MEGAURETERS is an uncommon condition that has been the subject of much medical speculation.¹ It has been a troublesome clinical problem for the physician inasmuch as the treatment has not been uniformly effective. Patients with this condition develop a gradual dilatation of the ureters and, as time progresses, the renal pelves and caliceal system become dilated. Gradually the renal tissue is compressed, and over a period of time complete destruction of the renal tissue may occur. Rate of progression of the disease varies from patient to patient and, undoubtedly, infection is a complication which intensifies kidney damage. In our experience fatalities have taken place as early as the second year of life; rarely a patient may reach middle age before renal failure occurs.

In reviewing a group of 60 patients with megaloureters, we have been impressed with the variety of complaints and physical findings which have initiated investigation of the urinary system. The paucity of complaints these patients may have is illustrated by the following case history:

A 9-year-old boy was admitted to our hospital in extremis and died a few hours after admission. Necropsy demonstrated megaloureters and hydronephrosis to be the cause of renal failure. A retrospect review of the history with this family failed to uncover any definite complaints that would have been referable to the genitourinary system. The child was smaller than normal for his age but outside of this the family had no clue which might have warned them of progressive renal disease.

In this group of 60 patients, 35 came for medical attention because of urinary tract infection. In 15, failure to gain prompted a general physical examination. Seven patients were found to have leukocytes in the urine on routine analysis, and 5 children had either palpable bladder or kidney on routine examination. This experience has made us more liberal in our indications for an intravenous urogram for patients who are not doing well or who have rather vague complaints with an otherwise normal history and physical examination.

PROCEDURE FOR STUDY OF URINARY SYSTEM

We have been particularly interested in this condition and have endeavored to perform studies of the urinary system in an attempt to classify these patients according to the etiology of the dilatation of the upper urinary tract.
Our routine is that the children are admitted to the hospital and those who prove to have a normal blood urea nitrogen are subjected to intravenous urography. Before any other tests which involve catheterization of the bladder are done, the residual urine is determined by catheterizing the child immediately after voiding. Children normally may have a residual urine volume as high as 10 to 15 ml. More than this amount, it is our belief, indicates some defect in function or an obstruction which prevents complete emptying of the bladder. At the time the residual urine is determined, a specimen is obtained for culture and antibiotic sensitivity studies. The catheter is then left in place for serial cystograms and cystometrograms. The cystometrogram has to be performed under ideal conditions, for if the patient had been catheterized or had an indwelling catheter, even a few days prior to the test, the resulting curve may be unreliable.

In order to standardize the cystometrogram study we have utilized an ink writing recorder with a transducer sensitive in the range of 0-100 ml. of water (Fig. 1). This apparatus makes a permanent and continuous record of intravesical pressure during bladder filling as well as of the timing and intensity of detrusor contractions. It is difficult to obtain good tracings on a child who is not co-operative. By amusing the children we are usually able to secure good tracings even with youngsters of 2 to 3 years of age. Below 2 years of age the cystometrogram is difficult to perform and interpret. To shorten the duration of the test, bladder filling is augmented with a slow drip of a solution consisting of 1 part of 30 per cent Diodrast® to 2 parts of saline. It is advisable to obtain 3 or 4 roentgenograms during filling of the bladder and to record the intravesicular pressure which is present at the time the film is taken. Such a procedure will not only reveal the presence of reflux but also at what stage of bladder filling it occurs. When the patient’s bladder is full and there is discomfort, the examination is discontinued, the catheter is removed from the bladder, and a voiding urethrogram is obtained (Fig. 2). This is essential to rule out mechanical obstruction at the bladder neck or along the course of the urethra. Such a urethrogram is far more informative than a retrograde urethrogram, since abnormalities are more readily outlined during
voiding than when the radio-opaque material is injected retrograde. On the following day cystoscopy is performed and the posterior urethra and bladder neck carefully observed for any form of mechanical obstruction.

**RESULTS**

**Mechanical Obstructions**

Applying these diagnostic tests to patients with megaloureter, only a small number have proved to have mechanical obstruction. Of 60 children, 2 had posterior urethral valves and 1 had a congenital stricture of the urethra. The diagnosis in these conditions is evident on voiding urethograms and on inspection during cystoscopy. These obstructions produce large trabeculated bladders and dilated upper urinary tract. Removal of urethral valves is most readily accomplished with a transurethral resectoscope. The child with a stricutured urethra was treated by dilatation. None of the 60 patients proved to have stricture of the distal part of the ureter. Four patients had a ureterocele as the cause of megaloureters; treatment consists of opening the ureterocele. Six patients with neurogenic bladders have been observed to have megaloureters. The etiology is an increased intravesicular pressure rather than a defect in the ureter itself. Treatment of these patients is too complex for a review of the subject in this place.

