Studies on Patients with
ILEAL CONDUIT DIVERSION
with special regard to
Renal Infection

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med.lic.

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   Brit J Urol 49, 503.

II. Ureteral reflux from ileal conduit.
   Scand J Urol Nephrol, in press.

III. Renal infection after ileal conduit urinary diversion. An autopsy study.

IV. Conduit urinary diversion and urinary tract infection. I.
   Serum antibody titers against Escherichia coli and Proteus mirabilis in relation to urographical findings.
   Scand J Urol Nephrol, in press.

V. Conduit urinary diversion and urinary tract infection. II.
   Serum antibody titers against Escherichia coli and Proteus mirabilis in relation to bacteriological findings.
   Scand J Urol Nephrol, in press.

The conditions for retrograde transport of urine and thereby bacteria in the urinary system of diverted patients (device and urinary tract) were studied with roentgenological technique. Back-flow from the urinary collecting device into the conduit occurred in a fifth of those patients who had a flat stoma. A nipple stoma of at least 2 cm height resisted back-flow better than any flat stoma. Ureteral reflux occurred to approximately 50 % of the ureters, both in the supine and erect body positions. The intraluminal pressure in the conduit was "low" ($\leq$ 12 cm H$^2$O) in approximately 50 % when reflux occurred. The autopsy study showed a higher frequency of renal infections in diverted patients than in non-diverted controls. 5 of 11 patients who died more than 2 months after diversion, and without cancer at autopsy, were attributed to death from renal infection.

There was a relationship between urographical abnormalities, recognized as associated with pyelonephritis, and raised serum antibody titers against *E.coli* and/or *P.mirabilis*. Most of the "not normal" renal units deteriorated after the diversion operation. The variable "kidney area" was found to be "small" in a higher frequency after a long postoperative period than after a short one.

Raised serum antibody titers occurred in 35 % of the patients and were correlated to growth of the corresponding bacteria (*E.coli* and *P.mirabilis* respectively) in the conduit urine. The frequency of raised antibody titers increased with the time after the diversion operation. After treatment with antibiotics of patients with bacteriuria and raised serum antibody titers, the titers were within normal limits ($< 512$), or decreased significantly, in 22 of 25 patients. Serum antibody titer determinations against *E.coli* and *P.mirabilis* are suggested as complement to urinary cultures in the follow-up of diverted patients.

The residual urine volume in the conduit was shown to be of importance for bacteriuria and raised titer against *P.mirabilis*.

Some measures, which possibly may reduce bacteriuria and thereby pyelonephritis, are suggested. A nipple stoma of at least 2 cm height ought to be constructed at the operation. To obtain a low residual urine volume the conduit should be short and unobstructed. The urinary collecting device should be emptied often and connected to a uribag during the night.
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BO BERGMAN

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La cystectomie totale est au point de vue opératoire une opération relativement facile -----. Mais une fois l'opération terminée, les difficultés commencent, et la question des uretères, question toujours discutée, se pose avec toutes les difficultés qu'elle comporte. Une fois la vessie enlevée, que faut-il faire des uretères?

M. Marion, 1908

To Birgitta, Mats, Åsa and Helena
INTRODUCTION

Supravesical urinary diversion is performed as a temporary or definitive measure. In some patients the urine is temporarily diverted before the effect of other treatment is achieved. Cystectomy necessitates permanent urinary diversion. These operations are performed in patients with the following: malignant diseases in the urinary bladder or urethra, neuropathic bladders, conditions of the urinary bladder after serious inflammations, congenital malformations of the urinary bladder or urethra, acquired strictures or fistulas in the urethra or urinary bladder.

Naturally the first urinary diversion operations attempted had to involve only small surgical trauma and a short anaesthetic period. Early reports on urinary diversion describe the creation of uretero-sigmoid fistulas (Lloyd, 1851; Simon, 1852). Simon in 1869 reported a cutaneous ureterostomy prompted by an operative ureteral lesion.

One hundred years ago Smith performed a direct uretero-intestinal anastomosis whereby the ureter was sutured into an opening made in the sigmoid (reported 1879). In 1881 Agnew performed an elective cutaneous ureterostomy and eight years later Pawlik (1889) performed a successful cystectomy and anastomosed the ureters to the vagina. In 1895 Wassaljew reported a cystectomy with cutaneous ureterostomy. However, most operative procedures reported around the turn of the century were designed to retain sphincter control of the urine. The development of acute pyelonephritis or chronic renal infection following uretero-sigmoidostomy was described early on and later well documented by Jacobs & Sterling (1952). Hyperchloraemic acidosis and potassium depletion are also well documented (Foster, Drew & Wiss, 1950; Clarke & Leadbetter, 1955; Williams, Davenport, Burkinshaw & Hughes, 1967).

To avoid ascending infections, new operative methods aimed at reducing the mingling of the faecal and the urine streams were introduced: ureteral implantation in the isolated rectum combined with a colostomy (experimentally, Maucraire, 1895) and a similar "rectal" bladder technique, but with the proximal part of the sigmoid brought to the anal area within the anal sphincter in order to establish faecal as well as urinary continence (Gersuny, 1898). Other operative methods designed to reduce the risk of ascending bacterial invasion of the upper urinary tract consisted of anastomoses of the ureters with their surrounding bladder wall to the intestine. Maydl (1894) used a bigger part of the bladder wall surrounding both ureters, whereas Bergenhem (1895) used two small parts of the bladder wall surrounding each ureter separately for implantation in the sigmoid. These two methods of ureteral implantation were devised to prevent ureteral reflux by preserving the natural uretero-bladder junction. The former method was combined with a by-
pass for the faecal stream, created by means of a sigmoido-sigmoidostomy, so as to protect the ureteral implantation site in the sigmoid (Borelius, 1903). Verhoogen (1908) abandoned the idea of keeping the urine within sphincter control and made a reservoir for urine by isolating an ileocecal segment of the gut. He used the appendix to divert urine to a cutaneous stoma in the right inguinal region. Seiffert (1935) described a jejunal conduit and Bricker (1950) an ileal conduit which is now the most popular method for urinary diversion. The conduit diversion method includes several advantages: only one cutaneous stoma is necessary, it is possible to shorten the ureters in patients with urothelial tumours, stoma strictures are not common if the cutaneous stoma is correctly performed and hyperchloremic acidosis is unusual compared with after uretero-sigmoidostomy (Mogg, 1967).

