Papers and Originals

PROBLEMS OF CHRONIC PYELONEPHRITIS*

BY

M. L. ROSENHEIM, C.B.E., M.D., F.R.C.P.*Professor of Medicine, University of London; Physician and Director of Medical Unit, University College Hospital, London*

The small contracted kidney of chronic pyelonephritis remains one of the enigmas of medicine. Ever since it was fully reviewed in the classical paper by Soma Weiss and Parker in 1939, chronic pyelonephritis has become an increasingly popular diagnosis. As a pathological process its progress is often slow and insidious, and, while it frequently presents clinically as a recurrent or refractory urinary infection, patients are often first seen because of hypertension or proteinuria, or because of one of the many manifestations of renal failure. It is now recognized as the commonest cause of the syndrome of renal failure with hypertension.

Despite the intensive clinical studies of the past fifty years and much experimental work in animals, many problems still remain unsolved. How does chronic pyelonephritis arise? Is it always the end-result of an acute bacterial infection? What part does obstruction in the urinary tract play in its production, and why does the condition so often appear to be relentlessly progressive? It is not possible in the course of a single lecture to present a complete survey, but I hope to review some of these problems in the light of recent advances in our knowledge.

Chronic pyelonephritis has been defined as the end-result of bacterial inflammation in the kidney (Kleeman *et al.*, 1960)—inflammation usually associated with the Gram-negative coliform bacilli. Until recently it has been essentially a pathological diagnosis, a diagnosis made with confidence only when the kidney could be viewed macroscopically and studied microscopically. The pathologist still has the final word; but modern radiology has provided a means of establishing the diagnosis during life, and now allows the clinician to follow the progress of the disease over years.

Unlike other forms of nephritis, chronic pyelonephritis is usually a focal disease, affecting discrete areas of one or both kidneys. The characteristic lesion is the localized pyelonephritic scar, an area of fibrotic renal substance with a sunken cortical scar, interstitial cellular infiltration, dilated tubules, and glomeruli either involved in cellular change or surrounded by periglomerular fibrosis.

A diffuse form of chronic pyelonephritis does occasionally occur with typical histology but no local scars. In such cases the possibility of some generalized tubular damage must always be considered; for the renal changes in gout, in hyperparathyroidism, and in chronic phenacetin poisoning may closely resemble those of chronic pyelonephritis. Whether tubular obstruction alone forms the link between these conditions or whether such obstruction predisposes the kidneys to superadded infection remains uncertain. In chronic phenacetin poisoning renal papillary necrosis is common, and Bengtsson (1962) has shown that, while there is no clear-cut pathological picture by which this form of nephritis can be

distinguished from chronic pyelonephritis, excess phenacetin consumption is common in Sweden in patients with true chronic pyelonephritis, and may precede the signs of infection by ten or more years.

The experimental work of De Navasquez (1950, 1956) and of Beeson (Rocha *et al.*, 1958; Freedman and Beeson, 1958) also suggests the importance of medullary scarring and tubular obstruction in the aetiology of the localized pyelonephritic scar, though Kincaid-Smith (1955) had postulated a vascular basis.

Although Braasch (1938) drew attention to the caliceal dilatation that could be recognized by urography, the criteria laid down by pathologists for diagnosis have rarely mentioned the atrophy of the renal pyramids and the resultant caliectasis. In a careful review of the morphology of chronic pyelonephritis published as recently as 1961 (Kimmelstiel *et al.*, 1961) no mention was made of these caliceal changes, which are now accepted by most radiologists and clinicians as the hallmark of the condition. J. F. Smith (1962) has studied the scars of chronic pyelonephritis. In 13 of the 14 kidneys in which collateral evidence suggested this diagnosis clubbing of the calix was present in association with the scar, while in only one of the 23 kidneys in which evidence had suggested an ischaemic aetiology for the scar was there any deformity of the underlying calix.

It is not my intention to discuss the criteria for making a clinical diagnosis of chronic pyelonephritis. The diagnosis is often difficult to establish, and the value of the history, of urinary bacterial and cell counts, of renal-function studies, and of radiology has been repeatedly stressed during the past few years. In my opinion radiology offers the best means of establishing the diagnosis in life, and the criteria laid down by Hodson (1959, 1961, 1962) in this country and by Dejdar (Dejdar and Prat, 1958; Dejdar, 1959) in Czechoslovakia are now widely accepted.

In order to establish a radiological diagnosis, the intravenous pyelogram must be a good one, with adequate concentration of the opaque medium obtained by proper dehydration, and a clear view of the renal outlines achieved by the careful preparation of the patient. One should be able to see the outlines of both kidneys so that their overall lengths can be measured and compared. The irregular scarred surface of the kidney should be evident, while the characteristic deformed or clubbed calix should be seen lying deep to the cortical scar. The focal nature of the scarring is often evident.

Dr. Hodson's careful studies and his follow-up of children with chronic urinary infections have greatly increased our understanding of chronic pyelonephritis. Unless the kidneys are symmetrically involved, and this is unusual, there will be a difference in size between them. He has shown that a scarred pyelonephritic kidney does not grow at a normal rate (Hodson, 1962), and the opposite kidney, if healthy, will grow more rapidly and to a greater size than normal.

*Lumleian Lecture delivered at the Royal College of Physicians of London on March 18, 1963.

