SOME USES OF THE ILEUM IN UROLOGY*

BY

L. N. PYRAH, Ch.M., F.R.C.S.

Department of Urology, University of Leeds, Leeds General Infirmary, and St. James's Hospital, Leeds

In this paper some operations are described in which an isolated loop of ileum has been incorporated into the urinary tract in order to assist in its reconstruction or its remodelling, for the relief of a variety of pathological conditions (Fig. 1); after the isolation of the loop, intestinal continuity has been restored. The conditions for which such a procedure has been employed in the Department of Urology at Leeds are:

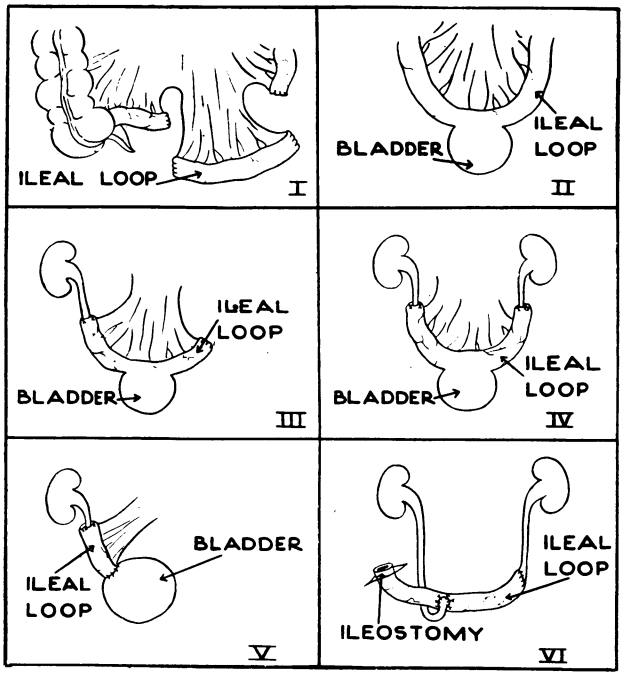

FIG. 1.—Schematic drawings to illustrate the procedures in which the ileal loop is used to reconstruct or remodel the urinary tract. I, Isolation of loop. II, Ileal loop anastomosed to the bladder. III, Ileal loop used to enlarge a contracted bladder and to relieve a hydronephrosis of a remaining kidney. IV, Ileal loop used for reimplantation of the two ureters into the bladder. V, Ileal loop used to replace the excised part of a ureter. VI, Ileal loop used to make an artificial bladder draining through an ileostomy.

	No. of Cases
To enlarge a contracted bladder	7
To replace part of a ureter excised for tumour or destroyed by injury	3
To enlarge a healed, contracted, tuberculous bladder and to correct an associated increasing hydronephrosis of a remaining kidney	3
To reimplant into the bladder ureters previously transplanted into the colon	2
To act as an artificial bladder	6
To replace an excised bladder, the ileal loop being anastomosed to the urethra	2
	23

A loop of lower ileum has been selected for these procedures partly because of its convenient anatomical position and structure. A loop of the required length can be isolated, and its blood supply maintained through its system of vascular arcades without impairment of its vitality, and continuity of the intestine can be restored above and below the isolated loop. The conveniently long mesentery allows the loop to be brought down to the pelvis into apposition with the bladder, or to be moved into the lateral part of the abdomen into the line of the ureter, without endangering its blood supply. The peristaltic movements and the power of contraction of the loop continue even when a segment is isolated. The mucosa of the loop continues to secrete mucus after its incorporation into the urinary tract, and that may occasionally be inconvenient. Because the ileum is a tube, a loop of it can be used as a conducting channel for urine, and because it is capacious it can be used as a reservoir to hold urine.

Advances in surgical technique in recent years, the greater control of infection by antibiotics and sulphonamides, the better understanding of surgical shock and fluid balance, and the great improvements in anaesthesia allow the surgeon to carry through longer and more complex operations with comparative safety; the employment of an isolated loop of ileum for the various purposes in the urinary tract which are described below is now a rational, safe, and in our hands a successful surgical procedure, though it must be regarded as being still on trial.

