present in varying degree in almost all cases (21 out of 22 in the writer's series). Usually there is continuous dribbling with very little urine retained in the bladder, which is consequently small and thin walled, with a short wide urethra without any evidence of bladder neck formation. Occasionally the urethra is longer and the bladder neck discernible though wide and the child may be dry for short periods when lying down.

Surgical correction aims at lengthening the urethra, forming and supporting a bladder neck. In mild cases this can be accomplished by trans-vaginal plication of the internal sphincter and WENDEL and KING (1970) report an encouraging series where this method was employed along with endoscopic control of the tightness of the closure. Sling procedures devised for the control of incontinence in women can also be adapted to this situation if the urethra is long enough and the Millin operation has been used in this way by the author with occasional success. Most urologists however, have concentrated their approach upon the retropubic exposure of the bladder and urethra, usually with section of the fibrous union of pubic bones so that the whole length of the urethra can be laid open. The standard

operation is the DEES (1949) modification of the original Young procedure: a urethral tube is formed from the base of the bladder up to the level of the ureteric orifices by the excision of triangular areas of mucosa from each side of a mid-line strip. The strip is then formed into a tube and the muscle layers are wrapped around this tube in an overlapping fashion. LEADBETTER and FRALEY (1967) have added to this operation the reimplantation of the ureters at a higher level: this has the advantage of securing reflux prevention which is often necessary in these children and at the same time makes more of the bladder base available for construction of a tubular urethra. However, the success of the Young-Dees operation seems related to the degree of development of the musculature in the region of the bladder neck rather than to the precise length of the urethral tube and there can be a disadvantage in reducing the bladder capacity by using a very large part of it to form a urethra. The reported success rate has varied. In the present author's series only 9 out of 17 children obtained perfect continence: second operations after an initial failure have a dismal record though they may be worth attempting if radiological studies show that the bladder neck has remained open and the muscle is still supple. HARROLD, CHAMPION and LORD (1972) have used a method completely severing the bladder from the short urethra and interposing a tube made from a long flap of anterior bladder wall. With this approach there may again be difficulty with a small bladder capacity. It appears that somewhere between a third and half of girls with epispadias will require urinary diversion.

V. Male Epispadias

In the male the bladder and bladder neck are as already described for the female, but the urethra narrows down at the level of the verumontanum and then takes a short direct course towards the dorsum of the penis, opening at the base or anywhere up to the glans itself. There is thus a greater degree of urethral resistance in the male and the mild examples are capable of normal or near normal continence: these numbered 17 out of a series of 54 boys old enough to be assessed in the author's practice. Moreover, the degree of success which can be obtained by surgery is more variable than in girls so that after operation a number are left with normal micturition but some stress incontinence.

The operations designed to achieve control by construction of a bladder neck and proximal urethra out of the base of the bladder are as set out in the previous section, though obviously the posterior vaginal approach is not available and the sling techniques are more difficult to apply in the presence of the developing prostate. As in the girl the exposure should be wide with release of the anterior wall at the base of the penis as well as a trans-symphyseal approach to the bladder neck area.

In a series of 25 boys operated upon by the Young-Dees procedure only 11 could be classified as good results in the author's series. This disappointing figure indicates that there is still room for improvement in technique, though as in girls a small bladder capacity was the factor responsible for some failures. Re-implantation of the ureters at a higher level was not always helpful. Incontinent boys with a good penile repair can be fitted with a penile urinal, others may require diversion.

The degree of penile deformity is variable (Fig. 165) and each child must have a programme of treatment adjusted to his particular problem (MAYS, 1972).The minor cases of glandar epispadias need only a minor correction; the penile cases

without upward chordee require a more formal approach, but an operation with an incision which isolates the urethral strip, rolls it into a tube and buries it between the corpora cavernosa will usually suffice. The tubing process may be carried forward through the glans up to the position of the normal meatus and the glans itself rolled up to give a normal appearance, for in contrast to hypospadias there is plenty of tissue here and little danger of stricture.

In cases with chordee there is a much more difficult problem: the deformity is due to the shortness of the urethral strip and the upward tethering of the corpora cavernosa, or very rarely to an intrinsic anomaly of the corpora themselves so that chordee is only evident upon erection. The techniques designed for hypospadias can be adapted for epispadias: two stage operations which lengthen the urethral strip first and later roll it up are safest, but some plastic surgeons have used free preputial grafts with success. In general men with epispadias are normally potent and have a normal ejaculation, though a few will have retrograde flow of semen due to the relaxation of the bladder neck. The semen was normal in all except one of the author's series reported by HANNA and WILLIAMS (1972).

Sometimes the penis is very small. In these boys the appearance at birth is shown in Fig. 166, the penis being entirely hidden by skin which cannot be retracted without anaesthetic. A short penis with upward chordee associated with complete duplication of the urethra may present an identical superficial appearance. By careful preservation and use of such skin as is available the penis can be made visible and given a shaft clothed with preputial or scrotal skin, but it remains very short and if the glans is exposed micturition in the standing position may be mpossible. However, this type of penis is often associated with a normally con-

Fig. 165

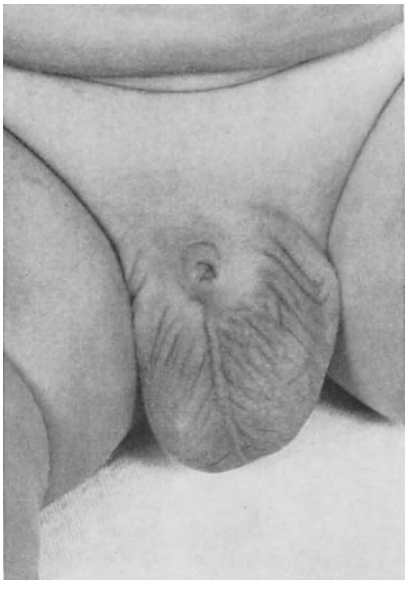


Fig. 166

Fig. 165. Epispadias in the male

Fig. 166. Epispadias with short penis completely buried beneath the abdominal wall skin

trolled bladder neck and at puberty with, if necessary, the addition of testosterone treatment, growth occurs which makes the situation manageable. There is therefore good reason for avoiding any radical treatment in early childhood and for this period it may be helpful to construct a tubular skin extension of prepuce which the boy can pull out through his trousers.

VI. Split Symphysis Variants

A wide range of fascinating variants of the exstrophy/epispadias abnormality are described. Many of them have been summarized by MARSHALL and MUECKE (1970). All of them have the characteristic separation of the pubic bones, though it is notable that many of them are normally continent or respond well to a simple operation for securing continence. The most minor example is the "pubic umbilicus" (Fig. 167) in which this misplacement and the open pelvic ring are the only evidence of the anomaly. A little more severe is the case with a urachal fistula but a covered lower part of bladder and urethra, or a child with a complete bladder but a patch of epithelium on the lower abdominal wall having the appearance of squamous metaplasia in bladder mucosa.

A complete but very thin walled bladder with a huge hernia through the mid-line defect between the separated rectus muscles (Fig. 168) may be associated with a short narrow urethra and poor control in either sex, but micropenis rather than

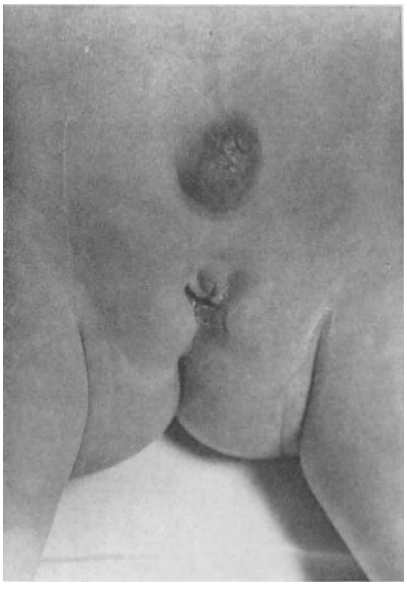


Fig. 167

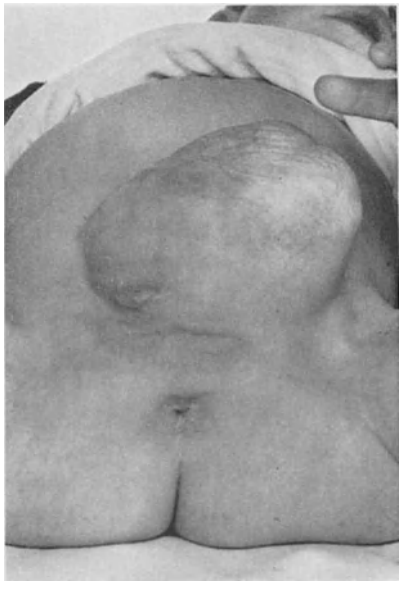
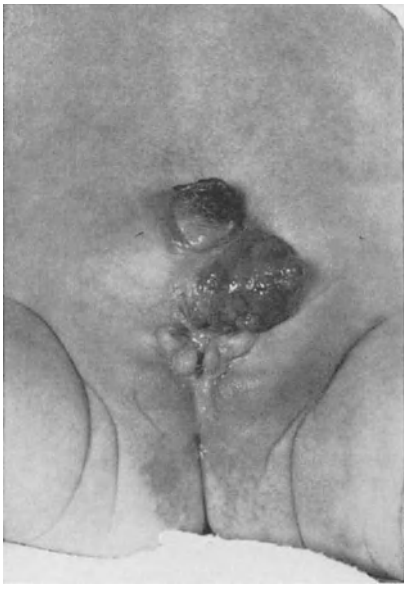


Fig. 168

Fig. 167. Split symphysis variant. A girl ultimately developing normal continence. Pubic umbilicus with metaplastic epithelium. Pubis widely separated

Fig. 168. Split symphysis variant. Boy with enormous mid-line hernia, minute but normally formed penis and short urethra with incontinence

epispadias is likely in such boys and in girls the clitoris is complete. Surgery can be effective in restoring continence and repairing the hernia but the problem of the micropenis remains.



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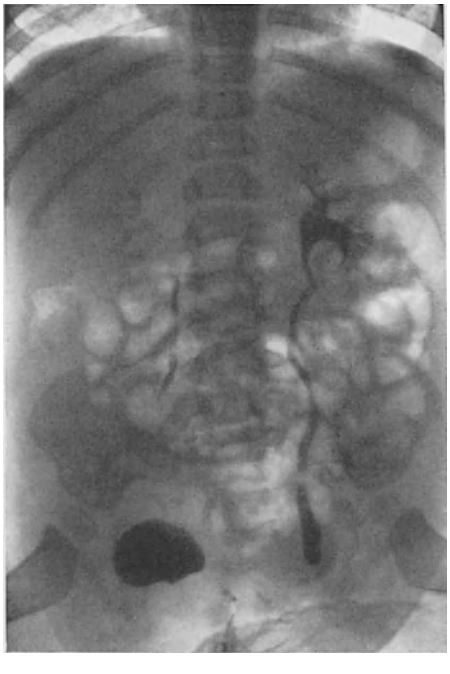

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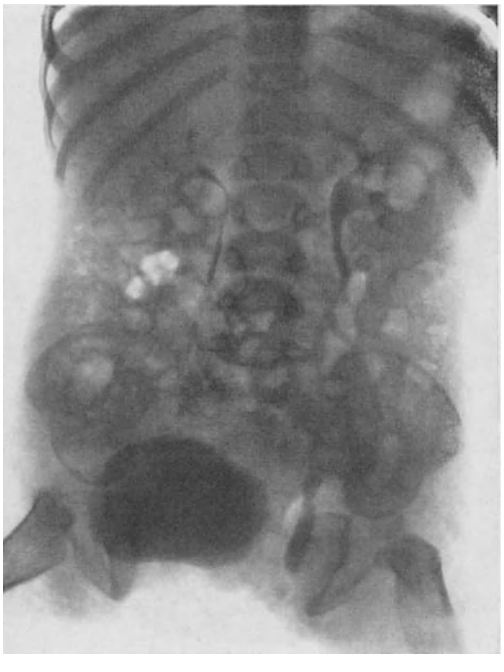


c

Fig. 169a–c. Duplicate exstrophy. a Clinical appearance: exstrophied left bladder. b Intravenous urogram showing normal kidneys, right ureter draining into a complete bladder, the left ureter into the exstrophied bladder. c Intravenous urogram after anastomosis of the two bladders: satisfactory control

U. Urolithiasis

T. M. Barratt and D. Innes Williams

With 9 Figures

I. Introduction

Both the incidence and clinical characteristics of urinary calculi vary greatly from one part of the world to another and from one historical period to the next. Although this variation is seen in adult disease it is even more evident in paediatrics, and recent contributions on the subject from different countries emphasise this wide range (Andersen, 1969; Aurora et al., 1970; Heras Perez, 1969; Lennert, 1967; Strohmenger et al., 1970; Thompson et al., 1967 and Troup et al., 1972). It is, however, possible to discern three patterns of incidence, each with its characteristic predominant form of urolithiasis.

1. The disease is very common and represents a substantial proportion of all admissions to hospital for paediatric surgery. This is the endemic type of disease, predominantly bladder stones in boys.

2. The disease is relatively rare, occurring in children's hospitals perhaps two or three times as often as nephroblastoma. This is the form common in Britain and many countries of Western Europe today: the calculi are largely of the infective, upper tract type.

3. The disease is rare: most of the cases are seen in older children and tend to follow the pattern of adult disease in the same area, so that oxalate calculi are relatively common as, for instance, in Scandinavia and the Southern parts of the United States.

In all countries metabolic calculi can be discovered, they are relatively more important where the overall incidence of calculous disease is small, but since many of them are genetically determined it is likely that they will vary from one population to another. Immobilisation calculi and foreign body calculi are obviously unrelated to the overall pattern of the disease. In this chapter no attempt will be made at a general survey of the stone problem. Recent work on endemic and metabolic disease is reviewed with a full description of the infective type of stone common in Britain.

II. Endemic Calculi

The classical endemic disease of children has a well documented history in many parts of the world, as recorded in the earlier volume. Eckstein (1968) gives a good clinical description of the condition as seen in Turkey, but similar observations have been made in many areas. Characteristically the stones were composed of uric acid, ammonium acid urate or oxalate (Lonsdale et al., 1968); they were found most often as bladder stones in boys (Fig. 171). The peak age incidence was about three years, some occurring during the first or second years

The duplicate exstrophy is another variant (ELLIS, 1971). In the example shown in Fig. 169 a complete bladder with a short narrow urethra was present on the right, a complete exstrophy on the left. Isolation of the exstrophied bladder with anastomosis to the normal resulted in satisfactory continence. All vesical duplications are apt to be associated with a split symphysis.

Isolated ectopic bowel segments may be present on the abdominal wall or in the genital area (Fig. 170). These are quite distinct from the cloacal exstrophies or from examples of exomphalos or dyschesis associated with vesical exstrophy, and the bowel segment can be completely removed: it has the histological features of colon. The bladder in such cases may be complete but the neck is usually incompetent with or without an epispadias deformity.

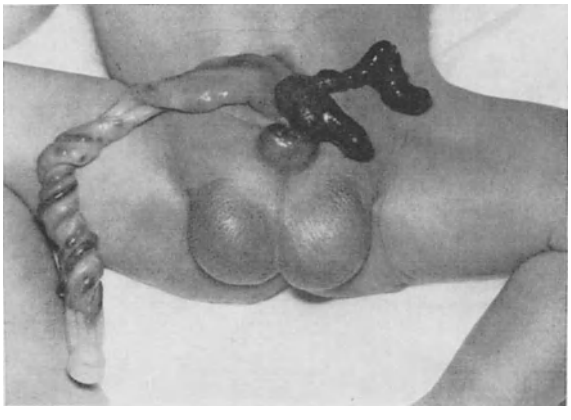


Fig. 170. Epispadias with ectopic bowel on the surface of the abdominal wall. Male neonate. The loop of bowel shown has no connection with the intestinal continuity

of life and relatively few later in childhood. They appeared to have been formed in sterile urine, but secondary infection was not uncommon and could lead to the deposition of mixed phosphates on the surface of the uric acid. The vesical calculi produced characteristic symptoms demanding urgent attention, and it may be that in earlier series in which radiological studies were incomplete the upper urinary tract calculi were more common than was suspected. In ECKSTEIN's series girls constituted only 8% of the total, a fact which he attributed to the shortness of the female urethra, but male predominance has been a characteristic of all stone disease in childhood whether the stone was in the kidney or in the bladder. In India (ANDERSEN, 1968) the endemic stones appeared to be more frequently oxalate than urate, but were otherwise clinically similar.

In England this type of stone was once common, but it ceased to occur with any frequency after the 1920's. LETT (1936) made a clear study showing a decrease in bladder stone in children in London. The change appeared to be the result of better nutrition: in East Anglia, particularly in the town of Norwich, where stone incidence was highest, agriculture depended very largely upon wheat growing and the poor lived almost entirely on wheat bread, often baked in insanitary bakehouses with highly adulterated flour. The improvement of the diet with the introduction of mixed farming co-incided with the abolition of adulteration of the flour and the exact factors responsible were therefore unclear (YUDKIN and

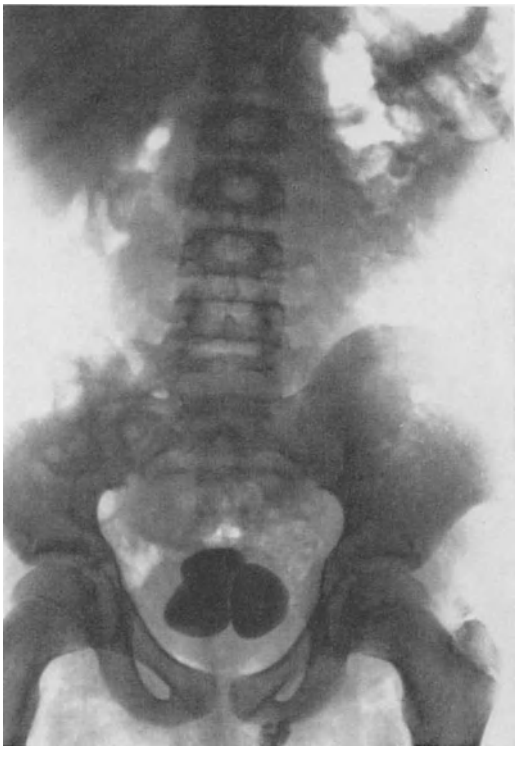


Fig. 171. Endemic calculi. Straight X-ray of an immigrant Pakistani boy with three large vesical calculi composed of oxalate and phosphate. No stone in the upper urinary tract

MACKENZIE, 1964). In other parts of the world the salient factor of the diet in endemic areas has again been a very considerable dependence upon cereal; this has been particularly evident in Mediterranean countries, but also in the Far East. A series of articles by CHUTIKORN et al. (1967) surveys the problem in Thailand: in certain country areas the bladder stone problem reached its peak, 78.9 per of cent all stones being bladder calculi of which 56.8 per cent were in boys under the age of 6 years. Almost all were ammonium acid urate or calcium oxalate. The villages most affected were not necessarily those least well provided with food in the shape of fish or vegetables, but many had seasonal deprivation of water. As far as the infants were concerned, however, it was traditional to supplement or replace breast feeding with a glutinous rice mixture from the first week of life. The authors note that there was a higher incidence in some households rather than in some groups of relatives, indicating perhaps some adulteration of the food rather than specific dietary or genetic factors. In Sicily and in Lebanon, ANDERSEN (1968) reports that the incidence of stone decreased over the past few years along with major changes in diet and standards of hygiene. The same decrease has been observed but not yet reported statistically in Palestine, in Turkey and in Greece. In all these areas a predominantly cereal diet for the poorest infant was customary, and in all episodes of dehydration associated with gastro-enteritis were not unusual. The diet is now largely supplemented by milk and milk products; better hygiene has cut the incidence of gastro-enteritis and better treatment lessened the chances of dehydration. It is interesting to note that in Ireland in the nineteenth century where the diet was extremely poor but consisted largely of potatoes stone was uncommon (YUDKIN and MACKENZIE, 1964). Endemic stone disease has never been common in the negro races, although occasional examples may be seen in boys in Central Africa. All forms of calculous disease appear to be rare in the negro, indicating perhaps some genetic factor.

III. Infective Calculi

The classification of infective calculi is necessarily imprecise since many stones of sterile origin become infected and grow as a result, while many infections consequent upon stasis, foreign body or operation on the urinary tract may predispose to stone formation. Nevertheless, amongst paediatric referrals as seen in Britain and many countries of Western Europe there is a group of stone cases which appear to have urinary infection as the most important factor in their causation, often without any anatomical abnormality of the urinary tract, and these form a sufficiently homogeneous clinical group to justify their description as a disease entity. It is a curious and unexplained fact that this type of disease is rare in Scandinavia and North America and since urinary infections appear to be just as frequent in these countries as in Britain there must be a strong suggestion that other important factors are concerned in the urolithiasis.

1. Incidence

The following account is based on two surveys of cases under the care of the author (WILLIAMS and ECKSTEIN, 1968; GHAZALI, BARRATT and WILLIAMS, 1973). Between 1951 and 1966 there was a total of 126 cases, between 1966 and 1972 120 cases. This may represent an increasing incidence of stone disease, but the

trend of the general referral pattern at the hospitals concerned prevents any firm conclusion. Boys were affected more often than girls in a ratio of approximately 3 : 1. The greatest majority presented before 5 years of age: there were none under 4 months and there was a sharp peak in the 2nd and 3rd years of life, largely due to cases with Proteus infection. This peak was discernible but flattened by a wider spread of age incidence where infection complicated stasis, but contrasts with the absence of a peak in children with sterile stones. Cases came from all social classes and from several immigrant groups. No negroes were affected, although negroes form a part of the ordinary clinical material of the hospitals.

2. Infecting Organisms

The infecting organism was a Proteus in 72 per cent of the second series. E. coli accounted for most of the remainder, though other organisms were cultured from time to time. The infection might change in the same child as a result of pre-operative medication, and in some cases culture of the stone itself revealed a Proteus even when the urine culture had grown an E. coli. There is therefore strong evidence that a Proteus infection is concerned in the causation of the disease, supported by the fact that in all recurrent stones in the second series a Proteus infection had not been adequately controlled. Taking all urinary infections in children, Proteus accounts for no more than 1–2 per cent but there are, nevertheless, still many examples of such infection without complicating stone, particularly in the neuropathic bladder of myelomeningocele. The urea splitting capacity of Proteus is a well known predisposing cause for triple phosphate deposition.

3. Composition of Calculi

The stones were composed of struvite (magnesium ammonium phosphate), apatite (basic calcium phosphate) and smaller proportions of other substances, such as calcium oxalate, urate and carbonate, together with a large proportion of organic material. This is in keeping with the composition of infective stones at all ages, but in children the organic matrix element appears to be particularly important: many children had large masses of partially calcified or completely translucent matrix in the bladder or kidney (Fig. 172) and at times this material was passed per urethram.

4. Site of Calculi

Stones were frequently multiple or formed a cast of the renal pelvis (Fig. 173). Ureteric calculi in dilated ureters with multiple renal calculi and even bilateral disease were relatively common. Sometimes a large vesical calculus was present with many calculi in one kidney and ureter, although the other side was free (Fig. 174).

5. Effects on the Urinary Tract

In the early stages the kidney may remain surprisingly healthy, even in the presence of numerous infected stones, so that removal of these stones can leave an apparently normal urinary tract. Untreated, however, the condition progresses

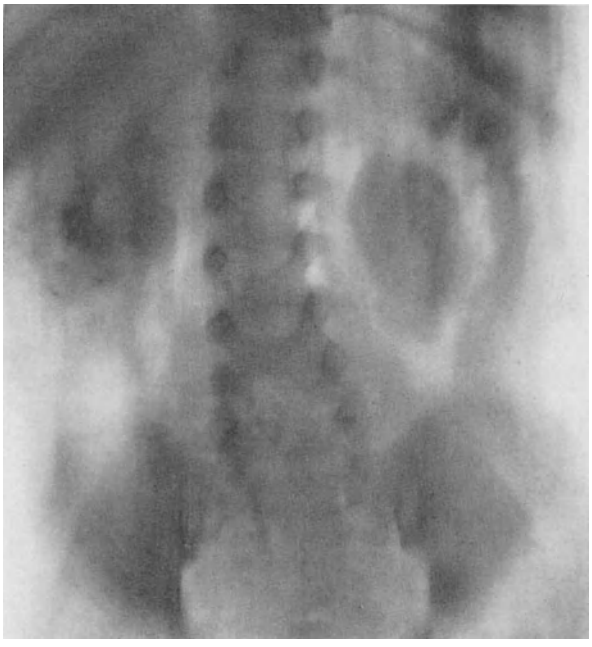


Fig. 172. Partially calcified matrix calculi. Tomogram (Straight X-ray) of a 3 year old boy with heavy urinary infection and renal failure

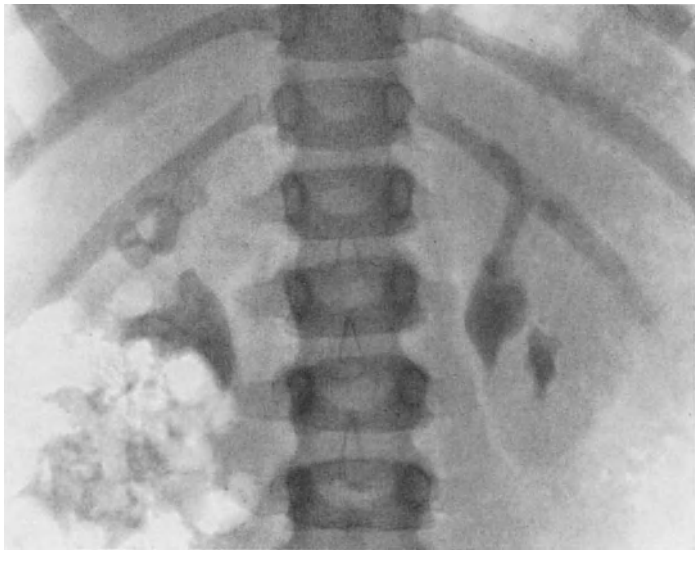
towards renal destruction, either as a chronic pyelonephritic contraction around the stone or as a pyonephrosis in an acute or chronic form (Fig. 175). Perinephric abscess sometimes complicates the picture. At the same time ureteric dilatation becomes irreversible with fibrosis and oedema of the musculature.

In about one quarter of the infected cases a urological abnormality was present which could produce urinary stasis, although it was not always possible to say beyond doubt that the ureteric dilatation or reflux were the cause and not the result of stone formation. CENDRON (1972) has noted an association between reflux and this type of infective stone, but reflux was by no means an invariable feature of our cases; particularly common was a mild degree of dilatation affecting predominantly the lumbar segment of the ureter without any obstructive cause and without reflux (Fig. 176): it was, perhaps, attributable to the paralysing effect of bacterial toxins on the ureteric musculature. Mild hydronephrosis associated with malrotated kidney was noted in a number.

6. Presentation and Progress

The presentation is with the general signs of urinary infection accompanied by fever and often loin pain; indeed there may be little to suggest the specific diagnosis, but haematuria is much more common where stone is present. Small stones may be passed spontaneously, sometimes even quite large ones become sufficiently moulded to allow passage through the lower ureter, but it is rare for the urinary tract to be cleared of stone by spontaneous evacuation. Occasionally

the child is said to have had a urethral discharge but will be found on examination to have passed matrix-like material per urethram. In bilateral disease with ureteric obstruction there may be an acute onset of renal failure, but in one kidney



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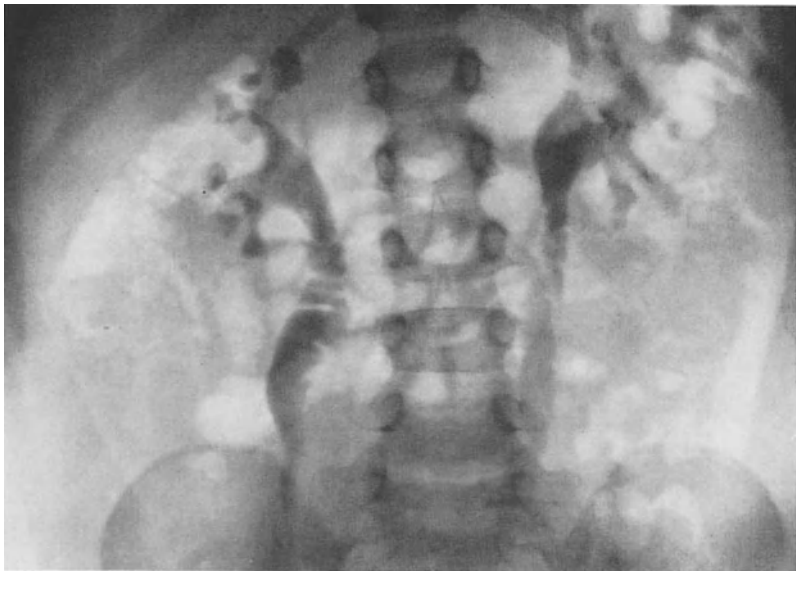

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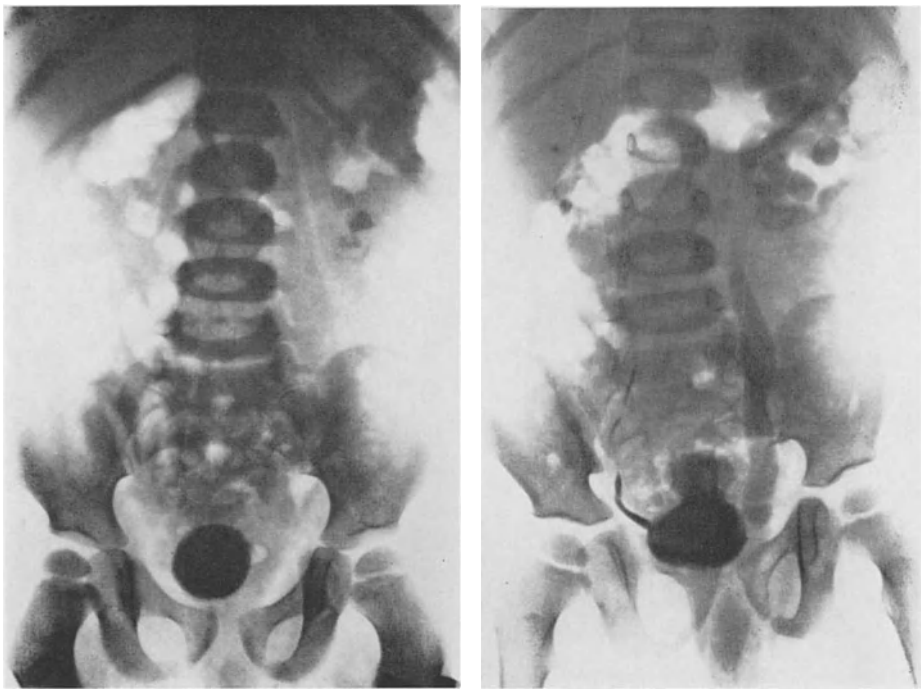
Fig. 173a and b. Staghorn calculi. Boy with haematuria and Proteus infection. a Straight X-ray. b Intravenous urogram showing dilated ureters; no reflux



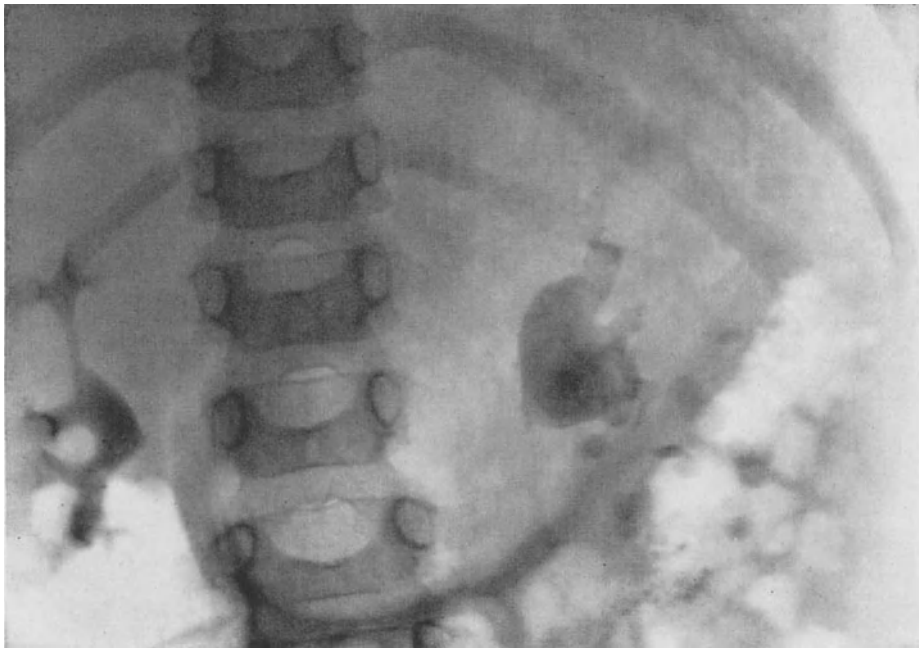
a b

Fig. 174a and b. Renal and vesical calculi. Boy with dysuria and Proteus infection. a Straight X-ray showing left renal and vesical calculi. b Intravenous urogram showing normal right kidney and dilated left ureter; reflux present

at least this is usually recoverable and very few progress to chronic irreversible failure during childhood, though naturally they carry their pyelonephritic scars into adult life and risk a late onset of hypertension and uraemia. With treatment the prognosis is surprisingly good, and provided the urine is effectively sterilised the recurrence rate is low. There is seldom anything in the history to give a clue as to the cause of the stone formation, though in a few infants there is a history of gastroenteritis with dehydration and some have obviously had an excessive milk intake. The investigation of the case will, of course, include the screening for metabolic disease as described in a later section of this chapter and the possible influence of hypercalciuria must be taken into consideration. The diagnosis is made from the pyelograms, though because of the low density of many stones good quality films must be obtained and need at times to be supplemented by tomograms to ensure that multiple stones are not overlooked. A cystogram should also be routine.

