MEDICAL GRAND ROUNDS

Clinical and Physiological Consequences of Urinary Tract Obstruction

James B. Gross, M.D.

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Introduction

Obstruction to the normal drainage of glomerular filtrate remains a clinically important problem. Its significance lies not only in the frequency with which obstruction is missed by clinicians but also in the potentiality for restoration of some degree of renal function. In general, the internist tends to consider the area of obstructive uropathy the province of the urologist and this attitude is often reflected in his general ignorance of clinically important principles related both to diagnosis and management of obstructive disease. Although the relief of urinary tract obstruction is in most cases a surgical problem, it should be obvious that the therapeutic efficacy of the urologist is directly dependent on the diagnostic skill of the primary physician; most patients with urinary tract symptoms do not consult a urologist initially. Thus, the responsibility for detection, evaluation and consideration of a proper therapeutic course rests largely with the internist and general practitioner, supplemented by the consultative and technical skills of the urologist.

I. GENERAL CONSIDERATIONS

A. Incidence

In autopsy series, the frequency of hydronephrosis varies from 3.5 to 3.8 per cent (1,3).

In children, hydronephrosis is the most common cause of an abdominal mass in the neonatal period. Since urine formation begins in the fourth month *in utero* an infant may be born with hydronephrosis. Complete obstruction of a kidney early *in utero* results in a dysplastic, cystic kidney, whereas later obstruction causes hydronephrosis. Experimental studies by Beck have confirmed this clinical observation (2). Obstruction occurs with about equal frequency as regards sex. Campbell found, in a post-morterm study of 16,000 children that 2% had hydronephrosis, 81% of whom were one year of age or less, and 60% of the cases were in males. In older children the incidence is less: 4.4% were aged 3-10, 3.5% were 11-15 years (3).

In young and middle aged adults, hydronephrosis is more common in females because of the frequency of pregnancy and carcinoma of the cervix. When hydronephrosis does occur in young males, it is usually due to calculous disease, which affects one in every 1,000 Americans yearly. In late adult life, obstructive uropathy is more common in men, reflecting the increasing incidence of benign prostatic enlargement and prostatic cancer with increasing age.

1. Hinman, F. and Hinman F., Jr.: Hydronephrosis. In *Urology*, Karafin, L. and Kendrall, A.R. (eds.) Harper and Row, New York, 1971.

2. Beck, A.P.: The effect of intra-uterine urinary obstruction upon the development of the fetal kidney. J. Urol. 105:784, 1971.

3. Campbell, M.F.: Urinary obstruction. In Urology, 3rd Ed., Vol. 2, Campbell, M.F. and Harrison, J.H. (Eds.). W.B. Saunders Co., Philadelphia, 1970.

B. Sources of Obstruction

Obstruction of the urinary tract may be either purely mechanical or functional (i.e., failure of normal urodynamic mechanisms). Causes of mechanical obstruction are obvious. Common functional lesions include: adynamic ureteral segment (congenital megaureter), vesicoureteral reflux, and neurogenic bladder.

The site of obstruction may exist anywhere from the level of the renal tubule (as in multiple myeloma, uric acid nephropathy) to the urethral meatus (as in phimosis). Both the site and type of obstruction varies in frequency with both age and sex. In childhood, urinary obstruction is most commonly caused by congenital malformations, such as ureteropelvic junction stricture, abnormal insertion of the ureter into the bladder, anomalous location of the ureter (retrocaval ureter, ectopic ureter), and posterior urethral valves. In fact, urethral valves are the most common cause of bilateral hydronephrosis in the male child. Other causes of obstruction in childhood are bladder malfunction secondary to myelodysplasia, congenital ureteric or urethral strictures, urethral meatal stenosis, and occasionally, duplication of the collecting system (4). Although obstruction frequently complicates the latter disorder, this is by no means invariable. Finally, the entity of "bladder neck obstruction," previously thought to be a common entity among obstructive lesions in childhood, is probably quite uncommon (5).

In the adult female, the most common causes of obstruction are pregnancy, calculi, and pelvic malignancies. In addition, ligation or injury to the pelvic ureter during pelvic surgery often results in undetected unilateral hydronephrosis. Routine pelvic surgery is associated with a 0.5% to 3.0% incidence of ureteral trauma, whereas radical pelvic surgery for carcinoma of the cervix results in ureteral injury in 10% of cases (6).

Urethral stricture is a frequently diagnosed condition in females with recurrent urinary tract infections or symptoms of urinary frequency and urgency. However, such "strictures" rarely cause sufficient obstruction to lead to impairment of renal function.

Extensive compression of the ureter by neoplastic or inflammatory processes must always be considered. In the latter category are several disorders, including retroperitoneal fibrosis, an entity which may be closely related to it pathogenetically--periureteritis plastica, pelvic endometriosis, and retroperitoneal inflammatory disease associated with regional enteritis and/or granulomatous colitis.

Listed in Tables I-III are the commonest causes of urinary tract obstruction in children, adult females and adult males, respectively. A more

comprehensive list of types of obstructive lesions according to anatomic location is provided in Table IV.