Preparation of the Ileal Loop

In all these procedures the isolation of the loop is the common factor, and it is the first stage in the operation. The patient is prepared by being given a low-residue diet and either 5 g. of streptomycin in 100 ml. of water daily by mouth, or 250 mg. of chlortetracycline four-hourly on the four days before operation in order to reduce the bacterial content of the intestine. The colon is washed out on the two mornings before the operation and an enema is given on the evening before. When the abdomen has been opened the loop of ileum is selected, the lower end of the loop being about 4 in. (10 cm.) above the ileo-caecal valve. The mesentery close to the intestinal lumen is incised at right angles to the intestine, dividing between ligatures one or two vascular arcades. Another opening in the mesentery is made at a suitable distance from the first, in order to provide an adequate length of loop for the required purpose. The intestine is divided between clamps at the selected places and intestinal continuity is restored by end-to-end anastomosis. The isolated loop is then available for whatever purpose the surgeon has in mind.

Ileal Loop to Enlarge a Contracted Bladder

Although the operation of ileocystoplasty had been carried out occasionally during the last 50 years, it was only in 1950 that it was advocated by Couvelaire, of Paris, as a suitable procedure for relieving the contracted bladder of healed tubercle; these bladders, which may be so contracted that their capacity may vary from 4–5 oz. (114–142 ml.) to a capacity almost nil—when the posterior urethra may also become dilated (Cibert *et al.*, 1954)—give rise to intolerable diurnal and nocturnal frequency of micturition and often to urinary incontinence, and sometimes to a harmful ureteric reflux also. In this series of seven cases the operation, in addition to its having been performed for a healed tuberculous bladder (one case), has been done for the fibrous type of contracture following long-standing recurrent cystitis. The operation has been performed by some surgeons for Hunner's ulcer, but with only temporary success, and it would appear that good results are obtained in those bladders in which the mucosa is soundly healed, a stable end-state of the bladder wall having been reached and active disease being absent.

The operation has been carried out in this series in seven patients. The abdomen is opened and the loop is prepared. A transverse incision is made through the peritoneum covering the posterior wall of the bladder some distance below

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its vault, and the peritoneum is dissected up and down to expose an adequate area of the detrusor. An anastomosis, as large as possible having regard to the size of the bladder, is then made between the centre of the loop of the ileum and the bladder wall. The peritoneum is stitched over the anastomosis and the abdomen closed, leaving a tube in the cave of Retzius.

Case 1

I first did this operation on a female patient aged 38. For 18 years she had had recurrent attacks of cystitis, followed after five years by very persistent frequency of micturition and suprapubic pain. She first came under my care in 1949, when she had frequency, half- to one-hourly in the daytime and eight to ten times at night. The urine sometimes contained pus cells and *Bact. coli*, but more often was sterile. Pyelograms showed normal kidneys. On cystoscopy there were localized red patches of inflammation on the left lateral wall and vault of the bladder, suggesting a type of interstitial cystitis. She received treatment for three years by distension of the bladder under anaesthesia and by light diathermy to the inflamed areas, but she always relapsed. The capacity of the bladder was usually 3 oz. (85 ml.), but during short phases of improvement it increased to 5–6 oz. (142–170 ml.).

I did an ileocystoplasty in January, 1952. Convalescence was normal; there was no leakage of urine from the wound or any wound infection. After recovery from the operation micturition was a little slower than normal, but frequency was reduced after a few weeks to three- or four-hourly by day and occasionally once at night. Intravenous pyelograms are normal and the urine is sterile. The other cases in the series have benefited similarly.

Comment

The operation of ileocystoplasty is a major surgical procedure, but it has been very well borne. In only one case in the series was there a temporary leakage of a small amount of urine for four days, but this did not lead to any wound infection, prolong the convalescence, or mar the end-result.