The discovery of a unilateral small kidney raises many points of interest. Chronic pyelonephritis is undoubtedly the commonest cause, and the diagnosis can usually be established by the presence of scars and clubbed calices. It has to be distinguished from the small ischaemic kidney due to the constriction or blocking of the main renal artery or one of its branches. Here the cortex may again be locally narrowed but the caliceal pattern remains undistorted. Angiography will often help by defining renal size and shape, but it must be remembered that the contracted pyelonephritic kidney will have a small artery, and the discovery of a small renal artery does not necessarily indicate that ischaemia is the primary cause of the shrunken kidney.

How often true hypoplasia of a kidney occurs remains a matter of dispute (Emmett *et al.*, 1952), but it is probable that many small, and perhaps non-functioning, kidneys that have in the past been ascribed to hypoplasia have been examples of pyelonephritis occurring very early in life, or even perhaps *in utero*.

Development of Atrophic Pyelonephritis

Many patients with chronic pyelonephritis first attract clinical attention at adolescence or in early adult life, when they present with hypertension, proteinuria, or renal failure, with or without active urinary infection and with or without a history of past infection. When, on investigation, either one or both kidneys are found to be shrunken and scarred, it becomes evident that the disease must presumably have been present and progressive for many years, and in many patients probably dates back to infancy or childhood.

Infants do not complain of frequency or dysuria, and many acute attacks of urinary infection are undoubtedly disregarded or misdiagnosed as teething, tonsillitis, bronchitis, or a stomach upset (Thompson, 1962). Joyce Burke (1961) found that anorexia, fever, and vomiting were the most prominent symptoms in 23 infants under the age of 1 year who had pyelonephritis. Abdominal pain was noted in only five and frequency of micturition and dysuria in only two. Porter and Giles (1956) reported five cases of pyelonephritis occurring in infants under the age of 1 month, and suggested that this diagnosis must be considered in any infant who vomits, loses weight, or goes off his food. A history of recurrent febrile attacks in childhood is often an invaluable clue to the diagnosis of chronic pyelonephritis in adult life.

It is interesting to contrast the views of general practitioners and of physicians interested in renal disease on the outcome of an acute attack of pyelonephritis. To the general practitioner acute pyelonephritis is rather akin to an acute chest infection, most patients responding rapidly to the appropriate antibiotic and apparently having no further trouble. Patients seen in hospital practice, however, have often suffered from recurrent attacks of acute urinary infection for years, sometimes responding well each time to treatment, but sometimes responding only symptomatically, the urine remaining infected between attacks. Several follow-up studies of pyelonephritis in children have been published (Wharton *et al.*, 1937; Woodruff and Everett, 1954; Macaulay and Sutton, 1957; Burke, 1961), and it is evident that the condition is far from benign.

Acute pyelonephritis must always be regarded as a serious condition. It requires prompt and adequate treatment. The criterion of cure is not that of symptomatic relief, but the urine should be shown to be sterile

on culture several days after the cessation of treatment. I believe that, once such a cure has been demonstrated, prophylactic sulphonamides should be continued for several months (Stansfeld and Webb, 1954). Recurrent or refractory infections always require full urological investigation.

When such patients with refractory urinary infections are investigated, abnormalities of the urinary tract are often found. Any obstruction to the normal flow of urine, any urinary stasis, predisposes the kidney to infection. This has, of course, long been known and amply confirmed in experimental animals. However, when series of patients with recurrent pyelonephritis are fully investigated, or when an atrophic pyelonephritic kidney is found in patients presenting with hypertension or renal failure, it has in the past frequently not been possible to demonstrate any underlying abnormality in the urinary tract. Atrophic pyelonephritis may occur with no obvious ureteric obstruction, with no clear congenital anomaly, and with no evidence of obstruction to the lower urinary tract.

Cabot and Crabtree (1916) subdivided pyelonephritis into primary and secondary. In the former, infection occurred in a kidney with no preceding lesion of the urinary tract, while in the latter there was present some antecedent lesion, such as a stone in the renal pelvis or ureter, or damage dependent upon some obstruction to the ureter or bladder.

This subdivision into obstructive and non-obstructive pyelonephritis was maintained for a long time. In 1960 Brod *et al.* reported that while in two-thirds of the cases of chronic pyelonephritis coming to post-mortem examination some condition causing partial or complete obstruction to the free flow of urine could be found, in about one-third of the cases there was no obvious abnormality in the urinary tract.

It has recently become evident that vesico-ureteric reflux, reflux of urine from the bladder into the ureter and renal pelvis, can be demonstrated in the majority of these patients with primary or non-obstructive pyelonephritis (Edwards, 1961). In my opinion this represents a major advance in our understanding of chronic pyelonephritis, and, since this discovery highlights many problems, I propose to discuss such reflux in some detail.

Vesico-ureteric Reflux

That ammoniacal putrefaction of the urine might follow catheterization was clearly demonstrated even before micro-organisms had been isolated from it. It was soon generally accepted that cystitis might follow an ascending urethral infection, but the route by which organisms reach the kidney has been hotly debated ever since the turn of the century. Do organisms reach the kidney from the bladder via the ureter, or is pyelonephritis the result of a blood-stream invasion? Convincing evidence in favour of each route can be adduced both from clinical observation and from experimental work, and, as is the case in so many fierce medical disputes, it is probable that both occur and that infection in man can follow either route.

With ascending infection in mind, the competence of the vesico-ureteric orifice soon came under discussion. The anatomy of the intramural portion of the ureter was fully described by Charles Bell (1812). Young (1898) discussed the possible occurrence of ureteric reflux in man, and Sampson (1903), who recognized reflux as a possible cause of renal infection, reviewed the subject

in detail. In normal man the oblique passage of the ureter through the bladder wall forms an effective valve. Pressure inside the bladder compresses the ureter against the posterior bladder wall, and post-mortem efforts to induce reflux by distension of the bladder fail. The anatomy of the intramural ureter has been discussed by Hutch *et al.* (1961) and by Stephens and Lenaghan (1962).

