

URETERIC INJURIES IN GYNAECOLOGY

I. JACOBSON, M.B., CH.B. (CAPE TOWN), F.R.C.S. (EDIN.), F.R.C.S. (ENG.)

Part-time Urologist, Groote Schuur Hospital, Cape Town

According to Ingersoll and Meigs¹ 'accidental injury to the ureter is the most serious complication of gynaecological pelvic surgery'. While there must be general agreement on the seriousness of this complication, it is almost impossible to obtain any reliable figures of its incidence, because a very definite proportion pass unnoticed, giving rise to minimal postoperative symptoms, and are, in fact, discovered only in the postmortem room. Newell² reports 6 such cases of ureteric ligation found at autopsy, none of which was even suspected before this examination. Many more such cases have since been recorded.

In a series of 857 hysterectomies performed in London at the Samaritan Hospital between 1952 and 1954, Ostry³ reports injury to 6 ureters, an incidence of 0.7%. Similarly, over a period of 5½ years, Conger *et al.*⁴ discovered 13 ureteric injuries in just under 2,400 major pelvic surgical operations at the Temple Hospital in Philadelphia—a percentage of 0.56. The most carefully controlled series is that of St. Martin,⁵ who carried out routine pre- and postoperative intravenous pyelograms on all of his cases, where necessary cystoscopy and doing retrograde pyelograms between the 6th and 18th postoperative days. In his total of 332 cases he found evidence of ureteral injury in 8 cases (or 2.42%). While these figures are far higher than in the previous series quoted, due allowance must be made for the fact that 5 of St. Martin's 8 cases, considered to be due to minor trauma of the lower ureter, had only temporary hydronephrosis and showed complete restoration to normal, without any treatment, by the 5th week after surgery. Of 3 cases of complete ureteric ligation in his series, 2 were completely asymptomatic. From the same hospital 6 of 20 cases of Wertheim hysterectomy for carcinoma of the cervix showed ureteric injury. Though this figure is far higher than might be anticipated, it is indicative of the high incidence of trauma to ureters in radical pelvic procedures. Lui and Meigs,⁶ analysing a series of 473 radical operations from a group of Boston hospitals, found 45 ureterovaginal fistulae, i.e. 9%. As it is common knowledge that only a proportion of ureteric injuries go on to fistula formation, the actual incidence of ureteric injuries in this series must have been much higher.

Anatomy

In a lecture at the Royal College of Surgeons, Howkins⁷ stressed once again the sites in the pelvis where the ureter is most prone to injury. These are:

1. Where the ureter is crossed by ovarian vessels contained in the ovario-pelvic fold of peritoneum—a healthy distance away in the normal individual, but often dangerously close following inflammation, or where adnexal tumours are present.

2. As the ureter clings to the peritoneum through most

of its pelvic course, inflammatory or malignant disease causing infiltration will make it susceptible to injury.

3. In its medial course in the base of the broad ligament, to reach the ureteric tunnel in Mackenrodt's ligament where it passes beneath the uterine vessels, 1.5-2 cm. from the cervix, the ureter lies in greatest peril during hysterectomies. This is also the common site of strangulation by parametric malignant infiltration.

4. After tunnelling the lateral part of Mackenrodt's ligament, the ureter traverses the anterior part of the same ligament—the so-called pubocervical ligament, at which point it is in special danger in all radical operations for carcinoma of the cervix. According to Grant⁸ it lies closer to the cervix here on the one side than on the other. (Usually closer on the left.)

5. Finally it is stressed that over-enthusiastic needle and suture reperitonealization of raw areas may easily produce piercing, occlusion, or kinking of the ureter, far more commonly than one normally imagines.

Duffy⁹ stresses, and shows radiologically, the very gross downward displacement of the ureters that occurs in severe genital prolapse, particularly in procidentia. This makes them especially vulnerable in operations designed to cure these prolapses or cystoceles, and in vaginal hysterectomies.