Pyelonephritis was reported to be considerably less common following ileal conduit diversion than after uretero-sigmoidostomy (Kerr, Robson, Russel & Bourque, 1962; Riches, 1967). Although this is indisputable, the frequency of renal infections after ileal conduit diversion is high and other adverse effects are reported such as stomal strictures, renal calculi and deficiency of vitamin B₁₂ (Parkhurst & Leadbetter, 1960; Butcher, Sugg, McAfee & Bricker, 1962; Susset, Taguchi, DeDomenico & MacKinnon, 1966; Rogers & Steyn, 1974; Johnson & Lamy, 1977). To minimize the risk of ureteral reflux from the ileal conduit different operative methods have been used (Kafetsioulies & Swinney, 1970; Mount, Susset, Campbell & MacKinnon, 1968; experimentally, Starr, Rose, Cooper & Snyder, 1974). However, ureteral reflux was often not prevented and strictures developed at the sites for the ureteral implantations in some cases. Pond, Texter, Harty & Sanders (1977) used the Maydl principle of anastomosing the ureters with the surrounding bladder wall to the ileal conduit and reported favourable results. The "trigono-intestinal" anastomoses can only be used in benign cases. Therefore, to avoid ureteral strictures after total cystectomy other reflux-preventing methods have been suggested (Bergman & Nilson, 1974; Zinman & Libertino, 1975). For the same reason colonic conduits have been used, as ureteral implantation can be performed with reflux-preventing technique in the colon with a greater degree of safety (Turner Warwick, 1960; Mogg, 1967; Skinner, Richie & Gottesman, 1974; Hendren, 1975; experimentally, Barry & Hodges, 1977).

To achieve urinary continence and maintain urine separation from faeces, new sorts of reservoirs for the urine have been proposed. In 1955 Smith and Hinman created reservoirs from the urinary bladder by interpolating an ileal conduit between the skin and the urinary bladder. By intussusception of the ileal loop a nipple was created which prevented outflow from the urinary bladder.
These "bladder" reservoirs must be emptied intermittently by means of inserting a catheter through the abdominal stoma. A similar principle has been used to create a valve from a flap of the bladder wall whereby intestinal surgery is avoided (Schneider, Reid & Fruchtman, 1977). Other operations to create reservoirs have also been suggested (Gilchrist, Merricks, Hamlin & Rieger, 1950; Blandy, 1961; Turner Warwick & Ashken, 1967; Ashken, 1974; Leisinger, Säuberli, Schauwecker & Mayor, 1976). Patients thus operated must also use intermittent catheterization to empty the reservoir. Intermittent transurethral catheterization has been used in some patients with neuropathic bladders and a high volume of residual urine, i.e. without any form of surgery at all. Fewer adverse effects upon the upper urinary tract in these patients have been reported compared to diverted patients (Comarr, 1972; Kyker, Gregory, Shah & Schoenberg, 1977). Before reservoir operations can be recommended for common use, further long-term studies of the adverse effects must be evaluated. The loss of a longer part of the gut must be considered if a reservoir is created from the intestine than if a cutaneous conduit is created.

Concerning the use of the colon as conduit or reservoir, one must bear in mind the risk of neoplasia of the colon in the long term. Adenocarcinoma in colon has been reported to occur 10-41 years (mean 22 years) following uretero-sigmoidostomy because of benign disease and 6-9 years (mean 8 years) following diversion because of malignant disease (Breken, Collén, Myrvold, Du Rietz, Schnürer & Fritjofsson, 1972). As many patients with urinary diversion, especially those with benign disease, have long anticipated survival times it must be wise to wait for the results of the long-term follow-up of series already done on colon conduit, before the colon can be recommended as a first choice for creating a conduit or a reservoir. In ileal segments used for urine transport to the bladder or to the cutaneous stoma, adenocarcinoma has not been reported. Furthermore, the frequency of pyelonephritis after colonic conduit may be higher than after ileal conduit diversion (experimentally, Spence, Esho & Cass, 1972).

On the basis of these facts it is not evident that the use of ileal conduits should be abandoned. Therefore, it is important to assess renal infection in patients with ileal conduit urinary diversion, as renal infection is the most common and serious adverse effect of ileal conduit urinary diversion.
Aim of the present study

The aim of the present study was to investigate patients with conduit urinary diversion with special regard to renal infection. Retrograde conveyance of contents from the urinary collecting device to the upper urinary tract in diverted patients was also studied because it serves as a possible route for spread of infection.

The study was performed in the following way:

1. The possibility of, and the conditions for, retrograde transport of urine and thereby bacteria in conduit diverted patients' urinary system (device and urinary tract) was studied under standardized conditions (I,II). The back-flow from the urinary collecting device through the stoma into the conduit and the upper urinary tract was investigated in paper I. The reflux from the conduit to the ureters was especially studied in paper II.