Reflux occurs naturally in certain animals, and this appears to be related to the shorter length of intramural ureter (Gruber, 1929), and Hutch (1961) has suggested that reflux is more likely to occur in infants than in adults because of the shorter length of the intravesical ureter.

Vesico-ureteric reflux occurs under many conditions in man; notably when there is obstruction to the outflow tract from the bladder or when neurogenic control of the bladder is upset. The Table lists the various causes of vesico-ureteric reflux: it is modified from that in a paper by Edwards (1961).

Causes of Vesico-ureteric Reflux

1. Abnormalities of the ureteric orifice:
 - (a) Congenital—e.g., ectopic and duplex ureters.
 - (b) Acquired:
 - Infection,
 - Tuberculosis,
 - Trauma—calculus.
 - surgical.
2. Infection—cystitis.
3. Obstruction of lower urinary tract.
4. Neurogenic bladder: congenital or acquired.
5. Megacystic-megaureter syndrome.
6. Unexplained—associated with chronic atrophic pyelonephritis.

Reflux occurs in its most extreme form in paraplegics. Hutch (1958) has made a special study of this and reports that reflux occurs in less than 5% of patients with paraplegia during the first three years of their disease, but the incidence rises until it reaches 17% some seven and a half years after injury. This rise in reflux rate is accompanied by the occurrence of hydroureter and hydronephrosis and by renal failure, and is almost invariably associated with urinary infection. Hutch has especially stressed the anatomic changes that occur to the intramural ureter; the posterior supporting wall becomes weak, leading to a sacculi or diverticulum just below the ureteric orifice, with shortening of the intramural ureter. He devised the operation of ureteroplasty, which relieves reflux in the majority of patients. L. Guttmann (personal communication), on the other hand, believes that infection plays a dominant part in the occurrence of reflux and that control of infection alone may restore vesico-ureteric valvular function.

Paediatricians and urologists have long been interested in children with obstruction of the lower urinary tract—with urethral valves or with the bladder-neck obstruction of Marion's disease. These children, the majority of whom are boys, are prone to recurrent or persistent urinary infection, develop hypertension and renal failure, and at post-mortem examination their kidneys show the characteristic features of atrophic pyelonephritis. Renal failure is often insidious and progressive, and these children may develop gross renal osteodystrophy.

The bladder-neck obstruction can be beautifully demonstrated by the micturating cystogram, and reflux is often present, sometimes accompanied by marked distension of the bladder and ureters. Marked hydronephrosis is unusual. Two characteristic and almost diagnostic features accompany such obstruction of the

lower urinary tract—residual urine and trabeculation of the bladder wall (Edwards, 1957).

While in many cases of chronic pyelonephritis in young children bladder-neck obstruction can be demonstrated and successfully treated, in a large number of children, especially girls, with typical atrophic pyelonephritis there is no residual urine, no trabeculation, and no demonstrable bladder-neck obstruction. Vesico-ureteric reflux has occasionally been noted in the past in patients with no obvious obstruction, but it has only been in the past few years, since radiological definition of chronic pyelonephritis has been achieved and the micturating cystogram has become a standard procedure, that the high incidence of reflux in so-called primary pyelonephritis has become apparent.

This requires emphasis, for there is a tendency to consider that, since vesico-ureteric reflux has long been known, its connexion with non-obstructive pyelonephritis has also long been recognized. This is not the case.

In 1957 Kjellberg and his colleagues reported that in a series of 290 consecutive children with infections of the urinary tract without demonstrable obstruction or neurogenic lesions reflux occurred in 99 (34%). In this country attention was drawn to the association of reflux with chronic pyelonephritis by Hodson and Edwards (1960). While Hodson was particularly interested in defining the radiological appearances of chronic pyelonephritis (Hodson, 1959), Edwards was investigating the outflow tract by fluoroscopy and cineradiography (Edwards, 1957, 1960). While investigating one of Professor Dent's patients, a boy with small kidneys and renal osteodystrophy, he observed normal emptying of the bladder with no obstruction, but reflux occurred right up into the pelves of both kidneys—kidneys which had the characteristic features of chronic pyelonephritis. This led to the investigation of children with so-called primary pyelonephritis, and in 1961 Edwards reported that 55 patients with radiological signs of chronic pyelonephritis had been examined and that vesico-ureteric reflux had been demonstrated in 42 (76%). He reported two cases in which the date of onset of reflux could be accurately determined; in one, reflux followed surgical intervention at the lower end of the ureter, and in the second it followed a chemical cystitis. Both patients subsequently developed the radiological changes of chronic pyelonephritis.

In America this association too has only recently been stressed. Hinman and Hutch (1962), both of whom had long been interested in reflux, published an article entitled "Atrophic Pyelonephritis from Ureteral Reflux without Obstructive Signs," and I quote their opening paragraph:

"We had always considered the end-point of vesico-ureteral reflux to be hydroureter and hydronephrosis until, while making cine-radiographic studies, we discovered a patient who clinically and radiologically appeared to have chronic non-obstructive pyelonephritis, but who actually had bilateral ureteral reflux. This finding was unexpected . . . and led us to suspect that other patients being treated medically for chronic pyelonephritis basically may have a urologic disorder."