Pathology

There is fairly general agreement that injury occurs most commonly during the following operations—in order of frequency:

(1) Radical abdominal hysterectomy, (2) total abdominal hysterectomy, (3) subtotal hysterectomy, (4) vaginal hysterectomy, (5) salpingo-oophorectomy, and (6) intra-ligamentous tumours.

However, there appears to be no gynaecological procedure, apart from the humble dilatation and curettage, that has not been complicated at one time or another by injury to one or other ureter, not excluding anterior colporrhaphies and Fothergill procedures. Nor is the work of the obstetrician entirely free from risk in this regard, for at least 5 cases have followed the application of forceps, and at least 3 cases, Caesarean section. Nor is ureteric injury the prerogative of the inexperienced or poor surgeon. There is unanimous agreement that injury to the ureter may occur in the hands of both the most highly skilled and adept surgeon, and his less able colleagues—perhaps even more so in the former group because of the greater tendency to carry out the many more radical procedures.

Types of Injury

The following list includes all possible types of injury: (a) Partial or complete ligation; (b) crushing of the wall, complete or incomplete; (c) complete division; (d)

resection, accidental or deliberate, as in carcinoma surgery; (e) angulation or kinking; and (f) necrosis due to interference with blood supply.

The incidence of each particular type of injury is very difficult to assess, but in Badenoch's¹⁰ series of 39 cases, more than 50% were found at operation to be due to suture or ligature. With such a high incidence of major injury it seems both illogical and dangerous to base therapy, or withhold therapy, on the premise that one or other less serious type of injury may be the cause of the obstruction.

Symptoms

Symptoms are extremely variable. Pain in the lower abdomen and the affected flank, accompanied by fever in the infected case, with or without some degree of ileus, can all be anticipated, particularly in those cases that are incompletely obstructed. Most authors agree that there may be no symptoms whatsoever that direct attention to the kidney, because loin pain is not a feature. In fact, Patton¹¹ states quite categorically that 50% of all cases of proved ureteric injury have no renal pain at any time. However, where pain is present, the relief following fistula formation is dramatic and complete. Anuria following operation, in the absence of any prerenal cause, is the obvious symptom of bilateral ureteric involvement. On the other hand oliguria, while tending to raise suspicion of unilateral injury, is much more difficult to assess and therefore of less consequence. Fistula, which is incontrovertible evidence of injury in the urinary tract, may occur at any time up to the 3rd or 4th week. In Badenoch's¹⁰ series 20% occurred in the 1st week, due, he thinks, to division or partial inclusion in a suture; 60% occurred in the 2nd week, due to ligation and subsequent sloughing; and the final 20%, which occurred in the 3rd week, are according to him, due to ischaemia. A healthy suspicion on the part of all gynaecologists should make daily renal palpation after all pelvic operations a normal, necessary, never-to-be-forgotten routine; any tenderness of one or other kidney should make intravenous pyelography imperative; unexplained pyrexia, abdominal distension, or ileus, should create a suspicion of ureteric obstruction, complete or incomplete.

Diagnosis

Apart from the symptoms and signs discussed, the only certain method of diagnosis is by pyelography. In St. Martin's⁵ series the injuries were asymptomatic in over 30% of the cases, the diagnosis being made solely by urography. (This is the series, mentioned before, where routine pre- and postoperative urographic studies were carried out.) Usually the ureteric catheter is held up at the site of injury. In some few cases of partial tear or partial injury, the catheter may rarely be manoeuvred past this site and, where this has been achieved, it can be left indwelling as a therapeutic measure. The site of injury is usually up to 8 cm. from the ureteric orifice, being as a rule at a higher level after abdominal surgery than after vaginal surgery.

TREATMENT

Prevention

A. Pre-operative

Wherever there is a possibility of ureteric damage in

major pelvic surgery, preliminary intravenous pyelography should be carried out. In all cases of carcinoma of the cervix this should be mandatory, not only because of possible damage at operation, but also to provide information concerning early ureteric involvement due to spread of the disease. Where intravenous pyelography reveals distortion or obstruction, it seems almost axiomatic for the cautious surgeon to have the ureters catheterized during the course of the operation. This is, in fact, the practice of many gynaecologists, among them Conger and his associates⁴ of Philadelphia, who remove these catheters before the abdomen is closed. In this way they check carefully for any resistance indicative of ureteric occlusion. Landsteiner,¹² Te Linde,¹³ and Thompson and Counsellor¹⁴ of the Mayo Clinic all advise indwelling ureteric catheters as a precautionary procedure in *difficult* gynaecological surgery.