2. The frequency of macroscopically recognizable infection in the upper urinary tract in diverted autopsy cases was compared with non-diverted controls (III). Deterioration of the upper urinary tract, especially the renal parenchyma, was estimated by urography, and the relationship between findings at urography and level of serum antibody titers against E.coli and/or P.mirabilis was analyzed (IV). The relationship between raised antibody titers against E.coli and/or P.mirabilis and bacteriological findings was studied and the frequency of pyelonephritis as judged from raised titers is given (V).
The patients in this study were operated upon at the Sahlgren hospital, Göteborg with a cutaneous conduit urinary diversion 1963 - 1974. The intention was to include all survivors with a postoperative follow-up time of more than 3 months still residing in Göteborg (51 patients), or in the hospital region (92 patients) in the clinical studies (I and IV, V respectively). All autopsied diverted cases were included in the autopsy study (III). The operative method for uretero-ileostomy was basically the one described by Bricker (1950). The uretero-intestinal anastomoses were performed without reflux-preventing technique. Only a few patients were operated upon with a high (≥2 cm) nipple stoma. During the first years after 1963, the patients, as a rule, had used devices for long term use (Giron). Later on nearly all patients used expendable devices. Both these types of devices were previously without non-return valve and only in recent years there has been a trend to replace them with expendable devices with non-return valves. 86 patients studied had an ileal conduit and 3 patients had a sigmoid conduit. All diverted autopsied cases had ileal conduits.

PATIENTS AND METHODS

STUDIES ON BACK-FLOW AND URETERAL REFUX IN THE URINARY SYSTEM OF DIVERTED PATIENTS

STUDIES ON BACK-FLOW FROM THE URINARY COLLECTING DEVICE (I)

Frequency of back-flow

The back-flow through the cutaneous stoma was investigated in 46 of 51 patients residing in Göteborg. The cutaneous stoma was inspected with the patient in the supine position. A stoma of at least 2 cm height was designated as a nipple stoma and the others as a flat stoma. A stoma allowing insertion of a 18 F catheter was designated as a wide stoma, the stoma which didn't as a narrow stoma. The frequency of back-flow was studied with 500 ml contrast medium in a device without a non-return valve. After a certain amount of physical activity roentgen exposures were taken of the conduit and the upper urinary tract. Where back-flow of contrast medium occurred to the conduit the patient was re-investigated another day with smaller amounts of fluid in the device. At this re-investigation the amount of contrast medium in the device was successively increased from 200 to 300 and to 400 ml.

Back-flow through nipple versus flat stoma

To determine the extraabdominal hydrostatic pressure necessary for fluid to enter the cutaneous stoma 16 patients were investigated; the 3 living patients
with a nipple were included and 13 chosen at random from the 42 patients without a nipple.

A cylinder was pasted watertight to the skin around the stoma and contrast medium was intermittently added to the cylinder in such a way that the fluid level rose 2 cm every other minute. The investigation was carried out until contrast medium entered the conduit through the stoma or until the pressure of the column corresponded to 35 cm H$_2$O. The conduit and the upper urinary tract were observed intermittently and the events registered by cine-radiology.

URETERAL REFLUX FROM THE CONDUIT (II)

To determine the frequency of ureteral reflux from the conduit and to study two factors which may influence the occurrence of reflux, namely: body position and intraluminal conduit pressure, 14 patients were investigated. They had 30 ureters implanted (2 patients had 3 ureters each). No signs of stricture of the uretero-intestinal anastomoses or of the stoma were present in any of the patients. Two fluid-filled catheters (infant feeding tubes, 8F) were inserted into the ileal conduit to a position corresponding to the uretero-intestinal anastomoses. Contrast medium was infused through one catheter and the intraluminal conduit pressure was continuously registered through the other. The pressures were recorded in the supine and erect body positions. The conduit and the upper urinary tract was observed intermittently by TV-fluoroscopy at regular intervals. Films were obtained by 70 mm fluorography. The investigation was carried on until ureteral reflux occurred to both ureters or for a maximum time of 60 min. The highest intraluminal conduit pressure recorded within 2 min. before the observation of reflux was settled as reflux pressure. Six patients in whom bilateral ureteral reflux was not observed were studied after occlusion of the conduit using an inflated Foley catheter balloon (5 ml). The reflux pressures obtained were divided into two groups: "low pressure" when the reflux pressure was 12 cm H$_2$O or less and "high pressure" when it was higher.

ASSESSMENT OF UPPER URINARY TRACT INFECTION

AUTOPSY STUDY (III)

Autopsy records from cases with ileal conduits were re-evaluated by one pathologist and compared with autopsy records from non-diverted control cases treated at the same clinic for the same disease, urinary bladder carcinoma. 54 conduit cases had autopsy records with detailed descriptions of the conditions in the urinary tract and such autopsy records were available in 181 controls. 21 of the conduit cases and 50 of the controls were without eviden-
ce of cancer at autopsy and were carefully re-evaluated.

**Evaluation of autopsy records**

Macroscopical evidence of urinary tract infection in kidneys, renal pelves and ureters were classed into four stages:

**Infection stage 0:** No signs of infection; i.e. normal mucosa, no purulent exudation. No renal abscess.

**Infection stage 1:** Reddish mucosa, usually with petechiae in the ureters and/or renal pelves. No renal abscess.

**Infection stage 2:** Inflamed mucosa with definite purulent exudation in the ureters and/or renal pelves. No renal abscess.

**Infection stage 3:** Macroscopical abscesses in the renal parenchyma.

**SERUM ANTIBODY TITERS AGAINST ESCHERICHIA COLI AND PROTEUS MIRABILIS IN RELATION TO UROGRAPHICAL FINDINGS (IV)**

It was possible to investigate 89 of 92 patients clinically and perform serological and routine laboratory investigations. In 83 subjects urography could be arranged within 3 weeks from the clinical and laboratory investigations. The uroographies were analyzed with respect to the following features: Scarring of the renal parenchyma, diagnosed according to Hodson (1967); calyceal distortions, i.e. flattening of the papilla and/or calyceal clubbing as described by Hodson (1967); wideness of the upper urinary tract, staged similar to the description by Edsmyr, Giertz & Nilson (1957), i.e. a ureter was staged as wide if the distal part of it continuously was wide on all X-ray exposures; kidney area was determined according to Möll (1961). The median kidney area in the different age classes was determined and the kidneys were designated either as "normal" size or "small" (< median size). A patient with at least one "small" kidney was referred to as a patient with "small" kidney. Some patients were excluded due to: a "silent" kidney, which made assessment of the renal unit impossible, solitary kidney because of a possible compensatory enlargement of the remaining kidney, acute pyelonephritis diagnosed at the time for urography, as such an infection may enlarge the kidneys temporarily (Bailey, Little & Rolleston, 1969) or technically unsatisfactory investigations.