They found eight more cases. Later they say:

"The traditional key diagnostic test to separate the non-urologic from the obstructive urologic groups has been the excretory urogram. If the urogram revealed no dilatation of the ureter or renal pelvis, the disease was called idiopathic or non-obstructive pyelonephritis. The evidence of reflux

in patients with urograms showing an obstructed and dilated urinary tract has long been recognized. But reflux has not been suspected in patients with non-obstructive pyelonephritis and the renal infection has been thought to be usually haematogenic in origin."

During the past four years 36 patients with apparent primary chronic pyelonephritis have been under the care of the Medical Unit at University College Hospital, and in 23 (64%) of these vesico-ureteric reflux has been demonstrated.

The ages of those with reflux ranged from 7 to 46, and more than half were between the ages of 10 and 20. There were 19 females and 4 males. This series is weighted by patients with hypertension. The presenting symptom or sign was hypertension in 11 patients, urinary infection in eight, and in all four men proteinuria drew attention to their disease. Radiology suggested a possible abnormality of the bladder neck in eight patients, a distal narrowing of the urethra in one, but demonstrated a normal outflow tract in the other 14 patients.

During this same period many cases of reflux have been detected in our paediatric department. Dr. Jean Smellie will be reporting these, but allows me to say that, out of 151 children with urinary infection, acute, recurrent, or chronic (sometimes only a single attack), 98 have been fully investigated with both pyelography and cystography, and of these 98, 41 (42%) have been shown to reflux.

Illustrative Cases

Case 1.—A girl aged 12 had three attacks of acute right-sided pyelonephritis during the previous two years. Each attack responded rapidly to treatment and there was no past history suggestive of renal disease. An intravenous pyelogram showed a smaller right kidney with caliceal clubbing and scarring of the upper pole (Fig. 1). The left kidney appeared normal. A micturating cystogram showed right-sided reflux with a normal bladder, with no residue and no trabeculation (Figs. 2 and 3). The bladder neck was narrow. She has recently had a right ureteroplasty and bladder-neck operation.

FIG. 1.—Case 1. Intravenous pyelogram showing smaller right kidney with caliceal clubbing. Note distensible ureter.

FIG. 2.—Case 1. Micturating cystogram, showing complete emptying of bladder and reflux up right ureter.

Case 2.—A girl aged 12 had been referred to hospital in the country because of severe headaches and transient diplopia. She was found to be severely hypertensive (diastolic 130–140 mm. Hg) and was treated with reserpine. In August, 1960, she was admitted to U.C.H. She had had enuresis up to the age of 7½, but, apart from nocturia once nightly, there were no symptoms referable to the urinary tract. Her urine was sterile and her renal function good. An intravenous pyelogram showed a small irregular left kidney (6.8 cm.) with hypertrophy of the right (12 cm.), and a micturating cystogram showed bilateral reflux with a normal bladder with no residue and no obstruction of the lower urinary tract. In October she had a right ureteroplasty and bladder-neck operation. In April, 1961, a cystogram showed reflux only on the left side, and in May she had a left nephro-ureterectomy. She is now very fit, with a blood-pressure of 150/80 on no drugs.

Case 3.—A girl aged 7½ was referred to U.C.H. in 1959 with a history of frontal headaches for a year and haematuria. There was no past history of urinary infection or of renal disease. She was found to have malignant hypertension with normal renal function. Intravenous pyelography showed bilateral chronic pyelonephritis with a small right kidney and distensible ureters, and a micturating cystogram showed bilateral reflux with a normal bladder and lower urinary tract. In December, 1959, she had a left ureteroplasty and right nephrectomy without bladder-neck operation. The kidney showed the typical changes of chronic pyelonephritis. A further cystogram five months later showed reflux persisting up the left ureter and into the stump of the right ureter. She is now very well, with normal fundi, growing well, and her blood-pressure is controlled on 10 mg. of guanethidine daily. (Case 5 of Hodson and Edwards, 1960).

Case 4.—A woman aged 20 was admitted to U.C.H. in September, 1959, for investigation of hypertension. She had no symptoms, but in February, 1959, had had a miscarriage at four and a half months and at that time had been found to be hypertensive and to have a contracted left kidney. There was no past history of renal disease, but on admission her urine was infected. Her blood-pressure was then 190/120 mm. Hg, and her renal function was good. An intravenous pyelogram had shown a small left kidney with irregular outline and hypertrophy of the right, and renal angiography confirmed the small left kidney and showed a small renal artery on that side (Figs. 4 and 5). A micturating cystogram showed reflux on the left side, right up into the renal pelvis, with no reflux on the right (Fig. 6). The bladder emptied completely and there was no obstruction of the lower urinary tract. Left nephro-ureterectomy was performed in October, 1959, the kidney showing the changes of chronic pyelonephritis. She has since had a normal full-term pregnancy, and her blood-pressure in March, 1963, was 130/75 mm. Hg on no hypotensive treatment.

FIG. 3.—Case 1. Micturating cystogram, showing complete emptying of bladder

Case 5.—A man aged 50, doing full-time work as a stoker, applied for a new job which necessitated a medical examination. He had always been well and had no history or symptoms of urinary disease other than long-standing nocturia. At routine examination proteinuria was found and he was referred to Dr. Kenneth Harris. He appeared

fit, but had 1 g. of protein/litre in his urine, the deposit from which showed no red cells, pus cells, or casts. His blood-pressure was 150/100 mm. Hg, and his blood urea 46 mg./100 ml. Intravenous pyelography showed a contracted left kidney (7 cm.) with a hypertrophied but scarred right kidney (14 cm.) (Fig. 7), and a micturating cystogram showed reflux right up into the left renal pelvis and also up the right ureter, with no residual urine in the bladder and no bladder-neck obstruction (Fig. 8).