B. At Operation

1. If there is a possibility of damage to the ureter, this structure should be isolated at the bifurcation of the iliac vessels, followed down carefully, and retracted out of harm's way, as a definitive preliminary procedure. Graham and Goligher¹⁵ do this as a routine in operations for excision of the rectum.

2. As severe and at times almost uncontrollable haemorrhage may occur in the pelvis, both arterial and venous, gynaecologists might be well advised to adopt the procedure normally used by urologists in dealing with the slipped renal pedicle, viz. packing the cavity with large packs for 20 minutes by the clock, and then clamping and ligating only the offending vessels.

3. Very careful reperitonealization so as to avoid puncture, occlusion by the stitch, or angulation of the ureter, should be carried out; with a catheter *in situ*, the ureter can be more easily avoided. Howkins⁷ feels that interrupted tacks, producing closure without tension, are far preferable in this respect to a continuous suture.

Injuries Recognized at the Time of Operation

The principles underlying treatment are: (1) Conservation of renal tissue, (2) restoration of normal anatomy as far as possible, and (3) the performance of the simplest procedure that suits the particular case.

(a) Crushing injuries noted at the time are treated by immediate removal of the clamp. Where no obvious injury appears to have been caused to the ureter, a ureteric catheter should be inserted at the end of the operation and should remain indwelling for 8-10 days.

(b) Where definite injury to the ureteric wall is noted, it is preferable to excise the injured area and to do an immediate anastomosis, if possible, preferably using the technique of Hamm and Weinberg;¹⁶ failing this, the ureter should be re-implanted into the bladder. Extraperitoneal drainage is mandatory in either case. Most of the injuries to the pelvic ureter can be dealt with in this way, but where there is marked loss of ureter, reconstruction by using a bladder flap after the method of Boari and Ockerblad may have to be substituted. Although some surgeons recommend transplantation to the unprepared sigmoid or caecum, this method is to be deplored because of the obvious danger of ascending pyelonephritis; temporary cutaneous ureterostomy is to be preferred.

Ligation of the cut ureter, unless a very large segment has been removed, making any other method impossible, cannot be too strongly condemned, as it was by John Bland-Sutton,¹⁷ who stated: 'Kidney tissue is very precious. Many persons get on very well in the world with very little brains, and some with none at all, but no one can live without a certain amount of kidney tissue'. Howkins contends that ligation of a cut ureter is the resort of the poor surgeon, and that it is a dishonest and dangerous shortcut out of a difficult situation. Moreover, according to Graham and Goligher,¹⁸ 5 out of 7 cases with tied ureters required nephrectomy eventually and others, still more unlucky, have reached the postmortem room, showing urinary extravasation and peritonitis as the cause of death.

Injuries Recognized After Operation

(a) *Bilateral*. There is much difference of opinion regarding the management of patients in whom injuries are recognized after operation, both because the patient is, on occasion, very ill and also because of the fact that the exact nature of the obstruction, which is itself so important, can never be ascertained with any degree of certainty until exploration is undertaken. Early diagnosis is most essential. If no urine is present in the bladder after 24 hours, immediate investigation must be undertaken. Cystoscopy and the passage of ureteric catheters will usually define the sites of obstruction.