Calyceal distortion was never attributed to patients in whom the widening of the upper urinary tract included the pelvi-calyceal system.
After these exclusions the kidney area could be calculated in 70 and the other features in 80 urographies. 64 of the available urographies taken preoperatively could be adequately analyzed.

SERUM ANTIBODY TITERS AGAINST E.COLI AND P.MIRABILIS IN RELATION TO LABORATORY AND CLINICAL FINDINGS (IV,V)

In each patient all the following investigations were performed on the same day.

Antibody determinations. Blood samples were taken for determinations of serum antibody titers against E.coli and P.mirabilis with a hemagglutination technique (Neter, Bertram, Zak, Murdock & Arbesman, 1952; Jodal, Lindberg & Lincoln, 1975). The titers are given as the reciprocal values of 1:2-step dilution of serum and were contiously controlled against standard serum. A titer level of 512 or more before and 64 or more after Mercaptoethanol treatment (ME-treatment) (Hanson, Holmgren, Jodal & Kaijser, 1971) was considered as raised and a two-step decrease of titer level as significant titer reduction. Urinary cultures were taken simultaneously and in patients with growth of E.coli and/or P.mirabilis in their urinary culture, these bacteria were used for making antigens. Thus, these patients were also tested specifically against their own bacteria.

Bacteriological methods. After conduit diversion urinary samples were taken through a sterile catheter inserted into the intraabdominal part of the conduit. The patients had all been without antibiotics 3 days before the urinary samples were taken. No patient had used aminoglycosides.

Clinical assessment of infection. The patients were investigated for signs of pyelonephritis and asked if they had experienced symptoms of the disease during the last two months. The patients' case records were also studied for evidence of upper urinary tract infection within this period.

Residual urine volume in the conduit was determined. A catheter was inserted into the conduit and the volume of urine obtained during slight manual compression of the abdomen was designated as residual urine. The volume was larger when urine was collected during compression of the abdomen than without.

Routine laboratory investigations. Blood samples were analyzed by the routine laboratories for ESR, CRP and serum creatinine.
Effect of treatment with antibiotics. Patients with bacteriuria were treated with antibiotics. 25 consecutive patients with raised antibody titers before ME-treatment of serum, i.e. with a possible acute kidney infection, were treated with antibiotics and followed by urinary and blood samples as described above.

Non-diverted control patients were investigated. Blood samples as described above were taken as well as urinary cultures from voided midstream urine in the 25 controls. Urinary cultures made from voided midstream bladder urine before urinary diversion were available in 75 operated patients.

The following statistical methods were used: \( \chi^2 \)-test, rank sum test according to Wilcoxon-Mann-Whitney, student's t-test, fourfold table test (Documenta Giegy) and lineal regression analysis.

RESULTS

STUDIES ON BACK-FLOW IN THE URINARY SYSTEM OF DIVERTED PATIENTS

Frequency of back-flow

Back-flow of contrast medium from the device into the ileal conduit occurred in 21 % of those patients who had a flat stoma (9/42) but was not observed in any of the 4 patients with a nipple stoma (Table I). In 6 of 9 patients with back-flow to the conduit, the contrast medium also passed into the upper urinary tract.

Table I. Frequency of back-flow from urinary collecting device into the ileal conduit. Devices successively filled with 200, 300, 400 and 500 ml of contrast medium.

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Flat stoma</th>
<th>Nipple stoma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>With back-flow</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Without back-flow</td>
<td>33</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>4</td>
<td>46</td>
</tr>
</tbody>
</table>

These investigations were carried out using devices without a non-return valve. However, re-investigating 4 of the 9 patients with back-flow also with a device with a non-return valve a back-flow could be registered in all 4 patients.
Nipple stoma versus flat stoma

Contrast medium flowed from the cylinder into the ileal conduit in all 13 patients with a flat stoma (wide or narrow) at extraabdominal pressures below 16 cm H₂O, but in 2 of 3 patients with a nipple stoma at higher pressures, 25 and 35 cm H₂O respectively (p<0.05). No contrast medium passed into the conduit in the third patient with a nipple stoma. Within the group of patients with flat stomas, the patients with narrow stomas resisted back-flow better than those with wide stomas.

URETERAL REFLUX FROM ILEAL CONDUIT (II)

Reflux was found to 20 of the 30 ureters (67 %). In the supine position reflux occurred to 17 of 30 ureters (57 %) and reached the renal pelves in 15. In the erect position reflux occurred to 10 ureters (42 %) and 6 renal pelves of 24 renal units tested.

The intraluminal conduit pressure was low (≤12 cm H₂O) in approximately 50 per cent when the reflux was registered.

Occlusion of the outflow from the conduit by inflating a Foley catheter balloon raised the intraluminal pressure approximately 20 cm H₂O. Occlusion did not, however, provoke reflux to any ureter where reflux was not observed in previous investigations in supine or erect positions. Thus, no correlation between ureteral reflux and intraluminal conduit pressure was traced.