7. Treatment

The treatment will almost always be surgical removal of the stone and in general the operations require little comment. Pyelolithotomy with extension into the calices or with supplementary nephrotomy incisions is usually an appropriate procedure. Often much time must be spent in irrigation of all the calices

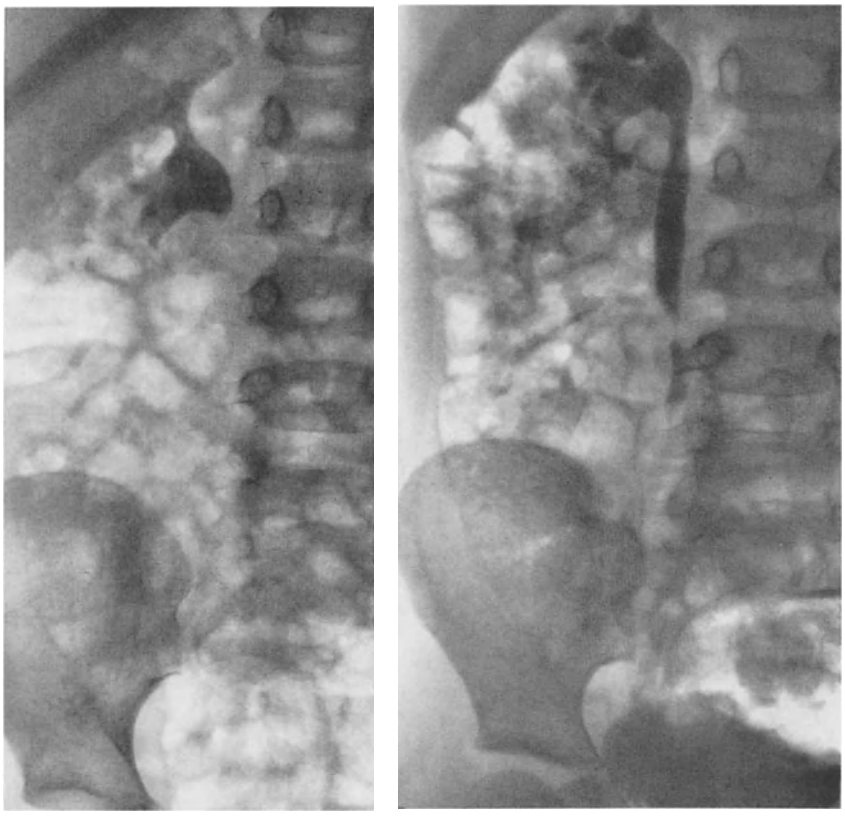


a

b

Fig. 175a and b. Left calculus pyonephrosis. Girl with renal mass and Proteus infection. a Intravenous urogram showing normal right kidney, multiple calculi in non-functioning left kidney. b Nephrectomy specimen

to free them from inspissated pus or matrix material, and at times it is worth leaving nephrostomy tubes for irrigation. There are clearly examples in which nephrectomy is inevitable for pyonephrosis or for a very small scarred kidney, but partial nephrectomy has a relatively small place in childhood stone disease since there are seldom individual dependent calices producing stasis and stone formation. Reconstructive operations at the pelviureteric junction or at the lower end of the ureter are required in some instances and may occasionally be undertaken at the same time as removal of the stones, but in the severely infected urinary tract the ureteric wall is often oedematous and friable, so that it is better to remove the stones and sterilise the urine, being prepared to perform reconstructive surgery at a later date. The completeness of stone removal must always be checked by X-rays of the exposed kidney on the operating table and again by plain film before discharge from hospital. Often the operative procedure must be covered by antibiotic treatment and post-operatively it is essential that the sterility of the urine is assured before the child is discharged. Follow-up should consist of monthly urine cultures for the first year, together with six monthly X-rays of the urinary tract.



a b

Fig. 176 a and b. Infective renal calculus. a Straight X-ray. b Intravenous urogram showing ureteric dilatation without either obstruction or reflux

IV. Metabolic Calculi

In spite of a considerable body of research, the metabolic factors underlying the formation of urinary calculi remain incompletely understood (SMITH, 1968; HODGKINSON and NORDIN, 1969; KING, 1971), particularly in children (DAESCHNER et al., 1960; DAVIS, 1965; WENZL et al., 1968). The physicochemical factors leading to the formation of urinary calculi are multiple and their interactions complex. It is therefore not to be expected in most cases that a single cause for urinary lithiasis will be found, and it is more probable that its genesis is multifactorial. Nevertheless, in certain situations, metabolic aberrations lead to one factor being dominant.

1. Disorders of Calcium Metabolism

a) Hypercalcaemia

The hypercalcaemic syndromes of early life are more commonly complicated by nephrocalcinosis than by urolithiasis. Causes of hypercalcaemia and nephrocalcinosis in this age group include vitamin D poisoning, idiopathic hypercalcaemia in its mild (LIGHTWOOD, 1952) or severe form (FANCONI et al., 1952), hypothyroidism (ROYER and MATHIEU, 1962) and hypophosphatasia (BARTTER, 1966). Hyperparathyroidism has only rarely been described in children (NOLAN et al., 1960; MACGREGOR, 1969), and bone lesions, which may be rachitic, predominate. In older children, however, renal calculi may be the presenting clinical feature (FOURMAN and ROYER, 1968). The rare neonatal (HILLMAN et al., 1964) and familial forms (endocrine adenomatosis; WERMER, 1964) have not usually been complicated by urolithiasis.

b) Hypercalciuria

Standards for the urinary excretion of calcium in healthy children are inadequately established. Data on American children collected in the 1940's (KNAPP, 1947; MACY, 1941) or in French children (ROYER, 1961; CUISINIER-GLEIZES et al., 1963; PAUNIER et al., 1970) may not apply to other nationalities or other decades for there are considerable variations in diet and habits of prescription of vitamin D. These authors report the upper limit of urinary calcium excretion to be about 6mg/kg/24 h. However, in 52 healthy British children aged 1–14 years, GHAZALI and BARRATT (1973a) found the upper limit to be 4mg/kg/24 h. Because of the difficulties of ensuring accuracy of a 24 hour urine collection in young children it is prudent to measure the creatinine excretion simultaneously. The upper limit of the normal calcium/creatinine concentration ratio in children is 0.25 mg/mg (GHAZALI and BARRATT, 1973a), slightly lower than the upper limit of 0.28 mg/mg reported by NORDIN (1959) in adults. The importance of dietary calcium intake in the definition of hypercalciuria (PEACOCK et al., 1967) has not been systematically examined in children, although in PAUNIER et al. 's (1970) study, there was no correlation between dietary and urinary calcium.

Urinary calcium excretion is increased in the hypercalcaemic syndromes described above. Normocalcaemic hypercalciuria may be due to increased gastrointestinal calcium absorption;-vitamin D excess and idiopathic hypercalciuria (ROYER et al., 1962; BEILIN and CLAYTON, 1964); to increased bone mobilisation of calcium;- immobilisation (WHEDON and SHORR, 1957), hyperadrenocorticism (MASSRY et al., 1968), and neoplastic deposits in bone; and to some renal tubular

disorders such as hypercalciuric rickets (DENT and FRIEDMAN, 1964), Wilson's disease (MORGAN et al., 1962) and renal tubular acidosis (see below).

During immobilisation, calcium is lost from the skeleton. Even slight activity reduces the negative calcium balance, and it is also important to maintain an adequate urine output in children at risk. A similar phenomenon occurs after any surgical operation; although rarely the cause of calculus formation, an erroneous diagnosis of hypercalciuria may be made in a stone patient if the urine samples are collected during the post-operative period.

Many children with apparently straightforward infected stones also have hypercalciuria (GHAZALI et al., 1973; GHAZALI and BARRATT, 1973b). The relevance of this observation to the formation of struvite (magnesium ammonium phosphate) calculi is not readily apparent, though all of these stones also contain apatites as well (LONSDALE and SUTOR, 1969). The hypercalciuria usually wanes after removal of the calculi, and may be merely an epiphenomenon of a severe infective illness.

Undue attention has perhaps been directed to the 24-hour calcium excretion: a more relevant observation might be the peak of urinary calcium concentration-see, for example, the exaggerated response of urine calcium concentration to oral carbohydrate loads in individuals with calcium oxalate calculi (LEMMAN et al., 1969). Most children with infective stones also have an exaggerated calciuretic response to an oral load of milk (GHAZALI and BARRATT, 1973b), and the peak incidence of such calculi is approximately at the age of maximum milk intake. Further studies are required in this field before any conclusions can be drawn.

c) Defects of Urinary Acidification

Of the hypercalciuric syndromes described above the paediatric urologist will be most troubled by distal renal tubular acidosis (RTA) (ALBRIGHT and RIEFENSTEIN, 1948; WRONG and DAVIES, 1959) since recurrence of calculi is typical. Two types of RTA have been defined (RODRIGUEZ-SORIANO and EDELMANN, 1969). Distal RTA (syn: gradient, ALBRIGHT) is characterised by a failure to establish a hydrogen ion gradient across the tubular epithelium. A metabolic acidosis with inappropriately alkaline urine develops and there is a renal leak of sodium, potassium and calcium. Osteomalacia may occur; this and the hypercalciuria diminish as the metabolic acidosis is corrected with alkali. Citrate excretion is low, particularly in relation to the urine pH (DEDMON and WRONG, 1962) which further facilitates calculus formation. The combination of nephrocalcinosis and urinary calculi is very characteristic of this condition (Fig. 177) but may also be seen in hypercalcaemic states. Methods for establishing the diagnosis of RTA are considered on p. 11. Treatment consists of the administration of alkali—Albright's solution or sodium bicarbonate—in a dosage of about 2 mEq/kg/24h with potassium supplements. Surgery is sometimes necessary to remove stones.

Proximal RTA (syn: RTA, bicarbonate losing) has only recently been described as an isolated entity (RODRIGUEZ-SORIANO et al., 1967). The defect lies in a quantitative failure of bicarbonate reabsorption: when the filtered bicarbonate load is low, urinary acidification occurs normally. In these children there is growth failure; hypercalciuria and nephrolithiasis do not occur. The condition appears to be transient in some (NASH et al., 1971).

It is now difficult to interpret the earlier reports of transient hyperchloraemic acidosis of infancy (LIGHTWOOD, 1936; LIGHTWOOD et al., 1953) for the condition has now largely disappeared (LIGHTWOOD and BUTLER, 1963). Some of the earlier

cases may have been examples of pyelonephritis, hypercalcaemia or mercury poisoning from teething powders. They were only rarely complicated by nephrocalcinosis.

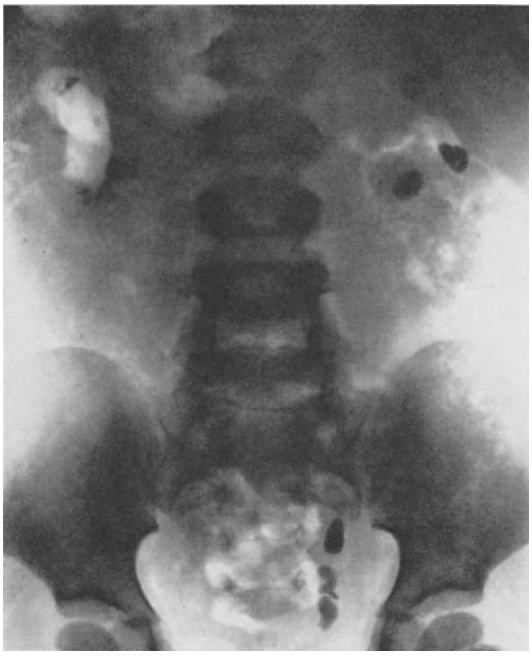


Fig. 177. Multiple calculi in renal tubular acidosis. There is both nephrocalcinosis and stone formation

2. Disorders of Oxalate Metabolism

The hyperoxalurias are genetic disorders of glyoxylate metabolism characterised by recurrent calcium oxalate nephrolithiasis progressing to chronic renal insufficiency and extrarenal deposits of calcium oxalate crystals (Williams and Smith, 1972). Both nephrocalcinosis and urolithiasis occur and acidification defects may also develop; the disease can resemble distal renal tubular acidosis rather closely (Dent and Stamp, 1970). In 12 per cent symptoms occur before the age of one year, and in 65 per cent before the age of 5 years. Cases may present with haematuria or the passage of stone during the first few years of life and multiple small calculi with nephrocalcinosis are characteristic whilst large branched renal calculi are rare. In some children the condition is rapidly progressive and death from renal failure occurs within four or five years. In others progress is slow (Fig. 178) and the disease is sometimes first recognised in adult life. The disease is inherited as an autosomal recessive, and clinical patterns are similar within affected sibships.

Considerable progress has recently been made in the elucidation of the biochemical abnormality in these diseases. In Type I hyperoxaluria there is increased

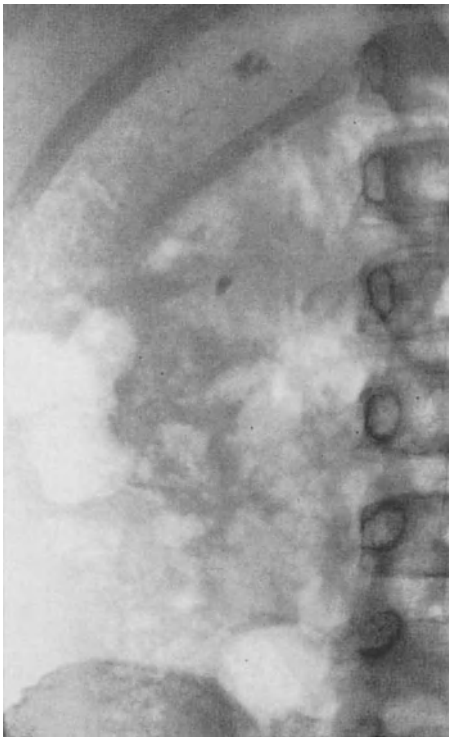


Fig. 178. Hyperoxaluria. Boy with recurrent formation of calculi in the right kidney, most of which have been passed spontaneously

urinary excretion of oxalic, glycolic and glyoxylic acid. Urinary oxalate excretion in healthy adults varies between 10 and 55 mg/24 hours, and it is similar in children if corrected to 1.73 m^2 surface area (Gibbs and Watts, 1969). In hyperoxalurics, excretion usually exceeds 100 mg/24 hours but falls with advancing renal failure. There is a deficiency of soluble 2-oxo-glutarate: glyoxylate carboligase activity (Koch et al., 1967) resulting in a failure of conversion of glyoxylate to α-hydroxy-β-keto-adipate and its diversion to oxalic acid synthesis.

A new variant of hyperoxaluria (Type II), which is clinically indistinguishable from Type I, has been described by Williams and Smith (1968). In this form there is increased excretion of L-glyceric acid and oxalic acid. The deficient enzyme is D-glyceric dehydrogenase; the mechanism by which this results in hyperoxaluria is discussed by Williams and Smith (1971).

Treatments directed at reducing oxalate production with, for example, dietary oxalate restriction, pyridoxine (Gibbs and Watts, 1967) or calcium carbimide (Solomons et al.; 1967) have met with only limited success. Dent and Stamp (1970), however, claim that substantial protection from urolithiasis is conferred by the administration of magnesium hydroxide: magnesium salts inhibit precipitation of calcium oxalate. Surgical treatment should be confined to removing obvious obstructing calculi since recurrences are almost certain and operative damage to the urinary tract must be minimised. Renal transplantation has been

complicated by the development of oxalate deposits in the transplanted kidney (WILLIAMS and SMITH, 1972).

It should be emphasised that not all individuals who form calcium oxalate calculi, even with a familial tendency (RESNICK et al., 1968), have hyperoxaluria.

3. Disorders of Purine Metabolism

a) Uric Acid Calculi

Uric acid is a weak acid with a pK of 5.6. Below this pH it exists predominantly in the unionised form, which is considerably less soluble than the ionised sodium urate; in contrast to calcium phosphate, acid urine favours its precipitation (GUTMAN and YU, 1968). These stones may develop in situations of uric acid over-production such as leukaemia or lymphoma (PASSWELL et al., 1970) especially after cytotoxic chemotherapy (KRAKOFF and MURPHY, 1968) but occasionally as the presenting feature of leukaemia (APPLEYARD, 1971). Uric acid gravel in both kidneys may lead to acute renal failure without radiological evidence of opaque calculus. Allopurinol reduces uric acid production and alkalinisation of the urine increases its solubility; both are valuable agents in the management of this complication of leukaemia therapy.

Primary gout with uric acid calculi occasionally occurs in older children (GUTMAN and YU, 1968), Another variant is the Lesch-Nyhan syndrome: a disorder characterised by progressive choreoathetosis, self mutilation and hyperuricaemia (LESCH and NYHAN, 1964; KELLEY and WYNGAARDEN, 1972) with uric acid calculi (HOWARD and WALZAK, 1967): the deficient enzyme is guanine-hypoxanthine phosphoribosyl transferase (SEEGMILLER et al., 1967). Hyperuricosuria with calculus formation may also occur in Type I glycogen storage disease (glucose-6-phosphatase deficiency); the mechanism is not clear (HOWELL, 1965).

In some patients, particularly males of Mediterranean stock, there is a tendency to uric acid stone formation without hyperuricaemia or hyperuricosuria; the syndrome is sometimes familial, and is occasionally seen in childhood (De VRIES et al., 1962). These individuals tend to produce excessively acid urine, favouring uric acid precipitation, but ammonia excretion is normal (METCALFE-GIBSON et al., 1965) and not, as had been previously suggested, reduced (HENNEMAN et al., 1958).

Bladder calculi in children in endemic areas of urolithiasis contain a high proportion of ammonium acid urate (GERSHOFF et al., 1963), as discussed on p. 280.

Uric acid crystalluria is common in the newborn and occasionally at post-mortem urate deposits are found in the renal medulla—uric acid "infarcts" (SMITH, 1969). Uric acid excretion on a body weight basis is less in infants than in adults, (BARLOW and MCCANCE, 1948) and the clinical significance of these observations is not clear.

b) Xanthinuria

Xanthinuria is a very rare condition (DENT and PHILPOT, 1962; WYNGAARDEN, 1972) in which there is a deficiency of xanthine oxidase and hence a failure of conversion of xanthine to uric acid. As xanthine is relatively insoluble in acid urine, calculi develop which may be radiotranslucent. A xanthine nephropathy may also be precipitated by the use of allopurinol in patients with very high uric acid excretion rates (BAND et al., 1970).

4. Disorders of Amino-Acid Metabolism

a) Cystinuria

In cystinuria there is a defective tubular re-absorption of the dibasic amino-acids cystine, ornithine, arginine and lysine from the glomerular filtrate (Dent and Rose, 1951; Crawhall and Watts, 1968; Thier and Segal, 1972); the transport defect is also present in the gut in some individuals (Milne et al., 1961). There is more than one mode of inheritance (Harris et al., 1955); Rosenberg et al. (1966) recognise three variants. The only clinical abnormality in these individuals is recurrent formation of urinary calculi. A presumptive diagnosis may be made on the basis of the purple colour which develops when the urine is mixed with cyanide-nitroprusside, and it should be confirmed with further studies of the urinary amino-acids by chromatography or high-voltage electrophoresis.

Cystine stones may occur in children at all ages. In the very young bladder calculi are not uncommon; later in childhood renal calculi are predominant, often large rounded stones or branched stones in the renal pelvis with multiple rounded calculi in the dilated calices. Some cystine stones may be passed spontaneously and in cases of renal colic where no explanation is evident the urine should always be tested for cystine. All cystine calculi are opaque to X-rays, though they are not as dense as many calcium containing stones and often not as dense as the opaque medium during intravenous urography (Fig. 179).

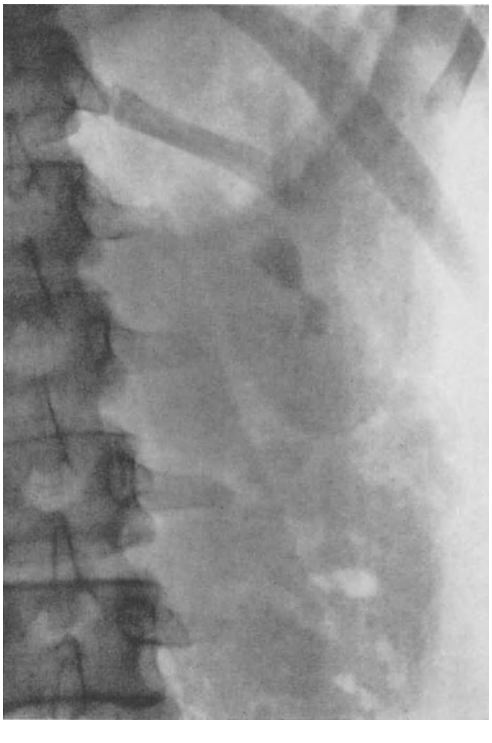


Fig. 179. Cystinuria. Renal calculi in a girl of 10 years with a familial incidence. Controlled by high fluid intake

The attractive simplicity of the view that cystinuria represents a genetic deficiency of the transport system of the dibasic amino-acids is threatened by the genetic heterogeneity alluded to above, by the observation that the cystine clearance frequently exceeds the inulin clearance (CRAWHALL et al., 1967) and by the recognition of phenotypes in which there is an isolated failure of re-absorption of cystine (BRODEHL et al., 1967) or of the other members of the group without involvement of cystine (hyperdibasicaminoaciduria: WHELAN and SCRIVER, 1968). To encompass these genetic variants SCRIVER (1969) has evolved a complex scheme to describe amino-acid transport systems.

The solubility of cystine in urine of pH less than 7.5 is about 300 mg/litre. Above this pH there is a substantial increase in solubility, but it is difficult to maintain the urinary pH consistently in this region with alkali therapy. A knowledge of the quantitative cystine excretion enables the minimum safe urine volume to be calculated: in adult patients who excrete about 1 g/24 hours this is approximately 4 litres daily.

A high fluid intake, sustained throughout the day and night prevents the formation of cystine stones and may result in their dissolution (DENT and SENIOR, 1955; DENT et al., 1965). The treatment is inconvenient and difficult to follow, but has the merit of being cheap and effective. An alternative treatment with D-penicillamine (CRAWHALL et al., 1963) results in the excretion of the mixed cysteine-penicillamine disulphide, which is more soluble than cystine. The drug is expensive and has many side effects (CRAWHALL and WATTS, 1968); the latter may, however, be less with the newer derivative N-acetyl-D-penicillamine (STOKES et al., 1968; STEPHENS and WATTS, 1971) These drugs should be reserved for cases in whom continuous hydration fails. Surgery is occasionally required for the removal of bladder stones, and of obstructing renal and ureteric stones, particularly if complicated by infection.

b) Glycinuria

One family has been described in which a renal leak of glycine was accompanied by the tendency to calcium oxalate nephrolithiasis (DE VRIES et al., 1957). SCRIVER (1972) considers this case to be a heterozygote manifestation of iminoglycinuria, and the relationship to nephrolithiasis is unclear.

5. Screening Investigations for Metabolic Stones

The extent to which a child with urolithiasis should be screened for metabolic abnormality varies in different clinical circumstances: thus sterile urine, nephrocalcinosis, recurrence and the development of calculi in older children should lead to close metabolic scrutiny; on the other hand the yield of metabolic diagnoses from screening children with renal calculi and Proteus infection is small, apart from the hypercalciuria described above.

In all children the plasma calcium concentration and 24-hour pre-operative urinary calcium excretion should be measured and the urine screened for cystinuria (amino-acid chromatography is preferable to the nitroprusside test). Under suspicious circumstances the 24-hour urinary oxalate excretion and plasma uric acid should be estimated. An observation of urine pH of 5.3 or less under any circumstances, either spontaneous or following ammonium chloride loading (see p. 11) excludes the diagnosis of distal renal tubular acidosis. If the urine is infected, particularly with Proteus, it may prove very difficult, however, to exclude this diagnosis, and formal examination of the capacity to acidify the urine should be deferred until the stone has been removed, and the urine sterilised.

V. Neoplastic Disease: The Kidney

D. Innes Williams
With the assistance of J. Bond

With 5 Figures

I. Introduction

Undoubtedly the most important advances of the past decade in the treatment of nephroblastoma have been the introduction of an effective form of chemotherapy and the trend towards concentrating affected children in a small number of centres able fully to study and treat this disease. There has been a definite fall in overall mortality as a result, but the process of concentration of cases and the devising of treatment trials have not been without their problems. With the increasing efficiency and enthusiasm involved in a more hopeful treatment, results improve, and this improvement may be wrongly attributed to the new drug in use. Once any improvement in such a dangerous malady has been reported it then seems unethical to refuse a similar treatment in subsequent cases: therapy thus becomes more aggressive and more prolonged. This may well bring a bonus in the shape of a cure for some children with disseminated growth but is not without its dangers, as shown by the disastrous results of cytotoxic drugs used in neonates. It therefore becomes increasingly important to distinguish the highly malignant growths with poor prognosis from the simpler forms responding to simple surgery, thus reversing the previous trend of including under the term nephroblastoma (a mixed tumour) all growths arising in the kidney in children. The neonatal forms and the multilocular cysts, for instance, have a very good prognosis and their inclusion in any trial would significantly distort the conclusions.

There is some hope that a scientific basis for drug treatment can be worked out experimentally: as reported by Priestley (1972) it has been possible to obtain tissue cultures of a spontaneously occurring animal (rat) Wilms tumour, and then to transplant it back into animals which can be treated by a variety of drugs or irradiation. Jasmin and Riopelle (1970) succeeded in inducing nephroblastoma in rats by dimethylbenzanthracene. Such methods have great potentialities but there is still some danger of applying animal results uncritically to human therapeutic problems.

II. Incidence

Nephroblastoma is second only to malignant disease of the central nervous system as the commonest single organ malignant tumour of childhood. Johnston et al. (1969) give an incidence of one for every 13500 live births; the tumour may appear at any age but has a peak incidence between six months and three years. Tumours presenting in the neonatal period are more likely to be hamartomatous or fibrosarcomatous. The sex incidence is equal though a few reports give a slight male predominance. There is no preference as to side, but bilateral disease

has been recognised more frequently in recent years and may constitute up to 10 per cent of tumours at first presentation.

A familial incidence is occasionally recorded (FITZGERALD and HARDIN, 1955) and a genetic factor must be suspected in the cases reported of co-incidence of congenital aniridia with nephroblastoma (WOODARD and LEVINE, 1969). Wilms tumour is not infrequently reported in horseshoe kidney and JAGASIA and THURMAN (1965) comment upon the association between congenital anomalies and Wilms tumour, but BERRY et al. (1970), reviewing embryonic tumours as a whole, did not find any remarkable correlation with other congenital mal-formations.

III. Pathology of Nephroblastoma

1. Histology and Origin of Neoplasia

The general pathological appearance of nephroblastoma is well known and needs no further description. Histologically all tumours contain some undifferentiated renal blastema with, in addition, masses of loose mesenchyme, collagenous connective tissue, cartilage, osteoid and adipose tissue and smooth or striated muscle. Primitive tubules and glomeruli may be formed, though they are less likely to be seen in metastases than in the primary tumour and appear to be discouraged by radiotherapy. The ultra structure of the epithelial cells has been studied by ITO and JOHNSON (1969) who find support for the view that tumour arises from metanephric blastema cells, and it is interesting to speculate upon the relation of the tumour to nodular renal blastemata found in otherwise normal kidneys or in association with congenital anomalies. BOVE et al. (1969) described these nodules consisting of primitive undifferentiated cells, often under the capsule of the kidney: it is presumed that most involute spontaneously, but if they develop into nephroblastomata then their multiplicity would account for the multicentric origin of some tumours.

2. Grading of Tumour

When assessing the results of most tumours some form of histological grading has been of value, but this type of classification is difficult to achieve in nephroblastoma. BODIAN and RIGBY (1964) described seven types based upon the degree of differentiation and claimed some relation to survival, but the variable appearance of the tumour as a whole makes it difficult to substantiate one grading for the whole tumour. It is sometimes stated that infants, who are known to have a better prognosis, have a better differentiated growth and it is certainly true that a well encapsulated tumour with cystic change is common in this age group. Moreover, the cystic tumours may sometimes be difficult to distinguish from multilocular cysts in which no true tumour tissue is present, as in the cases reported by USON and MELICOW (1963).

3. Staging of Tumour

Spread of nephroblastoma occurs within the renal substance by direct infiltration, though many cases remain well encapsulated locally despite metastases. Direct extension from the kidney to surrounding tissues is a relatively late occurrence. Lymph node metastasis is well recognised, though its exact frequency is a matter of dispute. In many nephroblastomata enlarged soft glands are found

in the para-aortic region, which are histologically free of tumour on ordinary examination. MARTIN and REYES (1969) claim, however, that a more careful examination will reveal a much higher incidence of lymph node involvement and advocate routine block dissection of the node area.

Spread down the ureter is uncommon, but cannot be ignored as a possibility (TAYKURT, 1972), and demands a full removal of the ureter. Spread occurs unto the spermatic vein on the left side and this, rather than simple pressure, is the cause of an occasional varicocele.

Pulmonary metastasis is the most striking feature of many cases and not infrequently appears for the first time within six months of operation upon an apparently well localised tumour. Although multiple secondaries are usual, solitary examples are well recognised and give an opportunity for local excision. These solitary metastases may well be pleural, or possibly mediastinal rather than pulmonary, but this does not preclude a good prognosis following surgery. In general it now appears to be possible to control the disease in approximately one third of children with pulmonary metastases.

Liver metastases are common, osseous and cerebral secondaries are very rare. All these forms carry a very bad prognosis and are scarcely ever amenable to treatment. Recurrence after primary nephrectomy sometimes takes the form of huge retroperitoneal masses of growth and it has been found in general that surgical excision of such tumours leads to no permanent improvement.