Micturition is not always perfect for some weeks after the operation, and there may be at first a sense of imperfect emptying of the bladder, which the patient can overcome by gentle manual pressure on the lower abdomen. Radiographic studies of the bladder after ileocystoplasty show that the loop can be filled quite easily with opaque medium and that a wide stoma has been preserved. Peristaltic contractions of the intestinal loop continue. Micturition appears to be biphasic in that, when the bladder contracts, some of the opaque medium enters the intestinal loop, which is then stimulated to contract; this mechanism may be responsible for the early delay in micturition.

Cystoscopic examination has shown that the anastomosis has healed well and there has been no evidence of contracture. The folds of the ileal loop have retained their normal appearance. The urine has been sterile in four cases, but in one there is a mild intermittent *Bact. coli* infection. Flakes of white inspissated mucus are always passed in the urine, and the reason for this should be explained to the patient.

It has been suggested that the intestinal loop may act as a diverticulum and may ultimately promote or perpetuate infection and even encourage stone formation. Although the intestinal loop is, in fact, a pouch leading from the bladder, it differs in many ways from an acquired diverticulum of the bladder, which may complicate prostatic enlargement or fibrosis. In an acquired diverticulum the wall is fibrous, whereas the intestinal loop of an ileocystoplasty has a muscular wall which has been demonstrated to be capable of active and vigorous contraction. An acquired diverticulum usually has a narrow neck and there may be associated muscular spasm, whereas in ileocystoplasty the stoma into the bladder can be made quite wide. Moreover, an acquired diverticulum usually complicates a bladder-neck obstruction of some kind; such obstruction has not existed in the cases of ileocystoplasty in this series.

Other cases in which we have performed the operation have been recorded elsewhere (Pyrah and Raper, 1955). The late results to date have been very satisfactory, and these cases have been among our most grateful patients.

Ileum Used to Replace Part of a Ureter

In the past the treatment for tumours of the ureter and for severe irreparable injuries of the ureter has usually been nephro-ureterectomy. Tumours which are shown by repeated radiography to be solitary, whether simple or malignant, and unassociated with tumours higher up the ureter or in the renal pelvis, may be treated by excision of the ureter, from a level above the tumour down to and including the ureterovesical orifice, with replacement of the removed segment by a loop of ileum. The central segment of the ureter, which is the seat of a tumour, cannot be treated by the interposition of a loop of ileum. A loop of ileum has been used to replace a segment of ureter in three cases of ureteric tumour.

Case 2

The patient, a man aged 52, had had three attacks of haematuria associated with left-sided renal pain. Investigation showed that the urine was sterile and the blood urea-nitrogen normal; the radiographs revealed a left-sided hydronephrosis of moderate degree and there was a filling defect in the lower half of the left ureter which appeared to be due to an obstruction resulting from a tumour situated a few centimetres from the bladder. On cystoscopy, blood was seen coming from the left ureteric orifice. A diagnosis was made of tumour of the left pelvic ureter.

At operation (February 2, 1953) the left ureter was exposed extraperitoneally through a left paramedian incision. A firm tumour, 5 cm. long and frankly malignant, was found in the wall of the lower ureter extending to within 1 in. (2.5 cm.) of the bladder. Five inches (12.5 cm.) of the ureter was excised extraperitoneally, including the tumour and the ureteric orifice. Since it was impossible to reimplant the divided ureter into the bladder, an ileal loop of the appropriate length was constructed and brought out through an opening in the lateral part of the peritoneum into the position previously occupied by the excised ureter. The lower end of the loop of ileum was anastomosed to the bladder, while the divided end of the ureter was implanted into the upper end of the loop. The opening in the peritoneum was sutured to the back and front of the ileal loop to prevent herniation of coils of intestine.

The patient had a normal convalescence. Post-operative pyelograms showed a reduction in the size of the hydronephrosis; cystoscopically the anastomosis of the ileum to the bladder showed perfect mucosa-to-mucosa healing. The tumour was found to be a poorly differentiated transitional-cell carcinoma. Nine months later the patient had recurrent haematuria caused by a recurrent tumour in the bladder 1 in. (2.5 cm.) to the inner side of the old ureteric orifice; the tumour was treated by diathermy. Fifteen months after the operation he developed metastases in the posterior part of the abdomen and he died 18 months after the operation. There was nothing in the post-operative course to suggest that he would have done better following a nephro-ureterectomy.