UPPER URINARY TRACT INFECTION

AUTOPSY STUDY (III)

Macroscopically recognized upper urinary tract infections were found in cases without evidence of cancer at autopsy more often in diverted cases (18/21; 86 %) than in non-diverted controls (14/50; 28 %). The frequency of infection was the same in patients autopsied at the University hospital as at other hospitals, although the frequency of autopsy varied (69 % and 37 % respectively). The frequency of bacteriuria premortally was the same in autopsied cases and non-autopsied cases. From these findings it was concluded that no bias in selection for autopsy had occurred. Excluding cases who died with cancer, at autopsy or diagnosed premortally as metastasis at X-ray, 18 (14 %) of the remaining 128 diverted patients died with infection in the upper urinary tract, 10 (8 %) of them with renal abscesses. The main cause of death, as settled by the pathologist at autopsy, in patients who died more than 2 months after diversion and without cancer at autopsy, was renal infection in 45 % (5/11).
RESULTS AT FOLLOW-UP OF CONDUIT DIVERTED PATIENTS (IV,V)

Findings at urography in relation to serum antibody titers

Both patients with raised antibody titers against *E.coli* and those with raised titers against *P.mirabilis* had normal urographies less often than patients with normal titers (p<0.01 and p<0.025 respectively). The results are summarized in Table II and Table III. Concerning the different findings at urography, wide upper urinary tract, calculi and "small" kidney were significantly correlated to raised titer against *E.coli*, whereas renal scarring, calyceal distortion, "small" kidney as well as calculi, were significantly correlated to raised *P.mirabilis* titer.

Table II. Relationship between raised *E.coli* and/or *P.mirabilis* antibody titers and wide upper urinary tract, parenchymal scarring, calyceal distortion and calculi (= "not normal" urography) in 80 patients with conduit urinary diversion. Normal urography = none of these features.

<table>
<thead>
<tr>
<th>Finding at urography</th>
<th>Normal Antibody titer</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal E.coli</td>
<td>Raised against E.coli and P.mir.</td>
</tr>
<tr>
<td>Normal urography</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>&quot;Not normal&quot; urography</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>Wide upper urinary tract (solely)</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Parenchymal scarring</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Calyceal distortion*</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Calculi</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>14</td>
</tr>
</tbody>
</table>

*Calyceal distortion was never attributed to cases in whom widening of the upper urinary tract included the pelvi-calyceal system.
Table III. p-values from statistical calculations ($X^2$-test, fourfold table test) of differences in frequency of raised antibody titer. Patients with the different roentgenological findings given in table were compared with those with normal urography. Calculations on figures given in Table I. Kidney area not considered in these calculations. Relationship between kidney area and antibody titers calculated separately.

<table>
<thead>
<tr>
<th>Findings at urography</th>
<th>Raised antibody titer against</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E.coli</td>
</tr>
<tr>
<td>in 80 patients</td>
<td>p&lt;</td>
</tr>
<tr>
<td>Wide upper urinary tract solely</td>
<td>0.02</td>
</tr>
<tr>
<td>Parenchymal scarring</td>
<td>0.10</td>
</tr>
<tr>
<td>Calyceal distortion**</td>
<td>NS</td>
</tr>
<tr>
<td>Calculi</td>
<td>0.05</td>
</tr>
<tr>
<td>Urographical abnormalities as above, total</td>
<td>0.01</td>
</tr>
<tr>
<td>&quot;Small&quot; kidney***</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*  Not significant  
** Calyceal distortion was never attributed to cases in whom widening of the upper urinary tract included the pelvi-calyceal system.  
*** Kidney area in 70 patients.

Diverted patients with long follow-up time had at least one "small" kidney in a higher frequency than patients with short follow-up time. 2/3 (12/18) of the patients with parenchymal scarring had developed the scars after the diversion operation and 50% (17/34) of the "small" kidneys diminished postoperatively from "normal" size.

In patients with raised antibody titers the kidney area diminished at mean by 5% on the right side and 11% on the left and in patients without raised antibody titer by 2% and 2% respectively. The kidney area was reduced by more than 10% in 16 of 23 patients (70%) with raised antibody titers and in 7 of 41 (17%) with normal titers (p<0.0005).

Several different roentgenological abnormalities were usually obtained in the same patient. Calyceal distortion was only found in patients who also had renal scarring and most patients with scarring had a "small" kidney (10/14).
Antibody titers in relation to bacteriological findings

A total of 35% of conduit diverted patients had raised antibody titers against E.coli or P.mirabilis. The frequency rose from 26% 3-11 months post-operatively to 59% in patients who had been diverted 5 years or more.

Table IV. Serum antibody titers against E.coli and/or P.mirabilis in 89 patients with different follow-up times after conduit urinary diversion.

<table>
<thead>
<tr>
<th>Antibody titer</th>
<th>No of patients</th>
<th>Postoperative observation time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3-11</td>
</tr>
<tr>
<td>raised</td>
<td>31 (35%)</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>normal</td>
<td>58</td>
<td>17</td>
</tr>
<tr>
<td>total no</td>
<td>89</td>
<td>23</td>
</tr>
</tbody>
</table>

Although patients with ≥10⁵ bacteria/ml urine had raised titers against E. coli and/or P.mirabilis most often, no definite number of bacteria could be established as "significant bacteriuria" as raised titers were found in patients with less bacteria/ml (Table V). In 79% of the patients who had a raised titer against P.mirabilis the corresponding bacteria was found in the urine whereas 35% with raised E.coli titer had growth of E.coli. 53% of patients with ≥10³ E.coli/ml urine and 52% of those with ≥10³ P.mirabilis showed a corresponding antibody titer increase.

Table V. Frequency of raised serum antibody titers against E.coli and P.mirabilis before or after ME-treatment in relation to number of the corresponding bacteria/ml urine.

<table>
<thead>
<tr>
<th>Antibody titer raised against</th>
<th>Number of bacteria per ml urine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10³</td>
</tr>
<tr>
<td>E.coli</td>
<td>17/72</td>
</tr>
<tr>
<td>P.mir.</td>
<td>3/68</td>
</tr>
</tbody>
</table>

Clinical findings

In this study the patients with bacteriuria and/or raised antibody titers were usually symptom-free. Only 2 diverted patients with raised titers and 1 with normal titers had had symptoms attributable to pyelonephritis.
Residual urine volume

The mean volume of residual urine in the ileal conduit was almost the same in patients with raised serum antibody titers as in patients without (17 and 16 ml respectively). 4 of 28 patients with raised titers before and/or after ME-treatment of serum and 13 of 46 with normal titers had less than 5 ml residual urine. However, none of 11 patients with less than 5 ml residual urine had raised titer against \textit{P. mirabilis} \((p < 0.05\), Table VI). 