In all controlled treatment studies staging of nephroblastoma is essential, and the following scheme is generally acceptable.

Stage I. Tumour encapsulated and removed entirely. The tumour does not reach the capsule of the kidney, there is no spillage of tumour at operation and no para-aortic node involvement.

Stage II. There is extension beyond kidney capsule by local infiltration, extension along renal vein or involvement of para-aortic glands, but the surgeon considers all macroscopic disease removed.

Stage III. There is extension of tumour beyond the kidney: spillage occurs at operation, or extensive tumour has been left. Peritoneal metastases are present.

Stage IV. Extension to lung, liver, brain and bones found at diagnosis.

Stage V. Bilateral renal involvement.

Some authors would prefer to put in Stage II very large tumours of greater volume than 550 ccs., shown by GARCIA et al. (1963) to have a relatively bad prognosis even though apparently confined to the kidney.

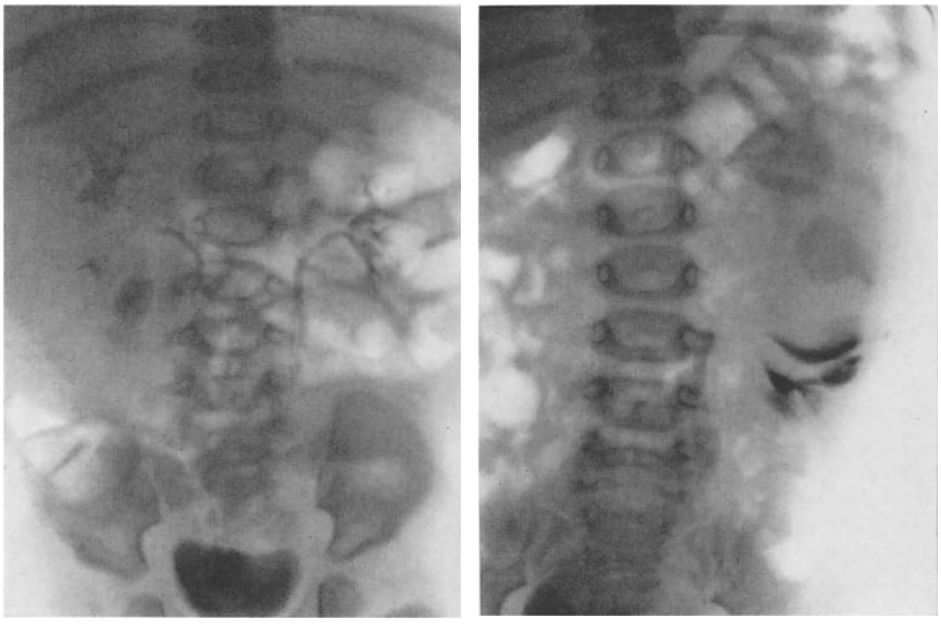
4. Growth Rate

Often the development of a renal mass, metastasis and death will occur within one year of the first symptom, but the growth rate is variable and very slow growing tumours are recorded as, for instance, the child described by HAAS and JACKSON (1961) where a nephrectomy was performed at the age of 4 years, a lobectomy for metastasis at 9 years, a laparotomy for recurrence at 12 years with death at 14 years. By contrast an example of very rapid growth is given by RABINOWITZ and BAGNASIO (1970): no abdominal mass was found at birth on very careful and deliberate search, yet a huge mass was present three months later. COLLINS (1955) suggested that the total growth period of the tumour, i. e. the child's age at presentation plus nine months representing the gestation period, might be valuable in testing the results of treatment, and that if there had been no clinical recurrence within a similar period after treatment a permanent cure was likely. PLATT and LINDEN (1964) tested this criterion of cure against a two year

survival rate and found little difference between the two: there were 5 exceptions to COLLINS' rule among 83 children and 4 exceptions to the two year survival rule. However, with the increased use of chemotherapy in repeated courses there can be no doubt that a longer survival time can be recorded without permanent cure.

5. Bilateral Disease

Bilateral Wilms tumours are now being reported at a rate of 6–11 per cent cases at presentation (RAGAB et al., 1972), and since in these there is no other evidence of metastasis it is usually assumed that a double primary is responsible. Most often the two tumours are concurrent, though asymmetrical, and it is obligatory to examine the apparently healthy kidney with care, both radiologically and at the time of operation, on order to detect a relatively small second primary. In such cases the growth process of the smaller tumour can be very slow, and a number are on record (LEEN and WILLIAMS, 1971) in which a prolonged survival has followed nephrectomy with radiotherapy to the remaining kidney. As with single primaries other cases present with enormous and rapidly growing tumours which are fatal within a few months. Perhaps the most discouraging are the cases in which the second primary appears two or more years after an apparently successful treatment of the first side (Fig. 180). In the author's experience such cases have had rapidly progressive disease and an early demise.



a b

Fig. 180a and b. Bilateral nephroblastoma. Infant girl presenting with abdominal tumour. a Intravenous pyelogram at presentation. The right kidney is distorted by a lower pole tumour, the left is normal radiologically and at operation. b Pyelogram 7 months after right nephrectomy. The left kidney is now enlarged by a rapidly growing tumour. Slight response only to radiotherapy and chemotherapy. Rapid deterioration

6. Nephroblastomatosis

One form of tumour is difficult to fit into the general classification. This is the bilateral nephroblastomatosis, described by LEE-TSUN and HOLMAN (1961), and later by ANDERSON et al. (1968). The two kidneys are symmetrically enlarged but not distorted by widespread infiltration by nephroblastoma-like cells. ANDERSON's case responded well to radiotherapy and was alive five years after the initial biopsy at the age of ten months. LIBAN and KOZENITZKY (1970) record metanephric hamartomata in one child and nephroblastomatosis in the sibling, and believe that the two have a similar origin, but LEBREUIL (1970), reporting a premature infant, regards the disorder as a form of dysplasia rather than tumour.

IV. Pathology of Other Renal Tumours

1. Neonatal Tumours

In older reports, neonatal Wilms tumour was mentioned as an interesting rarity and solitary examples with a good prognosis were recorded. In recent years, however, there has been a spate of papers on this subject, each describing many examples. It would be interesting to enquire whether this indicates a true increase in the incidence of the disease, and if so whether any environmental change could be responsible. It has been the author's experience at The Hospital for Sick Children, that neonatal tumour was exceptionally rare until about ten years ago, but has been seen rather frequently since then.

It has become clear that the majority of neonatal tumours cannot properly be classified as nephroblastomata, although perhaps some of them should be included in that category (FAVARA et al., 1968). The characteristic tumour was, however, better described by BOLANDE et al. (1967) as a congenital mesoblastic nephroma. Histologically the chief feature of the tumour is a leiomyomatous or fibrosarcomatous appearance. The mass is usually solid and appears at its margin to be infiltrating the parenchyma of the kidney (Fig. 181, 182), so that some renal elements are incorporated within it, but tubule formation within the tumour is rare. Metastases rarely, if ever, occur and it is probably correct to describe this tumour as a hamartoma (WIGGER, 1969). The term fibroma is applied by HAMANAKA et al. (1969), leiomyoma by MOLLARD et al. (1968). The ultra structure of the hamartomata has been described by GARCIA BUNUEL and BRANDES (1970).

Neonates with this disorder have ordinarily presented with a large abdominal mass which is exceptionally hard on palpation. They have not suffered haematuria. The results of treatment by nephrectomy alone have been exceptionally good and reported mortality has almost always been the result of chemotherapy, particularly with the use of Actinomycin D, operative accident or radiotherapeutic damage.

It is interesting to speculate on the fate of these cases if untreated; since they do not cause serious symptoms and are benign, it would be anticipated that they might be encountered later in childhood, but after the infantile period a fibroma or a leiomyoma is a very rare finding. The possibility that some undergo malignant change later in their growth period cannot be excluded.

2. Rhabdomyosarcoma

Some striated muscle may be found in nephroblastoma, but occasional cases of pure rhabdomyosarcoma are recorded in childhood (e. g. MALEK et al., 1971;

Reziciner et al., 1970). The author has recently treated a four month old infant presenting with an abdominal mass and vomiting; the latter symptom proved to be due to a cerebral metastasis rather than to the renal tumour.

3. Leiomyosarcoma

Apart from the neonatal cases, some of which are described under this nomenclature, leiomyosarcoma is exceptionally rare in children. The literature of this subject has been reviewed by Loomis (1972).

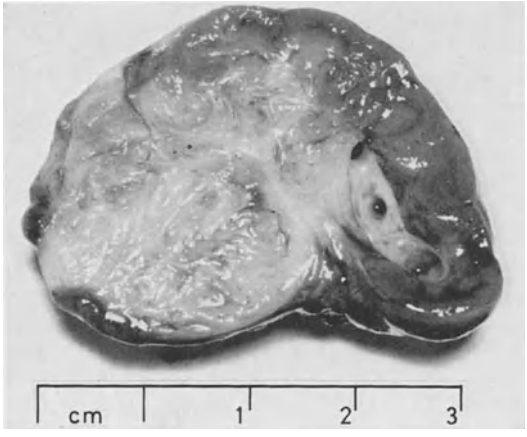


Fig. 181. Neonatal renal tumour. Nephrectomy specimen from a newborn infant showing fibrosarcomatous type of tumour infiltrating the renal substance, but without extra-renal spread

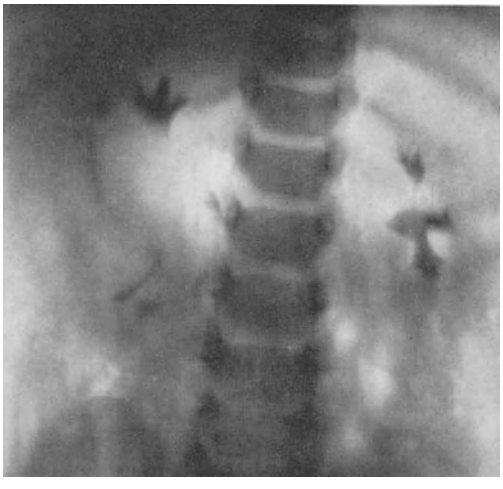


Fig. 182. Neonatal renal tumour. Newborn infant presenting with a hard mass in the abdomen. Intravenous pyelogram showing centrally placed lesion in the right kidney

4. Angiomyolipoma

Hamartomata containing angiomatous, myomatous and lipomatous tissue can be encountered at all ages, particularly in association with tuberose sclerosis. The latter condition is a familial disorder characterised by nodular areas of gliosis in the cerebral hemispheres causing epilepsy and mental deficiency, and ultimately symptoms of increased intra-cranial pressure. On the face, particularly around the nose, are nodules of adenoma sebaceum, and tumour-like nodules are found in the heart, lungs and bones. The renal lesions are multiple and bilateral; they seldom cause symptoms until later childhood or adult life, when they may reach a considerable size and cause haematuria or retroperitoneal haemorrhage. Malignant degeneration is exceptionally rare, and in view of the bilateral nature of the condition treatment is usually conservative (McCULLOGH et al., 1971).

Unilateral angiomyolipomata may also occur without tuberose sclerosis, but are usually encountered later in life and are difficult to diagnose, except by histology.

5. Haemangioma

Haemangioma of the kidney, although often considered as a possible cause of unexplained haematuria, is very seldom encountered. The lesions are apt to be very small and difficult to diagnose radiologically, causing nothing more than a slight deformity of one calix. The literature on the subject is reviewed by PETERSON and THOMPSON (1971).

6. Haemangiopericytoma

A renin-secreting tumour causing hypertension has been reported in an older child by LEE (1971): it is a small, benign neoplasm, only likely to be diagnosed by the very careful investigation of severe hypertension.

7. Adenocarcinoma

A renal cell carcinoma may occur in childhood, usually in the later years, and runs a course similar to that found in adult life. Recent reviews and reports are given by MANSON et al. (1970); DELMER et al. (1970), and YATES-BELL and CARDEL (1971). The disease is unlikely to be diagnosed except on histological examination of an excised tumour. The reported survival rate reaches 50 per cent.

8. Lymphosarcoma and Leukaemia

Both kidneys may be infiltrated by leukaemic deposits during the later stage of the generalised disease: very large palpable masses are present without serious impairment of renal function. The urographic appearance shown in Fig. 183 is not unlike that seen in adult polycystic disease, but should not give rise to any diagnostic difficulties in view of the haematological findings.

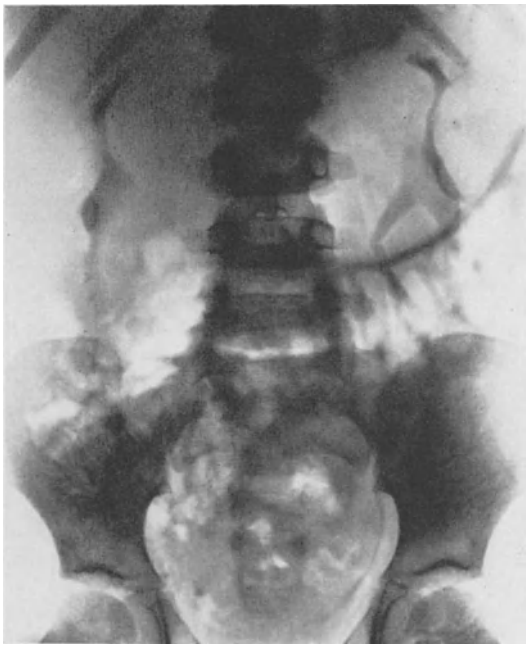


Fig. 183. Leukaemic infiltration of the kidney. Boy already under treatment for leukaemia presenting with abdominal masses. Intravenous pyelogram shows symmetrical enlargement of both kidneys but good preservation of function

9. Cystadenoma

This term is sometimes applied to the multilocular cysts of the kidney described on p. 77. Other pathologists have interpreted the disorder as a lymphangioma. A large encapsulated mass within the kidney contains many cysts, some of which may herniate into the renal pelvis and obstruct the ureter (Uson and Mellicow, 1963). In general this cannot be regarded as a true tumour, but at times it may contain cells suspected of being nephroblastomatous and there may be difficulty in making a firm diagnosis.

V. Clinical Presentation

Abdominal tumour is much the most common presenting complaint and masses are palpable in over 90 per cent of cases diagnosed during life. Abdominal pain is common but seldom severe unless rupture has occured or there is local infiltration of the posterior abdominal wall. Haematuria was the first symptom in approximately one third of the author's cases and appeared to be derived from obstructed vessels around the calices rather than from ulceration of the tumour; it did not adversely affect the prognosis.

Hypertension is a feature of nephroblastoma which has been extensively recorded, but since accurate measurement of the blood pressure is often difficult in the emergency circumstances of tumour treatment its exact incidence is unknown.

SUKAROCHANA et al. (1972) record a very high incidence with correction after nephrectomy. VERAGUTH and CHANSON (1969) report a fall in blood pressure with preoperative irradiation. A rise with the appearance of metastases is rare but has been recorded. MITCHELL et al. (1970) have recently investigated plasma renin in a 22 month old child with tumour and malignant hypertension. They found greatly raised levels which returned to normal after removal of the tumour, and it seems likely that the neoplastic cells were responsible for the production of the circulating renin, as in the haemangiopericytoma reported by LEE (1970). In other cases, however, the hypertension may result from ischaemia of the kidney due to pressure of the tumour upon the arterial supply.

Anaemia is a feature of cases with very large tumours, particularly when metastases are present, but a few have polycythaemia and KENNY et al. (1970) have recorded raised erythropoietin levels.

Approximately 40 per cent of children presenting to the author have had evidence of spread at the time of first consultation; this figure has been reduced only slightly during the past decade. It seems likely that at least a third of affected children will not have any symptoms or recognisable signs until after metastases have occurred. Nevertheless, there is the need for greater vigilance on the part of parents and doctors: the most encouraging cases are often those where an abdominal mass has been palpated during the course of routine examination of a young infant. Cases picked up in this way can clearly improve the overall results of treatment and are thus a justification for the regular medical examination of apparently fit children.

VI. Diagnosis

Although diagnosis may well be suspected on simple clinical examination, reliance is placed chiefly upon excretory urography, which shows enlargement of the kidney and distortion of the calices (Fig. 184). Sometimes the only calices opacified are remote from their normal situation and hard to recognise, but a lateral view is of great assistance in distinguishing the presence of a renal mass from a general renal enlargment. Since simple renal cysts are exceptionally rare in childhood, the differential diagnosis is concerned to distinguish nephroblastoma from other malignant disorders and from hydronephrosis, particularly if one half only of a duplex kidney is involved (Fig. 93). Complete failure of opacification is uncommon in tumour cases, but can occur in advanced disease with venous obstruction, whereas with high dose intravenous urograms and late films almost all hydronephroses will show some evidence of secretion of opaque medium. Arteriography can be valuable on occasions in the differential diagnosis between tumour and cystic lesions, particularly in bilateral cases or where the tumour is clearly inoperable and it is planned to start radiotherapy prior to surgery. The tumour mass can be clearly identified by the pooling of contrast and the presence of pathological vessels. Nevertheless, some tumours are avascular and difficulties may still arise: the characteristic arteriographic appearances have been described by MENG and ELKIN (1969); FOLIN (1969), and CREMIN and KASCHULA (1972). Inferior venocavograms have been advocated (BENNEK, 1966) as a method of detecting the presence of metastatic tumour in the great veins, but with a large growth the cava is so much compressed that findings are difficult to interpret. Isotope scans and urinary cytological studies have little practical value in the diagnosis.

The adrenal neuroblastoma is the tumour most easily confused with nephroblastoma, but help can be obtained in the diagnosis from skeletal surveys showing possible bone metastasis, marrow puncture which may reveal neuroblastoma cells, and estimation of catecholine amines, which are frequently raised. In practice the diagnosis of nephroblastoma is usually established without difficulty by the combination of clinical examination and excretory urography, though other forms of renal tumour cannot be recognised until after nephrectomy has been performed.

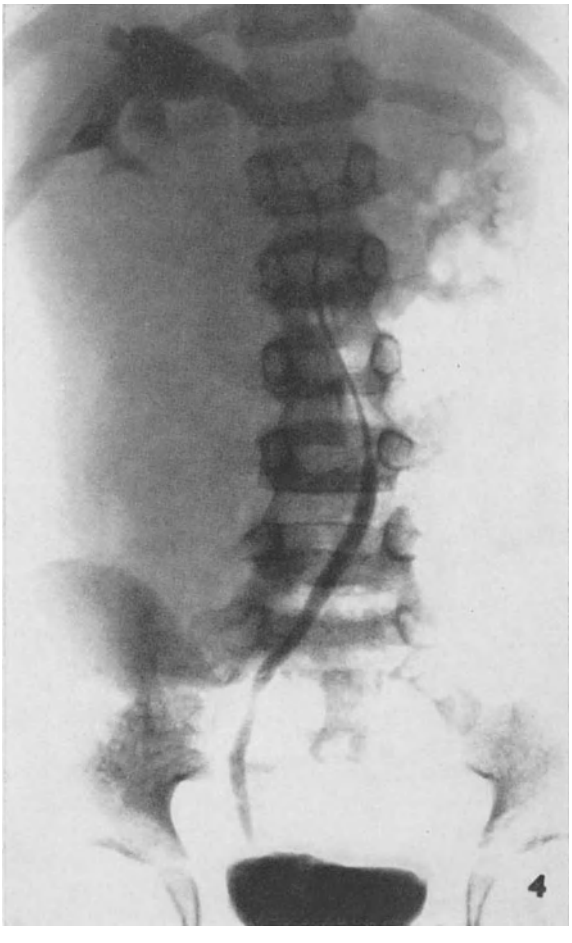


Fig. 184. Nephroblastoma. Infant presenting with abdominal tumour. Intravenous pyelogram shows large soft tissue mass occupying the lower pole of the right kidney with displacement and distortion of the entire caliceal system

VII. Treatment

It is now generally accepted that the routine treatment of nephroblastoma must include nephrectomy, radiotherapy and chemotherapy. An exception is to

be made, however, in the case of children under the age of one year: in the neonatal tumours, which are ordinarily hamartomata, simple nephrectomy is sufficient and other methods dangerous. RICHMOND and DOUGALL (1970) showed that of 9 neonates, 3 died as a result of treatment and 4 suffered permanent skeletal damage from radiotherapy. In the true nephroblastomata appearing later in the first year of life, nephrectomy is sufficient if the tumour is encapsulated within the kidney. For all other cases radiotherapy and chemotherapy will be required in addition to surgery, but there are varying opinions concerning the timing of operation, the dose and field for radiotherapy, and the dose and timing of chemotherapy.

1. Surgery

Nephrectomy must be performed through a very wide exposure; most urologists employ a transverse incision above the umbilicus, opening the peritoneal cavity and reflecting the colon medially. The tumour should not be mobilised until the renal vein is tied, but it is an advantage to have control of the renal artery before the vein itself is occluded. There can be no doubt that operation can release tumour emboli and the commonly observed pulmonary metastases appearing within six months of operation are almost certainly due to this cause. The adrenal vessels should also be secured before the tumour is mobilised laterally and the lymph nodes along the great vessels should be dissected out following the removal of the kidney mass. If the spermatic cord is involved it should be excised completely with the testicle on that side.

2. Radiotherapy

Radiotherapy is usually directed towards the tumour bed and lymph node area along the aorta, and doses usually vary between 3000 and 3500 R in 20–30 fractions over 4–6 weeks. The principles of radiation treatment are discussed by D'ANGIO (1968), HUSSEY et al. (1971) and WILLIAMS (1973). In Britain it has been customary to start the radiotherapy as soon as the wound has healed, whereas many centres in America start immediately after operation. The possible dangers of irradiation are damage to the skeleton and to the opposite kidney. The treated area usually includes the entire vertebral column and thus asymmetrical damage and consequent scoliosis are avoided. The opposite kidney is screened, unless it is known to contain tumour. The maximum dose for a child's kidney is approximately 1500 R, or 1200 R if co-incident with chemotherapy. With higher doses irradiation nephritis and progressive renal failure are likely to appear within six months of treatment. Irradiation is often required for the treatment of pulmonary metastases and can have dramatic effects, but here again the dosage has to be restricted as for the kidney to prevent irradiation fibrosis, which carries a serious late morbidity. Risks of pulmonary irradiation have discouraged most radiotherapists from using prophylactic irradiation to the chest after primary nephrectomy, though the occurrence of pulmonary metastases relatively soon after operation in Stage I tumours suggests that this measure might be of value. Pre-operative irradiation is not widely employed at present, except for cases in which the tumour is clearly inoperable. WAGGET and KOOP (1970) and DIETHELM and NEIDHARDT (1969) discuss the advantages of this form of treatment.

3. Chemotherapy

The chemotherapeutic agents most commonly used are Actinomycin D and Vincristine. D'ANGIO et al. (1959) first described the use of Actinomycin D combined with radiotherapy and found that the use of the drug potentiated the effect of radiation on Wilms tumour. Since that time many reports have been published showing, in general, beneficial results from the use of this drug, though some doubts have been cast on its efficacy by JOHNSTON et al. (1969). It is usually employed in doses of 15 μg/kg on four days, starting during the day of operation, and, as will be seen later, follow-up courses are now often employed. The dangers of Actinomycin in the very young have already been noted, in older children it may still produce severe toxic effects, the most obvious being leucopenia, alopecia and ulceration of the alimentary tract: wound healing is often poor during the use of this drug.

Vincristine has also been extensively employed and can have a dramatic effect; its use is described by SULLIVAN et al. (1967) and VIETTI et al. (1970). A dose of 1.5 mg/sq metre body surface is given at weekly intervals for up to six weeks. Neurotoxic effects are sometimes seen with, occasionally, difficulty in emptying the bladder, loss of hair and intestinal disturbances.

The chemotherapy of solid tumours in childhood is greatly influenced by experience in the leukaemia field, and in recent years there has been a tendency to employ multiple drug treatment and repeated courses. Other drugs now in use are cyclophosphamide (Endoxan) 200 mg/sq metre at weekly intervals and Adriamycin, 30 mg/sq metre. If Vincristine is used at the same time as these the dose should be reduced to 0.8 mg/sq metre. With combination chemotherapy it is hoped that there will be a summation of toxic effect on the tumour but that the doses are small enough to minimise toxic side effects, and if given at intervals of three to four weeks over six months the normal tissues may have time to recover between the doses.

The advantage of multiple dose Actinomycin D therapy was reported by WOLFF et al. (1968), and this type of regime has now been widely adopted, though it is disappointing that the prophylactic use of such drugs in Stage I cases with a satisfactory nephrectomy has not always prevented the later appearance of metastases.

The effect on kidney growth and function of long term chemotherapy has given rise to some concern, but reliable figures are not yet available to allow an assessment of this danger.

4. Treatment Regimes

The treatment regimes currently in use at The Hospital for Sick Children are as follows:

A child with a renal tumour but no clinical or radiological evidence of spread of the disease is subjected to nephrectomy as soon as possible after completion of investigations. A course of Actinomycin D is started at the time of operation and continues for four days afterwards in daily doses of 15 μg/kg. Radiotherapy, using a cobalt 60 source, is started as soon as the wound is healed, the renal bed and para-aortic areas are irradiated from the level of the inferior mesenteric artery to the crura of the diaphragm: the dose of 3000 R being given over four weeks. Following treatment the child is seen at monthly intervals for chest X-ray and at three monthly intervals for two years is given a further course of four doses of Actinomycin, 15 μg/kg/day. A child presenting with a clinically

operable tumour but metastases in the lungs is treated by immediate nephrectomy and the chemotherapeutic regime already described, but irradiation of the chest to 1500 R is included.

A child with a clinically inoperable tumour due to local fixation or intra-abdominal spread, receives pre-operative irradiation to the tumour mass, together with Actinomycin D or Vincristine, and operation is then attempted after about three weeks of treatment providing the tumour has shrunk satisfactorily.

In bilateral disease an individual decision has to be made as to the best form of treatment. In several a unilateral nephrectomy has been performed, removing the larger tumour; the smaller one has been treated by irradiation and chemotherapy. Other authors have reported the successful employment of partial nephrectomy (JOHNSTON and SHAH, 1965). JOCHIMSEN et al. (1969) have reported the use of bilateral nephrectomy and renal transplantation.

Solitary pulmonary metastases are best treated by surgical resection and many successful results have been recorded. (MARTIN and RICKHAM, 1970). Pulmonary metastases are also responsive to radiotherapy and a number of authors quote a 20–30 per cent salvage rate in children with lung metastases as a result of radiotherapy and chemotherapy. Liver metastases and abdominal recurrences are almost always fatal, however, and very little has been gained by second operations on abdominal tumour masses.

VIII. Results

In a relatively uncommon tumour, such as nephroblastoma, there has been a tendency to quote overall survival rates, but clearly unless the tumours are staged and the cases under one year, who have a better prognosis, are identified it is smpossible to compare one form of treatment with another. There has been a ateady improvement in the reported survival rates during the last three decades, and an important factor in this improvement has been the better surgical technique as well as the addition of radiotherapy and chemotherapy. LEDLIE et al. (1970) reported an overall three year survival rate in England and Wales of 33 per cent in the years 1962–1966, but at The Hospital for Sick Children in the years 1952 to 1959 there were 19 survivors among 22 Stage I cases treated by nephrectomy and abdominal irradiation, whereas there were no survivors amongst the 16 more advanced cases. This represented a very great improvement on previous figures for the same hospital (WILLIAMS, 1964), but suggested that surgery was the most important factor in treatment. The introduction of more aggressive radiotherapy and the addition of cytotoxic drugs has improved the survival of cases with established metastases, but has made little difference to the Stage I cases. Currently the overall 3 year survival rate is approximately 60 per cent: other clinics quote figures up to 80 per cent, but with differing case material, changing methods and the prolongation of life by chemotherapy in children with disseminated growth reliable figures are hard to obtain. The improvement with the multiple course Actinomycin D reported by WOOLFF et al. (1968) has not yet been assessed in terms of the ultimate survival rate (D'ANGIO, 1972) and there is no doubt that a longer follow-up period than the 2–3 years now usually reported is necessary for a final conclusion.

W. Neoplastic Disease: The Lower Urinary Tract

D. Innes Williams
With the assistance of J. Bond

With 9 Figures

I. Rhabdomyosarcoma

The commonest tumour affecting the lower urinary tract of children is a rhabdomyosarcoma, which, despite its name, has very little in common with the pleomorphic rhabdomyosarcoma arising in voluntary muscle during adult life. Horn and Enterline (1958) give the standard histological description of these childhood tumours, containing striated muscle or precursor, but often described as embryonic because of the immature nature of their constituent cells and mesenchyme. In some an alveolar arrangement of the cells with a characteristic histological appearance is present, but this cannot be correlated with any particular site or prognosis.

The childhood tumours may be found in the genito-urinary tract, in the orbit, in the pharynx and occasionally in the biliary tract. In spite of histological similarities, tumours in the different sites can have very different reactions to treatment; for instance, orbital tumours appear to be more sensitive to irradiation than those in the pharynx. It is therefore dangerous to apply conclusions drawn from the treatment of head and neck disease to the genito-urinary tumours, which still differ amongst themselves.

Rhabdomyosarcoma of the genito-urinary tract of childhood may have two distinct appearances; the botryoid or polypoid variety, where coarse lobulation gives the tumour a vaguely grape-like appearance, arises in the bladder or in the vagina and is clinically distinct from the solid tumour which is more commonly seen in the bladder base, prostatic area, broad ligament and paratesticular tissues. In general, the microscopic appearances are similar in all these sites, though possibly some solid tumours may be less differentiated.

Only tumours affecting the urinary tract are discussed in this chapter, but because there is a difference of clinical presentation and prognosis the polypoid and solid growths are treated separately.

1. Polypoid Rhabdomyosarcoma of the Bladder

The tumour characteristically presents during the first four years of life, boys being affected more often than girls: it consists of a polypoid lesion arising in the submucosal layer of the bladder (Fig. 185), most often at the base but occasionally at the apex, and sometimes multifocal in origin. Spreading from the base of the protuberant tumour is a submucous extension, often involving the ureters and urethra. The growth appears to arise primarily in the submucous and muscular layers and does not ulcerate the epithelium until later in the disease, often when infection is present. The pearly-grey lobules, which give rise to the descriptive

name of "sarcoma botryoides", prolapse into the urethra causing severe obstruction and the acute symptoms usually bring the child to hospital before metastases have occurred. Local spread and lymph node involvement will be seen before the appearance of lung secondaries.

Fig. 185. Polypoid rhabdomyosarcoma of the bladder. Total cystectomy specimen from a girl with "sarcoma botryoides"

The symptoms are characteristically those of obstruction and strangury, often complicated by infection and fever and only rarely by haematuria. On clinical examination the bladder is distended, but a mass is palpable in its base which remains after catheterisation. Excretory urograms may show upper tract dilatation, sometimes very severe; the lower ends of the ureters are characteristically widely separated and may turn laterally as they reach the bladder (Figs. 186, 187). The bladder itself exhibits a lobulated filling defect with prolapse into the urethra causing a cone-like dilatation down to the membranous area in the male. Radiologically, possible sources of confusion are ectopic ureteroceles, inflammatory polyps as seen in giant forms of cystitis cystica and eosinophilic cystitis, and other tumours and hamartomata; of the latter, haemangioma, neurofibroma and simple myoma are most likely to cause confusion. Endoscopy confirms that the bladder contains a lobulated grey tumour with some submucous infiltration at its base. Endoscopic biopsy can usually be performed without difficulty.