Ileal Loop Used to Enlarge a Healed Contracted Tuberculous Bladder and Correct an Increasing Hydronephrosis of the Remaining Kidney

The contracted healed tuberculous bladder, the end-result of extensive tuberculous ulceration, after nephro-ureterectomy and streptomycin therapy have been used in the treatment of the affected kidney, may often endanger the remaining healthy kidney by causing a spastic or fibrous contraction of its ureteric opening into the bladder; there may follow a gradually increasing hydronephrosis and hydroureter. In three such cases in which the urinary tract was pus- and tubercle-free, the bladder being contracted from

fibrosis and no longer from active tubercle, I have used an ileal loop to enlarge the contracted bladder and at the same time to relieve the hydronephrosis by anastomosing the ureter to the end of the loop.

Case 3

The patient, a man aged 31, had a left nephro-ureterectomy for tuberculous kidney in May, 1950, the bladder being then extremely ulcerated; later he was given sanatorium treatment and 1 g. of streptomycin with P.A.S. daily for 90 days. In December, 1950, the urine was pus- and tubercle-free, but he had hourly frequency by day and three to four times at night. Intravenous pyelograms showed a normal right kidney, but there was early dilatation of the lower ureter. During 1951 and 1952 he gradually developed hydronephrosis and hydroureter, which during 1953 became worse; the frequency increased to half-hourly by day and five or six times at night, and there was sometimes nocturnal incontinence. The blood urea-nitrogen was normal. On cystoscopy the bladder had a capacity of only 3 oz. (85 ml.), but the mucosa was completely healed.

The orthodox treatment for this condition has hitherto been a uretero-colic anastomosis in order to relieve the hydronephrosis. In May, 1953, an ileocystoplasty was done and the dilated ureter was anastomosed to one end of the loop. An intravenous pyelogram six months after operation showed reduction in the size of the hydronephrosis, and a cystogram showed a filling of the ileal loop but no reflux up the ureter. His clinical condition was satisfactory, he was back at work, frequency was normal in the daytime and only once at night. The urine was sterile but contained flakes of mucus.

Ileal Loop Used to Reimplant the Ureters into the Bladder

If it is desired to reconnect the ureters to the bladder when they are too short for direct implantation, a loop of ileum may be used. Such a procedure may be suitable following injuries to both ureters, portions of both having been destroyed, or if it is desired to reimplant into the bladder ureters which have been previously diverted to the skin or anastomosed to the colon. I have carried out this procedure in two cases in which uretero-colic anastomosis had been unsatisfactory because of severe attacks of ascending renal infection that threatened to invalidize the patient.

Case 4

The patient, a woman aged 42, had had a very large vesico-vaginal fistula following an operation for uterine prolapse in 1944, after which part of the bladder wall had sloughed. Several attempts had been made to close the fistula, and the patient was referred with a view to transplantation of the ureters into the colon.

In October, 1951, a bilateral uretero-colic anastomosis was performed, using a direct mucosa-to-mucosa technique. There was a rapid recovery from the operation, but a few weeks later the patient was readmitted to hospital with severe left-sided pyelitis; there were three further severe recurrent attacks of renal infection associated with hyperchloraemic acidosis during the next 20 months. The prolonged character of the attacks of infection was such that they were accompanied by a good deal of invalidism, and it was thought that permanent damage to the kidneys might result if further attacks supervened. Moreover, the vesico-vaginal fistula was now much smaller than when urine was passing through it, and it seemed possible that it could now be closed. Twenty-one months after the uretero-colic anastomosis the vesico-vaginal fistula was repaired: after waiting six months to make sure that the bladder was soundly healed the ureters were detached from the sigmoid and implanted into a long U-shaped ileal loop, the middle of which was anastomosed to the bladder; the operation was carried out in two stages. The patient made a good recovery; there has been no further attack of renal infection, the urine is sterile, and there is no hyperchloraemic acidosis.