Some Questions

The recognition of the association of vesico-ureteric reflux with atrophic non-obstructive chronic pyelonephritis raises many questions.

(a) Does Reflux Occur in the Healthy Urinary Tract?

From a study of published papers it is evident that there is now general agreement that reflux can rarely, if ever, be demonstrated in the normal healthy urinary tract (Eisendrath *et al.*, 1925; Campbell, 1951; Bunge, 1954; Stewart, 1955; Kjellberg *et al.*, 1957; Jones and Headstream, 1958; McGovern *et al.*, 1960; Politano, 1960; Leadbetter *et al.*, 1960; Gross and Sanderson, 1961; Turner-Warwick, 1962). It is of course not easy to investigate large series of normal individuals by

FIG. 4.—Case 4. Aortogram. Arrow shows small left renal artery below the splenic artery.

FIG. 5.—Case 4. Aortogram. Nephrogram stage, showing the small left kidney.

FIG. 6.—Case 4. Micturating cystogram, showing reflux up left ureter, complete emptying of bladder, and reflux into left renal pelvis.

FIG. 7.—Case 5. Intravenous pyelogram, showing small left and hypertrophied but scarred right kidney.

FIG. 8.—Case 5. Micturating cystogram, showing bilateral reflux with filling of left renal pelvis.

micturating cystogram, and Johnston (1962) noted that all volunteers have so far been either young children or convicted criminals.

(b) What is the Association of Reflux with Urinary Infection ?

There is considerable evidence that reflux may vary on repeated examination. It may not occur with every act of micturition. It is often associated with the presence of urinary infection, and it has been pointed out that reflux may disappear when urinary infection clears up (Campbell, 1951; Politano and Leadbetter, 1958; Williams, 1959; Hanley, 1963; L. Guttman, personal communication). Infection may lead to thickening of the bladder wall and to oedema and rigidity of the intramural ureter (Bumpus, 1924), and this may be reversible. If infection is a factor in the production of reflux it is probable that repeated attacks of cystitis may ultimately lead to permanent laxity of the vesico-ureteric valve. If this could be confirmed there would be added grounds for the early and effective treatment of urinary infection.

If infection precedes reflux, can we be confident that reflux is the cause of chronic pyelonephritis and not a chance association? There is good evidence that reflux is important, for it has been clearly shown that damage to ureteric orifices may be followed by atrophic pyelonephritis (Edwards, 1961). Reflux is not uncommon in double ureters (Lenaghan, 1962), and Williams (1962) reported a series of cases in which only one of the two ureters permitted reflux, and the segment of the kidney drained by the refluxing ureter showed pyelonephritis. Stephens and Lenaghan (1962) consider that reflux is primary and precedes infection and that it is due to a congenital absence of the submucosal segment of the ureter and to a deficiency of the ureteric musculature; and Hutch (1962) also considers that the basic defect in most patients with pyelonephritis is a damaged vesico-ureteric junction. Garrett *et al.* (1961) have stated that "regurgitation may precede, promote, and perpetuate pyelonephritis."

Of our 23 patients with reflux, 15 had evidence of active or past urinary infection and 11 had infected urine at the time of diagnosis. On the other hand, eight patients had no past or present evidence of infection. This raises the important question of whether renal infection invariably precedes the pathological appearance of chronic pyelonephritis, for I have already referred to the possibility that medullary scarring could lead to the changes of focal pyelonephritis without infection. Could reflux, occurring with every act of micturition, allow a wave, like the Severn Bore, to beat against the caliceal lining, and could this in turn lead to renal damage even in the absence of infection? We should not, at present, accept the view that infection invariably plays a part in the production of the pyelonephritic scar.

(c) What Part does Obstruction Play in the Production of Reflux ?

The relief of known bladder-neck obstruction in obstructive pyelonephritis may cure reflux, and some degree of obstruction may be present in all patients even in the absence of residual urine or trabeculation. Minor radiological changes were noted at the bladder neck in 8 of our 23 patients, and it is probable that a whole range of degrees of obstruction may exist. Most of the patients with chronic atrophic pyelonephritis and reflux are girls, and evidence does suggest that obstruction may be important, for repeated dilatation of the urethra may

relieve reflux, while operative widening of the bladder neck has become a recognized and effective part of surgical treatment (McGovern *et al.*, 1960; Williams *et al.*, 1961). There is great need for pressure and flow studies in these children, and much work is being done on this problem both in this country and in the United States.

(d) Is Reflux Congenital ?

It is clear that acquired anomalies of the intravesical ureter can cause reflux, and it is tempting to believe that congenital anomalies may occur. Kjellberg *et al.* (1957) reported the cases of 18 children with reflux in whom one or both kidneys were hypoplastic, suggesting that reflux occurred early in development, and we have some evidence suggesting that reflux may be hereditary.

Three main factors may thus play a part in the production of reflux—obstruction in the lower urinary tract, infection, and some anomaly of the intravesical ureter. Reflux is probably multifactorial, and certainly all three factors have to be considered when treatment is discussed.