The treatment of the condition is almost always total cystectomy, though an occasional solitary polypoid tumour may be encountered, arising from the dome

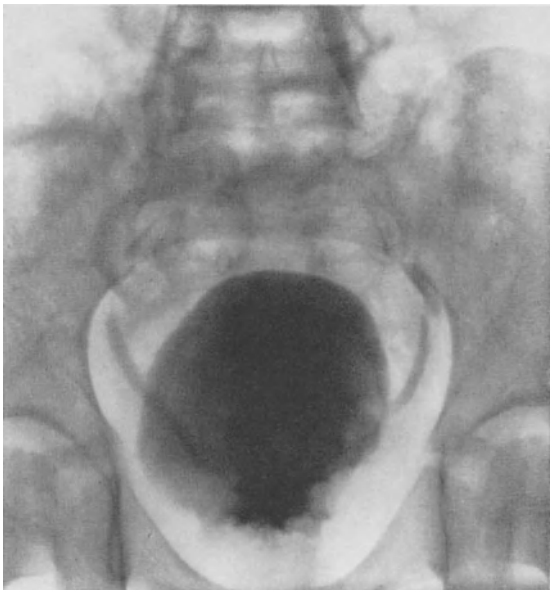


Fig. 186. Polypoid rhabdomyosarcoma of the bladder. Intravenous urogram showing polypoid filling defect at the base of the bladder in a three year old girl with retention of urine

of the bladder, and may be excised locally. If the urinary obstruction is severe it may require urgent relief by the use of an indwelling catheter, or in uraemic infants it is possible that the ureters are so severely obstructed that bilateral nephrostomy will be required as an emergency measure. The cystectomy should aim to remove the urethra in the male as far as the peno-scrotal junction, and it is therefore preferable to commence the operation from the perineum. In the female, the entire urethra and surrounding labial tissues should be excised together with the anterior wall of the vagina, or the entire vagina if this organ is involved. The uterus itself is not primarily affected, but hysterectomy may be required in cases of vaginal tumour. The dissection in the pelvis is greatly facilitated by splittling the symphysis pubis and retracting the pubic bones laterally. Great care should be taken in dissecting anteriorly and in clearing the lymph nodes. Urinary diversion by ileal conduit has given the best results.

Many authors have recorded good results from radical surgery in polypoid growths, even without the use of any other form of treatment (e. g. JARMAN and KENEALY, 1970). In the author's series, collected by GHAZALI (1973), out of 24 bladder rhabdomyosarcomata 11 were clearly of the polypoid variety. They were treated by cystectomy alone and all are surviving at the time of writing. With such a satisfactory prognosis for the early polypoid case there seems very little justification for the aggressive use of radiotherapy and cytotoxic drugs. The remaining 13 tumours had a considerable solid element to them, or clear extension into surrounding tissues: all have died. The appropriate treatment for these is considered in the next section.

2. Solid Rhabdomyosarcoma of Bladder Base and Prostate

The exact origin of a solid tumour is often hard to determine, but the rhabdomyosarcomata arising in the bladder base and prostatic area form a group clinically distinct from the polypoid tumours, even though they may have some

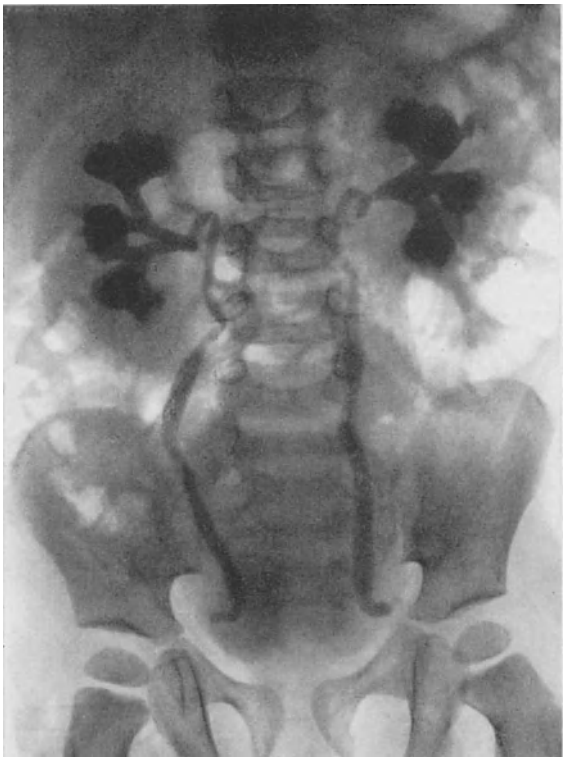


Fig. 187. Polypoid rhabdomyosarcoma of the bladder. Intravenous urogram showing lateral deflection of the lower ends of the ureters by the mass of tumour in the bladder base

superficial lobulation, and if allowed to escape into the bladder cavity as a result of incomplete surgery will form a polypoid mass. Typically there is a large lobular mass filling the pelvis, displacing the bladder upwards and stretching the urethra tightly over its surface. The base of the bladder is infiltrated and there is a mucosal extension along the urethra. Local spread into the adventitial tissues occurs and MARSHALL (1969) has drawn particular attention to the presence of tumour cells on the periosteal surface of the pubic bones. Local lymph nodes are involved relatively early, but distant metastasis to bones, brain or lung is a late feature.

The clinical presentation is likely to be later in the disease, and in older children than with the polypoid growth, though the disease may occur in infancy and by contrast with the nephroblastoma has as bad a prognosis at this age as in older children. The bladder is found to be distended and there is a huge pelvic mass palpable anterior to the examining rectal finger, often extending upwards and laterally, becoming fixed to the lateral pelvic wall. Radiologically the upper tract is obstructed with displacement and distortion of the ureters: the bladder is lifted out of the pelvis, the urethra elongated and compressed. Endoscopy may be possible and is a valuable method of obtaining a biopsy, but at times the displacement of the urethra makes this approach impracticable and a needle biopsy must be performed. The differential diagnosis to be considered is inflammatory disease due to prostatic abscess, or occasionally pelvic abscess resulting from intra-peritoneal

sepsis, but there will usually be very little doubt on clinical examination that some form of malignant disease is present.

Radical surgery followed by regional radiotherapy and chemotherapy is the standard method of treatment for this growth, but the results are very poor. A high dose of irradiation is necessary to obtain regression of the tumour (Williams, 1972). A long term survivor has been reported by Marshall (1969), who performed a pelvic exenteration with excision of the pelvic floor and inner table of the ischio-pubic ramus, and another by Goodwin et al. (1968). Tucker (1972), reviewing 53 cases in the literature found only these two survivors. Cukier et al. (1968) describe the method of radical excision which produced some encouraging short term results, but late recurrences occurred after three years (Debauchez et al. (1970). Pratt et al. (1972) and Grosfeld et al. (1972) have described encouraging results following radical surgery, extensive radiotherapy and combined use of Actinomycin D, Vincristine and cyclophosphamide in repeated courses. They appeared to use this form of treatment in the polypoid as well as the solid tumours. In the author's series (Ghazali, 1973) there were 9 prostatic cases, of whom 7 died soon after operation, while 2 are alive still less than two years from surgery. In the solid tumours at the base of the bladder, of whom 7 were male and 6 female, there were no survivors.

II. Transitional Cell Tumours

Transitional cell tumours of the bladder are exceptionally rare in childhood and are usually curable. Firstater et al. (1969) report a solitary lesion and Siegel and Pincus (1969) describe a papilloma and review the literature. Multiple and recurrent tumours are exceptionally uncommon but have been recorded by Li et al. (1972). Almost all have presented with haematuria and have been diagnosed by cystoscopy and biopsy. A simple diathermy excision or partial cystectomy appears to have sufficed.

III. Leukaemia

Leukaemic infiltration of the bladder may be seen in advanced cases, usually following prolonged treatment with chemotherapy. The disorder causes haematuria and distortion of the bladder wall, but it must be distinguished from the haematuria and spastic bladder contraction seen in cyclophosphamide cystitis, which is probably a commoner manifestation (Troup et al., 1972).

IV. Hamartomata and Benign Tumours

1. Neurofibromatosis

Generalised neurofibromatosis is a well recognised hamartomatous disorder characterised by multiple subcutaneous tumours along the course of the peripheral nerves and by pigmented café au lait spots on the skin. It is a hereditary disorder and appears to be transmitted as an autosomal dominant. Subcutaneous tumours are seldom evident at birth, but appear along with the café au lait spots during the first two or three years of life. Involvement of the skeleton with dwarfism and scoliosis are common complications; visceral manifestations are rare and only very few children have bladder involvement. Nevertheless, the distinction

between hamartoma in the bladder and malignant disease is of vital importance in treatment, and neurofibromatosis deserves attention for this reason.

Neurofibromatosis may affect the pelvic nerves generally producing a mass of plexiform tumours around the lower urinary tract and genitalia, or may be confined more specifically to the bladder area where the submucous layer is particularly involved. In this situation the irregular infiltration with neurofibromatous tissue gives the bladder a somewhat trabeculated or sacculated appearance on cystograms (Figs. 188, 189), and involvement of the intramural ureter causes serious obstruction to the upper urinary tract. Bladder emptying often remains surprisingly satisfactory in spite of extensive involvement of the wall, and it is usually infection or hydronephrosis which brings the child to hospital. The diagnosis may be immediately suspected from the superficial appearance of café au lait spots on the skin and on rectal examination by the irregular and somewhat spongy mass felt in the pelvis. Plexiform tumours may be found in the external genitalia. Cystoscopically the submucous infiltration with grey neurofibromatous tissue can be seen and a trans-urethral biopsy will confirm the diagnosis histologically. Treatment is largely concerned with overcoming obstruction: it will not, of course, be possible to eliminate the disease by excision of the involved organ, although this may be necessary to control local symptoms. In one of the author's cases, illustrated in Fig. 188, a pelvic neurofibromatous mass involved the bladder base but was not causing serious symptoms and is at present growing very slowly, if at all. No surgery has been undertaken. In other examples (Fig. 190), total cystectomy has been performed with ileal loop diversion to drain the upper urinary tract and to remove an infected obstructed bladder. Two of these earlier examples have been reported by PESSIN and BODIAN (1964). CAMERON (1964) has reviewed reported cases of neurofibromatosis of the bladder in adults, indicating that the progress of the disease may be extremely slow.

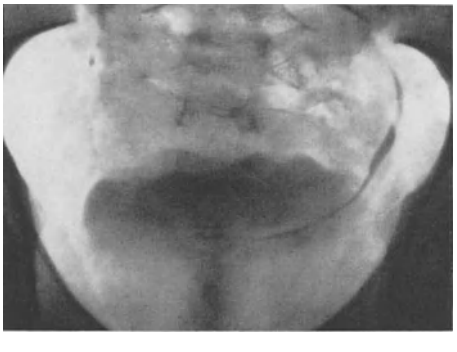
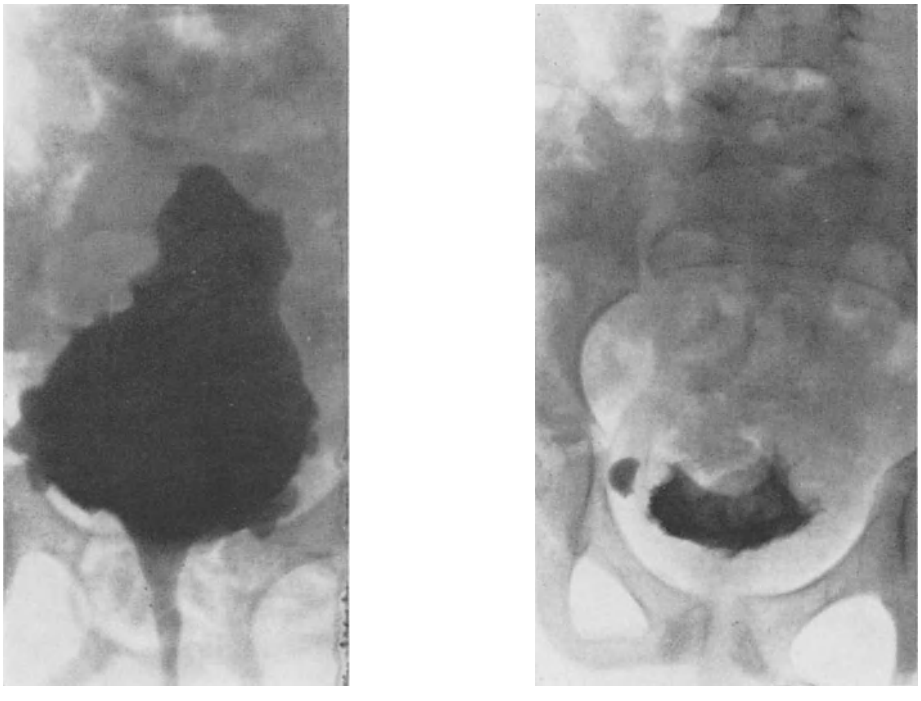


Fig. 188. Neurofibromatosis. Intravenous urogram showing irregularity of the superior aspect of the bladder in a 10 year old boy with pelvic mass, but no disturbance of micturition

2. Myoma

A simple myomatous polyp in the bladder has been recorded by RUSSELL et al. (1958) and by LANGE (1956). In both cases there was severe haematuria and a well localised polypoid tumour which, but for its solitary nature, would have been suspected of being rhabdomyosarcoma. A similar bleeding lesion with multiple polypoid is illustrated in Fig. 191, a case in which total cystectomy was undertaken because of suspected malignancy. The existence of these extremely rare benign lesions indicates the need for careful preliminary biopsy before surgery is undertaken.



a b

Fig. 189 a and b. Neurofibromatosis. Cystogram in a girl with gross bilateral hydronephrosis and neurofibromatous sub-mucous infiltration of the bladder wall producing an appearance similar to trabeculation

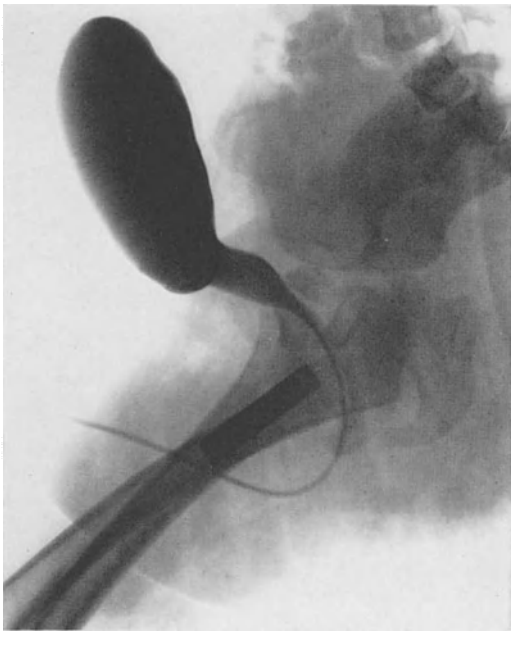


Fig. 190. Neurofibromatosis. Cystogram in a boy with extensive neurofibromatous involvement of the entire pelvis displacing the bladder upwards and outwards and compressing the rectum

3. Simple and Fibromatous Polyps

The common polypoid tumour in the lower urinary tract of the male arises by a long stalk from the region of the verumontanum; it has been reported on many occasions (Downs, 1970) and can occur at all ages of childhood, producing retention of urine or recurrent infection with or without haematuria. Williams and Abbassian (1966) note that reflux occurred in many such cases. The polyp may be palpable on rectal examination and radiologically it can be recognised by its extreme mobility (Fig. 192), so that in some films the filling defect is in the bulb, in others in the posterior urethra or the base of the bladder. Endoscopically the narrow stalk is easily recognised and may be resected, though removal of the polyp by open cystostomy is easier and more likely to be complete. A simple polyp in the bladder itself has been reported by Ganem and Ainsworth (1955), arising by a narrow stalk behind the trigone; it was responsible for haematuria.

4. Haemangioma

Haemangioma is a hamartoma which may present in childhood or in adult life. The subject has recently been reviewed by Fuleihan and Cordonnier (1969) and by Hendry and Vinnicombe (1971). The latter authors found 31 cases which

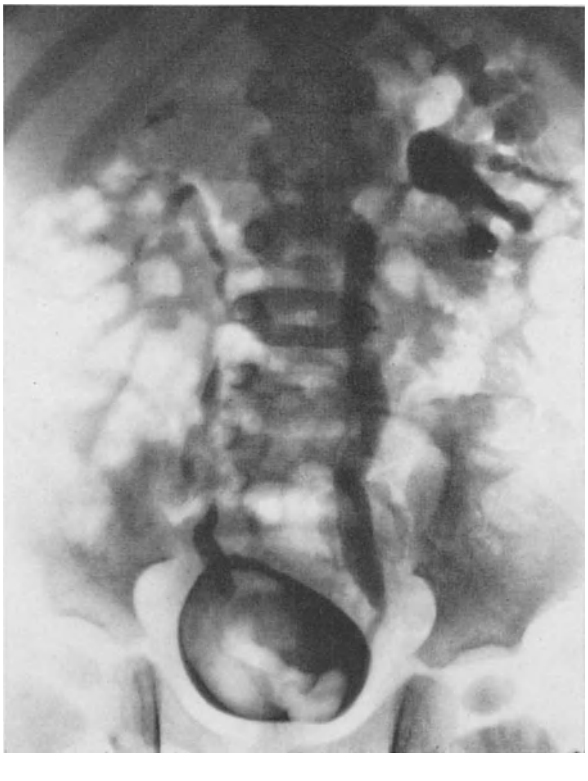
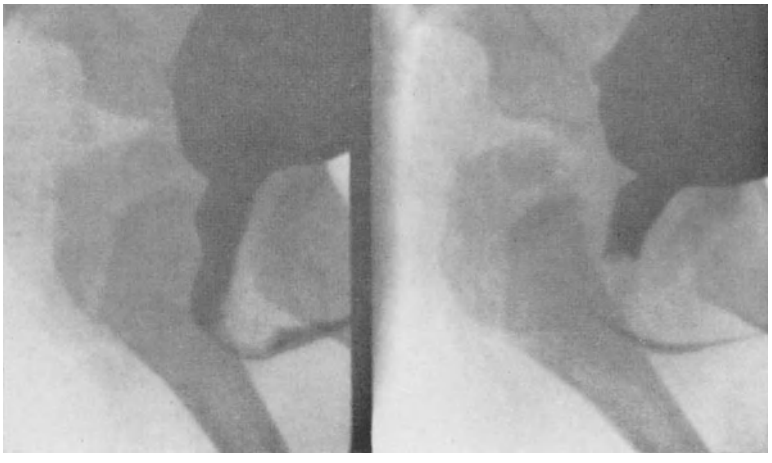


Fig. 191. Myoma of the bladder. A 1 year old boy presenting with haematuria and retention of urine. Intravenous urogram shows polypoid filling defect in the bladder due to myomatous tumour

had presented with haematuria during the first two decades of life; in approximately one third of instances haemangiomata were to be found elsewhere in the body. In the bladder the lesion may be well localised and is then liable to involve



a b

Fig. 192 a and b. Simple polyp of urethra. A boy presenting with retention of urine. Micturating cystogram shows mobile filling defect: a In the bulb of the urethra. b In the membranous area

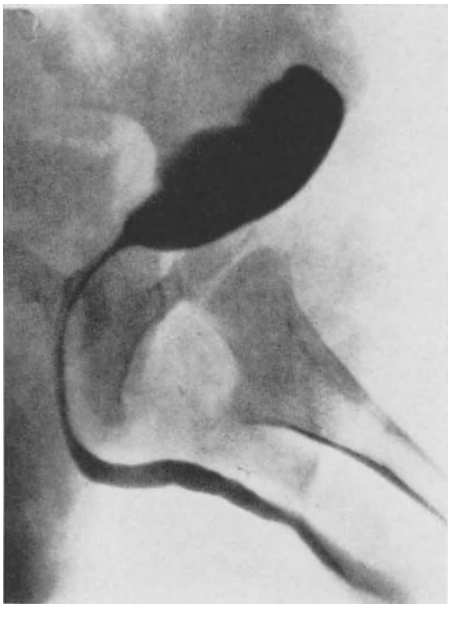


Fig. 193. Haemangioma. A boy with multiple superficial haemangiomata involving the lower limbs, and haematuria. Cystogram shows haemangiomatous involvement of the posterior bladder wall

the upper half of the bladder. Rather less commonly there is an enormous haemangiomatous infiltration of all muscular layers of the bladder and of the perivesical tissues. The diagnosis may be suspected from the skin lesions, or from the irregular filling defect in the wall of the bladder on cystography (Fig. 193). Cystoscopy reveals the characteristic appearance of a haemangioma, though this may be difficult to differentiate from a papillary tumour when a single lesion is present. Endoscopic biopsy runs some risk of precipitating severe haemorrhage, and in general an open exploration with resection of the involved tissue is advised.

5. Pheochromocytoma

Pheochromocytoma has been reported in the bladders of children as well as adults, producing paroxysmal hypertension, sometimes associated with micturition, and haematuria. Leestma and Price (1971) have published a recent review of the topic.

X. Congenital Adrenal Hyperplasia

G. H. Newns

With 4 Figures

I. Introduction

Congenital adrenocortical hyperplasia is a complex endocrine disorder of importance to the paediatric urologist because it produces an intersex state in the female and precocious virilisation in the male. The excessive secretion of androgens by the foetal adrenal cortex commences in early foetal life at some time after the differentiation of the internal genitalia from the Wolffian and Mullerian duct systems, but before complete differentiation of the external genitalia. Varying degrees of virilisation are present in the female at birth; the male does not at this stage exhibit any striking abnormality, though in both sexes there will be progressive virilisation of the untreated case.

II. Pathogenesis

The basis of all varieties of congenital adrenal hyperplasia is a block, varying in degree and site, in the biosynthesis of cortisol (hydrocortisone). Fig. 194 illustrates in a simplified form the biosynthetic pathways of cortisol, testosterone, and aldosterone.

In the production of cortisol, three hydroxyl groups are added to progesterone by specific enzymes in a definite sequence. C 17-hydroxylation occurs first with the formation of 17-hydroxyprogesterone. This is followed by 21-hydroxylation and finally by 11-hydroxylation (see Fig. 194).

As a result of enzyme deficiencies there is a reduction of varying degree in the production of cortisol. The plasma level of this steroid falls and, by a negative feed-back mechanism on the anterior pituitary, provokes a rise in ACTH-secretion. This stimulates the adrenal cortex and the resulting excessive production of androgens is the cause of the virilisation.

Other enzyme deficiencies have also been described. Desmolase is required for the conversion of cholesterol to pregnenolone, and 3 β-hydroxydehydrogenase is necessary for the conversion of pregnenolone to progesterone and for an important step in the biosynthesis of testosterone. Deficiency of these enzymes leads to defective virilisation in the male.

Approximately one third of patients with the 21-hydroxylase deficiency, all the patients with desmolase deficiency, and most of those with deficiency of 3 β-hydroxydehydrogenase have difficulty in conserving sodium which is associated with severe episodes of vomiting, dehydration, hyponatraemia and hyperkalaemia. Many such patients die unless active treatment is undertaken.

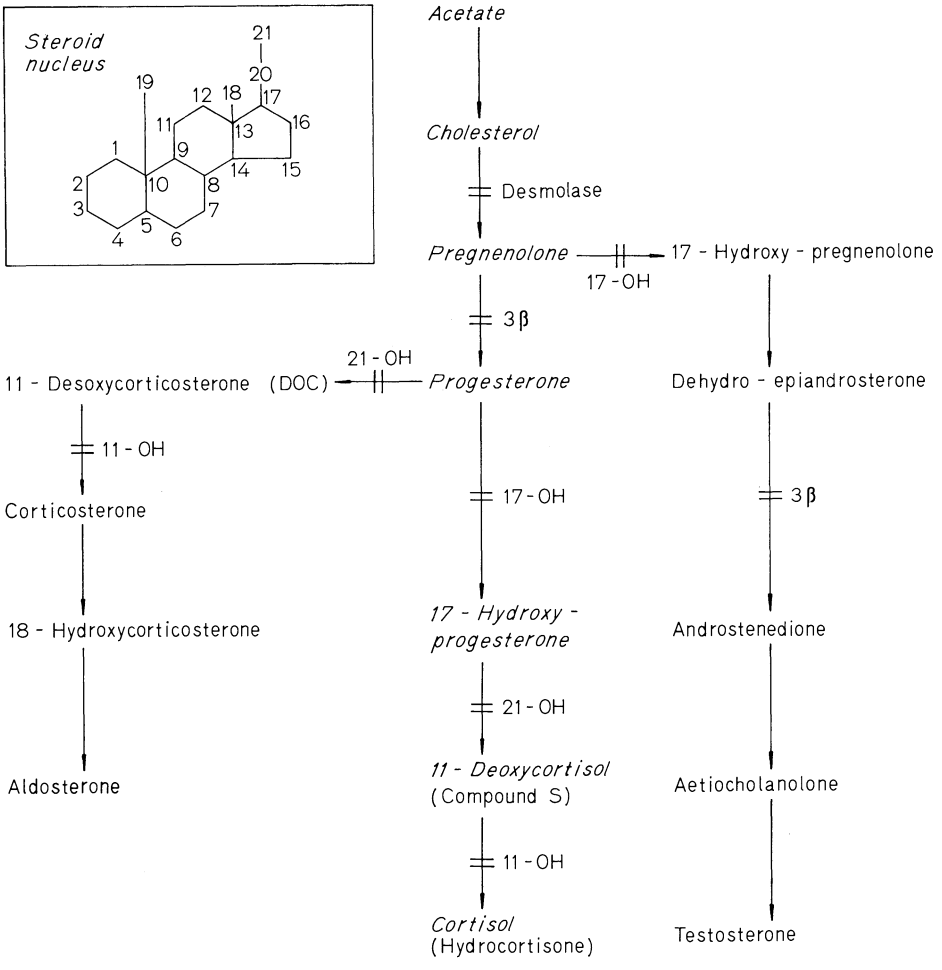


Fig. 194. Steroid biosynthesis in the adrenal cortex to show sites of enzyme blocks

1. 21-Hydroxylase Defect

This, which is by far the commonest enzyme deficiency, results in reduction in secretion of 11-deoxycortisol (Compound S) and cortisol, and a rise in its immediate precursor 17-hydroxyprogesterone whose plasma level is considerably elevated (Fig. 194). The main metabolite of this steroid is pregnanetriol which is excreted in the urine in excess. (In normal subjects the urinary level is very low.)

2. 11-Hydroxylase Defect

This is a rare type of congenital adrenal hyperplasia first described by Eberlein and Bongiovanni (1955a, 1956) and is associated with hypertension as well as virilisation. Since then several further cases have been reported.

11-Hydroxylase is necessary for the conversion of 11-deoxycortisol (Compound S) to cortisol and 11-desoxycorticosterone (DOC) to corticosterone. The metabolites of these substances, tetra-hydro S and tetra-hydro DOC respectively, are secreted in excess in the urine.

The hypertension is considered to be due to the hypersecretion of Doc. Nevertheless hypertension is not always present (Dyrenfurth, 1958). The typical steroid pattern with an increase in Compound S and its metabolites has been demonstrated in normotensive patients with 11-hydroxylase deficiency (Chaptal et al., 1959; Gandy et al., 1960).

The females are virilised as in 21-hydroxylase deficiency and both sexes virilise after birth if no treatment is given.

Administration of glucocorticoids brings the blood pressure to normal levels.

3. Lipoid Hyperplasia

This syndrome is caused by a deficiency of the enzyme desmolase which converts cholesterol to pregnenolone. This results in a complete absence of any steroid synthesis.

Prader et al. (1955, 1957) described a group of children who died of adrenal insufficiency, and O'Doherty (1964) reported another patient. There are large accumulations of cholesterol in the adrenal cortex. To date, none of the patients have survived owing to severe salt-loss. In female infants, the genitalia were normal. In the male, male gonaducts were present, but the external genitalia were feminised.

4. 3β-Hydroxydehydrogenase Defect

The enzyme 3 β-hydroxydehydrogenase is required for the conversion of pregnenolone to progesterone and for the conversion of dehydroepiandrosterone to androstenedione (Fig. 194).

The defect results in a severe reduction in glucocorticoid and aldosterone synthesis. In most cases, therefore, there is a severe, often fatal, salt-losing syndrome.

The androgen synthesis terminates in the formation of the weak androgen, dehydroepiandrosterone; very little conversion to testosterone occurs. As a result the males show incomplete male differentiation, the genitalia being of ambiguous appearance. Females may have normal genitalia though there is clitoral enlargement and some degree of labio-scrotal fusion in some cases. There is, however, a separate urinary orifice. This slight virilisation in the female is presumably caused by the milder type of androgens formed. Bongiovanni (1961, 1962) described the first example of the syndrome. He reported 6 cases, 3 female and 3 male, 5 of whom died. The males had hypospadias and the females were virilised.

Other cases have been reported by Kenny et al., 1971; Hamilton and Bush, 1964; and Zachmann, 1970.

There is an increased secretion of dehydroepiandrosterone and pregnenolone.

5. 17α-Hydroxylase Defect

17 α-hydroxylase is necessary for the conversion of progesterone to 17 α-progesterone and of pregnenolone to 17-hydroxypregnenolone, a step in the synthesis of androgens (Fig. 194).

Cortisol and androgen production is impaired but secretion of corticosterone which does not require 17-hydroxylation is considerably increased.

The males usually have ambiguous genitalia; the females are anatomically normal but have primary amenorrhoea and fail to develop secondary sexual characteristics.

This defect was first described by BIGLIERI et al. (1966) in a female aged 35. Further cases in females have been reported by SUTHERLAND et al. (1966), GOLDSMITH et al. (1967), MIURA et al. (1968), and MALLIN (1969).

NEW and PETERSEN (1967) described a 12-year-old pre-pubertal boy who later developed signs of puberty. NEW (1970) reported a male with ambiguous genitalia, absence of secondary sexual characteristics, and gynaecomastia. She considered he had a partial 17 α-hydroxylase defect. MANTERO et al. (1971) and BRICAIRE (1972) have also reported cases in males.

The chief features of the syndrome are benign hypertension, hypokalaemic acidosis, high plasma ACTH levels, hypervolaemia and low plasma renin activity unresponsive to low sodium intake. There are low levels of urinary 17-ketosteroids. Administration of glucocorticoids brings about a rapid fall in blood pressure, and normalisation of plasma corticosterone and aldosterone levels.

III. Cause of Virilisation

Until recently it was believed that the virilisation was caused by the weak androgens, dehydroepiandrosterone and androstenedione, normally produced by the adrenal cortex. Testosterone is not as a rule secreted in significant amounts by the adrenal.

It is now generally accepted that testosterone, the most potent of the androgens, is the cause of the virilisation which, in congenital adrenal hyperplasia, is secreted by the adrenal cortex. Improved methodology, notably the introduction of isotope dilution methods for the measurement of testosterone secretion rates, have enabled a number of workers to demonstrate that both the excretion and production rates are considerably elevated, often to the levels found in adult males (CAMACHO and MIGEON, 1963, 1966; HALL and HOFKELT, 1964, ZURBRÜGG et al., 1964; DEGENHART et al., 1965a and b; VISSER, 1966b; RIVAROLA et al., 1967; CONLY et al., 1967).

Plasma testosterone is derived mainly from the metabolism of androstenedione from the adrenal (DEGENHART et al., 1965a; RIVAROLA et al., 1967; HORTON and FRASIER, 1967). These high levels of testosterone secretion are no doubt responsible for the rapid virilisation and increase in height and bone age in untreated cases of congenital adrenal hyperplasia.

IV. Aetiology of Salt-Losing Defect

As mentioned above, about one third of the patients with 21-hydroxylase deficiency, most of those with 3 β-hydroxydehydrogenase deficiency, and all the patients with desmolase deficiency (lipoid hyperplasia) are salt-losers. The aetiology of the sodium loss is not yet clearly understood. The possibility of a salt-losing hormone has been postulated but no such specific hormone has been identified (GEORGE et al., 1965). BONGIOVANNI and EBERLEIN (1958) have suggested that

the tendency to lose salt is related to the severity of the enzyme defect. EBERLEIN and BONGIOVANNI (1958) postulate that a minimum of cortisol is necessary for aldosterone function. In the severe cases very little cortisol is formed.