4. Howards, S.S., and Wright, F.S.: Obstructive injury, In The Kidney, Brenner, B.M. and, Rector, F.C., Jr. (Eds), W.B. Saunders Co., Philadelphia, 1976.

5. Smith, D.R.: Critique of the concept of vesical neck obstruction in children. J.A.M.A. 207:1686, 1969.

6. Orkin, L.A.: Trauma to the Ureter. F.A. Davis Co., Philadelphia, 1964.

TABLE I

MAJOR CAUSES OF OBSTRUCTIVE UROPATHY IN CHILDHOOD

Ureteropelvic Junction Stricture
Abnormal Bladder Insertion of the Ureter
Anomalous Location of Ureter (Retrocaual, Ectopic)
Posterior Urethral Values
Congenital Ureteric "Stricture" (Congenital Megaureter) or Urethral Stricture
Urethral Meatal Stenosis
Myelddysplasia with Neurogenic Bladder
Duplication of the Collecting System

TABLE II

COMMON CAUSES OF OBSTRUCTIVE UROPATHY IN ADULT FEMALES

Pregnancy (Rarely a Cause of Severe Obstruction)
Calculi
Pelvic Malignancies
Ligation and/or Injury to Ureter
During Pelvic Surgery
U-P Junction Obstruction (With or Without Fibrous Bands or Aberrant Vessels)

TABLE III

COMMON CAUSES OF OBSTRUCTIVE UROPATHY IN ADULT MALES

Calculi
Benign Prostatic Enlargement
Prostatic Carcinoma
Urethral Stricture
Spinal Cord Injury with Neurogenic Bladder
U-P Junction Obstruction (with or without Fibrous Bands or Aberrant Vessels)

TABLE IV
(Taken from Reference 4)

CAUSES OF URINARY OBSTRUCTION

Level of Obstruction	Pathological Processes
I. All	Calculi
	Papillary tissue
	Trauma
	Blood clots
	Fungus balls
II. Tubule	Uric acid
	Polycystic kidneys (adult and childhood types)
	Protein in multiple myeloma
	Acute tubular necrosis (?)
III. Renal Infundibulum	Tuberculosis
	Peripelvic cyst
	Primary urothelial tumor
	Polycystic kidney
	Renal neoplasm
	Renal cyst
	Aberrant vessel
	Hydatid cyst
IV. Renal Pelvis	Wilms' tumor
	Ectopic kidney
	Tuberculosis

TABLE IV
(Taken from Reference 4, Continued)

CAUSES OF URINARY OBSTRUCTION

Level of Obstruction	Pathological Processes
IV. Renal Pelvis	Fibrous bands at UP junction
	Ureteropelvic stricture acquired or congenital
	Aberrant vessel at UP junction
V. Ureter	
A. Retroperitoneal Disease:	Lymphoma
	Metastatic or primary carcinoma
	Aortic aneurysm
	Retroperitoneal fibrosis
	Hemangioma
	Retroperitoneal hemorrhage
	Ovarian vein
	Retroperitoneal abscess
	Uroma post trauma
	Lymphocele
B. Congenital Disease:	Stricture
	Ureterocele
	Retrocaval ureter
	Ectopic kidney
	Ureterovesical reflux
	Diverticulum
	Ectopic position of orifice
	Adynamic ureteral segment
	Ureteral valve
	Mesenteric cyst
C. Primary Genitourinary Disease:	Carcinoma of the ureter and bladder
	Ureteral polyp
	Neurogenic bladder
	Ureteritis cystica
	Gumma of ureter
	Tuberculosis
	Schistosomiasis haematobia
D. Miscellaneous Disease:	Abdominal and pelvic neoplasm
	Granulomatous bowel disease
	Acquired traumatic ureteral stricture (postinstrumentation)

TABLE IV
(Taken from Reference 4, Continued)

CAUSES OF URINARY OBSTRUCTION

Level of Obstruction	Pathological Processes
V. Ureter	Congenital absence of the abdominal musculature ("prune belly")
	Endometriosis
	Pregnancy
	Obstetrical trauma
	Antituberculous therapy
	Nephrotosis
	Radiation therapy
	Renal artery aneurysm
VI. Bladder and Posterior Urethra	Benign prostatic hypertrophy
	Foreign body
	Hypertrophy of verumontanum (?)
	Müllerian remnant cyst
	Contraction of the bladder neck (acquired or congenital)
	Posterior or median bar
	External sphincter spasm (?)
	Hydrocolpos
	Carcinoma of prostate
	Carcinoma of the bladder
	Sarcoma of the bladder or prostate
	Sarcoma of the seminal vesicles
	Neurogenic bladder
	Inflammatory diseases of the prostate
	Hematocolpos
	Prostatic abscess
VII. Urethra	Valves (posterior and anterior)
	Diverticulum
	Phimosis
	Meatal stenosis
	Stricture (acquired-infections or traumatic)
	Stricture (congenital)
	Condyloma acuminata of the urethra
	Paraurethral abscess
	Foreign body

TABLE IV
(Taken from Reference 4, Continued)