**Aparasympathetic Bladders**

Thirty-two of the sixty patients have been found to have the following deviations from normal in their urinary tract: The residual urine volume is elevated, frequently being over 100 ml., and in some patients it has been as high as 600 ml. Ureteral reflux from the bladder is fairly common but does not invariably occur. The cystometrogram tracing deviates from the normal considerably. In a series of patients with normal bladders, in whom we have had an opportunity to perform cystometrograms with the type of recording apparatus described, the initial intravesical pressure has been near zero. During filling, the pressure gradually increases to 10 or 15 cm. (Fig. 3). In a 4- to 6-year-old child, when the bladder contains 150 to 200 ml. of fluid the patient has a strong urge to void and there are powerful detrusor contractions. Usually the pressure does not exceed 15 cm. of water prior to initiation of powerful detrusor contractions.

Patients with megalobladder and megaloureters have been found to have large bladder capacity (Fig. 4). A 4- or 5-year-old child with this condition may tolerate 400 to 500 ml. of fluid injected into the bladder without discomfort. Such patients seem to have a loss of sensation in the bladder, and it is the generalized abdominal discomfort at the extreme of filling rather than a specific bladder discomfort which prompts them to attempt to micturate. They empty the bladder by increasing intra-abdominal pressure; consequently the urinary stream is feeble, and voiding consumes more time than in normal individuals. The intravesicular pressure is excessive, averaging 20 to 25 cm. of water before abdominal discomfort is noted. One patient had an intravesicular pressure of 40 cm. of water. In view of the fact that the average ureteral peristaltic wave generates a pressure of 35 cm. of water, the patient with an intra-
vesicular pressure of 20 or 25 cm. of water requires more work of a ureter than when the bladder is normal, with a pressure of 12 cm. or less. In addition such patients have weak or completely absent detrusor contractions. Occasionally there may be a pro-
longed contraction, developing a pressure of 10 or 20 cm. of water, compared to a normal detrusor contraction which develops a pressure of 100 cm. of water or more. At cystoscopy no obstruction in the urethra, bladder neck or ureterovesical junction was found in these patients. The bladders were smooth in outline and showed evidence of chronic infection, and the urethral orifices were enlarged if reflux was present. Each ureter was catheterized and peristalsis recordings made employing the same equipment used for cystometrograms (Fig. 5). In normal ureters peristalsis occurs at 15- to 20-second intervals and each contraction develops a flow of urine with a pressure of 35 to 40 cm. of water. Anesthetic agents and preoperative medication have no influence on this function. In patients with mega-}

Fig. 4. Cystometrogram from patient with a parasym pathetic bladder.

Fig. 5. Ureteral peristaltic tracings showing one of normal amplitude and others diminished.
cult, tedious and time consuming to perform, retrograde pyelograms are made.

We have had an opportunity for histologic examination of 8 bladders from patients who seemed to fit all the clinical criteria of megalobladder and megaloureters, of the type outlined. It was found upon careful study of sections of the whole bladder that there is a marked diminution in ganglion cells as compared to the normal concentration and distribution (Figs. 7 and 8). This suggests the possibility of a congenital parasympathetic defect in the bladder to account for the dysfunction. Generally it is agreed that detrusor function, that is bladder contraction, is dependent on intact parasympathetic innervation. We have tested this in the laboratory by the following experiments. Ten healthy female dogs were subjected to catheterization, and cystometrogram tracings revealed normal pressure and active detrusor contractions. Bilateral division of the parasympathetic nerves were performed, and repeat cystometrograms revealed no bladder contractions and this absence persisted over a 3-month period. We do not consider this experimental lesion to be fully comparable to the congenital defect, however, it does indicate the relationship of the parasympathetic system to bladder contractions.

It has been interesting in studying patients with megacolon to demonstrate that about 50 per cent have some defect in bladder function detectable on careful cystometrogram studies, consisting of large capacities and absent detrusor contractions. However, they have normal residual urine volumes and intravesical pressures are normal. In about 3 per cent of patients with megacolon we have studied, the lesion in the bladder is more pronounced and then megaloureters are associated with megalobladder. In these patients the bladder has the same changes that we have noticed in patients with megaloureters and megalobladders but with normal colon. The changes referred to are: increased capacity of the bladder; feeble or absent detrusor contractions; high residual urine volume, and high intravesical pressure.