After operations for repair of the pelvic floor, the removal of *all* the sutures may be all that is required to reverse the anuric condition. After other procedures, providing the patient's general condition is good (and it usually is good 24-48 hours postoperatively) immediate bilateral deligation is recommended by Reisman and his associates,¹³ Badenoch,¹⁰ and Moore.¹⁹ Other surgeons prefer bilateral nephrostomies as a preliminary procedure, with surgery to the lower ureter at a much later date — up to 18 months later. The most impressive report in the literature is that of Reisman and his associates¹⁸ who detail 7 consecutive cases of unilaterally ligated ureters that were successfully deligated between the 5th and 33rd postoperative days, each as a primary procedure. They emphasize the necessity for cooperation between surgeon and urologist (or 2 urologists working together, one abdominally and the other cystoscopically) with ureteric catheters bringing into relief the site of obstruction. The approach is probably better extraperitoneally, through a clean field, rather than through the original approach. Badenoch¹⁰ favours this extraperitoneal approach. Deligation and splinting for 8-10 days seems, in the series mentioned, to have produced, in one operation, uniformly excellent results. While bilateral nephrostomy cannot possibly be justified as a life-saving procedure, unilateral nephrostomy must be accepted, in the very ill patient, as a necessary, but rather inferior, method of treatment. However, according to Reisman¹⁸ none of the patients appears to be so ill, even by the 6th postoperative day, so that the procedure of choice should be immediate deligation, so producing a normal urinary tract in one, and not multiple, operations. The plea that a small number of obstructed ureters may re-open after preliminary nephrostomy merely encourages delay and multiple

procedures that, in the light of Reisman's¹⁸ report and Badenoch's¹⁰ operative findings, would now be hard to justify.

(b) *Unilateral*. There is scant justification for preliminary nephrostomy in those cases where a normally functioning contralateral kidney is present; immediate deligation and splinting being the procedure of choice here. If a large section of the ureter is strictured, excision and re-anastomosis or re-implantation into the bladder is advocated. At this juncture, a word about the technique of re-implantation would not be out of place. All sorts of operative procedures have been devised from time to time in order to prevent reflux up the ureter after ureteroneocystostomy. While Patton²⁰ makes use of the original ureteric orifice, others produce elaborate oblique courses through the muscle coats, nipple anastomoses of different types, and various similar procedures. While Thompson and Counsellor¹⁴ have stated that re-implantation into the dome fails because of regurgitation, Riches²¹ believes that ureteric reflux is no more common using this method than after more ingenious procedures; nor is the method particularly liable to lead to stricture formation at the anastomosis. Certainly there has never been sufficient ureter to carry out Patton's²⁰ procedure in my cases, in all of which anastomosis to the nearest adjacent portion of the bladder, after fishmouthing the ureteric orifice in the manner of Marion, has been performed. A plastic ureteric splint is left indwelling for 10 days, the anastomosis at times being under very marked tension. Neither upper urinary tract dilatation nor pyelonephritis has so far resulted following the use of this simple method.

Ureterovaginal Fistulae

As many gynaecologists feel that a course of watchful inactivity is justified, believing, as Hinman²² did, that 50% of ureterovaginal fistulae heal spontaneously, this condition is one that should be investigated and treated by urologists as soon as it is even suspected. This is all the more so, since the investigation and plastic surgery that follows, are primarily urological procedures. The few ureterovaginal fistulae that do 'heal' spontaneously, heal by stricture formation and autonephrectomy. In many kidney function is irretrievably lost, but even where some function persists, the affected upper urinary tract is certainly not normal, particularly where the fistula has taken many weeks to heal, with attendant bouts of pyrexia and loin pain on the affected side. The urologist, interested as he is in primarily preserving renal function, and in the re-establishment of normal anatomy, will adopt a more active approach to the urinary leak — to the greater comfort of the patient and a reasonable expectancy of normal renal function. Although Thompson and Counsellor¹⁴ report that in as many as 8 out of 34 cases they could find no dilatation proximal to the site of leakage, other investigators have found not only dilatation but also gross pyelonephritis. There is no doubt, as may be seen from the pyelograms here reproduced, that dilatation is extremely rapid, and although kidneys obstructed by ligature for up to 33 and 81 days have recovered function after re-implantation of the ureter into the bladder, it would be foolish to anticipate as a routine such unexpected and happy results. My plea

is for treatment to be undertaken as soon as the condition is diagnosed, and with this Millin²³ concurs. Howkins⁷ advises delay of up to 6 months, during which period the unfortunate patient is either confined to her wet

bed, with a packed vagina, connected to a low suction drainage apparatus, or gets around most uncomfortably in pads and waterproof panties — a form of management that merits the strongest condemnation. While ideal treat-