Earlier reports that in congenital adrenal hyperplasia there was an excess of aldosterone were based on inadequate methodology but with the development of isotope dilution techniques for measuring aldosterone secretion, it has been conclusively shown by a number of workers that there is a diminished production of aldosterone which cannot be increased significantly on a low sodium intake (BLIZZARD et al., 1959; BRYAN et al., 1962, 1965; MATTOX et al., 1964; KOWARSKI et al., 1964, 1965; NEW et al., 1964, 1966).

In the uncomplicated form of the disease aldosterone production is adequate and may even be high (KOWARSKI et al., 1964). The secretion rate could be further increased by a low sodium intake. Treatment with glucocorticoids brought the aldosterone secretion rate to normal levels. These findings have recently been confirmed by DAHL et al. (1972).

It has been shown that progesterone and 17-hydroxyprogesterone have a salt-losing action by antagonising the renal tubular effects of mineralocorticoids (JACOBS et al., 1961; VISSER et al., 1964). Their plasma level is much elevated in congenital adrenal hyperplasia. Such an effect may be the explanation of the temporary "salt-losing" phase sometimes seen in untreated cases of the simple form of congenital adrenal hyperplasia. When treatment is instituted, the salt-loss ceases. The high secretion rate may be a compensatory phenomenon to offset the natruretic effects of the excess metabolites. The salt-losing action of progesterone and 17-hydroxyprogesterone may have an additive effect in the salt-losers and exacerbate the salt loss.

The impaired capacity to secrete aldosterone appears to lessen with age though it is never completely outgrown. The cause of this phenomenon is so far unexplained. It is usually possible to withdraw mineralocorticoids after the age of 4–5. Nevertheless in later childhood, under stress, a child may develop an addisonian crisis requiring emergency treatment with intravenous saline and DOCA (NEW, 1966). In such cases it may be necessary to re-introduce maintenance therapy with small doses of mineralocorticoids.

V. Clinical Features

1. Females

Cases of congenital adrenal hyperplasia are recognisable at birth because of the abnormal genitalia (Fig. 195). An exception is the rare type of virilisation where there is complete fusion of the labio-scrotal folds; the urethra opening is at the tip of the clitoris (Fig. 196). Such patients are usually mistaken for cryptorchid boys with hypospadias.

The usual appearances are those of a female intersex (female pseudohermaphrodite). There are varying degrees of labio-scrotal fusion. The labia minora are absent and the scrotum-like labia majora are fused. There is a single perineal orifice of varying size and position which opens into a urogenital sinus. The clitoris is considerably enlarged and has a well-formed prepuce. In a very few cases the vulva is normal, there being separate openings for the urethra and vagina; there is usually some clitoral enlargement.

The ovaries, uterus and Fallopian tubes are normal. According to QAZI and THOMPSON (1972) a much higher proportion of salt-losers have the more advanced degree of virilisation. The variable degree of virilisation probably depends on the timing in foetal life of the appearance of excess androgen secretion.

In the untreated female, progressive virilisation takes place. The clitoris enlarges, pubic hair, axillary hair and later facial hair appears and the voice deepens. In adolescence, breast development and cyclical menstrual bleeding fail to appear because the excessive androgen production suppresses gonadotrophin release. There have been a few reports of females with 21-hydroxylase deficiency who were completely normal at birth, but who have exhibited progressive virilisation with clitoral enlargement and hirsutism in later childhood, adolescence or early adult life (VISSER, 1966 b).

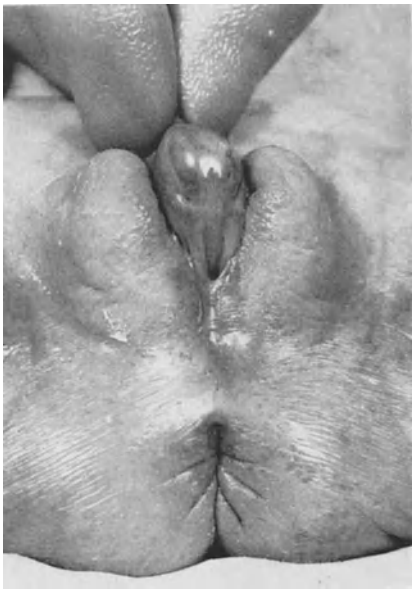


Fig. 195

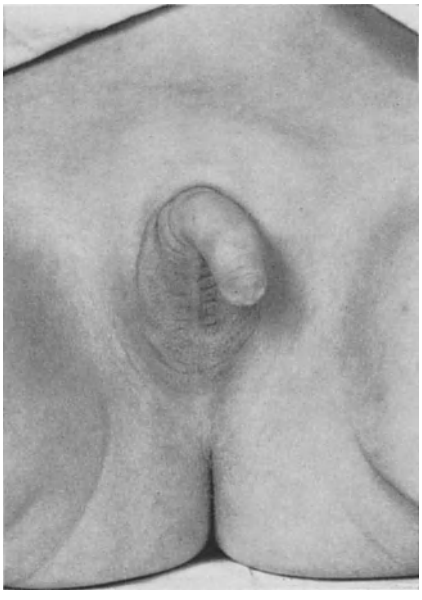


Fig. 196

Fig. 195. Congenital adrenal hyperplasia. Typical appearance of external genitalia in a female infant

Fig. 196. Congenital adrenal hyperplasia: a completely virilised female aged 4 years

2. Males

In the male, the genitalia appear normal at birth in spite of the high level of testosterone. The cause for this is not known. The exceptions are in patients with the 3 β-hydroxydehydrogenase defect and in lipoid hyperplasia where the males are incompletely masculinised.

Virilisation rarely begins before 6 months of age and usually develops at 1–2 years (Fig. 197). Occasionally it is delayed beyond 3 or 4 years. In these cases it is important to differentiate the condition from virilising adrenal tumours.

The penis enlarges and pubic hair appears. The testes remain small, however; the excessive androgen secretion suppresses release of LH by the pituitary.

In both sexes, in untreated cases, somatic growth is excessive. There is rapid increase in height and advance in skeletal age. Growth ceases early owing to the premature fusion of the epiphyses so that the ultimate height is much below normal.

Muscular development is particularly marked in the males and the voice becomes very deep at an early age.

In both sexes, pigmentation of the genitalia may be present at birth. This is usually greater in the male and in salt-losers.

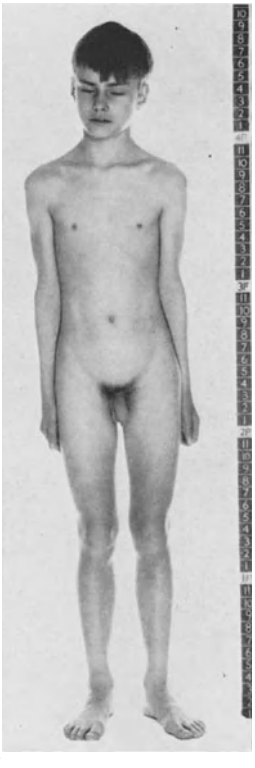


Fig. 197. Congenital adrenal hyperplasia. Untreated 4 year old boy showing virilisation and excessive height

VI. Salt-Losing Syndrome

Symptoms rarely occur in the first week and usually appear between the 2nd and 5th week. The onset is sudden and resembles that of an acute addisonian crisis. The infant becomes irritable, fails to gain weight, vomits and may have diarrhoea. Dehydration rapidly develops and the plasma volume falls with consequent peripheral circulatory failure. The infant may go rapidly downhill and die within 48 hours of onset of symptoms if treatment is not instituted. The vomit is often semi-projectile and in boys a mistaken diagnosis of congenital pyloric stenosis may be made, and even a Rammstedt's operation performed. Many of

the males are diagnosed incorrectly, or remain undiagnosed because of the normal-looking genitalia. In view of the presence of diarrhoea as well as vomiting, a mistaken diagnosis of gastro-enteritis may be made.

The serum electrolytes show a typical pattern. The serum sodium is low and may be less than 125 mEq/100 ml. The serum potassium is high, often 9–10 mEq/100 ml. In spite of this level, cardiac complications are rare.

These findings distinguish the disease from congenital pyloric stenosis and gastro-enteritis where both the serum potassium and serum sodium are low.

The blood urea is usually moderately elevated, probably from extra-renal causes, namely the fall in plasma volume and reduction in the glomerular filtration rate. These electrolyte changes slowly return to normal when treatment with saline and DOCA is instituted.

VII. Genetics

Genetic studies by Childs, Grumbach and Van Wyck (1956) and others indicate that congenital adrenal hyperplasia is inherited via an autosomal recessive gene, the disease occuring only in the homozygotes. Most large series have examples of 2 or 3 cases in one family.

The above-mentioned authors studied 76 affected individuals among 181 siblings in 56 families. In only one family was there consanguinity. They estimated the incidence of the disease in the State of Maryland, U.S.A. as 1 in 67000 births with a gene frequency of 1 per 128 persons in the general population.

Prader (1958) calculated the incidence for the Canton of Zurich, Switzerland at about 1 per 5000 births with a gene frequency of 1 per 35 persons. There are probably therefore considerable differences in gene frequency in various parts of the world.

The various types of congenital adrenal hyperplasia "run true". If the patient has a 21-hydroxylase defect, and is a non-salt-loser, other siblings will be non-salt-losers. Similarly the siblings of salt-losers are also salt-losers. These forms of congenital adrenal hyperplasia are probably genetically independent.

No diagnostic test for heterozygotes has been found.

VIII. Diagnosis

The differential diagnosis in females is between:

1. Those whose mothers have been given androgenic hormones in the first trimester of pregnancy.
2. Cryptorchid males with perineal hypospadias.
3. Certain types of male intersex (male pseudo-hermaphroditism) with ambiguous genitalia.
4. Males with some defect in the synthesis of testosterone such as occurs in patients with 3 β-hydroxydehydrogenase deficiency and lipoid hyperplasia.
5. Certain female intersexes (female pseudohermaphrodites) with no endocrine cause, possibly of genetic origin.
6. Certain cases of true hermaphroditism with ambiguous genitalia of female type.
7. Maternal virilising arrhenoblastoma in pregnancy (very rare).

In boys:

1. Virilising adrenal tumour.
2. Premature pubarche (premature growth of pubic hair).

The family history may be informative. There may have been previous affected siblings, or there may be a history of early deaths with wasting and dehydration usually diagnosed as gastro-enteritis. These are generally boys. A careful history to exclude administration of androgen hormones in pregnancy is essential.

IX. Diagnostic Tests

1. Demonstration of a positive (female) chromatin pattern in the buccal smear indicating an XX karyotype. It will not exclude true hermaphrodites, the majority of whom have a female chromatin pattern.

Caution, however, should be exercised in interpreting this test since several reports of low chromatin-positive counts in buccal smears in untreated cases have recently been published (Garets et al., 1971; Riccardi et al., 1972). This test will eliminate the cryptorchid male with perineal hypospadias, and the male intersex (male pseudohermaphrodites.)

2. Demonstration of increased secretion of 17-ketosteroids in the urine. These are the excretion products of adrenal androgens. It is important to remember that in the first two weeks of life, the urinary 17-ketosteroids may be physiologically high, up to 2–2.5 mg/24 hr. The level then falls to below 0.5 mg/24 hr and levels higher than this are significant. If a high value is found it must be repeated after the baby is 2–3 weeks of age.

3. Demonstration of increased secretion of abnormal metabolites depending on the site of the metabolic block.

In 21-hydroxylase deficiency, there is a considerable increase in the plasma level of 17-hydroxyprogesterone which is normally very low. This metabolite can be measured at present only in special laboratories. In untreated cases the level may be from 5–10 μg/100 ml from as early as the 6th day of life (normal controls up to 1.5 μg/100 ml). The estimation can be done on a small quantity of capillary blood and takes less than 2 hours (Atherden et al., 1972).

The most important urinary metabolite of 17-hydroxyprogesterone is pregnanetriol and is a specific indication of increased plasma levels of this hormone, and, therefore, a valuable indication of 21-hydroxylase deficiency. Normally the urinary levels are very low or undetectable, but in congenital adrenal hyperplasia, the levels may be raised to 2–6 mg/24 hr or even higher (Barnes and Atherden, 1972).

In patients where a quick diagnosis is required, especially in those who have a salt-losing crisis, the rapid diagnostic test which has been devised by Edwards et al. (1964) is useful. The "oxygenation index" is the ratio of the non-11-oxygenated steroids to the 11-oxygenated ones, chiefly cortisol. In normal individuals the ratio is below 0.7 but in patients with congenital adrenal hyperplasia it is usually over 1.0. An advantage of the method is that only small quantities of urine are required and the results are obtainable in 3–4 hours.

In 11-hydroxylase deficiency there is an accumulation of tetrahydro S, the metabolite of 11-deoxycortisol (Compound S) in the urine. An excess of tetrahydro DOC is also usually found.

In 3β-hydroxylase deficiency, the secretion of dehydroepiandrosterone is increased. Because of the block in the formation of androgens the urinary 17-

ketosteroids are low. There is also an excess of pregnanolone and its urinary metabolites.

In 17-hydroxylase deficiency, there is a low urinary excretion of 17-ketosteroids, low or normal pregnanetriol levels, and elevated plasma levels of progesterone and corticosterone and DOC.

Urethroscopy and/or radiological examination of the lower genital tract may give useful information about the anatomy which will be of value when surgical treatment is undertaken.

Suppression of 17-ketosteroids with glucocorticoids in low dosage, e. g. Dexamethazone, 4–8 mg/day, serves to differentiate congenital adrenal hyperplasia from virilising adrenal tumour in which suppression does not take place with these doses, because the hormones secreted by the tumour are independent of control by ACTH. In adrenal tumours there is usually a high secretion of dehydroepiandrosterone.

When the diagnosis is in doubt and the patient has been treated with glucocorticoids, injections of Synacthen (a synthetic ACTH analogue) for several days stimulates the adrenal cortex causing a rise in urinary 17-ketosteroids and pregnanetriol, and in the plasma 17-hydroxyprogesterone level.

X. Treatment

The object of treatment is to prevent progressive virilisation and to secure normal growth and normal skeletal development. As mentioned above, untreated patients grow at an excessive rate and their bone age advances rapidly so that early fusion terminates growth before adult height is reached.

Before the introduction of cortisone by WILKINS et al. in 1950, it was not possible to arrest the virilisation and excessive growth. If treatment is commenced in early infancy normal growth and development take place.

The administration of glucocorticoids raises the level of plasma cortisol and by the feed-back mechanism leads to suppression of the excessive ACTH secretion by the pituitary gland, and the stimulation of the adrenal cortex ceases. The level of androgen falls and this is reflected by the normalisation of the urinary excretion of 17-ketosteroids.

Cortisone acetate or hydrocortisone are the usual glucocorticoids employed. Both are effective suppressors of ACTH. Hydrocortisone, since this is the hormone normally secreted by the adrenal, would seem more physiological. ZURBRÜGG (1969) claimed that he has had better results with this hormone than with cortisone. Hydrocortisone has an extremely bitter taste and requires sweetening. Fluid Cortef (Ubjohn) in a concentration of 10 mg/5 ml, in a suitable fruit-flavoured medium is well tolerated. This preparation is not available in some countries and individual dispensing of a weighed powder incorporated in a sweetened mixture will be necessary. Alternatively, Cortisone Acetate which is still available in 5 mg tablets may be used by making a mixture of the crushed tablets.

Both these glucocorticoids have to be given at least three times daily as their duration of action is short (6–8 hr); otherwise good control of ACTH secretion will not be obtained. Even so, there seems to be an "escape" from control in the early hours of the morning when the last does is given to an infant at 6 or 7 p.m.

ATHERDEN et al. (1972) have recently shown in a group of adolescent patients treated with cortisone a persistence of the circadian rhythm as shown by high

levels of plasma 17-hydroxyprogesterone between 2 and 4 am, indicating a rise in ACTH secretion at this time.

Other glucocorticoids have been employed for suppressing ACTH secretion, e. g. Beta-methazone (HUBBLE, 1965), triamcinolone, dexamethazore. Some workers use prednisolone in small doses and claim that there is no growth retardation. The dose is approximately one quarter that of cortisone. The author, however, has had to transfer several patients from prednisolone to cortisone because of slowing of growth velocity. Some steroids have a greater growth suppressing effect than cortisone or hydrocortisone (VAN METRE et al., 1960; LARON and PERTZELAN, 1968).

If cortisone is given, a relatively high initial dose is necessary for 7–10 days to suppress the ACTH secretion. Thereafter the dose is reduced to a maintenance level.

Doses of 50–60 mg orally daily in 3 divided doses are given in a small infant. After 7/10 days the urinary 17-ketosteroid level will have dropped to less than 1 mg/24 hr; the plasma 17-hydroxyprogesterone level falls within a few hours. If given intramuscularly the dose is one-third i.e. 15–20 mg/day.

Maintenance doses should be the smallest required to maintain the urinary 17-ketosteroids at normal levels for the age. This varies from patient to patient. The average dosage is 15–20 mg daily for infants under the age of 2 years; 20–30 mg daily from the age of 2–5 years; 30–50 mg/days from 5–10 years, and 50–75 mg/day thereafter.

Doses should be given preferably three times a day at approximately equal intervals. The evening dose should be given as late as possible so as to maintain control in the early hours of the morning when ACTH secretion is high.

Even in patients treated with cortisone and hydrocortisone reports of retardation of statural growth have recently appeared in the literature (BERGSTRAND, 1966; RAPPAPORT, 1968).

Rappaport's 16 patients (all of whom were salt-losers) had severe growth retardation, the growth failure being greatest in the first year of life. He considered that growth retardation was due to over-treatment related to increased dosage during infections and afterwards.

SPERLING et al. (1971) reported that 76 per cent of children with congenital adrenal hyperplasia were below the 3rd percentile by the age of 2 years. RAITI and NEWNS (1971), on the other hand, found that 27 of 35 salt-losing patients and all 10 non-salt-losers grew within the 3rd–97th percentile in height. All were treated with cortisone. Eight of the salt-losers were below the 3rd percentile, all of whom had received excessive doses of cortisone in infancy.

MIGEON (1968) recommends a dose of cortisone not more than two to three times the normal cortisol secretion rate for the age (Table 9).

The oral dose would thus range between 12–36 mg/sq.metre daily which is close to that suggested by LARON and PERTZELAN (1968), i. e. 10–30 mg/sq.metre. These doses are somewhat lower than those recommended above.

Growth suppression seems to be greatest during the period of active growth in the first 2 years of life. Frequent monitoring of urinary 17-ketosteroid levels should be carried out during this age period which would necessitate a 48 hr period of admission to hospital for the 24 hr urine collection.

Glucocorticoid therapy must be continued throughout life. A high plasma androgen level inhibits gonadotrophin secretion and may impair fertility. Some adolescent females treated with cortisone or hydrocortisone do not menstruate and the regime recommended by HAYEK et al. (1971) should be considered. He found that a single dose of 0.5 mg of dexamethazone administered at midnight suppressed 17-ketosteroid action throughout the 24 hours. The female patient menstruated after a long period of amenorrhoea.

The females appear to be fertile. Numerous reports of normal pregnancy and delivery have now appeared and the infants are normal (GANS and SER, 1959; LARON, 1959; MASON, 1961, and SWYER and BONHAM, 1961).

Patients with congenital adrenal hyperplasia must be observed regularly. The height should be carefully measured and 6-monthly estimations of bone age and urinary 17-ketosteroids made. If the 17-ketosteroid level is too high or too low the dose of glucocorticoids must be adjusted.

Table 9. Oral cortisone doses based on cortisol production rate (CPR)

Age in years	Surface area in m^2 for 50th. percentile (both sexes)	CPR (12 ± 3 mg/m^2/day)	Approximate oral cortisone dose (CPR x 2–3) (mg/day)
0.5	0.25	3.0	6– 9
1	0.47	5.6	11–17
2	0.55	6.6	13–20
4	0.68	8.2	16–25
8	0.91	11.0	22–33
12	1.30	15.6	31–47
Adult females	1.60	19.2	38–58
Adult males	1.75	21.0	42–63

XI. Treatment of the Salt-Losing Syndrome

1. Emergency Treatment

Severe salt-losers present in the early weeks of life and develop rapidly an addisonian crisis with severe dehydration and circulatory failure. They must be regarded as medical emergencies.

Isotonic saline should be administered intravenously. 100 ml/kg of body weight in infants is adequate and 25 per cent of the total calculated volume for 24 hr should be given in the first 2–3 hours.

2–5 mg desoxycorticosterone acetate (DOCA) should be given in twice daily doses. The blood pressure and electrolytes should be measured frequently and the above treatment continued until the serum sodium and potassium have reached normal levels.

Circulatory collapse should be counteracted by either intramuscular injection of 100 mg of hydrocortisone twice daily or intravenous injection of hydrocortisone hemisuccinate in a dose up to 10 mg/kg several times a day. There is little danger of overdosage in the emergency period. After the infant is rehydrated and the serum electrolytes are normal, suppressive doses of glucocorticoids (cortisone or hydrocortisone) are begun and the dose of DOC reduced and finally discontinued. Oral treatment with sodium chloride, 3–6 G daily is started.

2. Maintenance Treatment

Maintenance treatment with mineralcorticoids should be instituted. DOCA may be given as 125 mg pellets (2–4) implanted below the skin in the scapular

area. Each pellet is approximately equivalent to 0.5 mg of intramuscular DOCA daily. They will need to be replaced when they can no longer be palpated.

DOCA may also be administered as a depot preparation (Percorten) 25-50 mg intramuscularly every month.

Many endocrinologists use the powerful salt-retaining steroid, 9α-fluorohydrocortisone providing one can be sure it will be given regularly. The average dose is 0.1 mg/day in two divided doses. Larger doses up to 0.2 mg/day may be given but these carry a greater risk of the development of hypertension. This has also been reported in a few patients treated with Percorten. It is, therefore, essential to measure the blood pressure regularly and if it begins to rise the hormone must be stopped.

Even when patients are receiving mineralcorticoids a salt-losing crisis may be precipitated by an infection or injury or by a surgical operation. Any attack of vomiting must be taken seriously and medical aid sought immediately.

Parents should be given a pamphlet detailing measures to be taken in these circumstances, including increasing the dose of steroids.

The mother should be given supplies of DOCA and hydrocortisone and taught to give injections if the doctor cannot come immediately. The parents or doctor should always be able to telephone someone at the hospital in the Endocrine Service who can give the instructions for treatment, and if necessary, arrange admission to hospital.

Most salt-losers can stop taking salt-retaining hormone at 4–5 years of age and can usually be maintained on cortisone or hydrocortisone and added salt.

Nevertheless even in later childhood, a salt-losing crisis may develop requiring emergency treatment as indicated on p. 330. In such cases it is advisable to reinstate the administration of small doses of salt-retaining hormone.

Y. Sex Chromosome Anomalies and Intersex States

P. E. Polani, Sheila M. Kohlinsky and J. D. Singer

With 21 Figures

I. The Normal Chromosomes

It is not often possible to pinpoint the origin of a whole new branch of science accurately in time and place because, as Isaac Newton said, "there are usually so many precursors on whose shoulders the successor stands and is thereby able to see further than they". However, genetics is an exception, for it owes its origin to one man, Gregor Johann Mendel, who expounded its basic principles at Brno on 8th February and 8th March 1865. After Mendel's studies there was a gap of neglect until the turn of the century when Mendel and the principles enunciated by him were rediscovered. By then cytology had made rapid and great strides and interest was beginning to centre around the chromosomes and their behaviour in cell division, their integer individuality and their numbers. After Flemming's (1882) studies of cell division in the human cornea came Hansemann's (1891) attempt to count human chromosomes, followed by many others, and then von Winiwarter's (1912) study of human spermatogenesis where he concluded that in the male there were 47 chromosomes, in the female 48 and that the chromosomal sex-determining mechanism of man was of the XO–XX type. However, Painter (1923) clearly demonstrated a small Y chromosome in spermatogonial metaphases and the X and the Y in first meiotic divisions, and, after some indecision as to whether the correct count was 46 chromosomes, he concluded that the chromosome number for man was 48. By then cytology and genetics had been successfully married.

Though most subsequent observers agreed with Painter's conclusions, a number followed von Winiwarter's ideas on XO–XX man until Koller (1937) finally settled the matter of the presence of a Y chromosome in man and 48 became the accepted chromosome number. During the period 1935 to 1955 workers in Western laboratories were inhibited by the presence of fixed ideas, now known to be fallacious. Human cells were supposed to be exceptionally difficult to cultivate. It was thought that the karyotype varied in different somatic tissues so that only germ cells were reliable material. Higher anthropoids and man were alleged to be tetraploid because 4 nucleoli were found in somatic cells so 28 was a likely diploid number. Finally human zygotes with aberrant chromosome complements were not thought to be viable. However, the real block to progress was technical and useful work in human cytogenetics was limited until Hsu (1952) announced the method of dispersing chromosomes by hypotonic treatment—the result of a laboratory mistake. Equally important was the use of colchicine to arrest cell division at metaphase. Four years later Tjio and Levan (1956) proved that in fact the chromosome number of man was 46. Ford and Hamerton (1956) quickly confirmed the discovery with the study of meiotic cells at first metaphase. Thus it was established that man's chromosome complement was of 23 pairs of

chromosomes, 22 pairs of autosomes, or non-sex chromosomes, and a pair of sex chromosomes, XX in the female and XY in the male.

Meanwhile BARR in Canada had discovered sexual dimorphism of non-dividing so-called resting nuclei: the presence of a sex-specific chromatin mass in normal females and its absence in males (1949). Soon this discovery was applied to the study of patients with hints of anomalous sex determination, first women with Turner's syndrome (POLANI et al., 1954; WILKINS et al., 1954), and a little later males with Klinefelter's syndrome with results that confirmed the hints of sex chromosome "abnormality". In 1958 FORD and his colleagues introduced the bone marrow technique to the study of human somatic chromosomes and this work led—in parallel with the fibroblast culture methods used by others, particularly LEJEUNE and TURPIN (1960)—to practical applications and the demonstration of sex chromosome and autosome anomalies in man. The next practical advance was the development of techniques for obtaining chromosome preparations from cultured lymphocytes (HUNGERFORD et al., 1959), the feasibility of which had been discovered by CHRUSTSCHOFF and BERLIN in 1935. This has led to the wide applicability of human chromosome investigation.

The chromosomes are most clearly seen in dividing cells at the metaphase stage and preparations are made after three days' culture in the case of leucocytes or approximately three weeks' culture in the case of skin fibroblasts. The preparations are examined under a light microscope and at this stage in cell division each chromosome is divided longitudinally into two chromatids. A metaphase spread seen under the microscope is shown in Fig. 198. A photograph of the cell is then taken and the chromosomes cut out and arranged in pairs to make a karyotype (Figs. 199 and 200). In general a "karyotype" is first constructed by doing a direct visual analysis under the microscope and, usually, a number of cells are so analysed, numbers depending upon the object of the investigation. The members of a pair of chromosomes are homologous and complementary in function as well as being similar in appearance; the only exception to this being the XY pair in males. For convenience chromosomes are classified in order of decreasing length and by the position of their centromere, the organelle concerned with chromosome movement during cell division, the site of which is at the so-called 'primary constriction' of the chromosome. Chromosomes with centromeres positioned midway are called metacentric chromosomes. Chromosomes with centromeres placed slightly more towards one end are called sub-metacentric; those with sub-terminal centromeres are acrocentric and the term telocentric is also used, generally to imply the presence of the centromere at the very end of the chromosome. These normally are not found in man.

The chromosomes are grouped into seven classes, from A to G, and the autosomes are numbered from 1–22, as shown in the karyotypes in Fig. 199 and 200. The twenty-third pair of chromosomes is the pair of sex chromosomes (XX in females and XY in males, the X belonging to the C and the Y to the G groups).

A convenient, concise and standard way of describing the karyotype is first to give the total number of chromosomes, then the sex-chromosome status and then the autosomal abnormality if present (Table 10).

If a piece of chromosome material is missing this is known as a deletion and if part of the short arm (in shorthand notation: p) is deleted it is denoted as p–, e.g. a girl with part of the short arm of a B chromosome missing is 46,XX,Bp–. The long arm of a chromosome is designated q, so a male with part of the long arm of a D group chromosome missing is 46,XY,Dq–. If a piece of chromosomal material is added to an arm of a chromosome this is noted by a plus sign after the shorthand form of the appropriate arm, therefore p+ or q+.

Table 10. Examples of karyotype description (Paris 1972 Nomenclature)

1. Normal male	46,XY
2. Normal female	46,XX
3. Female with three X chromosomes	47,XXX
4. Male with extra X chromosome	47,XXY
5. Female with single X chromosome	45,X
6. Male with extra 'G' group chromosome	47,XY,+G
7. Male with missing 'G' chromosome	45,XY,–G
8. Female with an additional chromosome 18 with a deletion of the long arm of the extra chromosome	47,XX,+18q–

The chromosomes are collections of genes and each chromosome presumably contains many hundreds of them. However, the chromosome assignment, and even more so, the position of only a few of the human genes are known. In some respects the X chromosome is similar to an autosome in that it contains a collection of non-sex genes; indeed, it is the one chromosome to which many genes have been successfully assigned and for which a reasonable "map" is beginning to emerge. Thus it contains genes for colour vision, for the Xga blood group, for blood clotting, for G6PD and some 60 other genes recognised from their mutations

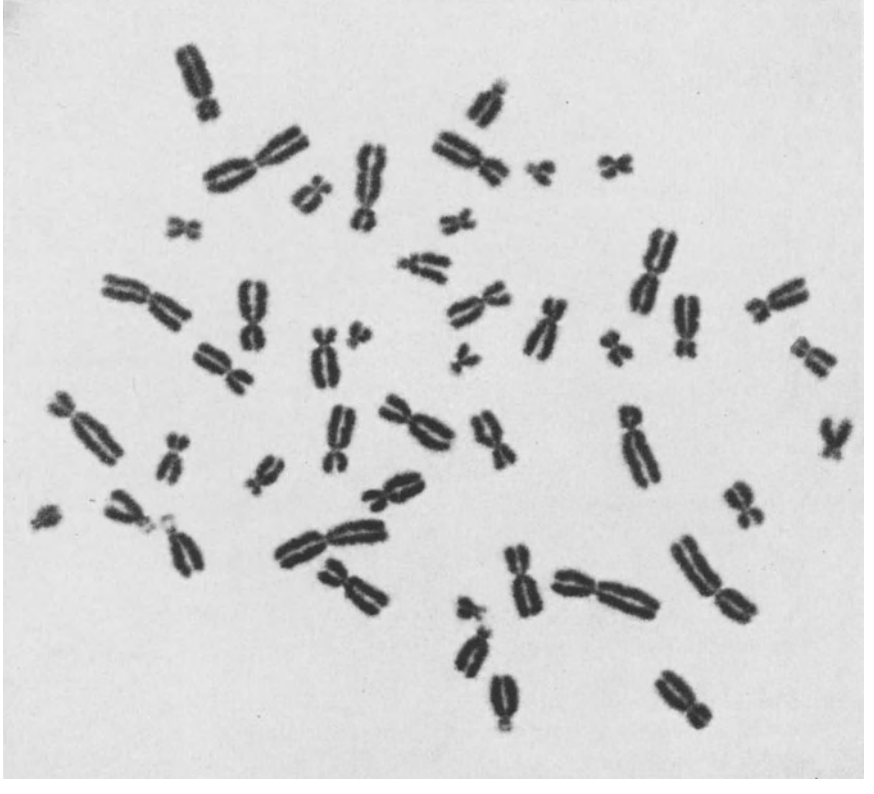


Fig. 198. A metaphase spread (aceto-orcein × 1,500) of a normal male cell (46,YX); five G chromosomes are seen. The Y chromosome is the small acrocentric at 8 o'clock

(colour blindness, haemophilia A and B, etc.). At present only one gene has been detected on the Y chromosome though this chromosome plays a key role in sex determination. This odd gene would seem to produce hairy ear rims in males (a trait fairly common in parts of India) and is transmitted from father to son (holoandric transmission).