Ileum Used as an Artificial Bladder

A long ileal loop may be made to serve as a collecting-tube for urine, the two ureters being transplanted into it and the lower end of the ileum being brought through the abdominal wall as an ileostomy opening. A Rutzen bag can be attached to the abdominal wall and the patient can be kept dry. This procedure has been used by Bricker (1950) to collect the urine after pelvic exenteration for extensive cancer. Wells (1953) favours this operation as an alternative to uretero-colic anastomosis, following cystectomy for carcinoma of the bladder, in order to avoid ascending renal infection and hyperchloraemic acidosis.

The indications which we have used for the operation, or where it would seem to be suitable, are: (1) Severe urinary incontinence in patients with spina bifida in whom the anal sphincter is partly or totally paralysed and who are therefore unfit for uretero-colic anastomosis. (2) Patients with late ectopia vesicae untreated in childhood, who have suffered recurrent attacks of pyelitis, resulting in grossly impaired renal function; the risk of dangerous hyperchloraemic acidosis following uretero-colic anastomosis is considerable in such cases. (3) Cases of total cystectomy for carcinoma of the bladder in which renal function is poor and in which severe hyperchloraemic acidosis may be expected to develop. (4) Patients in whom uretero-colic anastomosis failed, who have had recurrent attacks of renal infection with severe hyperchloraemic acidosis with or without potassium deficiency.

Case 5

The patient, a man aged 42, had spina bifida with urinary and faecal incontinence, anaesthesia in the saddle area, and hypoaesthesia of the feet. Faecal incontinence was largely controlled by constipation. At the age of 7 he was fitted with a rubber urinal, and gradually the pressure from this produced a fistula at the peno-scrotal junction. He found he could best control the incontinence through the fistula by placing a spigoted catheter bandaged to the penis through the fistula, removing the spigot in order to micturate; this was possible because the penis and scrotum were anaesthetic. During the ensuing years the pressure of the urethral catheter caused a gradual enlargement of the urethral orifice, and in order to achieve continence the patient increased the circumference of the catheter by wrapping insulating tape round it. When he was seen in the out-patient department he had a large opening at the base of the penis, and he was incontinent by reason of being no longer able to keep the catheter securely in position. The penis was reduced to a fibrous remnant and there was a large hole at the base of the scrotum that would admit a thumb. The anal sphincter being lax, transplantation of the ureters into the colon was impossible. The ureters were therefore implanted into a long ileal loop, the end of which was brought out in the right iliac fossa as an ileostomy; the urine has been collected in a Rutzen bag and complete continence has been achieved.

In the cases in which we have employed it the artificial bladder of this type has been highly satisfactory and a great boon to the patient.

Ileum Used as an Artificial Bladder Voiding per Urethram

In the cases referred to in the previous section the ureters were transplanted into an isolated loop of ileum draining by way of an ileostomy opening, because an incontinent anal sphincter or badly functioning kidneys made the operation of transplantation of the ureters into the colon unsuitable. I have not carried out this operation for cases in which the bladder has been removed for carcinoma, though this procedure has been advocated by Wells (1953), on account of the risks of ascending renal infection and consequent hyperchloraemic acidosis following uretero-colic anastomosis; in such a procedure the disadvantages of an ileostomy opening (unassociated with electrolyte imbalance) have to be weighed against a somewhat greater risk of renal infection and electrolyte imbalance when the ureters are transplanted into the