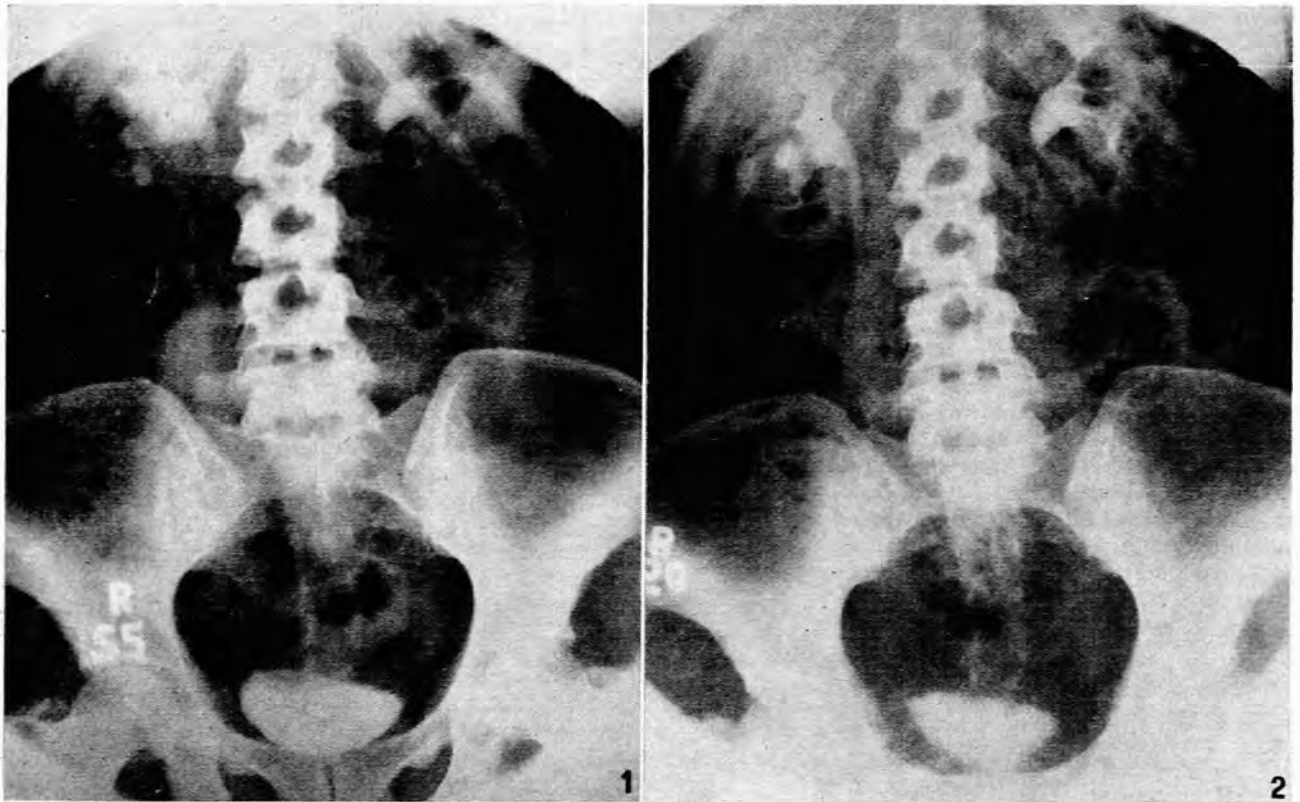


Fig. 1. M.P. Pre-operative (1 month post-hysterectomy); showing hydronephrosis and hydro-ureter. Site of obstruction obscure.
Fig. 2. M.P. Postoperative; showing restoration of function and anatomy.