When ordinary somatic cells undergo division, a process known as mitosis, the two daughter cells produced are identical to the parent cell. Prior to mitosis the chromosome produces an identical copy of itself, a replica, and duplicates of all the genes it carries. When cell division takes place, original and copies of chromosomes separate to the two daughter cells. Therefore, these carry the same chromosome pairs as the mother cell with the same complement of genes. However, in the germinal cells prior to the formation of gametes a special sequence of two cell divisions has to occur, known as meiosis or reduction division. In this process, the cell divides twice but the chromosomes divide only once with the result that the two members of each chromosome pair separate, giving each gamete only one member of each pair. Preparatory to the first meiotic division each chromosome replicates and pairs with its corresponding partner homologue. Exchange then occurs between the chromatids of the paired chromosomes which results in reshuffling (recombination) of the genes. Subsequently at first meiotic division chromosomes of a pair separate from each other, while at second meiotic division the two chromatids of each chromosome separate from each other as at an ordinary mitotic division. However, now there are only 23 chromosomes (instead of 46), only one representative of each original pair present in somatic tissues. Furthermore, because of the reshuffling of the genes, the two chromatids of each chromosome need not be wholly but may be only partly identical unlike what happens at mitosis. A mature ovum or spermatozoon contains in its nucleus 22 autosomes and a single sex chromosome (haploid number, n). Fertilisation thus produces a zygote with the full number of 46 chromosomes, 44 autosomes and two sex chromosomes (diploid number, 2n). This zygote subsequently divides by mitosis, each daughter cell having the full number of 46 chromosomes.

The sex of the zygote is determined by the segregation of the father's sex chromosomes (X and Y) at the first meiotic division preparatory to sperm formation. A Y-bearing chromosome thus produces an XY zygote and an X-bearing sperm an XX zygote. However sex determination and the subsequent differentiation of the genital tract is a complex phenomenon which involves not only sex factors and genes on the sex chromosomes: there are also genes on the autosomes which may affect sex development.

II. Chromosome Abnormalities

Chomosome abnormalities consist in an excessive or deficient number of chromosomes or in their abnormal structure. The commonest origin of numerical chromosome anomalies is an error in the complex process of meiosis so that one chromosome too few or one too many enters the gamete and hence the zygote. This process is generally known as non-disjunction (Fig. 201) and is due to failure of one pair of chromosomes to separate at the first cell division of meiosis or, alternatively, it is caused by two chromatids failing to separate at the second cell division of meiosis. Both members of a chromosome pair (or both chromatids if non-disjunction occurs at the second division) enter one daughter cell and the other daughter cell receives none thus so unbalanced gametes will form. In the first case the zygote will therefore have three of the particular chromosomes

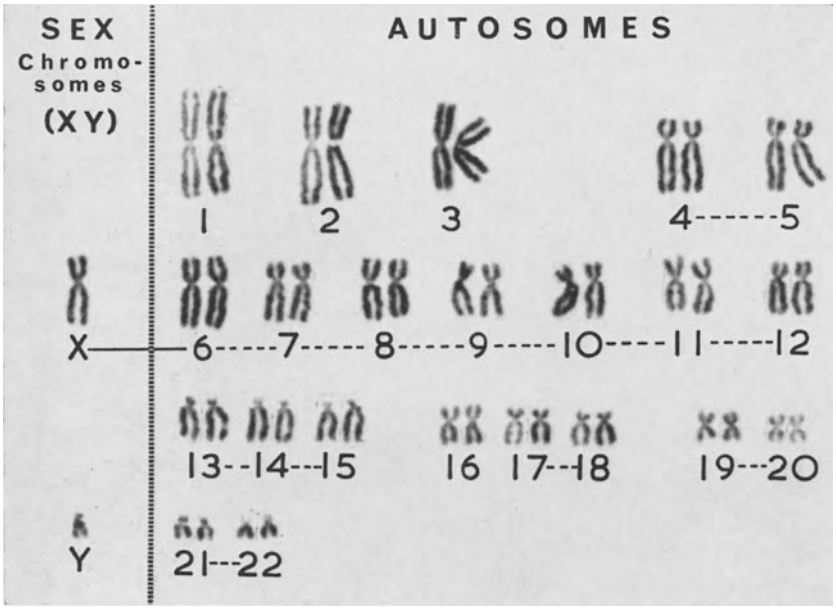


Fig. 199. Karyotype of a normal male (aceto-orcein × 1,500) 46,XY

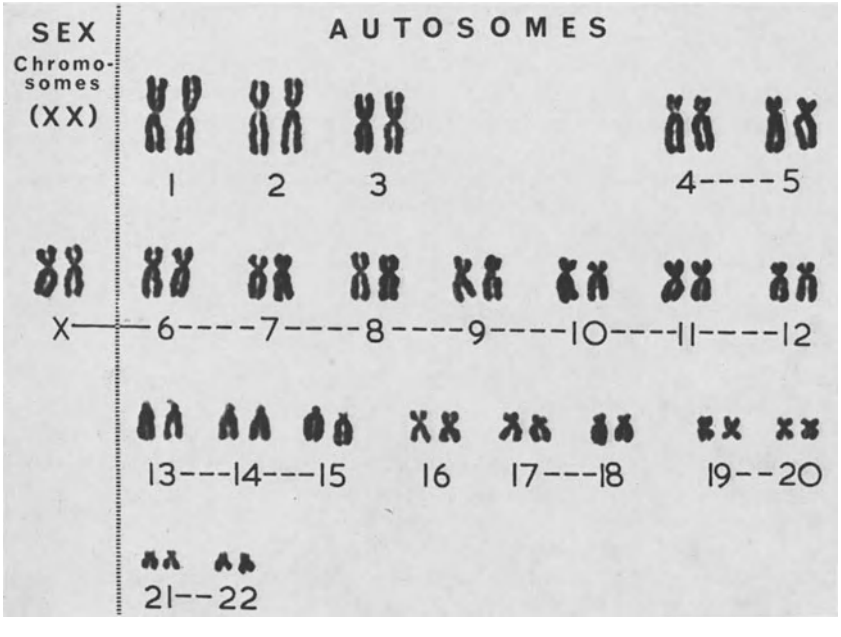


Fig. 200. Karyotype of a normal female (aceto-orcein × 1,500) 46,XX

involved instead of the normal pair and will be trisomic. In the second case the zygote will have only one chromosome instead of two of the given pair and is, therefore, monosomic. On occasions, although disjunction or segregation of chromosomes may occur regularly, one of the chromosomes lingers on the equatorial cell-division plane and is thus excluded from either daughter cell. This process is sometimes referred to as anaphase lag and results in the formation of a normal cell and a cell that misses a particular chromosome. Such a nullosomic gamete will, at fertilisation, produce a monosomic zygote. Few autosomal monosomic zygotes have been described in man probably because the condition is incompatible with embryonic development—whereas trisomy need not be—but sex chromosome mono-somy (XO) is common in early conceptions. It is also possible for non-disjuction (or anaphase lag) to occur at mitosis, e.g. at an early division of the zygote, and in this case the zygote will have two or more cell lines with different chromosome complements (i.e. it will be a mosaic). The example in Fig. 202 shows a normal 46,XX zygote which produced two cell lines, one with normal 46,XX cells and the other with one X chromosome missing, i.e. a 45,X cell line. However, mosaicism can arise in an abnormal zygote and tend to normalize it, and obviously may affect autosomes as well as sex chromosomes.

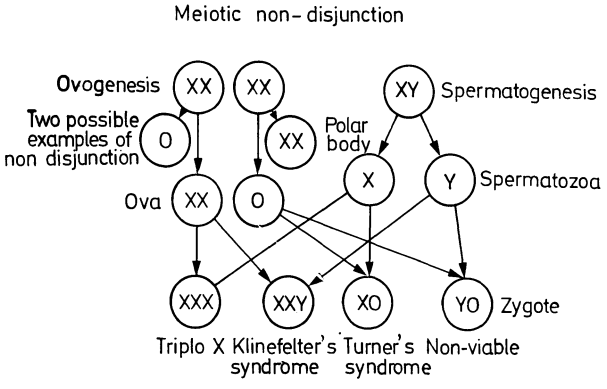


Fig. 201. This simplified diagram suggests that an error can occur at first or second meiotic division. The error illustrated here is of oogenesis, but could occur at spermatogenesis. Indeed, there is some evidence that the XO (45,X) condition may often arise from such an error

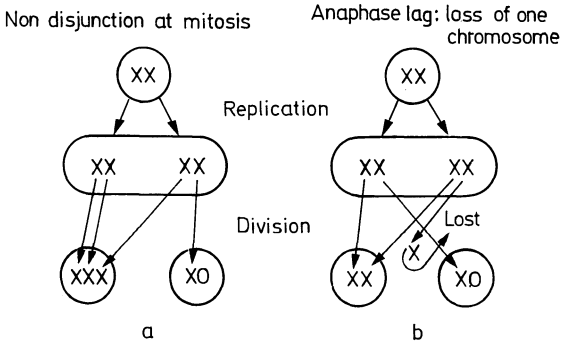


Fig. 202a and b. Mosaic formation due to a) non-disjunction at mitotic division of a normal zygote, b) anaphase lag

At this point a little should be said about chimaerism which is to be distinguished from mosaicism. The term chimaera refers to an individual with two or more cell types each of which has a different zygotic lineage. Therefore, in chimaeras, in contrast with mosaics, the two or more cell lines present arise from two or more different zygotes, for example as a result of fertilisation of the ovum and of the polar body by two sperms. In this case we speak of complete or dispermic chimaeras. But chimaeras can be partial and involve only the blood cells or discrete tissues as from cross circulation through the placenta between dizygotic twins.

The source of chromosomal structural abnormalities is breakage of one or more chromosomes. These breaks are not uncommon but usually the broken ends reunite without any loss or damage to the chromosome. Two breaks may occur in the same chromosome and the fragment of chromosome may rotate and therefore a whole block of genes may be replaced in the reverse order. This is known as inversion which may involve one chromosome arm (paracentric inversion) or may straddle across the centromere (pericentric inversion) and involve both arms. Either event may lead to abnormalities. When a break or double break occurs the fragment broken off may be lost leading to a partly deleted chromosome. However, instead of this a terminal fragment from one broken chromosome may become attached to the broken end of another chromosome whose terminal end becomes attached in turn to the first chromosome (reciprocal translocation). Provided the genetic material is all present there is usually no disturbance in that individual (balanced reciprocal translocation, or interchange, carrier). However, when the subject comes to make germinal cells only the one or the other chromosome may be selected at meiotic division and hence the zygote may lack material of one chromosome and have an extra dose of material of the other (duplication-deficiency). Other more complicated outcomes of segregation from a balanc-

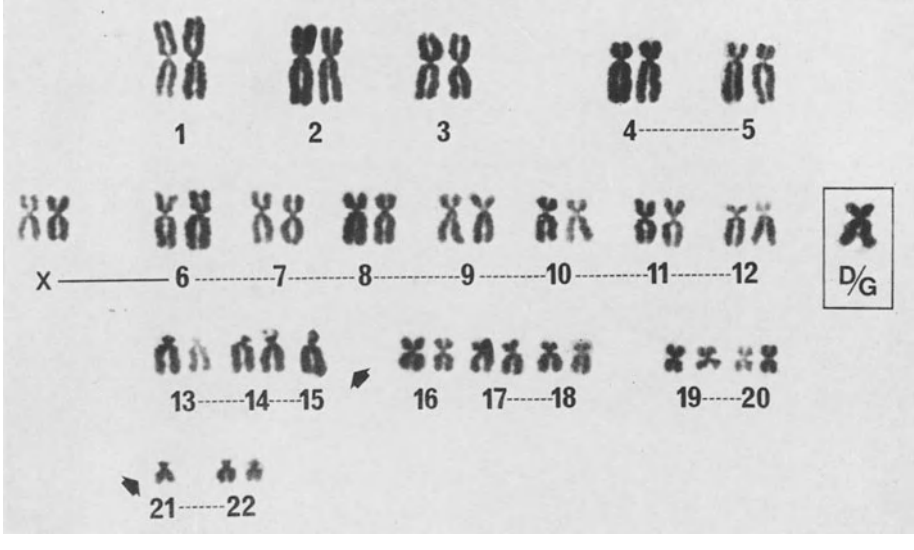


Fig. 203. Karyotype of a balance D/G translocation female carrier (aceto-orcein × 1,500). The translocation is of a special type (centric fusion) and the small product of the reciprocal exchange is usually lost during cell division. In this event, as in this karyotype, the chromosome number is 45 (see text)

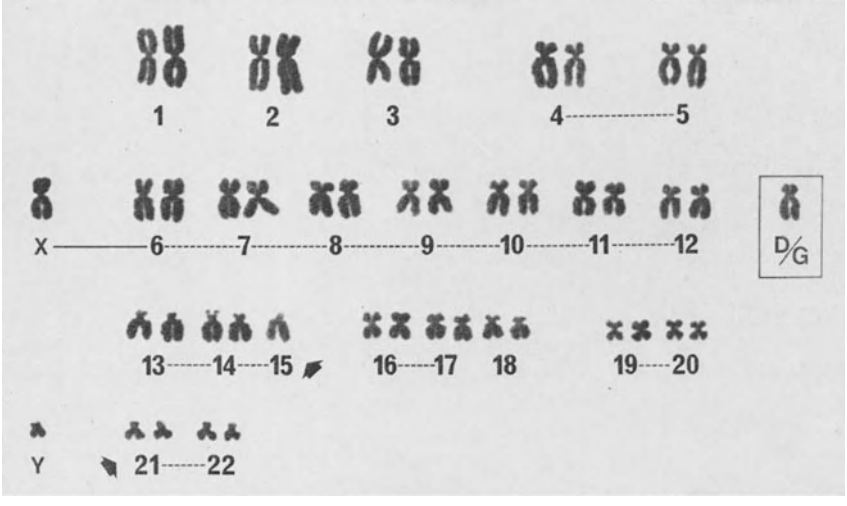


Fig. 204. Karyotype of a male D/G translocation Down's Syndrome (aceto-orcein × 1,500). This type of unbalanced translocation mongol is a special type and is often derived from a translocation carrying parent (see Fig. 203). Unlike primary trisomic 21 Down's Syndrome these subjects have 46 chromosomes but have practically all the material of three chromosomes 21

ed translocation carrier are possible. If in making a germ cell the individual happens to provide both the chromosomes which took part in the reciprocal translocation, then the resulting zygote will have the same chromosomal constitution as the parent, i.e. it will be a balanced translocation carrier.

There are also some special relatively common and important human translocations which occur between acrocentric chromosomes and in which some small amount of chromosome material seems to be lost without detriment to the" balanced" carriers, but with resulting oddities in chromosome number (Fig. 203 and 204).

Chromosomal anomalies are not uncommon and recent studies of spontaneous abortions occurring before the third month of gestation reveal that approximately 25–30 per cent of these have chromosomal abnormalities. As one in six or one in seven pregnancies ends as a spontaneous abortion the overall risk of any conception bearing a chromosomal abnormality is not small and may amount to, at least, $3\frac{1}{2}$–4 per cent of conceptions. However, by contrast, only about one in 150 to one in 200 live born infants has a chromosomal abnormality because chromosomally abnormal conceptions have an 85–90 per cent prenatal mortality. Of the chromosomally abnormal surviving infants above half of the anomalies affect the autosomes and half the sex chromosomes.

III. Sex Chromatin

Full chromosome analysis is both an expensive and rather complex undertaking but is essential for a study of the autosomes and for detailed investigation in general. However, there are useful indirect methods of studying the sex chromosomes without resorting to full chromosome analysis. The number of X chromosomes present can be simply established by the use of the oral smear technique.

In the nucleus of non-dividing cells (i.e. in the resting or interphase stage) if two X chromosomes are present as in normal females one of them is highly condensed and is seen, generally, at the edge of the nucleus, as a darkly staining body. This is known as the Barr body or sex chromatin mass. The discovery of the sex chromatin in mammals was made accidentally in the course of studies on neurone fatigue in 1949 by BARR and BERTRAM who observed a difference between neurones of the medulla of male and female cats. Only in the female was a darkly staining mass present which lay against the inner wall of the nuclear membrane. It has since been determined that the mass is due to the interphase condensation of one of the two Xs when two are present. In a normal male with a single X, and similarly in an abnormal female with only a single X chromosome (45,X), no Barr body can be seen. In an individual with two X chromosomes, e.g. normal female (46,XX) or a male with Klinefelter's syndrome (47,XXY), a single sex chromatin mass is present. This person is described as chromatin positive in contradistinction to a person with no sex chromatin mass who is chromatin negative. If there are three X chromosomes present (47,XXX) two sex chromatin masses are noted and with four Xs there are three sex chromatin masses in the resting nuclei. Hence the number of X chromosomes equals the number of sex chromatin masses plus one (Fig. 205). Sex chromatin studies are cheap and fairly simple to perform and can best be done by scraping cells from the buccal mucous membrane inside the cheek, fixing them and examining them under an ordinary light microscope. However, they only can tell about the numbers (and sometimes the structure) of X chromosomes present.

Apart from the practical usefulness of Barr-body sexing, this body has an important theoretical meaning. As we have seen each sex chromatin mass corresponds to one condensed X (this is referred to as the heterochromatic X) and there is good evidence that the Barr-body forming X is genically inert. This means that ordinarily all or most of its genes are "masked off" from a very early stage, say two weeks, of embryonic development. This inactive—X hypothesis—the Lyon hypothesis—states also that the process of embryonic inactivation of the X is random, so that different cells have not necessarily all the same X (or Xs) inactivated. It is thought that inactivation of extra Xs is the fundamental reason why humans are so tolerant to X chromosome polysomy, i.e.trisomy, tetrasomy, etc.

Recently a method of assessing the presence or absence, indeed the number of Y chromosomes, has also become available without having to resort to full blood chromosome tests. This method is based on the principle that part of the Y chromosome takes up fluorochromes such as quinacrine (or quinacrine mustard) much more intensely than any other chromosome or chromosome segment and that the intensely fluorescent area is quite large. Thus cell preparations (e.g. blood smear), treated with these fluorescent stains, when studied under U. V. light, can be seen to have a brightly fluorescent spot when a Y chromosome is present, (Fig. 206), or more than one when more than one Y is found. There are few pitfalls to the tests which may however be applied to a variety of interphase nuclei (oral mucosa cells, amniotic cells, fibroblasts, etc.). Hence by the combination of sex chromatin and fluorescence studies the number of X chromosomes can be established together with that of Y chromosomes.

IV. The Identification of Chromosomes

Over the past few years workers have succeeded in identifying chromosomes more accurately than is possible by simple assessment of size and shape, using

ordinary light microscopy and conventional methods of preparation and staining. These methods include: (1) autoradiography and two recent techniques; (2) fluorescence studies and, (3) Giemsa banding.

1. Autoradiography

This is a technique for studying the location or amount of a substance using a radio-active isotope tag and recording the resultant disintegrations on photographic emulsion. This technique has been applied to many cytogenetic problems, amongst them the accurate identification of some specific chromosomes and the organisation of the chromosomes, and the method of replication and the segregation of the genetic material.

By this method, studies of DNA synthesis, particularly the terminal synthetic patterns (v.i.) can aid in the identification of human chromosomes as the patterns of a number of different chromosome pairs tend be characteristic. Dividing lymphocytes or fibroblasts are incubated with radio-actively labelled DNA precursor, e.g. tritiated thymidine. A record of zones of radio-activity over the chromosomes can be obtained by using a photographic emulsion on the chromosome preparation slides that are subsequently made. If the radio-active material was supplied to the cells towards the end of the long period during which DNA is synthetized as a means of replicating the chromosomes, those chromosomes and/or segments which are late replicating incorporate and later reveal the radio-active label. The resulting pattern in many homologous chromosomes, members of the same pair, is, as said, distinctive. Thus numbers 13, 14 and 15 can often (sometimes using statistics as well) be identified; equally chromosomes 4, 5 and 17 and 18 have generally special labelling patterns. Also the Y chromosome and, less clearly, chromosome 21 tend to label late. In an individual with two X chromosomes, one X chromosome can usually be identified by its heavy

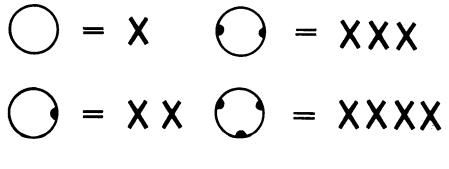


Fig. 205

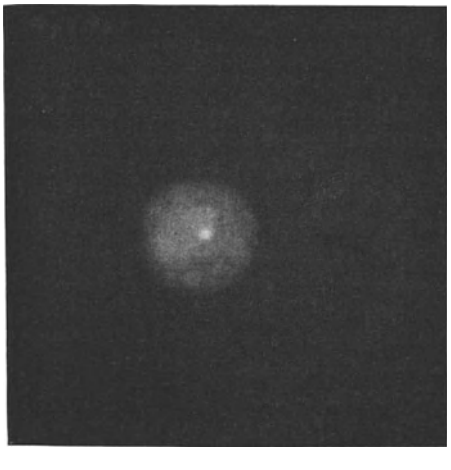


Fig. 206

Fig. 205. Each X chromosome in excess of one forms a sex-chromatin-mass. The sex-chromatin in relation to the number of X chromosomes

Fig. 206. Interphase nucleus stained with quinacrine mustard showing the fluorescent terminal portion of the Y chromosome (quinacrine mustard × 1,500) (see text and Fig. 208)

labelling with tritiated thymidine. This again is due to its later replication during the phase of DNA synthesis of the chromosomes, preparatory to cell division. If additional X chromosomes are present they also tend to be late replicating and labelling (Fig. 207). As in the case of sex chromatin, so with late labelling, there is always one less late labelling X chromosome than X chromosomes present and the late labelling X or Xs are those that form the heterochromatic sex chromatin mass in the resting nucleus.

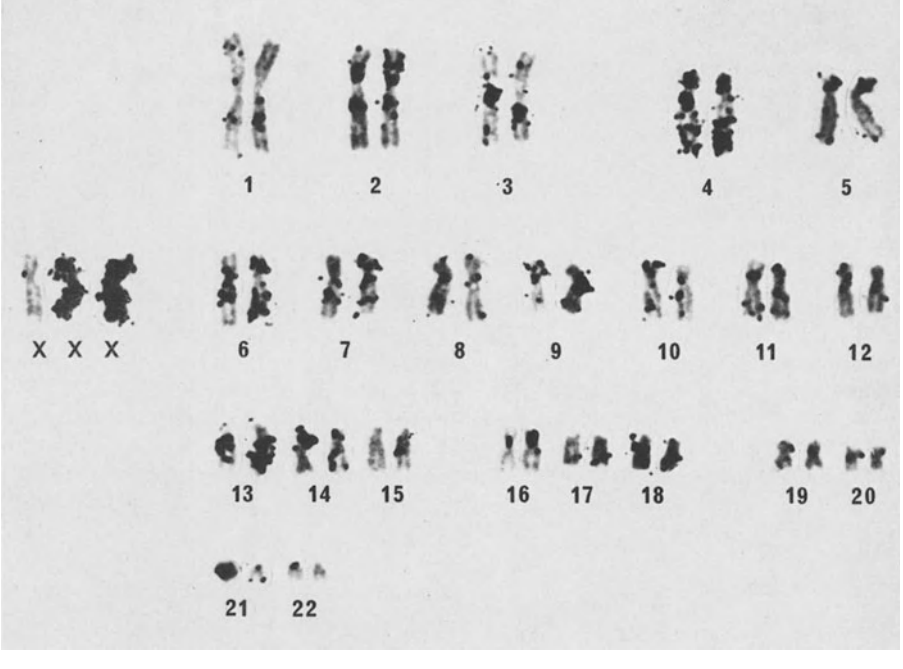


Fig. 207. Karyotype from an autoradiograph of a triplo-X female (× 1,500). 2 of the 3 X chromosomes are late labelling and show the greatest number of grains (see text)

2. Fluorescence Studies

For some time CASPERSSON and his colleagues have made studies in plant and animal cells designed to show differential binding of chemical substances in areas of DNA rich in two of the four bases, for example rich in guanine and cytosine as against thymine and adenine. For this they had used agents which not only bind firmly to DNA of chromosomes but also causes them to fluoresce, for example quinacrine mustard. During the course of these studies both CASPERSSON's group and workers in England observed a very strongly fluorescing region in the long arm of the Y chromosome. As we have already seen this observation has great practical and clinical value. But they also noted a "striped" or banded pattern of fluorescence in other chromosomes and soon CASPERSSON found that these special characteristics were the same when the chromosomes from different individuals were compared. The banded pattern (Q-banding) of homologous chromosomes was distinctly similar and each pair of chromosomes could, in good

preparations, be distinctly and unequivocally identified (Fig. 208). One of the points of clinical interest was the differentiation of the two "G" group chromosomes, Numbers 21 and 22. It has now been established from these studies that mongolism (Down's syndrome) is due to trisomy of the brighter, and shorter, "G" autosome, number 21.

The high staining capacity of the Y chromosome in comparison with other chromosomes can be exploited by the study of interphase cells as we have seen. In 47,XYY individuals two Y fluorescent spots are visible. Hence, large scale population screening for this abnormality has become a much more feasible proposition. Use of these fluorescent dyes on fixed sperm can detect Y containing sperm heads and it is of interest that 1–2 per cent of sperm of normal males contain two Ys though they are otherwise haploid. They must be the source of 47,XYY sons and that these are less frequent than might be expected could depend on selection against the male gametes with two Y chromosomes. However, as always with technical procedures, there have been some problems and it has been noted that the fluorescent body may be unusually small in some normal males. This limits the usefulness of the indirect Y chromosome test.

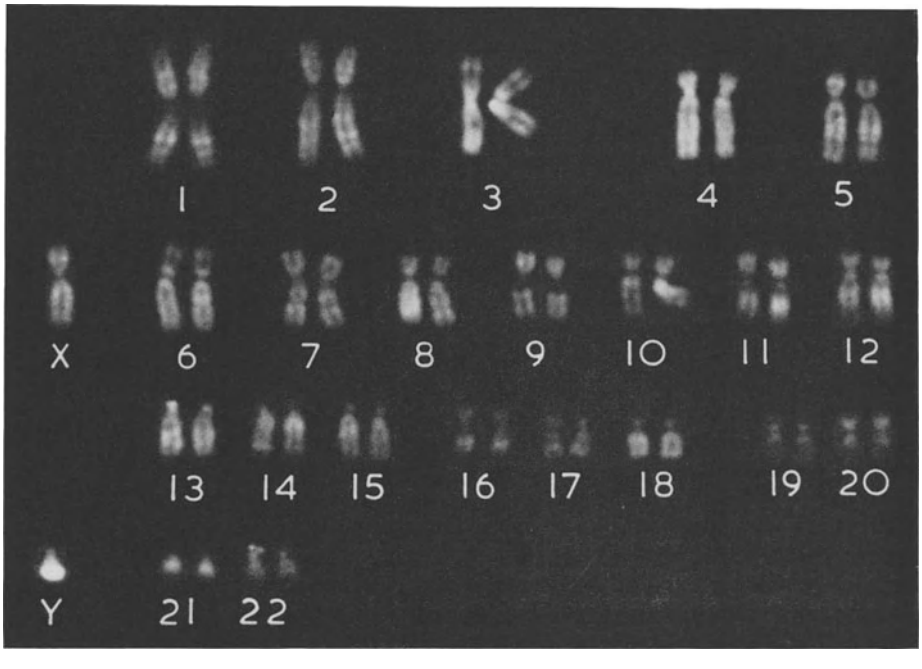


Fig. 208. Karyotype of chromosomes of normal male stained with quinacrine mustard (×1,500). Note the bright fluorescence of the terminal portion of the Y chromosome (see text)

3. Other Chromosome Banding Techniques

Recent developments in cytochemical techniques have resulted in three new methods of producing chromosome banding patterns or "stripes" similar to those observed when using fluorescent dyes. All three types of banding known as cen-

tromeric (C), Giemsa (G) and reverse (R) respectively, depend on denaturing the chromosomes by the action of heat, dilute alkali or enzyme solutions and then staining with Giemsa dye.

The C-banding pattern may be obtained by treating the chromosome with dilute alkali followed by a long period of incubation in a saline solution. Staining with Giemsa then reveals the "constitutive heterochromatin" that is localized around the centromeric regions of all the chromosomes. In certain cases, i.e. chromosomes 1, 9 and 16, the heterochromatic region is very prominent and often shows considerable variation in size.

G-bands may be produced in several different ways. One of the simplest methods involves treating the chromosomes with a dilute solution of trypsin. Naturally enough, the synonym Trypsin-banding has been coined for this variation of the G-banding technique. The specific banding patterns produced by all the G-banding techniques are the same as those observed in fluorescence banding (i.e. a dark G-band corresponds to a region of bright fluorescence and vice versa). G-banding is useful for the accurate identification of whole chromosomes and also for identifying the segments involved in chromosome translocation.

R-banding (Fig. 209) may be achieved by incubating the chromosome in saline solution for short periods at relatively high temperatures (about 87° C) followed by Giemsa staining. The banding patterns achieved by this method are more or less the reverse of the G-banding (i.e. a light band with G-banding will be seen as a dark band with R-banding and vice versa) and thus of fluorescence or Q-banding. In particular, the chromosome ends (telomeres) are usually darkly stained and

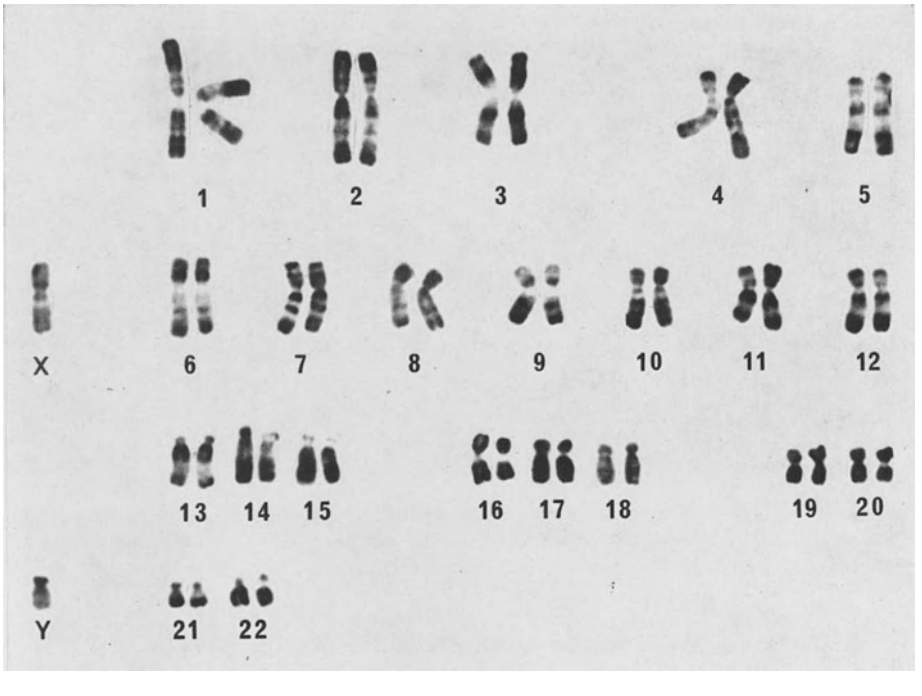


Fig. 209. Karyotype of a normal male showing characteristic banding patterns obtained by the reverse banding technique (×1,500) (see text)

because of this especially this technique is a useful tool in identifying the different parts of translocation chromosomes, especially where small terminal portions are involved.

More detailed descriptions of and references to these new techniques, as well as a revision of the basic chromosome nomenclature together with a system of nomenclature to describe the banding patterns can be found in "Cytogenetics", 1972.