It would seem reasonable that in patients with a congenital defect in the pelvic parasympathetic system, and consequently no ganglion cells in the distal part of the colon, a few would have a defect in the parasympathetic innervation of the bladder. A congenital defect in the pelvic parasympathetic system may produce 3 types of patients. If limited to that portion of the pelvic nerves which supply the distal part of the colon, the patient would have congenital megacolon with a normal urinary system. A second type of patient might have a more extensive malformation and consequently function of both the colon and urinary bladder might become defective. We have observed such patients in the group of children with congenital megacolon and megaloureters we have studied.
Logically there should be a third type of patient with normal colon and a defect in that part of the pelvic parasympathetic system which supplies the bladder. We believe that this comprises the group of patients with megalobladder and megaloureters, and we have designated them as having an aparasymathetic bladder. Such patients have a defect in function which is less pronounced than that noted in cord bladder, for they are never incontinent. From these studies we concluded that patients in the group with aparasymathetic bladder have dilatation of the upper urinary tract secondary to a defect in bladder function. Should this be true, bladder drainage would be effective treatment. With this in mind, 24 such patients were treated by either suprapubic drainage or a catheter in the urethra and improvement occurred in all.

Prolonged drainage of the bladder is not a convenient method of treatment either for the child or parent. In order to reduce the residual urine and to aid the children in emptying the bladder, resection of the bladder neck has been performed. The rationality of this treatment is appreciated upon realization that opening of the internal sphincter or the bladder neck is a function of the detrusor muscle (Fig. 9). These children have a defect in detrusor contractions and as a result there appears to be ineffective opening of the bladder neck; this, plus feeble contractions of the bladder, probably results in the large residual urine volume which is common in this condition. The internal sphincter has no essential functions and can be eliminated without endangering the child's continence. Either transurethral resection of the bladder neck, or resection through open cystotomy, has been performed on 15 patients with an aparasymathetic bladder.

The most important feature of treatment consists in having the patient make a sustained effort to empty the bladder completely. Usually this can only be accom-
Sections of bladder neck showing detrusor fibers before and after resection.

1)lished by the aid of manual suprapubic pressure. Because these children have no sense of bladder fullness until the bladder contains excessive amounts of urine under high pressure, it is equally important to have them void at regular intervals despite the absence of a sense of bladder fullness. A schedule of 4 or 5 voidings a day and 1 or 2 at night is ideal, for under such circumstances the intravesical pressure is never greatly above normal.

Treatment of urinary infection is also important and should consist of small doses of sulfisoxazol for long periods of time. These patients should be regarded as having a chronic disease and regular visits to the physician should be made. At monthly intervals urinalysis will give an indication of the amount of infection. A large number of leukocytes in the urine should prompt catheterization for residual urine and culture to determine the organism and test the sensitivity to various therapeutic agents. When exacerbations of infection occur, a more potent agent than sulfisoxzol is desirable for short periods. Roentgenograms should be made annually to determine the course of the disease. It has been necessary to do a second resection on some of these patients in order to maintain normal residual urine volumes. Our longest follow-up is on a patient 18 years of age, first seen at 11 years (7 years ago), with fairly advanced hydronephrosis, megaloureters and megalobladder (Fig. 10). Initially the blood nonprotein nitrogen was 66 mg./100 ml. A period of bladder drainage was beneficial. This was followed by 2 transurethral resections in order to reduce the large residual urine volume to normal. Until this was accomplished the infection could not be controlled. This co-operative patient has voided on a regular schedule of 5 times a day and once at night to prevent development of high intravesical pressure. The blood urea nitrogen has remained normal and urorograms are now essentially normal. Out of a group of 15 patients subjected to resection all but 2 have done well. For a period of time we were resecting a large part of the fundus. The 2 patients who have not done well had more extensive removal of the bladder wall than the others, and the intravesical pressures are higher now than prior to operation. This experience has prompted us to discontinue resection of part of the bladder. There has been 1 death—a child who died of monilia infection after prolonged intensive antibiotic treatment.