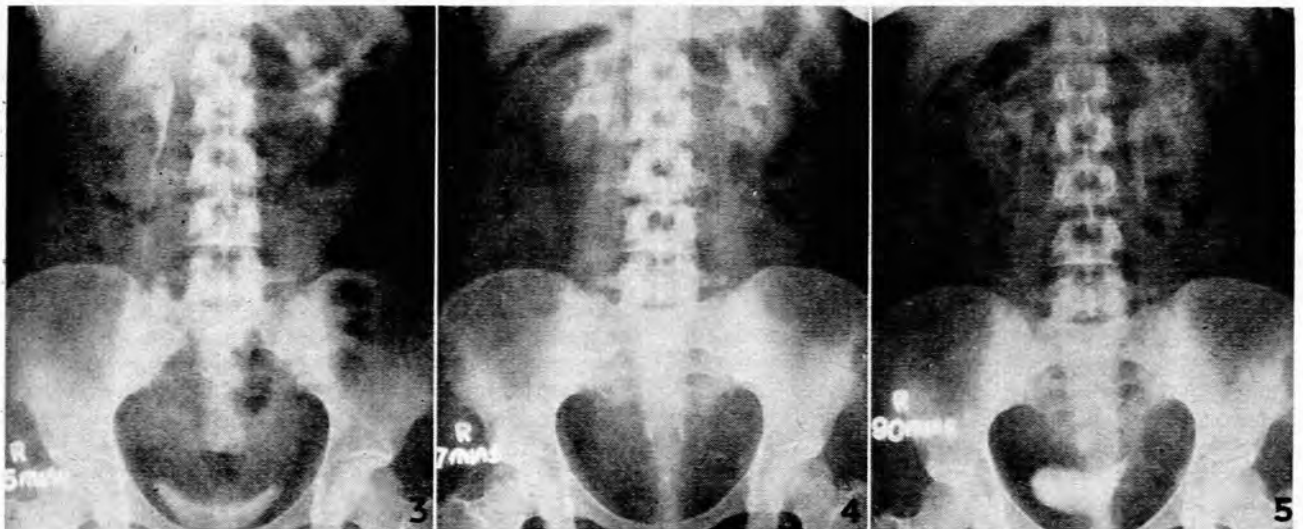


Fig. 3. J.S. Pre-operative; showing gross dilatation on the left side and puerperal dilatation on the right side.
Fig. 4. J.S. Postoperative (1 month); showing rapid return of function.
Fig. 5. J.S. Postoperative (1 month); showing diminished dilatation with marked tenting of the bladder at anastomosis. (This disappears gradually)

ment should consist of re-anastomosis of the ureter, Millin²³ and Badenoch¹⁰ state that this concept is largely theoretical and usually impracticable, and that the best that can be hoped for is a successful re-implantation into the bladder. This is my impression too, and probably that of all urologists who tackle these cases early, since the pelvic mass in which the stricture and fistulous track lie is formidable and better left well alone.

The following case histories of 3 ureterovaginal fistulae illustrate some of the points mentioned—the first 2 cases are routine, simple and straightforward; the third presents a somewhat more complex picture.

Case 1

M.P., aged 37 years, had a right ovarian cystectomy 10 years previously. For the last 2 years she had complained of pain in her right groin with irregularity of her periods. A subtotal hysterectomy and right oophorectomy, for chocolate cyst of the ovary, were carried out 1 month previously without any apparent untoward incident at operation.

About 10 days after the operation she started complaining of pain in her lower abdomen which persisted for 2 days, after which urine started leaking vaginally. With the leakage of urine the lower abdominal pain disappeared.

Intravenous pyelography (1 month after hysterectomy) showed normal function and anatomy of the upper urinary tract on the left side. On the right side there was grossly delayed function with hydronephrosis and hydro-ureter. The level of the obstruction could not be made out (Fig. 1). Cystoscopy and retrograde pyelography showed no efflux on the right side with complete blockage of the right ureter at 6 cm. Attempted retrograde pyelography resulted in reflux of dye back into the bladder.

Operative findings (5 weeks after hysterectomy): The right ureter was found to be grossly dilated, disappearing into a mass of scar tissue at the level of the iliac bifurcation. The ureter was divided just above the bifurcation and re-implanted into the bladder, at the most convenient site on the dome and under slight tension, over a No. 3 polythene tube, using the technique of Marion.