Table VI. Relationship between serum antibody titers against \textit{E. coli} and/or \textit{P. mirabilis} before and/or after ME-treatment of serum in 74 diverted patients.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Volume of residual urine in ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;5</td>
</tr>
<tr>
<td>Normal against \textit{E. coli} and \textit{P. mirabilis}</td>
<td>13</td>
</tr>
<tr>
<td>Raised against \textit{E. coli}</td>
<td>4</td>
</tr>
<tr>
<td>\textit{P. mirabilis}</td>
<td>0</td>
</tr>
<tr>
<td>\textit{E. coli} and \textit{P. mirabilis}</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
</tr>
</tbody>
</table>

Patients with less than 5 ml residual urine volume never had \(10^5\) bacteria/ml urine or more. In contrast 8 of 11 patients with at least 30 ml in residual urine volume had \(10^5\) bacteria/ml or more (Table VII).

Table VII. Relationship between bacteria/ml urine and residual urine in 74 diverted patients.

<table>
<thead>
<tr>
<th>No of bacteria/ml</th>
<th>Volume of residual urine in ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;5</td>
</tr>
<tr>
<td>(&gt;=10^5)</td>
<td>0</td>
</tr>
<tr>
<td>(&gt;=10^3 &lt; 10^5)</td>
<td>7</td>
</tr>
<tr>
<td>(&lt;10^3)</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
</tr>
</tbody>
</table>
Non-diverted control patients

None of the 25 controls had raised titers, 2 of them had $\geq 10^5$ bacteria/ml urine.

Antibody titer level at administration of antibiotics

Fig. 1 describes the titer response to antibiotic treatment. 21 of 25 patients with raised titers had normal titers after administration of antibiotics. In 1 of the remaining 4 the titer level was significantly reduced from 8 192 to 512. One patient was followed less than 2 months.

**Fig. 1.** Serum antibody titers against *E.coli* and *P.mirabilis* followed during treatment of bacteriuria with antibiotics in 25 patients with raised titers before ME-treatment of serum ($\geq 256$).
Discussions on the possibility of kidney infection after urinary diversion started simultaneously with the operations during the 19th century. It has been shown experimentally in rats that pyelonephritis is usually caused by intracanicular ascending infection but may be caused by haematogenous or possibly lymphogenous spread, which was demonstrated in renal units with the ureter ligated (Cotran, Vivaldi, Zangwill & Kass, 1963; Hjort, 1977). It is commonly accepted that pyelonephritis in man usually is caused by intracanicular retrograde conveyance of infection. Although this fact is well-known it seems that in diverted patients attention has only been paid to ureteral reflux (Lusted, Ship, Smith & Jude, 1959; Jude, Lusted & Smith, 1959; Campbell, Oliver & McKay, 1965; Koehler & Bowles, 1966; Nogrady, Petitclerc & Moir, 1969) but not to the back-flow of infected urine into the conduit and the upper urinary tract from the collecting device. The frequency of this back-flow, shown to occur in a fifth of patients without a nipple stoma in this study, must be considered as a minimum, as the patients were only screened once and then with the patient performing a small amount of physical activity. Besides, back-flow occurred from the cylinder into the conduit in all patients with a flat stoma. In non-diverted patients vesico-ureteral reflux carries a risk that a urinary infection is maintained in the urine. The "residual urine" which consists of the refluxed urine may counteract a complete emptying of the lower urinary system, which is a simple defence mechanism against urinary infection. Also, ureteral reflux may convey the infecting agent to the kidneys.

In diverted patients "reflux" may occur at two different levels, from the conduit to the ureters and from the device to the conduit. Ureteral reflux from the conduit or back-flow from the urinary collecting device may maintain a urinary infection and convey it to the upper urinary tract in a similar way. "Residual" urine in the conduit may consist of urine refluxed to the ureters and then again returned to the conduit. However, conduit "residual" urine may also consist of "back-flow" urine from the device.

It has been shown that radioactive particles, ranging in size from 2-5 microns, simulate the movement of bacteria in the urinary tract (Corriere, Lipschutz, Judson & Murphy, 1970). When such particles were refluxed from the conduit to the kidneys they remained 2-10 times longer than simultaneously refluxed contrast medium (Corriere, Sanders, Kuhl, Schoenberg & Murphy, 1970). The frequency of ureteral reflux as investigated in the present study, without occlusion of the conduit, corresponds to the frequency reported using an isotope conduitography technique (Woodside, Borden, Damron & Kiker, 1978). The finding
of ureteral reflux at low intraconduit pressures are in accordance with recent findings by Magnus (1977). The ureteral reflux at low intraluminal pressures implies a risk of conveying microbes from the conduit to the kidneys in all patients without reflux-preventing ureteral anastomoses.

Although back-flow from the device to the conduit may increase the volume of "residual" urine in the conduit temporarily, no connection between back-flow and volume of residual urine could be shown as the 9 patients with demonstrable back-flow from the device had 13 ml at mean in residual urine compared to 16 ml for the total material.

Bergman & Kaisers (to be published) found that 9 of 19 non-diverted patients (45%) who kept voided sterile urine in a urinary collecting device pasted on the abdomen had \( \geq 10^5 \) bacteria/ml in the urine in the device after 24 hours. These bacteria most certainly originate from normal skin bacteria, which are numerous on normal skin (Marples, 1969). Thus, sterile urine from the conduit kept in the device may be a substrate for growth of skin bacteria. The microbes may then be conveyed to the conduit and the kidneys.

Urine in contact with the peristomal cutis contained \( \geq 10^5 \) bacteria/ml in 6 of 14 patients, which was more frequently than urine obtained from the conduit through an inserted catheter (Bishop, Smith & Gracey, 1971). This is in accordance with a recent finding of \( \geq 10^5 \) bacteria/ml in 4 patients and \( 10^3-10^4 \) in conduit urine in another 4 of 24 patients compared to \( \geq 10^5 \) in 19 specimens and \( 10^4 \) in 1 of 24 specimens of urine simultaneously obtained from those patients' collecting devices (Bergman, unpublished observations).