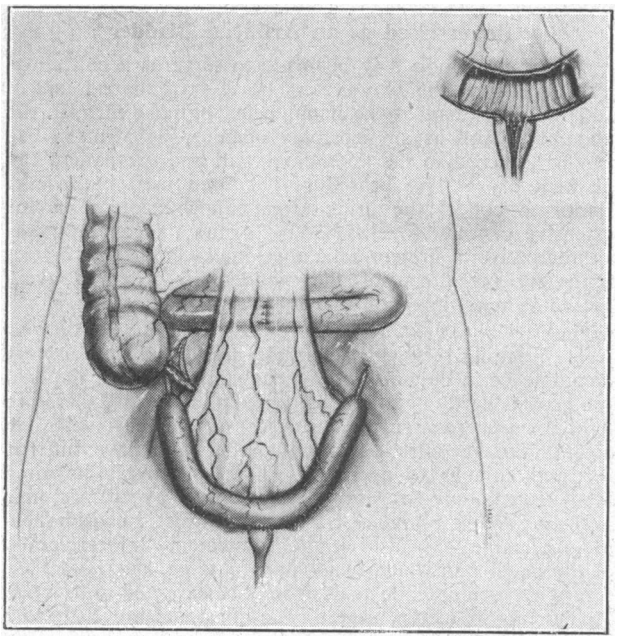

FIG. 2.—A long isolated loop of ileum to which the ureters have been anastomosed after total cystectomy is joined at its centre to the prostatic urethra, forming an artificial bladder emptying *per vias naturales*.

faeces-laden colon. The decision depends upon the views and experience of the individual surgeon. If, however, the centre of the ileal loop (to which the ureters have been joined) can be anastomosed to the divided urethra after the bladder has been removed, the patient may achieve urinary continence, with micturition through the natural channel, and probably avoid the main risks of electrolyte imbalance.

I have carried out this operation for carcinoma of the bladder in two cases. In the first case the operation has been successful. The second patient died four weeks after operation from a sudden and unexpected pulmonary embolism after an apparently normal convalescence; necropsy showed that the technical result was completely satisfactory. The first case is described.

Case 6

The patient, a man aged 54, on investigation for recurrent haematuria, was found to have multiple papillary tumours of the bladder, which biopsy showed to be low-grade papillary carcinoma; the tumours were treated by perurethral resection and diathermy. In September, 1953, he had multiple recurrences which were treated by diathermy and then by radium placed in the centre of a distended Foley catheter and inserted into the bladder through a perineal urethrostomy. During 1954 there were further recurrences with persistent haematuria, and further cystodiathermy treatment was given. In December, 1954, a considerable area of radionecrosis in the vault of the bladder was seen. The persistent bleeding indicated the need for cystectomy.

Total cystectomy was performed across the peritoneal cavity. The bladder, with the seminal vesicles and the proximal two-thirds of the prostate, was removed, the prostate being sectioned transversely so as to leave its distal third for anastomosis to the ileum. An ileal loop 22 in. (56 cm.) in length was prepared and the ureters were anastomosed by a direct mucosa-to-mucosa technique to the ends of the loop. The centre of the ileal loop was anastomosed to the prostatic urethra, using two rows of sutures. The broad stump of the prostate was big enough to allow a row of stitches to be inserted to secure the seromuscular coat of the ileum to the fibromuscular tissue of the prostate posteriorly. A small opening was then made into the ileum through all layers, large enough for construction of an anastomosis between the ileum and the urethra by mucosa-to-mucosa apposition, first posteriorly, then anteriorly. Finally, the seromuscular coat of the ileum was sutured to the stump of the prostate in front of the actual anastomosis. A catheter was passed along the urethra into the ileum, where it was retained for ten days.

Convalescence was accompanied by a slight urinary leak, but this did not mar his progress. When the catheter was removed on the tenth post-operative day, normal micturition was established. In a very few days the patient learnt to know when the new "bladder" was distended, and slight straining caused an easy act of micturition. There is complete control (since the external vesical sphincter is intact) during the day, but it is not yet complete at night. The post-operative "cystogram" is shown in Fig. 3, and Fig. 4 shows the presence of a small amount of residual urine. His condition is satisfactory nine months after operation.

Physiological Considerations

At the beginning of this paper I referred to the anatomical suitability of a loop of ileum for the operations that have been described. I now refer briefly to some factors in the physiology of the ileum which had to be investigated before we could accept these operations as being sound.