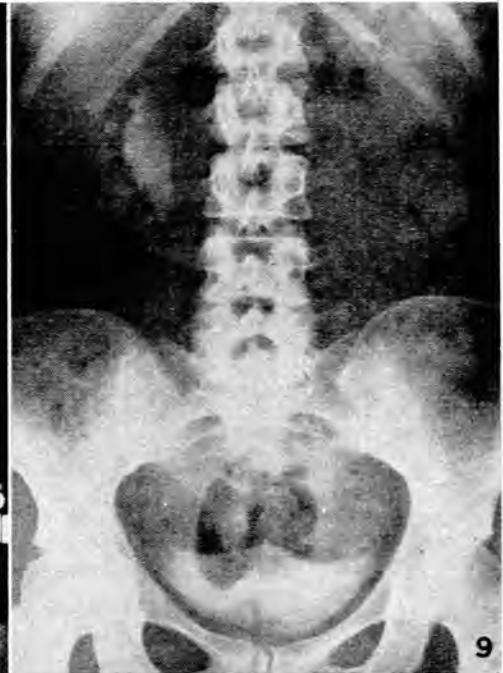


Fig. 6. G.S. Pre-operative; showing gross dilatation of the minor calyx of the right kidney with severe depression of function.

Fig. 7. G.S. Retrograde pyelogram showing dye extravasation through a small cavity into the vagina.

Fig. 8. G.S. Postoperative restoration of good function.

Fig. 9. G.S. Postoperative restoration of near-normal anatomy. Note the congenitally dilated atonic kidney pelvis.

Postoperative films show normal function and anatomy on the right side (Fig. 2).

Case 2

J.S., aged 26 years, had 3 Caesarean sections over the last 6 years for toxæmia of pregnancy. The last one was performed 3 weeks previously and, according to her gynaecologist, was a very difficult procedure with a bleeding vessel on the left side of the pelvis constantly slipping away. This bleeding vessel was finally underrun to control the haemorrhage.

Her postoperative course was grossly pyrexial despite anti-

biotics, and she complained of intermittent pain in the left loin from the 4th day onwards. Vaginal urinary leakage commenced about 10 days postoperatively, from which time the pyrexia had settled.

Physical examination revealed a tender, slightly enlarged, left kidney with tenderness over the course of the left ureter down to the level of the anterior superior iliac spine.

Intravenous pyelography (3 weeks after Caesarean section) showed normal function on the right side and grossly delayed excretion on the left. The right kidney and ureter showed normal puerperal dilatation, and the left kidney and ureter showed evidence of marked obstruction, the exact site being obscure (Fig. 3).

Left retrograde pyelography showed obstruction at 7 cm. with extravasation of dye outside the ureter. Ureteroneocystostomy was performed 5 weeks after the birth of her child. The left ureter was found to be dilated down to the brim of the true pelvis where it disappeared into a mass of tissue extending down to the broad ligament. This ureter was divided above the mass and re-implanted into the dome of the bladder, over a polythene splint, under very considerable tension. Despite this tension, which is visible in the postoperative pyelograms shown, there was rapid return of function (Fig. 4) and marked diminution in dilatation of the upper urinary tract, 1 month after re-implantation (Fig. 5).

Case 3

G.S., aged 40 years, complained of urinary incontinence for 2 weeks and gave a complicated history.

She was last well about 4 months previously when a hysterectomy was performed for persistent menorrhagia. Her gynaecologist reported that a fibroid uterus and a right cystic ovary were removed and that there was more than average oozing throughout the operation, particularly during wound closure. Her convalescence was quite uneventful and she was discharged after 11 days. Two months later she complained of severe lower abdominal pain of rather sudden onset without any other sign than abdominal distension. Diagnosed as a case of subacute intestinal obstruction, she was re-operated on for adhesions, which were divided, the surgeon finding that the site of right oophorectomy was adherent to the rectal wall. Following this operation she was well for about 5 weeks, when she experienced severe burning high up in the vagina for a week. This burning was relieved when urinary leakage commenced *per vaginam*; she had been incontinent since. Intravenous pyelography (4 months after her hysterectomy) showed a normal left upper urinary tract, both functionally and anatomically. On the right side there was poor concentration though the dye appeared early, with very gross hydrocalycosis. Neither pelvis nor ureter showed throughout the series (Fig. 6).