V. Errors of Sexual Development

Many errors of sexual development, some very and some less obvious, are based on anomalies of the sex chromosomes. The majority of these are the result of anomalies of structure or of the number of sex chromosomes, but a few are associated with a sexual phenotype not in agreement with an apparently normal chromosomal sex. Yet other errors depend on gene rather than chromosomal mutations and, finally, some are more strictly of environmental origin, though even these depend on an interplay of genetic factors and factors external to the developing embryo.

Before considering in some detail the main errors of sex development a few words should be said about the normal processes of embryonic sex determination and differentiation, remembering that it is really from the study of these errors in man and animals as well as from contrived animal experiments that many of the present ideas of the normal steps in sex development have been derived.

It is known that in man the Y chromosome is strongly sex determining, namely that the Y chromosome is necessary for the formation of a testis though there is no precise knowledge of the mechanism whereby this is achieved: to some the evidence, especially from induced freemartin states, suggests a possible humoral influence on gonadal induction; others believe that control of gonadal development depends on discrete gene effects from the Y while others still believe in a more generalised, almost non-specific growth promoting effect of the whole of the Y or at least of a large portion of it. At any rate, in the absence of the Y chromosome, or of a key fraction of it, sexual development is usually essentially female. Thus the Y chromosome is a switch mechanism in sex determination which is thus controlled by the presence of an XX or an XY sex chromosome complement. On the other hand differentiation of accessory sex structures together with that of the external genitalia is governed by the presence or absence of hormonal stimuli. During embryonic development, at first the gonads are morphologically identical in both sexes with equally developed cortical and medullary parts, but subsequently they develop into testes or ovaries according to the sex chromosome constitution, always provided that the sex chromosomes themselves are normal. The germ cell precursors arise in the wall of the extra-embryonary gut, whence they actively migrate to the undifferentiated gonadal anlage. The embryonic differentiation of the gonads begins at about 35 days after fertilisation in the male when the cortical part undergoes involution (eventually to form the albuginea) whereas the medullary sector develops tubules and grows considerably. In the absence of the Y, ordinarily the primitive gonad develops into an ovary which can begin to be recognised as such by about the 10th week. Experimental evidence suggests that the gonad of the homogametic sex—the female in mammals—is less strongly determined so that, for example, hormonal influence can *relatively* easily transform it, at least partly, into that of the opposite sex.

Following testis formation, it is believed that the male embryonic gonad secretes two hormones one of which, perhaps a protein hormone, inhibits the Müllerian derivatives of possible pronephric origin, while the other, presumably testosterone or other androgenic steroid, specifically acts on male target cells to influence their growth and thus the hypertrophy, cell-division and development particularly of the Wolffian derivatives of mesonephric origin. Subsequently, during the third stage of sex organogenesis (12–16 weeks) and possibly under the influence of tropic hormones, heightened testis activity provides the stimulus for external male genital development. As for the ovary, its formation normally proceeds when the absence of the Y chromosome, or of a normal Y chromosome with its male inducing elements, allows growth and continued differentiation of the cortical sector of the indifferent gonad. For this one X suffices. Once the ovary has developed, in later foetal life and after birth, maintenance of the oocytes and of the primordial follicles, and their further evolution, seem to depend on the presence of a second X chromosome, the Barr-body forming, heterochromatic and "genically inert" X.

As we have said the numerous types of deviations and abnormalities of sex development have allowed us to recognise a number of basic components of sex and these should be listed briefly as they may serve as a basis for an overall classification of sex errors. Thus we can distinguish the following elements which add up to the totality of what is called the sexual make-up of the individual, male or female as the case may be. These are:

1. the anatomy and function of the gonads;

2. the production of hormones by the foetal gonad and their effect on the anatomy of the internal genital tracts;

3. the output of tropic hormones and development of the external genitalia;

4. a variety of other sex elements, anatomical (e.g. skeletal development, secondary sex characters), physiological (hormones, brain patterns), cultural (baptismal sex or sex of assignment, sex of upbringing or rearing), socio-psychological (adaptive sex or gender role).

The foundation of sexual dimorphism rests on the sex chromosome constitution (XX or XY) but the sex chromosomes (or their sex genes or factors) interact with the sex genes and/or factors present in the autosomes, some of which appear to be capable of overcoming the influence of the sex chromosome make-up and of counteracting their gonad inducing role. Therefore in errors of sex development one must not only be aware of possible anomalies of the complement of sex chromosomes or of their sex genes and factors but also of the sex genes located on the autosomes; and sometimes errors of physical sex development are caused by essentially exogenous or environmental events.

Classification of errors of sex development is difficult particularly if the classification is to be fairly comprehensive and aims at being aetiological or pathogenetic. Furthermore, as different classifications may be useful in different practical or in more academic situations it is difficult to arrive at a compromise classification though we shall attempt to do so. We shall confine our attention mainly to the errors of physical sex development involving the components (1), (2) and (3) listed above and will consider these under two broad categories: Errors of sex determination (and of sex determining mechanisms) and Errors of sex differentiation (Table 11).

Table 11. Classification of errors of sex development (Modified, from POLANI, 1972)

1. Errors of sex determination (i. e. with deviant gonadal induction) and of the Sex Determining Mechanism (i. e. with abnormal sex chromosome complements)
   - i) Complete sex inversions (46,XX males and ? 46,XY "females")
   - ii) Incomplete sex inversions (true hermaphrodites)
     - a) with apparently normal sex chromosomes (46,XX or 46,XY)
     - b) with sex chromosomes anomalies (e.g. mosaics and chimaeras: 45,X/46,XY; 46,XX/46,XY, etc.)
   - iii) Other abnormal sex chromosome complements (47,XXY; 47,XYY; 47,XXX; 45,X; 48,XXYY; 48,XXXY; 48,XXXX, etc.)
   - iv) Other presumptive errors of gonadal induction
2. Errors of sex differentiation
   - i) Female pseudohermaphrodites
     - a) Androgenic
       - I) Foetal: Adreno-genital Syndrome (21- and 11-hydroxylase deficiencies)
       - II) External (iatrogenic)
       - III) Maternal
     - b) Non-androgenic
       - I) With urinary tract anomalies
       - II) Without urinary tract anomalies
   - ii) Male pseudohermaphrodites
     - a) Testicular Feminisation Syndrome (complete or incomplete)
     - b) Adreno-genital Syndrome (3-β-hydroxysteroid dehydrogenase deficiency)
     - c) Lipoid Hyperplasia of the adrenal cortex
     - d) Chromosomal
     - e) Others
3. Other "intersexual" states (hypospadias, familial persistence of Müllerian structures in males, etc.)

Although the term sex determination is sometimes used in a general sense we will restrict its meaning to describe the events which, under the influence of the sex chromosomes and sex genes generally, eventuate in the formation of the normal embryonic gonad; errors of sex determination are those which involve these events and consequently gonad formation. By sex differentiation we will mean the series of developmental events, steered by the genetic controls, which lead to the involution of some and the formation of other sex structures (ducts, external genitalia, etc.). Errors of sex differentiation are those in which the gonad is normal and appropriate to the sex chromosome complement of the individual but the ducts and/or external genitalia are abnormal. Hence primary gonadal development has proceeded to an ovary or a testis in a subject with XX or XY sex chromosomes respectively, but ductal and/or urogenital sinus development does not correspond with the gonadal sex or is more or less intermediate.

Errors of sex determination and of the sex determining mechanisms fall into two broad sub-groups: (a) that sub-group in which the gonads are completely (Table 11) or partly inappropriate. The wrong gonad appears to develop (completely or partially) in the face of a sex chromosome make-up that seems appropriate to a normal female or male, but when the gonad is bisexual the underlying mechanism can be a sex chromosome anomaly. These errors have been called "heterogonadal" (POLANI, 1972). (b) In the second sub-group, sex determination, i.e. gonad formation, does not seem to be faulty though the sex-determining mechanism is clearly upset and abnormal, and primarily deranged because of the presence of a numerical or structural, or combined, sex chromosome anomaly. However embryonic gonad formation seems normal and is not inappropriate to

the sex complement, nor generally is its function; but development and function become abnormal with the passing of time and noticeably so at puberty.

Errors of sex differentiation with a normal gonad and normal sex chromosomes in keeping with the gonad often result from the action of mutant genes of large effect, either autosomal (e.g. adrenogenital syndromes including lipoid hyperplasia) or X chromosomal (probably testicular feminisation) or possibly even Y chromosomal (see 46,XY pure gonadal dysgenesis). There are also some more minor deviations of sex development which may be inherited and may arise in a complex way as, for example familial persistence of Müllerian derivatives and hypospadias.

VI. Errors of Sex Determination

1. Complete Sex Inversions

There is a small but most interesting group of patients who present clinically with Klinefelter's syndrome but who have a 46,XX chromosome complement like that of a normal female. Their testes may look like those in Klinefelter's syndrome or in the germinal cell aplasia syndrome of Del Castillo. The frequency of 46,XX males has been estimated at about 1:45000 males but it may be somewhat more common. Various explanations have been proposed for the origin of the condition which is aetiologically heterogenous. Almost certainly some patients might be hidden or undetected mosaics with a 47,XXY cell line, in which case the hidden line would be responsible for testis formation. But in many patients no evidence of mosaicism has been found and normal male sex determination has occurred apparently in the absence of a Y chromosome. Another suggestion is that in some of these apparent 46,XX males the male determining part of the Y chromosome is present on one of the Xs (or on an autosome) as an interchange. The behaviour in two families of the Xga blood group which is X linked gives some support to this hypothesis. Also some facts about the frequency of Xg(a+) 46,XX males may lend some little support to this suggestion in respect to a group at least of these males. Fluorescence studies have been done on a number of these patients and have revealed no unusual fluorescence on the X chromosome or autosomes. Another suggestion is that a mutant gene, probably autosomal, could be responsible for overriding the effect of two X chromosomes, and for causing male sex determination, and this would be in keeping with observations on similar mutant genes in domestic animals. It is also possible that at least some of these 46,XX males may be linked aetiologically with the 46,XX true hermaphrodites for some of whom, too, an interchange hypothesis has been suggested.

As a 46,XX male may have testes, thus being an example of sex inversion, one might enquire if a comparable but reverse situation, an XY sex chromosome complement together with a female phenotype with ovaries, also exists. Only one possible case of this has so far been detected. However, there is a well known condition where a patient has a female habitus and a male sex chromosome complement, and in addition she has a uterus and fallopian tubes; the gonads however are sterile "streaks". It could be speculated that a proportion of these 46,XY females, who clinically fall into the category of pure gonadal dysgenesis (v.i.), might be examples of sex inversion in whom the germinal tissue has undergone involution, i.e. the embryonic ovary has been transformed into a sterile streak, a fate shared by the 45,X gonad and attributable in both instances to the absence of the second X chromosome. However, it seems unlikely that all 46,XY pure gonadal dysgenesis

cases could be of this type. It is possible that some may be related to the rudimentary testes syndrome, or to forms of male pseudohermaphroditism of which they represent extreme examples in whom testis formation and embryonic function are completely disrupted. It could also be suggested that some cases may be related to the so-called mixed gonadal dysgenesis syndrome (v.i.).

2. Incomplete Sex Inversions: True Hermaphrodites

These subjects generally present with ambiguous external genitalia (i.e. they are intersexes) as do most of the pseudohermaphrodites, but in contrast to them both ovarian and testicular tissue are present in the same individual. In some cases a testis and an ovary are on opposite sides of the body, or on the same side, or else there is an ovo-testis, i.e. a gonad with both types of tissue. A clinical classification of true hermaphroditism and the frequencies of the three types is shown in Fig. 210. The condition is rare and less than 400 cases have been described in detail to date. A sex chromosome anomaly exists in many patients. In more than half the patients who have had chromosome studies a normal female chromosome complement was found, in one fifth the sex chromosome make up was normal male and the remainder were mosaics (Table 12).

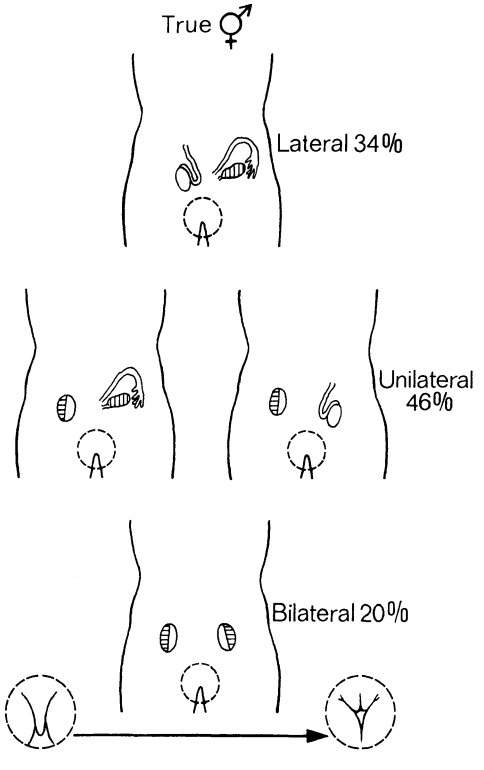


Fig. 210. Clinical classification of true hermaphroditism. The oval half stippled structure symbolizes an ovotestis. The external genitalia vary from rather masculine to frankly feminine (see text) (Polani, 1970)

Table 12. Chromosomal studies in true Hermaphrodites (POLANI, 1970)

46,XX	59		
46,XY	21		
Mosaics and chimaeras	28	with a Y chromosome	45,X/46,XY 11
			46,XX/46,XY 6
			46,XX/47,XXY 5
			Others 4
		without a Y chromosome	2

Of about 400 true hermaphrodites described in detail in the literature, chromosomal studies were available in 108 (excluding 29 cases with 45,X/46,XY Mixed Gonadal Dysgenesis) including a few personal unpublished observations.

The testicular tissue may be devoid of germ cells, there may or may not be a uterus, and other Müllerian or Wolffian derivatives may be found. The external genitalia are usually ambiguous, sometimes more masculine, and at other times more feminine. The internal genitalia other than gonads are variable. However, in general they tend to correlate with the appearance of the external genitalia and to some extent with the make-up of the gonad, in so far as presence of a fallopian tube or of an epididymis is concerned. Interestingly, it appears that in the course of abnormal gonadal differentiation the right gonad has a greater tendency to become a testis and the left gonad an ovary.

These intersexual patients, in common with the pseudohermaphrodites may present as a problem of sex assignment in the neonatal period. It is obviously important that a decision about this should be made (see p. 363) as soon as possible and that the internal, gonadal and other sex structures be assessed by operation, biopsy, etc. as soon as is feasible. If it is decided to bring the child up as a female then obviously all testicular elements must be removed surgically, to avoid virilisation at puberty. Similarly in cases brought up as males the presence of ovarian tissue may cause gynaecomastia together with monthly bleeds at puberty, and therefore surgical removal is mandatory at some stage before expected puberty. Often there will also be the need to deal with the external genitalia. As would be expected the sex of assignment and rearing of true hermaphrodites is highly correlated with the anatomy of the external genitalia. Approximately 80 per cent of true hermaphrodites with feminine external genitalia were reared as females and over 90 per cent of those externally more masculine were reared as males. Of those with very ambiguous external genitalia, 80 per cent of those rather more masculine than feminine were reared as males as compared with over 50 per cent of those who were intersexual but more feminine. By contrast with the importance of the external genitalia in the assignment of sex, the sex chromosomal make-up is of secondary importance though it is to some extent correlated with the state of the gonads and hence with the rest of the genital tract. Once sex assignment has been made and while the genital structures are dealt with as indicated, the upbringing of the child is of paramount importance and therefore reinforcement of the assigned sex must be carried out by the parents, and physical and psychological clashes and ambiguities should be avoided as far as possible. The HAMPSON, MONEY and their colleagues have carried out many psychological studies on intersex patients and their work indicates that early assignment of sex with reinforcement is very important in these cases.

In 1963, SOHVAL described with the name "mixed gonadal dysgenesis" a condition in which one gonad was noted to be a fairly well recognisable testis and the other a so-called sterile "streak", a connective tissue structure with some resemblance to ovarian stroma but without germinal elements. Most subjects with this gonadal make-up appear to have female external genitalia though sometimes these are somewhat masculinised and indeed previously cases of this condition had been described in the group of "gonadal dysgenesis with phallic enlargement". These patients usually are chromosome mosaics of the 45,X/46,XY type but it is to be noted that patients with this type of mosaicism may present as true hermaphrodites or with one of the syndromes of ovarian dysgenesis. The definition of true hermaphroditism does not exclude sterility of the gonad but, while a testis can still be positively identified as a testis by histology even if sterile, sure recognition of a sterile streak as an ovary is generally impossible. Nevertheless, because a 45,X ovary though originally with ova tends to become a sterile streak, we feel that patients with mixed gonadal dysgenesis could be classified as true hermaphrodites. It is rather difficult to assess the numbers of these patients that have been described and even more difficult it is to know the real frequency of the anomaly but perhaps it is not quite so rare as would appear (Table 12).

VII. Errors of the Sex Determining Mechanism

There is no anomaly of gonadal induction and from the somatic and sexual aspects the error of development is often relatively unobtrusive. In fact it may not be apparent in early life but may only reveal itself at puberty. The gonads are neither bisexual (as in true hermaphrodites) nor heterosexual (as in sex inversions). They conform in general to the external sexual phenotype and the errors have accordingly been described as "orthogonadal". The conditions which will be discussed here are the 45,X anomaly, i.e. Turner's syndrome and related conditions, the 47,XXX chromosome complement or Triplo-X female, the 47,XXY complement with Klinefelter's syndrome and the 47,XYY chromosome complement.

Before describing the syndromes it is perhaps relevant to reiterate the possible mechanisms of production of these chromosome abnormalities and Table 13 describes the origin of the possible errors that may occur.

Table 13. Mechanism of production of the following Chromosome Anomalies

1. *45,X (XO)* An abnormal sperm without a sex (X or Y) chromosome unites with a normal ovum with an X chromosome or a normal sperm with an X chromosome unites with an abnormal ovum without the X chromosome.
2. *Klinefelter's Syndrome (47,XXY)* A normal sperm with a Y chromosome unites with an abnormal ovum with two X chromosomes, or an abnormal sperm with both an X and a Y chromosome unites with a normal ovum with its single X chromosome.
3. *Triplo-X (47, XXX)* A normal sperm with its X chromosome unites with an abnormal ovum with two X chromosomes, or an abnormal sperm with two X chromosomes unites with a normal ovum with its single X chromosome.
4. *47,XYY* An abnormal sperm with two Y chromosomes unites with a normal ovum with its single X chromosome.

There are in addition a variety of corresponding mosaics with two or more cell lines. Structural anomalies of either the X or Y chromosomes can also arise and usually occur in patients with Turner's syndrome. Most of these are various types of deletions but other structural errors such as translocations and pericentric inversions have been described. However, the commonest structural anomaly is an isochromosome for the long arm of the X chromosome. An isochromosome of this type is symmetrical about the centromere and consists of two long arms of the X while the short arm is missing. In a sense such a chromosome is an extensive duplication-deficiency. In a large percentage of structural anomalies there is mosaicism, often with a 45,X cell line.

1. Turner's Syndrome

(XO sex chromosomes; 45,X chromosome complement)

In 1938, H. H. TURNER described a syndrome of sexual infantilism, congenital neck webbing and cubitus valgus in seven females whose heights ranged from 123 to 139 cms. Since the original description, many other somatic anomalies have been described in Turner's syndrome. These include shield chest with widely spaced nipples, congenital heart disease mainly coarctation of the aorta, multiple pigmented naevi, a tendency to keloid formation, characteristic facies (with epicanthic folds, ocular hypertelorism, broad forehead, small chin and antimongoloid slant of the palpebral fissures), malrotated or malformed ears and a low neck hairline which is shaped like an inverted "M". The hands often show short (fourth) metacarpals and hypoplastic, narrow, deeply set nails. In addition there may be a high arched palate, deafness and renal anomalies such as horseshoe kidney and pyelon duplex. Mild mental retardation may be present.

In adult life there is absence of the secondary sex characters including menses, but the vagina, uterus and fallopian tubes are normal though infantile. Gonadotropins levels are raised from the age of 11–12 years and often earlier. The gonads, which are dysgenetic, are represented by narrow elongated streaks of tissue in a normal ovarian position. On section, they are found to be composed of connective tissue elements arranged in sheets and whorls. Ova are not found at maturity: however, they are present in normal numbers in 45,X foetuses (many of which are spontaneously aborted) and many be present in small numbers (5–10 per cent of normal) at birth and for a short while thereafter. Thus ova are present originally but degenerate rapidly. By puberty the great majority of 45,X patients will be left with ovaries reduced to sterile streaks. However, occasionally they have sufficient ova left at puberty to produce spontaneous menarche though sustained cycles are exceptional. Nevertheless, two apparently non-mosaic 45,X women, who produced normal children, have been described.

Infants with Turner's syndrome may escape detection although a few of them are discovered by virtue of the fact that they have congenital lymphoedema. The facies in infancy is often characteristic with a broad forehead, widely spaced eyes, a rather flat nose and excessive skin folds below the eye lids. The chin is small and the neck skin folds extremely loose but true neck webbing is not present. The finger and toe nails are usually hypoplastic, sometimes invisible. While the nails progressively emerge the lymphoedema generally recedes in early life. It seems to be caused by hypoplastic lymphatic vessels and as a part of the disorder of the lymphatic circulation some new-born infants with Turner's syndrome have serosal effusions, e.g. in the pleural cavities.

The incidence of the 45,X condition at birth is in the order of 1 in 2500 females. However, it is the commonest sex chromosome anomaly in conceptuses but has a very high prenatal mortality (as early spontaneous abortion). It is estimated that $\frac{3}{4}$–1 per cent of conceptions are 45,X, and that their prenatal mortality is probably in the order of 97 per cent and only about 3 per cent with this chromosome constitution are born. Interestingly, embryos with this constitution are often noted to have huge cystic hygromata in the neck which may be the forerunners of the neck webbing and clearly are related to their abnormal lymphatics.

Clinically the patients may present in a number of ways:

a) with lymphoedema of hands and feet in infancy, with or without the additional anomalies listed above:

b) with webbing of the neck and other "Turner's stigmata" in early childhood;

c) with congenital heart disease, generally coarctation of the aorta, short stature and some or many "Turner's stigmata" in childhood;

d) with otherwise unexplained short stature in childhood;

e) with short stature, primary amenorrhoea and absent secondary sexual characteristics at expected puberty.

Although already in 1956 it had been proposed that Turner's syndrome might be caused by an XO sex chromosome complement, the test of this suggestion became technically possible only in 1959 when Ford and his colleagues reported, by direct visualization of the bone marrow chromosomes, that this was indeed the case. They showed that one X chromosome was present and therefore either an X chromosome or a Y chromosome was missing. As there is only one X chromosome, the patients are chromatin negative and as no Y chromosome is present fluorescence studies are also negative. It has since been established that the sex chromosome complement in the majority of patients with Turner's syndrome is 45,X. However, patients may be mosaic, e.g. 45,X/46,XX or occasionally 45,X/46,XY. Other more complex forms of mosaicism are occasionally found as well as structural anomalies of either the X or, sometimes, the Y chromosome with or without mosaicism.

Some workers reserve the eponym "Turner's syndrome" strictly for patients with webbing of the neck as in Turner's original description. Those patients without neck webbing but with the anomaly of sex development found in patients with full Turner's syndrome are designated as having Ovarian Dysgenesis (Fig. 211). There is a further group of patients who do not fall into either the category of Turner's syndrome or of Ovarian Dysgenesis but who are designated as having Pure Gonadal Dysgenesis. These patients are of normal stature or tall and do not show the somatic anomalies of Turner's syndrome. They do, however, have dysgenetic ovaries. Chromosome studies in these patients show that most have a normal female chromosome complement, a few have a normal male chromosome complement or may be mosaics, 45,X/46,XX or 45,X/46,XY or with structurally abnormal sex chromosomes. In the patients with dysgenetic gonads and an XY cell line there is danger of malignancy occurring in the gonadal tissue and for this reason prophylactic gonadectomy should be considered even when the gonad is a sterile streak. As a result of the gonadal abnormality, patients with pure gonadal dysgenesis almost always have absent or poorly developed secondary sex characters and therefore exogenous hormone therapy is required. The external genitalia, uterus and tubes are however normal.

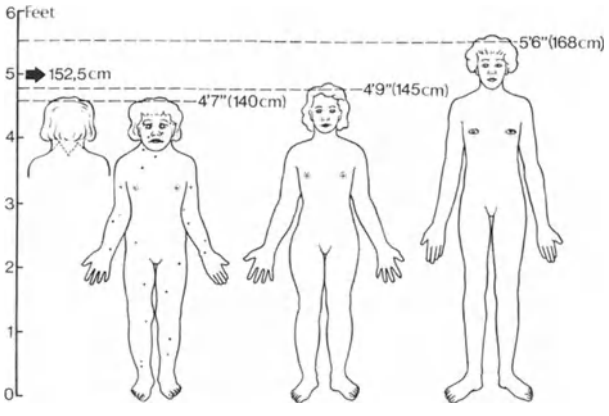


Fig. 211. Classification of Turner's Syndrome, ovarian dysgenesis and pure gonadal dysgenesis based on external appearance and height (POLANI, 1970)

Diagnosis, especially before puberty and in the absence of nuclear sexing and chromosome studies is made more complex because there is a group of patients with the somatic anomalies of Turner's syndrome but who generally have normal fertility and normal stature, and often have congenital heart disease, usually pulmonary stenosis. They may also have arthrogryposis, muscle ageneses and various types of nuclear palsy and other neurological anomalies. They have normal sex chromosomes. These patients are often designated as having the Ullrich's or Bonnevie-Ullrich's syndrome. This condition occurs in both males and females. Among the males, however, there is a sub-group in whom in addition to the somatic anomalies of Turner's syndrome, there is short stature, undescended testes with or without hypospadias and infertility. These patients are often referred to as having "Turner's syndrome in the male". They, too, usually have normal sex chromosome complements (Fig. 212).

In females with Turner's syndrome the main problems are obviously the infertility, for which there is no treatment, the absence of secondary sexual characteristics and the short stature. The secondary sexual characteristics, including menses, can be brought on at puberty by the administration of exogenous oestrogen and progesterone. This may have the added value of preventing osteoporosis in later life due to oestrogen lack and perhaps premature senescence. Regrettably, no adequate treatment for the short stature is available. These patients rarely achieve a height of more than 147 cms. However, after the administration of exogenous hormones, the appearance of secondary sexual characteristics often causes considerable improvement psychologically. Their sexual orientation is perfectly feminine and many of these women are attractive, though petite. Many, but by no means the majority, are therefore happily married. The intellect in this condition is sometimes slightly impaired, particularly in those patients with marked neck webbing and many other somatic anomalies. Interstingly, in 45,X subjects the performance I. Q. is lower than the verbal I. Q. and there may be an inability to deal with spatial concepts.

The risk of recurrence of Turner's syndrome (with a 45,X chromosome constitution) in a future pregnancy is extremely small. By contrast, in a small proportion of families the Ullrich syndrome may be inherited as a recessive or occasionally as a dominant condition from a parent who shows some stigmata.

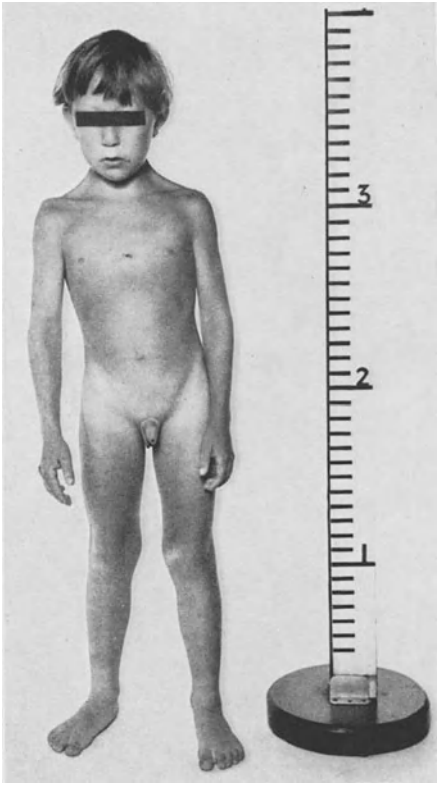


Fig. 212. Male Turner's Syndrome in a boy of 7 years with webbed neck, undescended testes and pulmonary stenosis (see text)

2. Klinefelter's Syndrome

This condition was described originally in 1942 as a syndrome of gynaecomastia, absent spermatogenesis (but without a-Leydigism) and increased excretion of follicles stimulating hormone. However the syndrome was later expanded to include other cases with small testes and histological changes of a similar type in whom an androgen deficiency might be present and gynaecomastia absent. Phenotypically these males present with poorly developed secondary sexual characteristics, gynaecomastia, small testes, mild mental retardation and infertility. They are tall and eunuchoid. The distribution of sex hair may be female as may be the distribution of the body fat (Fig. 213). There is often infrequent shaving and absence of the recession of the temporal hair line. The degree of intellectual impairment is usually relatively slight but the performance I. Q. is often higher than the verbal I. Q. There may be behaviour disturbances associated with this condition. Usually there is complete azoospermia. The testis shows hyalinisation and atrophy of most seminiferous tubules but this is a progressive feature and may not be found until some time after puberty. In the tubules, Sertoli cells may be seen and their appearance may vary somewhat from mature to immature though eventually, as the tubule basement membrane thickens and hyalinization progresses, the cells disappear. The Leydig cells are hypertrophied and form large intestitial clumps,

though their total bulk is usually not increased (Fig. 214). Before puberty the testis is almost normal but the proportion of spermatogonia is well below normal. Exceptionally spermatogenesis has been recorded.

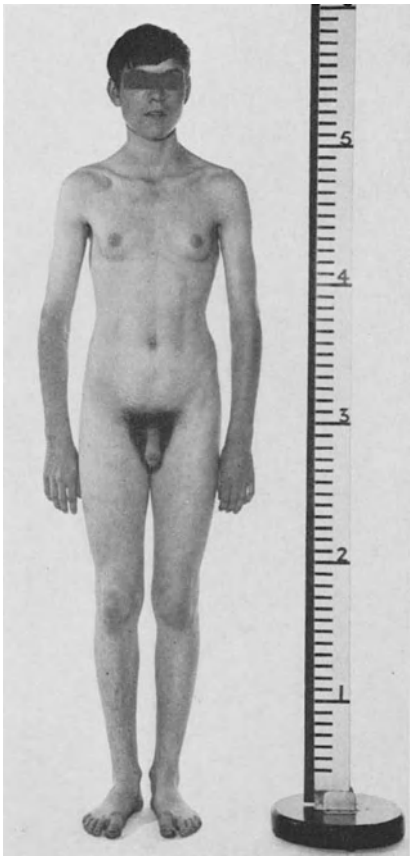


Fig. 213. 47,XXY Klinefelter's Syndrome with gynaecomastia and small testes (see text)

Sex hormone activity in the syndrome is disturbed and whilst 17-keto-steroid output may be normal the output of urinary gonadotropins is increased. Ferguson Smith (1966) has suggested that within the clinical spectrum of Klinefelter's syndrome three types of case may be recognised:

a) a chromatin positive variety caused by sex chromosome errors (the most usual type);

b) a chromatin negative (46,XY) variety with post pubertal testicular atrophy;

c) a variety with absence of germ cells and without testicular fibrosis, and normal male sex chromosomes.

Two thirds of the cases of chromatin positive Klinefelter's syndrome have a chromosome complement of 47,XXY (Fig. 215). Many of the rest are mosaics with

a normal cell male line (46,XY) but in a few the second cell line is 46,XX. The overall frequency at birth of chromatin positive males is about one in 400 male infants.

In this condition there is nothing that can be done to help the infertility. However, administration of exogenous androgens will improve the secondary sex characters and muscular development with a consequent improvement in some of the psychological problems.