In this condition direct operations on the ureter are not indicated. Actually the ureter has normal peristalsis without evidence of ureterovesical obstruction, and attempts to shorten such ureters or to re-implant them into the bladder are of no avail; the fundamental defect is in bladder function.4 Operations on the lower end of the ureter are
contraindicated due to the fact that additional damage to the innervation of the bladder may be sustained during such procedures. We have seen 1 patient who had bilateral operations on the lower end of the ureter, and there was inability to empty the bladder postoperatively, and the patient was committed to permanent catheter drainage. Our interpretation of this result is that the patient initially had considerable defect in parasympathetic innervation of the bladder and that inadvertently during operation on the lower end of the ureter, an area where innervation enters the bladder, the meager nerve supply was damaged with the result that the patient was unable to void postoperatively. In other patients the residual urine volume has risen considerably after this type of operation, indicating damage to the bladder innervation. In this disease it is far more logical and effective to attack the basic pathology which is in the bladder. We have observed 2 patients with agenesis of the abdominal wall associated with megalobladder and megaloureters; these patients have not fared differently from other children with this condition except that they seem to do better as the abdominal wall grows more firm later in life. Perhaps, this is due to the fact that they are able to empty the bladder more effectively with increased intra-abdominal pressure.

Absence of Ureteral Peristalsis

In the course of studies of patients with megaloureters, 15 have been found to have essentially normal bladders with no residual urine. In studying these patients for ureteral peristalsis we found an absence of, or only feeble, contractions. Some of these children apparently have a congenital defect in the ureter to account for the absence of peristalsis. It has been suggested that infection is the cause of the absence of ureteral peristalsis. However, we have studied some patients who had quite extensive urinary tract infection with perfectly normal ureteral peristalsis. It is true that some of the
patients have had some slight return of function after prolonged treatment of the infection. This may indicate that in certain instances infection may play a role in dampening or diminishing ureteral peristalsis, but where there is complete absence of peristaltic activity, after repeated studies, we are inclined to believe that it is probably on a congenital basis. Unfortunately one cannot gain the answer to this question from studying the ureters histologically, for normally there are few if any ganglion cells in this structure. Therefore, this method of studying the autonomic innervation of an organ which has been so useful in the colon and bladder is of no avail in the ureter. Regardless of the etiology of absent peristalsis, the defect in function leads to considerable enlargement of the ureter and of the renal pelvis. It has been extremely difficult to control infection in these patients. Providing infection is eradicated, these children may go on with very little progression of the disease and do well generally. In some instances control of infection has been impossible and in some, dilatation of the ureters and pelves has occurred. One patient in this group died with renal failure. The lack of effective therapy for such patients prompted us to seek a substitute for ureters deficient in peristalsis.

In dogs, segments of the small intestine were isolated and the lumen reduced in size by excising three-quarters of the wall. This left a narrow strip of intestinal wall attached to the mesentery which could be sewed into a small tube not much larger than a normal ureter. At a second stage, the ureter on one side was removed and replaced by this previously prepared narrow ileal segment. We were gratified with the results in the laboratory. The function seemed to be adequate and infection was not a problem. Furthermore, there seemed to be no perceptible reabsorption of electrolytes through the small surface area of ileal mucosa exposed to urine. In the past, full-size segments of ileum had been used to replace the ureter.

![Fig. 11. Intravenous pyelogram of patient with right aperistaltic ureter before (left), and 10 months after replacement with narrowed segment of ileum (right).](http://pediatrics.aappublications.org/)
was faced with anastomosing the full-sized lumen of the small intestine to the bladder, and chances of reabsorption were greater because of the enlarged ileal surface area. We concluded that narrowing the lumen would overcome all of the objections to a large extent. Because of our favorable experience in the laboratory, 6 patients were subjected to this procedure with gratifying results. It has been interesting to study the peristaltic activity of these narrow segments of small intestine. Peristaltic contractions with pressures as high as 70 and 80 cm. of water have been recorded, which indicate that these "ureters" made from small intestine have considerably more effective pumping action than a normal ureter. One patient has been followed for 10 months after replacement of the right ureter (Fig. 11). The problem in this particular patient preoperatively was uncontrolled infection. There has been no urinary infection since the aperistaltic ureter was replaced with a segment of small intestine, and the hydronephrotic kidney has returned to normal. It would seem that in patients with aperistaltic ureters or ureters with defective peristalsis, where infection cannot be controlled or where there is progression of the disease, replacement with ileal segments offers a practical form of treatment.

SUMMARY
Studies on 60 patients with megaloureters are described.
Thirty-two patients proved to have a defect in parasympathic innervation of the bladder. The defect in bladder function was the cause of ureteral dilatation. Bladder neck resection is the treatment of choice.
Fifteen patients proved to have defects in ureteral peristalsis as the cause of ureteral dilatation. Replacement of some of these defective ureters with narrowed segments of ileum has proved successful.

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