Retrograde pyelography showed an obstructed right ureter 7 cm. from the ureteric orifice. A small cavity communicating with ureter and vagina was outlined (Fig. 7). Speculum examination showed the fistulous opening in the vaginal vault on the right side.

Right ureteroneocystostomy was performed 4½ months after hysterectomy. At the operation a thickened, grossly dilated, ureter was seen to disappear into a mass of tissue in the neighbourhood of the superior vesical pedicle. The ureter was cut across above the mass and re-implanted into the side of the bladder with minimal tension.

Postoperative films (5 months after the operation) showed normal function (Fig. 8) with a congenitally large atonic pelvis. It is probable that renal function was conserved so long because of this atonic pelvis relieving the calyces of maximal back-pressure after obstruction had commenced (Fig. 9).

SUMMARY

1. The vulnerability of the pelvic ureter in gynaecological surgery is stressed.

2. The aetiology, pathology, diagnosis, and management of ureteric injuries at all stages, are discussed.

3. A plea is made for greater awareness which will lead to earlier recognition of injury, earlier definitive urological care, and restoration of renal function.

4. Three cases of ureterovaginal fistulae are specifically quoted to illustrate some of the above points.

REFERENCES

- Ingersoll, F. M. and Meigs, J. V. (1945): *New Engl. J. Med.*, **232**, 335.
- Newell, Q. U. (1939): *Ann. Surg.*, **109**, 981.
- Ostry, E. I. (1959): Quoted by Badenoch, A., *loc cit.*¹⁰ Clinical report from Samaritan Hospital for Women, London. Privately printed.
- Conger, K., Beecham, C. T. and Horrax T. M. (1954): *Obstet. and Gynec.*, **3**, 343.
- St. Martin, E. C., Tritchel, B. E., Campbell, J. H. and Locke, C. M. (1953): *J. Urol. (Baltimore)*, **70**, 51.
- Lui, W. and Meigs, J. V. (1955): *Amer. J. Obstet. Gynec.*, **69**, 1.
- Hawkins, J. (1954): *Ann. Roy. Coll. Surg. Engl.*, **15**, 326.
- Grant, J. C. B. (1944): *A Method of Anatomy*, 3rd ed., p. 348. Baltimore: Williams & Wilkins.
- Duffy, D. B. (1957): *Brit. J. Urol.*, **29**, 26.
- Badenoch, A. (1959): *Proc. Roy. Soc. Med.*, **52**, 101.
- Patton, J. F. (1952): *J. Urol. (Baltimore)*, **67**, 852.
- Landsteiner, E. K. (1954): *Surg. Gynec. Obstet.*, **98**, 653.
- Te Linde, R. W. In Falk, H. C. and Bunkin, I. A. (1954): *Obstet. and Gynec.*, **4**, 4.
- Thompson, G. J. and Counsellor, V. S. (1951): *J. Int. Coll. Surg.*, **15**, 479.
- Graham, J. W. and Goligher, J. C. (1954): *Brit. J. Surg.*, **42**, 151.
- Hamm, F. C. and Weinberg, S. R. (1957): *J. Urol. (Baltimore)*, **77**, 407.
- Bland-Sutton, J. In Carter, R. G. (1954): *Ibid.*, **71**, 200.
- Reisman, D. D., Kamholz, J. H. and Kantor, H. I. (1957): *Ibid.*, **78**, 363.
- Moore, T. D. (1948): *Ibid.*, **59**, 712.
- Patton, J. F. (1939): *Ibid.*, **42**, 1021.
- Riches, E. (1959): *J. Roy. Coll. Surg. (Edinb.)*, **5**, 22.
- Hinman, F. (1940): *West. J. Surg.*, **48**, 486.
- Millin, T. J. (1949): *Proc. Roy. Soc. Med.*, **42**, 37.