Treatment of Vesico-ureteric Reflux

There is again a voluminous literature concerning the treatment of reflux in patients with bladder-neck obstruction and in those with neurogenic bladders. The importance of the adequate control of infection has been frequently stressed and reflux has been observed to disappear when infection has been cured. On the other hand, chronic and recurrent infection may be curable once reflux is relieved. Many authors have advocated the training of children in double or triple micturition (Lattimer *et al.*, 1956). The ability to produce more urine from a bladder a few minutes after micturition is almost diagnostic of reflux, the distended ureters emptying back into the bladder as it relaxes (Stephens, 1954; Stansfeld and Smith, 1962). Repetitive micturition helps to empty the bladder of stagnant urine and assists in the prevention or cure of infection. It is possible that children with reflux with no true residual urine or bladder trabeculation should be taught this trick of multiple micturition and should be maintained on long-term chemotherapy. Repeated dilatation of the urethra has also been advocated (Lattimer *et al.*, 1961). Many operations have been devised for the treatment of reflux. In patients with paraplegia, Hutch believes that ureteroplasty, placing the lower end of the ureter inside the bladder and repairing the bladder wall behind it, is an effective means of cure, but in children with bladder-required (Williams *et al.*, 1961). This combined neck obstruction operation on the bladder neck is also operation has proved highly successful in such children (McGovern *et al.*, 1960; Leadbetter and Leadbetter, 1961).

In our cases of atrophic pyelonephritis with reflux, Mr. D. R. Davies at first operated only on the ureters, but in three patients in whom ureteroplasty was not accompanied by widening of the bladder neck reflux persisted post-operatively. He now usually combines ureteroplasty with plastic reconstruction and widening of the bladder neck, and in the majority of patients this leads to disappearance of reflux. Forty-three refluxing ureters have been treated by this combined operation and 35 (81%) showed no reflux in a subsequent cystogram.

Where one kidney is badly damaged and atrophic and reflux is bilateral, we believe that bladder-neck recon-

struction and ureteroplasty on the better side should precede nephro-ureterectomy, for prophylaxis of the sounder kidney is clearly most important. If a kidney is removed the ureter should always be removed as well, for reflux will otherwise continue up the ureteric stump, which will act as a bladder diverticulum and may predispose to continuing infection.

It is only by long and careful follow-up of patients who have had their reflux corrected that it will be possible to tell whether the tendency to repeated urinary infection can be controlled and whether the relentless progress of chronic pyelonephritis can be prevented. Such evidence is urgently required.

Some Other Aspects

While paediatricians and urologists have been trying to clarify these problems of reflux and pyelonephritis, renewed interest in urinary infection has been aroused by the work of Kass (1957, 1960) in Boston.

He has drawn a clear distinction between bacterial contamination and true urinary infection and believes that symptomless infection of the urinary tract is not uncommon. He has shown that it is not necessary to use catheter specimens of urine in women for the diagnosis of infection, but that mid-stream clean specimens will do as well, provided that cultures are set up early, before contaminant organisms have had time to multiply. Using the pour-plate technique, which permits estimation of the number of organisms present in the urine, Kass has found that counts of over 100,000 organisms per ml. indicate a true infection, while counts of under 10,000 indicate contamination. He has found a considerable number of women to have symptomless infection without pyuria and believes that such women are especially prone to develop pyelonephritis. By the prophylactic use of sulphonamides during pregnancy in patients with such asymptomatic bacilluria he has achieved a reduction in the incidence of pyelonephritis of pregnancy and a reduction in the perinatal infant mortality.

In this country, it has long been customary to culture urines on solid media and to report upon them on a rough quantitative basis. Provided that cultures are made early, the complicated pour-plate technique is probably not essential (Hinkle *et al.*, 1960; Schneierson, 1962; Cattell and Lefford, 1963; McGeachie and Kennedy, 1963). At U.C.H., Guttman and Stokes (1963) have compared the results of our routine laboratory technique with the pour-plate method and have found an excellent correlation.

The experimental work of Beeson and his colleagues has thrown further light on the aetiology of pyelonephritis. They have shown that the renal medullary tissue is particularly susceptible to infection. Minute lesions were produced in the kidney by cautery, and coliform bacilli were then injected intravenously. Multiple lesions in the renal cortex did not lead to an increased incidence of infection, but a single medullary lesion was followed by localized infection in 85% instances, the infection being restricted to the distribution of those nephrons whose collecting tubules passed through the area of injury (Rocha *et al.*, 1958). Similar results were obtained by the direct inoculation of organisms into the kidney. An injection of less than 10 organisms into the medulla provoked infection there, while some 100,000 were usually necessary to infect the

cortex (Freedman and Beeson, 1958). If organisms were injected into the ureter, no renal infection followed in the absence of obstruction. If the ureter was obstructed very few organisms in the ureter led to rapid renal infection, but large numbers of bacilli in the urine failed to cause such infection in the absence of obstruction (Freedman and Beeson, 1958). Beeson and Rowley (1959) have shown that renal tissue exerts an anti-complementary effect on the normal bactericidal action of serum on coliform bacilli and suggest that this effect may be related to the production of ammonia in the renal tubules.

The close association of infection and obstruction has thus again been demonstrated, and this emphasizes the possible importance of vesico-ureteric reflux as a factor predisposing to infection of the kidney, without reference to whether the organisms reach the renal medulla from the urine or the blood-stream.

Thus gradually a picture of chronic pyelonephritis is being pieced together and we are beginning to appreciate why urinary infections occur, why infection may persist, and how repeated or persistent infection may lead to progressive renal damage, while recent work holds out some hope of preventing the relentless progress of this fascinating disease.

My sincere thanks are due to all members of the U.C.H. Renal Club who have, over the past six years, discussed and disputed the problems of chronic pyelonephritis. In particular thanks are due to Dr. C. J. Hodson and Dr. David Edwards, our radiologists; to Mr. D. R. Davies, urologist; to Dr. J. F. Smith, morbid anatomist; and to Dr. Eric Ross, first assistant in the Medical Unit. I am also especially grateful to Dr. Hywel Jones for his assistance in following up our patients.