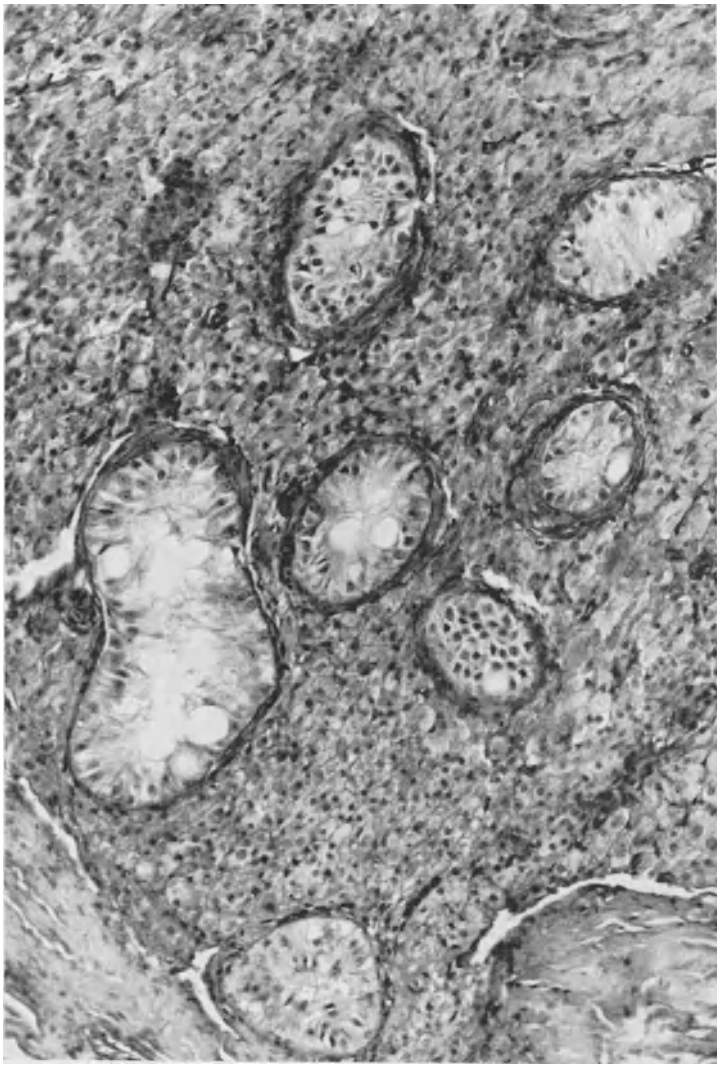


Fig. 214. Testis histology in Klinefelter's Syndrome. The basement membranes of the tubules are thickened and hyalinized and the interstitial cells are relatively prominent. Only Sertoli cells line the tubules and are disappearing from some of them. Spermatogenesis is absent. (H. and E. × 600)

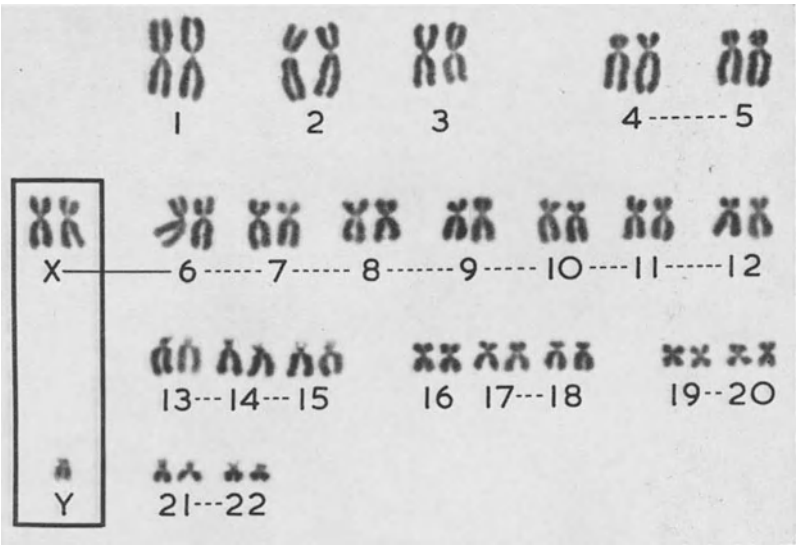


Fig. 215. Karyotype of patient with Klinefelter's Syndrome, 47,XXY. (Aceto-orcein × 1,500)

There are a number of clinical and other chromosomal variants of Klinefelter's syndrome and it is clear that an increasing number of X chromosomes results in a much greater intellectual impairment, i.e. patients with a 48,XXXY chromosome complement are more likely to be intellectually impaired than those with a 47,XXY chromosome complement. Subjects who are 49,XXXXY, clinically do not present merely with the stigmata of Klinefelter's syndrome, but in addition have many somatic anomalies including often cardiovascular malformation, a distinctive round facies with epicanthic folds, ocular hypertelorism and prognathism together with skeletal anomalies, e.g. radio-ulnar synostosis. Indeed the syndrome is so striking that it is possible to confidently and successfully predict the chromosome anomaly. There is, compared with the 47,XXY males, greater anomaly of the genitalia, and the scrotum, testes and phallus are often minute.

3. 47,XYY Males

Studies of hard-to-manage patients in Swedish mental hospitals and in Special Security State Hospitals in England revealed a tenfold increment in expected frequency of chromatin positive males, presumptive 47,XXY. However, in the English survey a high proportion of 48,XXYY subjects was found and this led to the hypothesis that the antisocial behaviour may have been caused by the extra Y rather than the additional X chromosome. A study of a Scottish Special Security Prison Hospitals confirmed these findings and in this study a high proportion of 47,XYY males was also detected. It has been estimated that among institutionalised violent criminals, such males may be thirty to fifty times more prevalent than among the newborn and ten or more times more common than in mental or mental subnormality hospitals. This evidence, therefore, suggested that 47,XYY males were at risk of social maladaptation which might lead to criminal behaviour;

hence the over-representation of these males in prison hospitals. However, it should be emphasised that not all males with a 47,XYY chromosome complement come into disaccord with the law, far from it. First, since the original studies were done figures have become available about the frequency, at birth, of 47,XYY perhaps one in 700 male infants. Secondly, it has been estimated in Scotland that possibly only 2 per cent of these males may find their way into Special Security Hospital. Thus it would be that the individual "criminality risk" for a male with XYY sex chromosomes is small, albeit greater than average.

Typically, the 47,XYY male found in prison hospitals stands out above all because of his excessive height which on average exceeds 181 cm, or more than 12 cm more than the average height of his fellow inmates. Approximately 50 per cent of 47,XYY males are taller than 183 cm. compared with 10 per cent of normal males. I. Q. tends to be borderline and they tend to a higher performance than verbal score. Their personalities are often aggressive, and especially impulsive, and it is characteristic of their criminal careers that they begin these early and that their crimes are directed more against property than against people. As regards sex development, some males with this chromosomal complement have been identified because they presented with testicular maldescent, hypospadias or with features of hypogonadism. However, many of these males are fertile and their sons generally have been chromosomally normal. Nevertheless, there is something quite unusual about gametogenesis in this syndrome. The early stages of meiosis appear to be normal and pachytene cells are plentiful, but an undue proportion of them undergo degeneration. First meiotic metaphases are few and usually are chromosomally normal in that they mostly display only one Y chromosome. Also, spermatogonal mitoses seem to be often normal 46,XY (in the absence of detectable somatic mosaicism!). Finally, YY sperm, as judged from fluorescence studies are possibly only just more plentiful than in normal males, about 5 per cent compared with 1–2 per cent, whereas many more would be expected. All this suggests some selective disadvantage to the cells with two Y chromosomes which tend to undergo atresia while any normal male cells that happen to arise would seem to have a proliferative advantage and emerge as mature gametes.

4. 47,XXX Females

This abnormality of the sex chromosomes found in about one in 1 200 newborn girls does not produce a clearly identifiable clinical syndrome and there are no distinctive features in the 47, XXX female, though in a few patients the appearances are sufficiently reminiscent of Down's syndrome to make one suspect this diagnosis or the possibility of Down's syndrome mosaicism. Oral smear on these patients reveals that they have two sex chromatin masses present. Irregular menstruation or secondary amenorrhoea are variable features of the condition and correlate well with the presence of rather small ovaries and with the decrease in the number of ova observed in the few cases studied by laparotomy and biopsy. There is some intellectual impairment in this group of females as shown by the fact that 47,XXXs are five times more common among patients in subnormality hospitals than in the newborn population. Similarly, 47,XXX females are found among mental hospital patients diagnosed as chronic schizophrenics. Studies by Kidd and collaborators (1963) confirm the tendency to mental illness in at least a proportion of these patients. However, it should be pointed out that many females with three X chromosomes have been found to be normal mentally, psychologically, somati-

cally and from the point of view of reproduction. The risk of recurrence of this anomaly in a future pregnancy is extremely small.

As in the case of males, there are examples of females with more than three sex chromosomes, i.e. 48,XXXX and 49,XXXXX. Their most striking feature is severe intellectual deficit but neither sexual nor physical development seem greatly disturbed. It has been estimated that each extra X chromosome lowers the I. Q. by about 15 points. Incidentally, the Y chromosome might have about one third this effect. It is interesting that additional sex chromosomes exert similar quantitative effects on other metrical characters.

VIII. Errors of Sex Differentiation

The overall classification of pseudohermaphrodites is complex (Table 11).

1. Female Pseudohermaphrodites

These patients have ovaries, but the external genitalia are virilised. In a proportion of patients the developmental genital anomaly is caused by virilising hormones. Female pseudohermaphrodites are dealt with in detail in Chapter X.

2. Male Pseudohermaphrodites

Among the male pseudohermaphrodites, the testicular feminisation syndrome is an important clinical entity which will be discussed here. The condition was first reviewed by MORRIS in 1953 and the cardinal features of the complete or classical form are:

a) female habitus with good breast development and normal female external genitalia without clitoral enlargement;

b) absence of axillary and pubic hair;

c) complete or almost complete absence of Müllerian or Wolffian derivatives;

d) the presence of testes without spermatogenesis in the inguinal canal or intra-abdominally.

MORRIS drew attention to the risk of often malignant gonadal tumours in these patients. He also noted the strong familial tendency in the complete or classical form (Fig. 216), a feature which was later studied in greater detail. Although these patients are tall they are not particularly muscular and do not excel at athletics. Breast development is normal, the nipples being somewhat hypoplastic and under pigmented. Pubic and axillary hair is generally absent, but may be very sparse and fine (Fig. 217). The external genitalia are feminine and the vagina is present although sometimes short. It ends blindly and there is no cervix. There is no clitoral enlargement in the classical form although it may be present in the incomplete form where slightly more virilisation is found with correspondingly less breast development and more sex hair. Inguinal herniae, usually rare in females, are present in about two-thirds of these patients. They almost all contain a testis and may be bilateral. The testes are relatively small and brown on section. They may contain Sertoli cell adenomas. There is generally no spermatogenesis and usually there are no spermatogonia, and the tubules are usually lined only with Sertoli cells.

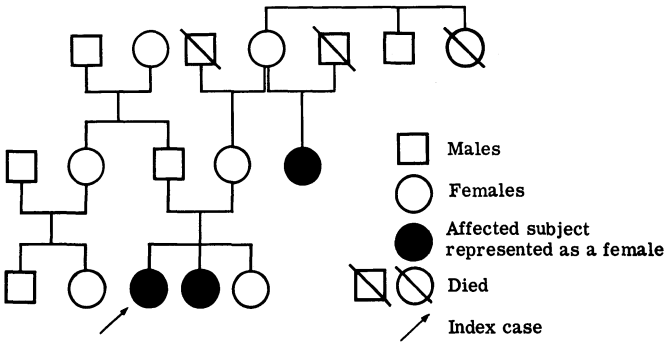


Fig. 216. Pedigree of a kinhsip with familial testicular feminisation syndrome. This diagram shows transmission of the testicular feminisation syndrome through the maternal line. The carrier woman in the first generation had two husbands: from the first she had an affected child and from the second she produced a carrier daughter who had two affected children (kindred PRU 985)

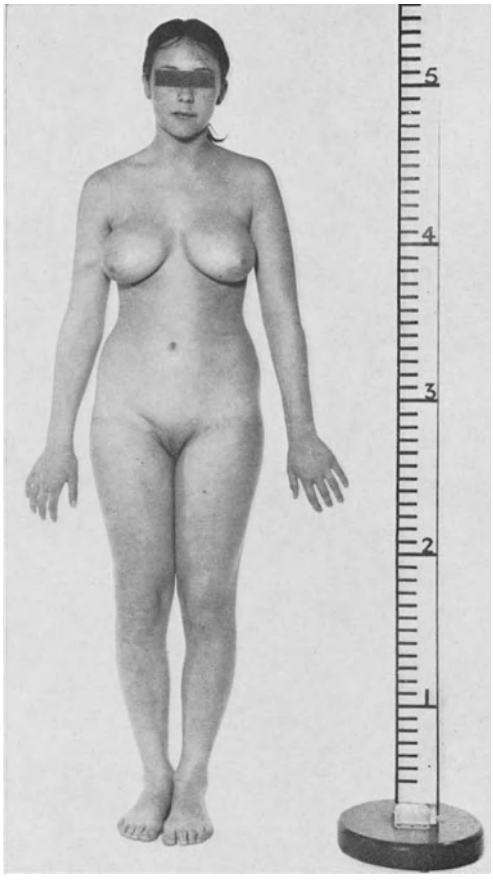


Fig. 217. Patient with testicular feminisation syndrome with excellent breast development and lack of pubic hair. Chromosomally 46,XY

There often is hyperplasia of Leydig cells (Fig. 218). Occasionally, attached to the testis is found a small body of connective and muscle tissue which has been interpreted as being similar to myometrium or some other structure of Müllerian origin. In a small proportion of cases structures interpreted as a Fallopian tube or epididymis may be detected histologically in the connective tissue near the gonad. Interestingly, despite the testicular tissue, these patients are not virilised though the testis produces androgens as well as oestrogens. However the patients do not respond to the former nor do they respond to exogenous testosterone in large doses. It has, therefore, been postulated that there is an end organ lack of response to this steroid (see below).

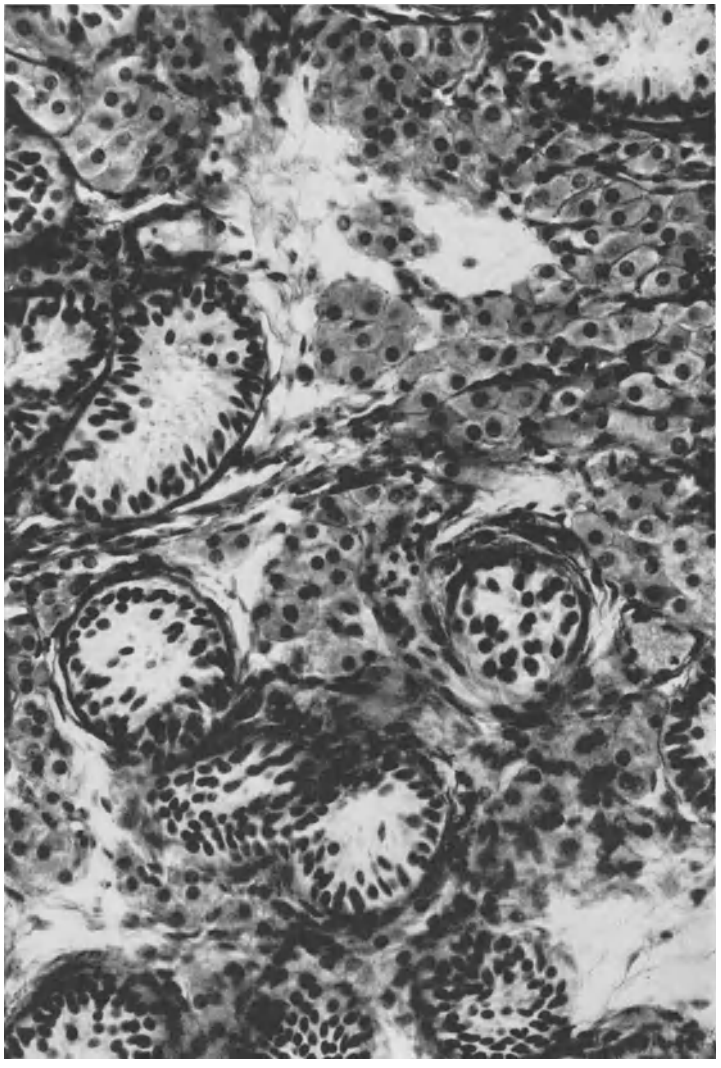


Fig. 218. Testis in testicular feminisation syndrome. There is no spermatogenesis. The tubules are lined with Sertoli cells and the interstitial cells are hyperplastic. (H. and E. × 500)

The testicular feminisation syndrome appears to be inherited as an X-linked recessive, but could possibly be an autosomal sex limited condition, the trait behaving as a dominant in males and as a recessive in females. So far linkage studies with known X chromosomal markers like Xga or colour blindness have failed to reveal measureably close linkage to these loci or to the few autosomal loci tested and thus have not provided conclusive evidence for the location of the testicular feminisation gene. At any rate the condition is transmitted by apparently unaffected carrier mothers to half the chromosomally male offspring who are transformed into apparent females. Thus the ratio of "females" to males in testicular feminisation families is about 3:1. Evidence for maternal transmission also comes from women who have affected offspring by different husbands.

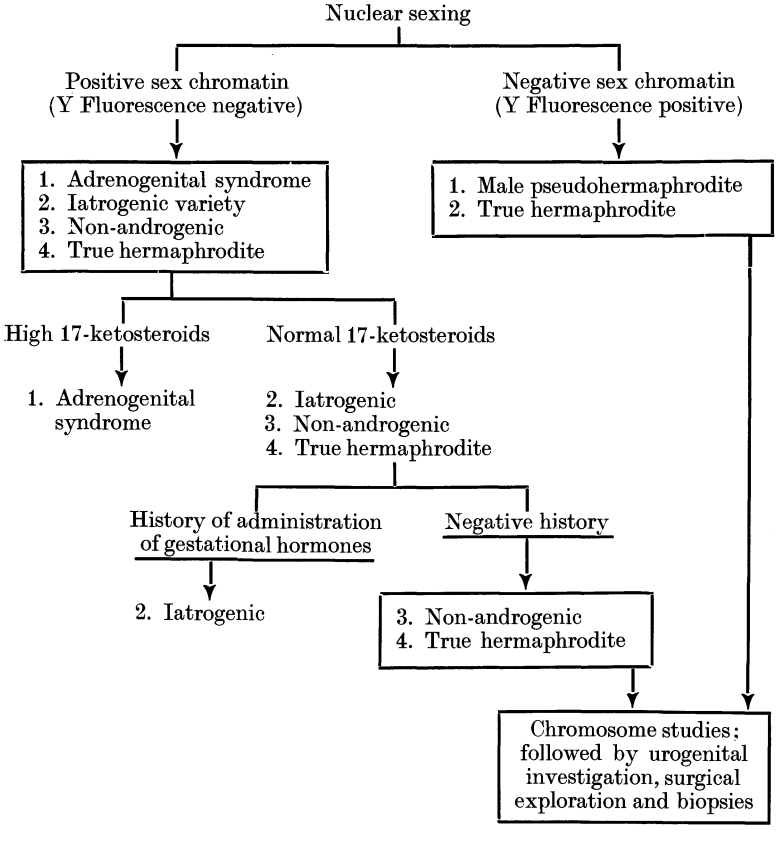
Conditions similar to testicular feminisation have been described in domestic animals, for example in the cow. However, some interesting information has come especially from the discovery of a testicular feminisation mutation in the laboratory mouse by LYON and HAWKES (1970). First this has enabled the gene in the mouse to be located in the X chromosome because breeding tests have shown it to be closely linked with a known X-linked coat colour gene locus. Secondly, largely through the work of OHNO and his collaborators, insight has been gained into the mechanism of action of the gene mutation and from this, interesting concepts about normal sex differentiation have emerged. The action of testosterone in producing target cells hypertrophy and the method whereby this seems to be normally achieved by translational and RNA polymerase control and, conversely, appears to be blocked in testicular feminisation (with consequent target organ resistance) have been well investigated in the animal model. The ideas would seem to be applicable to the human situation and, because of the alleged conservation during evolution of the genes on the X chromosome of mammals generally, we could accept the view that it is likely indeed that testicular feminisation in man is also X linked. The lowest estimate of the frequency of the testicular feminisation syndrome is one in 120000 index cases but seemingly taking all cases, frequencies which may be 3 to 6 times higher have been suggested. The condition is thought to account for one in five of all examples of male pseudohermaphroditism.

IX. Sex Assignment

We should conclude this review with a comment on a practical issue. Sex assignment in the neonatal period of an infant with ambiguous genitalia is very important and Table 14 outlines the steps often helpful in reaching a correct diagnosis. The doctor who encounters a newborn infant with ambiguous genitalia must assume responsibility for the early determination of the nature of the anomaly and for the assignment of the sex of rearing. Sex assignment in the newborn period of an infant with ambiguous genitalia requires that studies appropriate to an unequivocal assignment should be completed during the newborn period, so that with baptismal sex finally fixed, appropriate plans for rearing, management and reinforcement can be instituted, preferably before the child leaves hospital.

Table 14. Differential diagnosis of Commoner Intersex States

(Based on history, nuclear sexing and urinary neutral 17-ketosteroids output)



Appendix:

Z. Urological Manifestations of Multi-System Disease

T. M. Barratt

Tables 1—3 see following pages

Table 1. Inherited syndromes with urological manifestations. Conditions listed are those with urological features (excluding genital abnormalities) considered by McKusick (1971) to have an established mode of inheritance

Syndrome	General features	Urological manifestations	Catalogue number	
			McKusick	Smith
	Dominant inheritance			
Alport syndrome	Hereditary nephropathy and deafness	Haematuria. Renal failure[a]	10420	—
Aniridia	Absent iris	Wilms tumour	10620	—
Ehlers-Danlos	Hyperextensibility of joints and skin	Ureteropelvic anomaly	13000	T 125
Haemoglobin S	Sickle cell trait	Haematuria. Polyuria. Papillary necrosis in heterozygote	14170	—
Marfan syndrome	Arachnodactyly. Lens subluxation. Aortic lesion	Renal anomaly	15470	T 123
Nail-Patella syndrome	Nail dysplasia, patellar hypoplasia	Haematuria, renal failure[a]	16120	R 110
Neurofibromatosis (Von Recklinghausen)	Café-au-lait-spots Fibromatous skin tumours	Phaeochromocytoma Renal Artery stenosis Bladder involvement	16220	M 67
Neuromata (mucosal) with endocrine tumour (Sipple)	Multiple neuromata Medullary carcinoma of thyroid	Phaeochromocytoma	16230	—
Polycystic kidney ("adult" type)		Haematuria, loin mass, renal failure[a]	17390	—
Renal tubular acidosis (gradient; distal; Albright)	Metabolic acidosis Hypokalaemia	Nephrocalcinosis Urinary calculi[a]	17980	—
Telangiectasia, hereditary haemorrhagic (Osler)	Mucosal telangiectasia	Bladder telangiectasia	18730	U 131
Tuberous sclerosis	Adenoma sebaceous, epilepsy, mental retardation	Renal hamartoma	19110	H66

Syndrome	General features	Urological manifestations	Catalogue number	
			McKusick	Smith
Von Hippel-Lindau	Retinal angiomata, cerebellar haemangioblastoma	Renal cysts Hypernephroma Phaeochromocytoma	19330	M63
	Recessive inheritance			
Asphyxiating thoracic dystrophy (Jeune)	Small chest; respiratory failure	Medullary necrosis	20850	087
Cerebro-hepato-renal syndrome (Zellweger)	Maldeveloped skull. Intrahepatic biliary dysgenesis	Polycystic kidneys[a]	21410	E28
Cystinosis I and II	Dwarfism Corneal clouding	Tubular disorder Renal failure[a]	21980 21981	—
Cystinuria I, II, III		Renal calculi[a]	22010	—
EMG syndrome (Beckwith-Wiedemann)	Exomphalos Macroglossia. Gigantism	Medullary dysplasia[a]	22560	L60
Fanconi's pancytopaenia	Anaemia. Leucopenia. Thrombocytopenia. Aplasia of radius. Skin pigmentation	Abnormalities of fusion and rotation of kidneys[a]	22790	I49
Hyperprolinaemia I	Mental retardation Deafness	Haematuria. Renal failure[a]	23950	—
Hypophosphatasia	Skeletal anomalies	Nephrocalcinosis	24150	—
Lawrence-Moon syndrome	Obesity. Retinitis pigmentosa, Hypogonadism. Polydactyly	Renal anomaly	24580	E25
Meckel syndrome	Encephalocoele Polydactyly	Polycystic kidneys[a]	24900	—
Mediterranean fever, familial	Recurrent fever, amyloidosis	Proteinuria[a] Renal failure	24910	
Nephronophthisis, familial, juvenile	Sometimes retinitis pigmentosa	Polyuria[a] Renal failure	25610	

Table 1 (continued)

Syndrome	General features	Urological manifestations	Catalogue number	
			McKusick	Smith
Nephrosis, congenital		Nephrotic syndrome[a] Renal failure	25620	—
Oxalosis I and II		Oxalate calculi[a] Renal failure	25990 26000	—
Polycystic kidney, infantile, Type I	Cystic liver and kidneys	Loin masses[a] Renal failure	26320	—
Renal dysplasia and retinal aplasia	Tapeto-retinal degeneration, blindness	Medullary cystic disease[a]	26690	—
Renal tubular acidosis with progressive nerve deafness	Metabolic acidosis Hypokalaemia. Deafness	Nephrocalcinosis[a]	26730	—
Thrombocytopaenia absent radius (TAR) syndrome	Thrombocytopaenia without leucopenia. Absent radius	Renal anomaly	27400	I50
Wilson's disease	Athetosis, Cirrhosis	Tubular defects, renal calculi	27790	—
Wolman's disease	Malabsorption Hepatosplenomegaly	Adrenal calcification[a]	27800	—
Xanthinuria		Urinary calculi[a]	27830	—
	X-linked inheritance			
Angiokeratoma (Fabry)	Cutaneous lesions Burning feet	Proteinuria[a] Renal failure	30150	U130
Diabetes Insipidus, nephrogenic	Polyuria	Ureteric dilatation	30480	—
Granulomatous disease due to leucocyte malformation	Recurrent sepsis	Granulomata around bladder	30640	—
Hypoxanthine guanine phosphoribosyl transferase deficiency (Lesch-Nyhan)	Athetosis, self-mutilation. Mental retardation	Urate calculi	30800	—

[a] Urological involvement common (more than 25 per cent)

Table 2. Syndromes of congenital malformation with urological manifestation, but without defined genetic basis. Conditions listed are those given by SMITH (1970) with urological features (excluding genital abnormalities) not recognised by MCKUSICK (1971) as having an established mode of inheritance

Syndrome	General features	Urological manifestations	Catalogue number	
			MCKUSICK	SMITH
	Chromosomal abnormality			
18 Trisomy	Clenched hand, short sternum, low arched dermal ridge patterning on finger tips	Horseshoe kidney, ectopic kidney, double, ureter, hydronephrosis, polycystic kidneys[a]	—	A3
13 Trisomy	Defects of eye, nose, lip and forebrain of holoprosencephaly type. Polydactyly. Scalp defects	Polycystic kidneys. Hydronephrosis, horseshoe kidney, double ureter[a]	—	A4
Long arm 18 deletion	Mid-facial hypoplasia, prominent antihelix, whorl digital patterns	Horseshoe kidney[a]	—	A7
Long arm 21 deletion (Antimongolism)	Down-slanting palpebral tissue, malformed external ears, micrognathia	Unitaleral renal agenesis	—	A8
Cat-eye syndrome (small extra chromosome)	Coloboma of iris, down-slanting palpebral tissue, anal atresia	Unilateral renal agenesis	—	A9
Cri-du-chat syndrome (partial deletion of short arm 5)	Cat-like cry in infancy, microcephaly, antimongoloid slant of palpebral tissue	Unilateral renal agenesis	—	A6
XO Syndrome (Turner's syndrome)	Short female, broad chest with wide spacing of nipples, lymphoedema	Horseshoe kidney, double pelvis[a]	—	A11
	Miscellaneous Syndromes			
Absent abdominal muscles	Prune belly, cryptorchidism	Renal dysplasia, dilated ureters[a]	10010	7
Hypercalcaemia	Peculiar facies, Aortic stenosis	Nephrocalcinosis Renal failure	23800	L59
Potter syndrome	Abnormal facies and ears. Pulmonary hypoplasia	Bilateral renal agenesis[a]	—	6
Prader-Willi syndrome	Obesity, hypogonadism	Renal anomalies	26400	E26
Rubenstein-Taybi syndrome	Broad thumbs, odd facies	Renal anomalies	26860	B14

[a]Urological involvement common (more than 25 per cent)

Table 3. Syndromes of congenital malformation with abnormalities of the external genitalia. As given by SMITH (1971)

Syndrome	General features	Hypospadias		Micropenis[a]		Cryptorchidism	
		Common	Rare	Common	Rare	Common	Rare
Absent abdominal muscles	Prune belly, renal anomalies					+	
Carpenter's syndrome	Acrocephaly; polydactyly and syndactyly of feet.			+		+	
Cerebro-hepato-renal syndrome (Zellweger)	Hypotonia; high forehead; hepatomegaly		+				+
Cockayne's syndrome	Premature senility.						+
Cornelia De Lange syndrome	Short stature, abnormal eyebrows, micromelia.				+		
Cri-du-chat syndrome	Cat-like cry, microcephaly.						+
Diastrophic nanism	Short tubular bones, club foot.						+
Down's syndrome (mongolism)	Hypotonia, flat facies, slanted eyes			+			+
Ellis-van Creveld syndrome	Short limbs, polydactyly.		※				
Fanconi syndrome	Hypoplasia of radius, pigmentation, pancytopenia		+				+
Fraser syndrome	Cryptophthalmus; auricular defect.	+				+	
Hallermann-Streiff syndrome	Microphthalmia, hypotrichosis, small nose.			+		+	
Hypercalcaemia	Peculiar facies, aortic stenosis	+					
Hypertelorism-hypospadias (Opitz)	Hypertelorism,	+				+	
Laurence-Moon-Biedl syndrome	Retinitis pigmentosa, obesity, polydactyly.		+				
Oculo-cerebro-renal syndrome (Lowe)	Hypotonia, cataract, renal tubular dysfunction.					+	

Syndrome	General features	Hypospadias		Micropenis[a]		Cryptorchidism	
		Common	Rare	Common	Rare	Common	Rare
Popliteal Web syndrome	Popliteal web, cleft palate		+				+
Prader-Willi syndrome	Hypotonia, obesity			+		+	
Rubenstein-Taybi syndrome	Small stature, broad thumbs, hypoplastic maxilla	+					
Seckel's syndrome	Short stature, microcephaly, prominent nose					+	
Smith-Lemli-Opitz syndrome	Anteverted nostrils, ptosis, syndactyly	+				+	
Silver's syndrome	Short stature, skeletal asymmetry		+				
Turner-like (Noonan)	Webbing of neck, short stature, heart lesion			+		+	
XXXXY	Odd facies, fixed elbow flexion		+			+	
13 Trisomy	Eye, nose, lip, scalp defects, polydactyly		+			+	
18 Trisomy	Clenched hand, short sternum		+			+	
4 Short arm deletion	Hypertelorism, microcephaly	+				+	
18 Long arm deletion	Mid facial hypoplasia			+		+	
21 Long arm deletion	Antimongolism, micrognathia	+					+

[a] In the absence of hypospadias or epispadias.

N.B. (1) Many of the syndromes listed in Tables 1–3 are also characterised by mental retardation and short stature—in general omitted from the general features given to conserve space.

(2) "Urological manifestations" include haematuria and renal failure, but not other disorders of renal function.

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