The possibility of conveyance of infected urine from the collecting device into the conduit and the upper urinary tract can be reduced by some simple measures. Thus, the stoma ought to be constructed as a nipple stoma at least 2 cm high and the patients should be advised to empty the device frequently and to connect it to a uribag, at least during the night. It is evident that the ratio between length and width of the nipple is of importance when the nipple functions as a valve. However, the optimal length could not be assessed in the present study. Although the non-return valves tested did not prohibit back-flow, back-flow is probably reduced by such valves. The massive back-flow conveyed the contents of the device not only to the conduit, but also to the renal pelvis. Thus, bacteriological findings at different levels in the conduit are less relevant with respect to the possibility of inducing kidney infection. As symptoms from the urinary bladder and urethra are absent in diverted patients, it is certain that these patients run a considerable
risk of developing symptom-free pyelonephritis.

There are earlier reports of serious infection with renal abscesses following conduit diversion (Parkhurst & Leadbetter, 1960; Butcher, Sugg, McAfee & Bricker, 1962). 45% of diverted cases in this study who were without evidence of cancer at autopsy had serious renal infection as the main cause of death. Although it may be difficult to assess the importance of such a finding, as many of the diverted patients were still alive, it is indisputable that excluding known "cancer" and calculating frequency on the remaining 128 diverted subjects, 14% of those were dead within a relatively short follow-up period with evidence of pyelonephritis at autopsy.

The relationship between raised serum antibody titers against E. coli and/or P. mirabilis and kidney deterioration at urography shows that the antibody titers relevantly reflect pyelonephritis in diverted patients. 35% of the diverted patients had renal parenchymal infection during a limited follow-up period.

When evaluating pyelonephritis after conduit diversion by means of urography, it is more relevant to pay attention to renal scarring, calyceal distortion and kidney area than to the wideness of the upper urinary tract. A main aim of urinary diversion in patients with benign disease is to preserve kidney function and the diversion is consequently done in many patients with wide upper urinary tract before the operation. Obstructed ureters due to bladder carcinoma may be found in as much as 27% of patients before treatment (Bergman & Wahlqvist, 1978). Therefore, it is by no means surprising that some patients promptly improve after urinary diversion with regard to wideness of the upper urinary tract. The majority of kidneys with scarring and "small" kidneys had deteriorated after the diversion operation and, furthermore, it was shown that "small" kidney as well as raised titers are more frequent after a long follow-up time than after a short one. The lower frequency of pyelonephritis after a shorter postoperative follow-up time in the present study may possibly depend on a more adequate antibiotic treatment during the last few years. However, the treatment had been in accordance with the sensivity of the bacterial strains according to the case records. Furthermore, the adverse effects of diversion should be expected to develop with time. The present observation of such a time-dependent development is in accordance with those by Minton, Kiser & Ketcham (1964) of a higher frequency of bacteriuria in patients diverted more than 5 years previously (78%) than in those diverted 1-4 years previously (30%) and with the report by Koehler, Bowles & McAlistler (1967) that 7 of 29 children followed more than 5 years were dead.
or anticipating a soon renal death in contrast to 2 of 25 of those followed less than 5 years postoperatively. Schwarz & Jeffs (1975) reported deterioration at urography in 10 of 18 children (56 %) followed more than 10 years after conduit diversion, in contrast to 2 of 14 (14 %) followed 2-4 years.

Serum creatinine determinations showed reduced function in patients with "small" kidneys. However, it is a rough method of assessing kidney function. Therefore kidney function was further studied through radiorenograms in 50 diverted patients. 7 of 19 patients with raised titers (37 %) and 6 of 31 without (19 %) had reduced kidney function (unpublished observations). This difference is not statistically significant. However, 10 of 21 patients (48 %) with "small" kidney and 3 of 23 with "normal" size kidney (13 %) had reduced function as shown by radiorenogram (p<0.05). Thereby it was shown that assessment of calculated kidney area as used in the present study is adequate. Therefore it can be recommended to calculate kidney area in follow-up studies when kidney deterioration shall be assessed. Many "small" kidneys diminished after the diversion operation. These "small" kidneys had reduced function. This finding implies that the reduced kidney function is an adverse effect of the operation and it is of clinical importance. The fact that the serum creatinine values indicated reduced kidney function when one kidney was "small" implies that the elaborate functioning structures had deteriorated in both kidneys.

Antibiotic treatment of patients with bacteriuria and raised serum antibody titers reduced the titer level, which argues for an active attitude in treatment of urinary infection in diverted patients at least when the titers are raised. The attitude that the diverted patients live in symbiosis with their urinary bacteria cannot be accepted from results in the present study. However, it is not problem-free to treat patients with antibiotics adequately for a long term when the patients easily are re-infected. Therefore, other measures to prevent or reduce infection in conduit urine should be used: construction of a nipple stoma of at least 2 cm height, frequent emptying of the device, use of a non-return valve in the collecting device, use of a uribag, at least during the night. The volume of residual urine in the conduit is of importance. Thus, a short conduit with unobstructed out-flow should be created. This is preferably achieved by the use of an intraperitoneal ileal conduit. A retrocolically placed conduit is longer and has a higher intraluminal conduit pressure than an intraperitoneally situated one (unpublished observations). Furthermore, the hole through the abdominal wall for the conduit must be created with sufficient excision of muscles, fascia and skin. The nipple stoma reduces the possibility of back-flow. It is also less usual for patients with nipple stomas to develop stomal complications such as strictures (McEwan & Clark, 1973). Conduits with stomas constructed with the mesenterium
to the everted ileal nipple preserved empty better than those with other stomata types (McEwan & Clark, 1973). These facts imply a low volume of residual urine in a conduit with an adequate nipple stoma.