REFERENCES

- Beeson, P. B., and Rowley, D. (1959). *J. exp. Med.*, **110**, 685.
 Bell, C. (1812). *Med.-chir. Trans.*, **3**, 171.
 Bengtsson, U. (1962). *Acta med. scand.*, Suppl. No. 388.
 Braasch, W. F. (1938). *J. Urol.*, **39**, 1.
 Brod, J., Prat, V., and Dejdar, R. (1960). In *Biology of Pyelonephritis*, edited by E. L. Quinn and E. H. Kass. Little, Brown, Boston.
 Bumpus, H. C. (1924). *J. Urol.*, **12**, 341.
 Bunge, R. G. (1954). *Ibid.*, **71**, 427.
 Burke, J. B. (1961). *Lancet*, **2**, 1116.
 Cabot, H., and Crabtree, E. C. (1916). *Boston med. surg. J.*, **174**, 780.
 Campbell, M. (1951). *Clinical Pediatric Urology*. Saunders, Philadelphia.
 Cattell, W. R., and Lefford, M. J. (1963). *Brit. med. J.*, **1**, 97.
 De Navasquez, S. (1950). *J. Path. Bact.*, **62**, 429.
 — (1956). *Ibid.*, **71**, 27.
 Dejdar, R. (1959). *Fortschr. Röntgenstr.*, **90**, 196.
 — and Prat, V. (1958). *Z. Urol.*, **51**, 1.
 Edwards, D. (1957). *Brit. J. Urol.*, **29**, 410.
 — (1960). In *Modern Trends in Diagnostic Radiology*, edited by J. W. McLaren, 3rd series. Butterworth, London.
 — (1961). *Proc. roy. Soc. Med.*, **54**, 1096.
 Eisendrath, D. N., Katz, H., and Glasser, J. M. (1925). *J. Amer. med. Ass.*, **85**, 1121.
 Emmett, J. L., Alvarez-Ilerena, J. J., and McDonald, J. R. (1952). *Ibid.*, **148**, 1470.
 Freedman, L. R., and Beeson, P. B. (1958). *Yale J. Biol. Med.*, **30**, 406.
 Garrett, R. A., Rhamy, R. K., and Carr, J. R. (1961). *Trans. Amer. Ass. gen.-urin. Surg.*, **53**, 120.
 Gross, K. E., and Sanderson, S. S. (1961). *Radiology*, **77**, 573.
 Gruber, C. M. (1929). *J. Urol.*, **21**, 567.
 Guttman, D., and Stokes, E. J. (1963). *Brit. med. J.*, **1**, 1384.
 Hanley, H. G. (1963). *Lancet*, **1**, 22.
 Hinkle, N. H., Partin, J. C., and West, C. D. (1960). *J. Dis. Child.*, **100**, 333.
 Hinman, F., and Hutch, J. A. (1962). *J. Urol.*, **87**, 230.
 Hodson, C. J. (1959). *Proc. roy. Soc. Med.*, **52**, 669.
 — (1961). *Ibid.*, **54**, 1094.
 — (1962). In *Renal Disease*, edited by D. A. K. Black. Blackwell, Oxford.
 — and Edwards, D. (1960). *Clin. Radiol.*, **11**, 219.

- Hutch, J. A. (1958). *The Ureterovesical Junction*. Univ. of California Press, Berkeley and Los Angeles.
- (1961). *J. Urol.*, **86**, 534.
- (1962). *Ibid.*, **88**, 354.
- Ayres, R. D., and Loquvam, G. S. (1961). *Ibid.*, **85**, 531.
- Johnston, J. H. (1962). *Ann. roy. Coll. Surg. Engl.*, **30**, 324.
- Jones, B. W., and Headstream, J. W. (1958). *J. Urol.*, **80**, 114.
- Kass, E. H. (1957). *Arch. intern. Med.*, **100**, 709.
- (1960). In *Biology of Pyelonephritis*. Little, Brown, Boston.
- Kimmelstiel, P., Kim, O. J., Beres, J. A., and Wellmann, K. (1961). *Amer. J. Med.*, **30**, 589.
- Kincaid-Smith, P. (1955). *Lancet*, **2**, 1263.
- Kjellberg, S. R., Ericsson, N. O., and Rudhe, U. (1957). *The Lower Urinary Tract in Childhood*. Year Book Publishers, Chicago.
- Kleeman, C. R., Hewitt, W. L., and Guze, L. B. (1960). *Medicine (Baltimore)*, **39**, 3.
- Lattimer, J. K., Dean, A. L., and Furey, C. A. (1956). *J. Urol.*, **76**, 656.
- Leuzinger, D., Justice, M., and Knappenberger, S. (1961). *Ibid.*, **85**, 275.
- Leadbetter, G. W., Duxbury, J. H., and Dreyfuss, J. R. (1960). *Ibid.*, **84**, 69.
- and Leadbetter, W. F. (1961). *J. Amer. med. Ass.*, **175**, 349.
- Lenaghan, D. (1962). *J. Urol.*, **87**, 808.
- Macaulay, D., and Sutton, R. N. P. (1957). *Lancet*, **2**, 1318.
- McGeachie, J., and Kennedy, A. C. (1963). *J. clin. Path.*, **16**, 32.
- McGovern, J. H., Marshall, V. F., and Paquin, A. J. (1960). *J. Urol.*, **83**, 122.
- Politano, V. A. (1960). *J. Amer. med. Ass.*, **172**, 1252.
- and Leadbetter, W. F. (1958). *J. Urol.*, **79**, 932.
- Porter, K. A., and Giles, H. M. (1956). *Arch. Dis. Child.*, **31**, 303.
- Rocha, H., Guze, L. B., Freedman, L. R., and Beeson, P. B. (1958). *Yale J. Biol. Med.*, **30**, 341.
- Sampson, J. A. (1903). *Johns Hopk. Hosp. Bull.*, **14**, 334.
- Schneerson, S. S. (1962). *J. Urol.*, **88**, 424.
- Smith, J. F. (1962). *J. clin. Path.*, **15**, 522.
- Stansfeld, J. M., and Smith, K. M. (1962). *Brit. J. Urol.*, **34**, 280.
- and Webb, J. K. G. (1954). *Brit. med. J.*, **1**, 616.
- Stephens, F. D. (1954). *N.Z. J. Surg.*, **23**, 197.
- and Lenaghan, D. (1962). *J. Urol.*, **87**, 669.
- Stewart, C. M. (1955). *Ibid.*, **74**, 749.
- Thompson, H. T. (1962). *N.Y. St. J. Med.*, **62**, 1376.
- Turner-Warwick, R. T. (1962). *Proc. roy. Soc. Med.*, **55**, 419.
- Weiss, H., and Parker, F. (1939). *Medicine (Baltimore)*, **18**, 221.
- Wharton, L. R., Gray, L. A., and Guild, H. G. (1937). *J. Amer. med. Ass.*, **109**, 1597.
- Williams, D. I. (1959). *Bull. N.Y. Acad. Med.*, **35**, 317.
- (1962). *Postgrad. med. J.*, **38**, 520.
- Scott, J., and Turner-Warwick, R. T. (1961). *Brit. J. Urol.*, **33**, 435.
- Woodruff, J. D., and Everett, H. S. (1954). *Amer. J. Obstet. Gynec.*, **68**, 798.
- Young, H. H. (1898). *Bull. Johns Hopk. Hosp.*, **9**, 100.