It was thought desirable to study the behaviour of the urinary electrolytes when urine was brought into permanent contact with the mucous membrane of the ileum. When urine is in permanent contact with the *colon*, we have shown that chloride ions are absorbed from the urine into the blood stream and sodium ions are also absorbed but to a less extent (Parsons, Powell, and Pyrah, 1952; Parsons, Pyrah, Powell, Reed, and Spiers, 1952; Pyrah, 1954); there is, in fact, a differential absorption of electrolytes across the colonic mucous membrane into the blood stream, the absorption of acid ions exceeding that of alkaline ions. If the renal tubules are healthy no harm appears to result from this, but if the renal tubules have been damaged by ascending infection and their function has been impaired a hyperchloraemic acidosis results which, so long as it is of minor degree, may not produce clinical symptoms; but dangers exist for the patient if further renal damage gradually follows, and in some instances hyperchloraemic acidosis in cases of uretero-colic anastomosis has led to impaired health and in some cases to drowsiness and fatal coma.

When the *ileum* has been incorporated into the urinary tract we have not, in our series, found any instances of

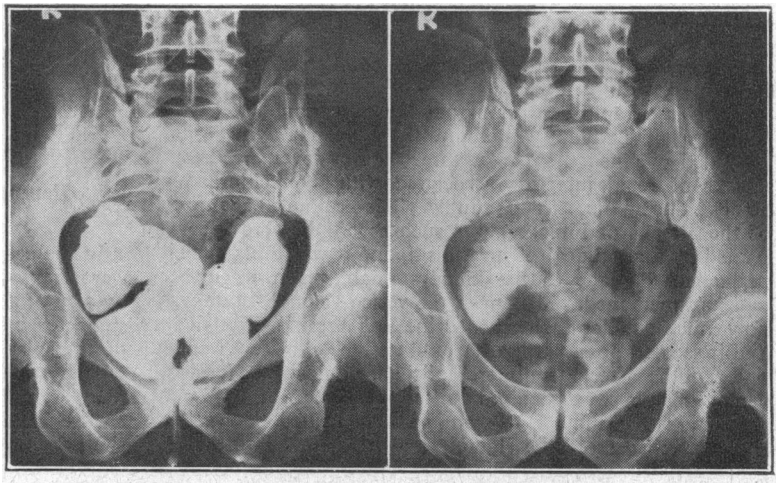

FIG. 3 FIG. 4

FIG. 3.—Case 6. "Cystogram" of the artificial bladder made from a 22-in. (56-cm.) loop of ileum; the loop was anastomosed to the urethra. FIG. 4.—Case 6. The artificial bladder has been voluntarily evacuated, leaving a small amount of residual urine.

hyperchloraemic acidosis. Occasional instances have been reported in the still scanty literature, which has been reviewed elsewhere (Pyrah and Raper, 1955; Pyrah, Care, Reed, and Parsons, 1955), but such examples can sometimes be explained by collateral circumstances such as urinary obstruction. Biochemical investigations carried out in the Department of Urology at Leeds have shown, by a series of perfusion experiments using artificial urine, that chloride and sodium ions in almost equal proportions can pass across the mucous membrane of an isolated excluded bladder, and also across that of a bladder to which a loop of ileum has been joined, into the blood stream and also in the reverse direction: there is a small net uptake of both ions equally. Only in the case of potassium ions does there seem to be any danger: if in the fluid perfusing the ileum the potassium concentration is more than three times that in the blood plasma, the cellular potassium being normal, there is a net movement of potassium ions from the lumen of the ileum into the blood plasma. If kidney function is greatly impaired, an elevation of the blood potassium may result, which could be dangerous; with the average healthy kidney in the cases which we have operated on, however, we have not so far clinically detected, nor found biochemically, any dangerous rise of serum potassium (Pyrah, Care, Reed, and Parsons, 1955).