The finding of a smaller kidney on the left side than on the right side after the diversion is in contrast to the normal status where the left kidney is bigger than the right one (Møll, 1961). In the patients in the present study the left ureter had been placed behind the colon. This fact may be of importance. So far, it has not been shown that it is safer to place the ureter intraperitoneally in front of the colon.

There was a closer relation between occurrence of _P. mirabilis_ in the urine and raised _P. mirabilis_ titer than the corresponding relationship for _E. coli_. This fact may be explained by difficulties in treating _Proteus_ and therefore _Proteus_ infections may be long lasting. It may also depend on aggressive properties of _Proteus_ bacteria (Cotran, Thrupp, Hajj, Zangwill, Vivaldi & Kass, 1963; Cotran, Vivaldi, Zangwill & Kass, 1963).

Determinations of antibody titers against _E. coli_ and _P. mirabilis_ are important complementary methods to urinary cultures at follow-up of diverted patients, especially in patients with a low bacterial count in the urine as, so far, the critical bacterial count for "significant" bacteriuria has not been settled for diverted patients. In these cases the titers may be helpful during therapy. The value of titer determinations is further stressed by the fact that the infection is also often symptom-free in patients with pyelonephritis. Besides, the bladder "wash-out" technique with antibiotics in diagnosis of the infection level (Fairley, Carson, Gutch, Leighton, Grounds, Laird, McCallum, Sleeman & O'Keefe, 1971) is unreliable when free ureteral reflux exists.

CONCLUDING REMARKS

Bacteriuria in diverted patients, who often have ureteral reflux may cause renal parenchymal lesions. From a theoretical point of view it should be of great value if ureteral reflux could be prevented. So far, a safe reflux-preventing ureteral implantation technique without risk of anastomotic strictures has not been described. Therefore, it is obvious that the natural uretero-vesical junction with its reflux-preventing properties should be preserved, if possible. In patients with benign diseases this may most easily be achieved by leaving the urinary bladder intact to be emptied by means of intermittent catherization through urethra or through a continent vescicostomy. If the urinary bladder is too small to serve as a reservoir or for other
reasons must be resected in patients with benign diseases it is wise to preserve the "trigone" with the uretero-vesical junction intact for implantation in an ileal conduit or in a reservoir. If possible, the colon should be avoided in patients with a long anticipated life due to the risk of developing carcinoma.

In patients with malignant diseases cystectomy is performed and the "trigone" cannot be preserved. Since more than two decades most diversion operations in these patients are basically performed as ileal conduit as described by Bricker (1950). In spite of this fact it has been difficult to assess the importance of the construction of the stoma, residual urine volume in the conduit and bacteriuria.

Raised antibody titers against E.coli and P.mirabilis show that pyelonephritis due to these bacteria is a common finding in diverted patients. Thus, bacteriuria may imply pyelonephritis. Few of the diverted patients have clinical signs or symptoms of pyelonephritis. Urography can reveal renal parenchymal lesions due to pyelonephritis but does not specify if these lesions are caused by present infection. Therefore, bacteriuria should be treated and, when the antibody titers are raised, treated over a long period of time. As bacteriuria in diverted patients is difficult to assess and difficult to treat, every preventive measure against infection is of value. This prevention starts at the operation by construction of a short, unobstructed conduit with a nipple stoma at least 2 cm in height. Back-flow of infected urine from the device ought to be minimized. This may be achieved by the use of devices with non-return flap valves and by connecting the device to a uribag, at least during the night.

When adequately operated patients, properly examined for infection with urinary cultures and serum antibody titer determinations and adequately treated, have been followed over a long period of time, the ileal conduit method for urinary diversion can be more fully assessed.
GENERAL SUMMARY

In an autopsy study cases with ileal conduit diversion and without cancer at autopsy, had macroscopically recognized infection in the kidneys more often than non-diverted control cases. 45% of diverted cases without cancer at autopsy were attributed to deaths from renal infection. Thus, pyelonephritis is a serious disease in these patients.

In order to assess the possibility of retrograde transport of urine and thereby spread of bacteria from the device and the conduit to the kidneys 89 diverted patients without reflux-preventing ureteral implantation and 25 non-diverted controls were investigated. In 46 patients the back-flow from the urinary collecting device was investigated. Such a back-flow into the conduit was shown to occur in 9 patients (21%). In 6 of these 9 patients the back-flow continued to the renal pelves. A 2 cm high nipple stoma was shown to resist such back-flow better than any flat stoma.

Ureteral reflux occurred in diverted patients at low intraluminal conduit pressure (< 12 cm H₂O) both when the patients were investigated in the supine and in the erect body position. The reflux could not be correlated to intraluminal conduit pressure.

Thus, it was shown that the contents of the device, including bacteria, may easily be conveyed to the kidneys. As sterile urine may be infected, when placed in a collecting device pasted on normal skin, it was concluded that diverted patients may be infected with the ordinary skin bacterial flora as a result of this back-flow from the device. Some measures to reduce this possible conveyance of infection retrogradually are suggested. Thus, a nipple stoma of at least 2 cm height is recommended at the diversion operation. The collecting device should be connected to a uribag during sleep. It is probably wise to use an expendable device with a non-return valve, to empty the device often and to change devices daily.

A relationship between urographical abnormalities recognized as associated with pyelonephritis, and raised serum antibody titers against E. coli and/or P. mirabilis was shown. Most of the "not normal" renal units deteriorated after the diversion operation. It was shown that kidneys deteriorated with time at the same time as the frequency of raised serum antibody titers increased with time after the diversion operation.

The pyelonephritis was usually symptom-free in the diverted patients. However, there was a relationship between occurrence of bacteria in the urine and an
increase in the corresponding serum antibody titers. No specific bacterial count could be settled as "significant" bacteriuria as settled from the antibody titers as patients with a low bacterial count or without bacteria in the urine also had raised titers.

Determination of serum antibody titers against *E.coli* and *P.mirabilis* are valuable complementary methods to urinary cultures in the follow-up of diverted patients.

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