PRESENTATION AND DIAGNOSIS OF CHRONIC PYELONEPHRITIS

BY

H. M. LEATHER, M.D., M.R.C.P.

Consultant Physician, Plymouth Clinical Area; Late Senior Medical Registrar, Medical Unit,
Bristol Royal Infirmary

Chronic pyelonephritis may be very difficult to diagnose. In some large surveys as few as 20% of cases have been diagnosed during life (Kleeman *et al.*, 1960). In recent years new methods of diagnosis have become available and include renal biopsy and the "pyrogen" test. Between July, 1959, and January, 1962, 30 cases of chronic pyelonephritis were diagnosed in the medical unit, Bristol Royal Infirmary. The way these cases presented has been analysed and an attempt made to determine how useful were the new methods of investigation.

Methods

Full clinical details were taken and at least four specimens of urine from each case were examined for proteinuria and centrifuged deposit. Quantitative urine culture was carried out by the loop technique (Gillespie *et al.*, 1960). Infection was considered to be present when the bacterial count exceeded 10,000/ml. A urinary W.B.C. count (Houghton and Pears, 1957) was made in each case and the effect of pyrogen (Pears and Houghton, 1958) or steroid (Katz and Moore, 1960; Katz *et al.*, 1962; Little and de Wardener, 1962) on the output of W.B.C. determined. Renal biopsies were taken by the method of Kark and Muehrcke (1954) with the modification in later cases in the series that an image intensifier was used throughout the course of the biopsy to locate the kidney. Other investigations included excretory urography and, when necessary, cystoscopy and retrograde pyelography.

Diagnosis.—The diagnosis of chronic pyelonephritis was made on any one of the following criteria: (1) a history of infection of the urinary tract together with changes on excretory urography, which included distortion and clubbing of calices with focal parenchymal narrowing; (2) a positive pyrogen or steroid test provided this was associated with other evidence of pyelonephritis obtained from the history, excretory urography, or biopsy; and (3) conclusive histological

evidence of pyelonephritis from renal biopsy. Since the investigations were made five cases have come to necropsy and in three others a nephrectomy has been carried out. In all eight cases the diagnosis of chronic pyelonephritis has been upheld. In one other case a diagnosis of primary hyperparathyroidism has been made subsequent to the diagnosis of pyelonephritis.

Findings

There were 22 women and 8 men; their ages ranged from 5 to 60 years.

Presentation.—Thirteen cases presented with symptoms of infection of the urinary tract. All complained of dysuria and frequency, and eight of them had had loin pain. Only 2 of these 13 cases had hypertension, and in these two dysuria and frequency dated from 7 and 16 years previously. A further case presented with acute epididymitis. There had been no history of infection of the urinary tract prior to this. Sixteen cases showed evidence of intrarenal infection: five with hypertension, seven with renal failure, and four with proteinuria. Only six of these (three with hypertension and three with renal failure) had had dysuria and frequency, which had occurred from 16 to 30 years previously. Hypertension was present in 14 of the 30 cases. Only two of these came with dysuria and frequency; the remaining 12 had hypertension itself (five cases), renal failure (four cases), albuminuria (two cases), and acute epididymitis (one case). The clinical presentation of these 30 cases thus fell into two broad groups. Approximately half complained of symptoms of infection of the urinary tract. The remainder showed evidence of renal damage.

Urinary Findings.—Proteinuria was usually present but never heavy. Three cases were repeatedly protein-free and in these the urinary deposit was also normal. In three other cases proteinuria was absent between acute episodes of urinary tract infection. In eight cases the