Conclusion

The cases which I have described demonstrate that a loop of lower ileum is suitable anatomically and physiologically for incorporation into the urinary tract. There appears to be little if any risk of hyperchloraemic acidosis, but further experience is needed before we can be completely happy about the absorption of potassium from the loop. The cases for which I have used an ileal loop have been very worth-while, in that troublesome symptoms such as frequency of micturition have been relieved, kidneys have been preserved which would gradually have deteriorated or would have had to be excised, and, finally, a procedure for a true artificial bladder, with micturition *per vias naturales*, has been developed. Further experience of more cases is needed before the final place of such operations in surgery can be assessed.

I wish to thank my colleague, Mr. F. P. Raper, for permission to include the description of Case 5.

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Daily visiting by mothers of their children in hospital, and assistance with their nursing, are now accepted as valuable in many hospitals. There remain a number, however, where there is little enthusiasm for the practice or even opposition to it. According to the annual report for the year 1954–5 of the Royal Alexandra Hospital for Children, Sydney, Australia, daily visiting was introduced into some of the wards of the hospital during the twelve months covered by the report. Difficulties arose in the larger wards of obsolete design, as there the sisters-in-charge were too busy to be able properly to supervise free visiting by the mothers. In the smaller wards, however, the scheme for daily visiting is progressing satisfactorily, and good understanding between the mothers and the nursing staff has been established. It is intended, the report states, to extend the scheme as far as possible.

CLINICAL TRIAL OF "DORIDEN," A NEW HYPNOTIC

WITH NOTE ON USE OF RANKING METHODS IN ASSESSING THERAPEUTIC EFFECT

BY

M. RUSHBROOKE, M.B., B.S.

E. S. B. WILSON, M.B., B.S.

J. D. ACLAND, B.M., B.Ch.

AND

G. M. WILSON, M.D., F.R.C.P.Ed., M.R.C.P.

From a General Practice in Sheffield and the Department of Pharmacology and Therapeutics, University of Sheffield

The clinical trial of a new hypnotic presents several difficulties. Tests in a general hospital are often unsatisfactory and difficult to plan, since in most cases sleeplessness diminishes as familiarity with new surroundings develops and the acute stage of an illness passes. Insomnia is common in the elderly, and the assessment of a hypnotic is clearly most valuable if it can be done while the patients are living at home. In such circumstances it is impossible to measure accurately either the time in getting off to sleep or the duration of sleep. Nevertheless, patients can usually make a definite statement on whether they have had a restful night, and can compare how they have slept on different occasions. Accordingly, if suitable precautions are taken a reliable assessment should be possible in a general practice.

A trial of α-phenyl-α-ethyl glutarimide ("doriden") has been attempted under such conditions. Animal experiments had not demonstrated any serious toxic effects (Gross, Tripod, and Meier, 1955). Preliminary observations, in which single doses of either 0.25 g. or 0.5 g. of doriden were given, suggested that the larger amount produced approximately the same effect as 0.2 g. of cyclobarbitone. The results of Lanz (1955) and of Müller and Rohrer (1955) also provided evidence that 0.5 g. of doriden was a suitable hypnotic dose. The investigation was designed in two parts. In the first place a controlled trial of the action of the drug as a hypnotic was carried out, and, secondly, the effect of courses of doriden was studied both in hospital and in general practice, with particular reference to the development of undesirable or toxic features.

Design of Trial

Twenty patients living at home agreed to take part in the trial. The experimental design required a multiple of six subjects, 18 being a convenient number, and the two additional patients were kept in reserve. They had all previously been taking a barbiturate, and whenever attempts were made to stop this medication they complained of insomnia. Contributory factors in producing the insomnia in several patients were cough and rheumatic disorders. Cases in which pain rather than insomnia was the predominant feature were excluded. None of them was confined to bed during the day. In view of the difficulty in determining the real necessity for a hypnotic in many patients, it was considered essential to include a placebo in the trial. Accordingly the action of doriden has been compared with the effect of cyclobarbitone and of an inert tablet.

Doriden, 0.5 g., cyclobarbitone, 0.2 g., and inert tablets were prepared so that they were identical in appearance.