CUASES OF URINARY OBSTRUCTION

Level of Obstruction	Pathological Processes
VII. Urethra	Polyp Meatal atresia Hypospadias Carcinoma of the urethra Carcinoma of the penis Epispadias Ectopic ureter

II. SPECIFIC CAUSES OF OBSTRUCTION

A. Prostatic Hypertrophy

Prostatic Hypertrophy is clearly the most common cause of obstructive uropathy in males. Although the symptoms are those of bladder outlet obstruction (hesitancy, intermittency, frequency, nocturia, decreased size and force of stream, post-void dribbling) many patients deny any symptoms except, possibly, nocturia, and will not present to the physician until obstruction is far advanced. In many cases the first presentation is that of acute urinary retention, often occurring in patients already hospitalized for other reasons. Acute retention may develop in patients previously minimally symptomatic as a result of systemic illness, prolonged immobilization, or administration of drugs which interfere within the normal function of the bladder detrusor musculature, e.g. anticholinergics.

It is well established that both the symptoms as well as physical findings on digital exam of the prostate correlate poorly with the actual degree of functional obstruction of the bladder outlet. Moreover, even cystoscopy and cystography/urethrography may fail occassionally in delineating the degree of anatomic obstruction. Trabeculation of the bladder may not be related causally to prostatic enlargement in all cases, but rather may be caused by the functional obstruction of a neurogenic or dystonic bladder. Conversely, absence of trabeculation is not an invariable accompaniment of significant bladder outlet obstruction.

As a result of these considerations, the urodynamic evaluation of bladder function has gained increasing recognition in many centers as an

important asset in the evaluation of the nature and extent of bladder outlet obstruction. Although it is probably not necessary in most cases, urodynamic evaluation can be very useful in selected problem cases--e.g., patients with major discrepancies between symptomatology and radiographic findings and those in whom other common causes for bladder dysfunction are likely. An example of the latter cases would be a diabetic with prostatic enlargement and symptoms of prostatic obstruction as well as peripheral neuropathy. In this situation, it may be difficult to determine by standard investigative techniques whether the obstruction is functional, resulting from a neurogenic bladder, or mechanical (due to urethral encroachment by the large prostate). Here urodynamic assessment of urine flow as well as intravesical pressure determinations can provide critical data which would allow accurate assessment of the potential efficacy of surgery.

It should also be emphasized that not all patients with BPH experience progressive worsening of symptoms with time. Thus, a patient with only modest symptoms, who is free of infection and who has normal upper tracts can be managed medically until a clear indication for surgery arises.

A more detailed discussion of the use of urodynamics and radiographic techniques is given in the subsequent section on diagnostic evaluation.

B. Retroperitoneal Fibrosis

This uncommon disorder is probably one manifestation of a generalized disease process which includes cases of mediastinal fibrosis, ischemic non-a theromatous heart disease, fibrosing cholangitis, Riedels thyroiditis, protein-losing enteropathy, cutaneous vasculitis, and pseudotumor of the orbit. Comings has reported familial instances of this syndrome in which varying combinations of its components have been observed in members of the same family who were the offspring of a consanguineous marriage (7). Retropenitoneal fibrosis, however, is clearly the most common clinical manifestation. Although there may be a genetic component in some cases, other cases appear to be related in some way to pre-existent pelvic inflammation. In addition, the development of the disease has been frequently related to administration of one of several drugs, including ergotomine, dihydroergotamine, hydralazine, and most commonly, methysergide. It has been estimated that 50-60 cases of retroperitoneal fibrosis have resulted from methysergide in over 500,000 individuals receiving the drug for treatment of migraine (8). Although an autoimmune etiology has been implicated on the basis of the typical high sedimentation rate and occassional association with Raynaud's phenomenon, hypergrammaglobulinemia, presence of antinuclear factor, and coexistence of systemic lupus erythematous (9), the etiology of this disorder remains unestablished.

The disease process most commonly involves the retroperitoneal tissue in the midline at the L_4, L_5 level and may entrap one or both ureters; in

most cases both ureters are eventually involved. Because of the insidious progression of ureteral obstruction, most patients are minimally symptomatic until renal failure has developed. When symptoms are present they are usually vague, dull back, flank or abdominal pain, anorexia, weight loss, low grade fever, and symptoms related to anemia. Many patients first present with symptoms only of uremia. Laboratory findings include and elevated sedimentation rate, mild to moderate anemia, azotemia, and hypergommaglobulinemia.

Pyelography has been classically described as demonstrating gradual tapering of ureteral outlines and medial deviation of the ureters at the level of the pelvic brim. This observation has been recently challenged by Arger, et al, who compared the course of the ureters visualized by intravenous pyelography with that of 60 normal individuals. There was no significant difference in the course of the urefers in the two groups, indicating that the "medial deviation" is only apparent and that the fibrosing process merely entraps the ureters in the normal course over the pelvic brim (10). Although extension of the process to the upper ureters and pelvis has been reported, involvement of the lower 1/3 of the ureter does not occur. At cystoscopy, it is usually possible to pass a catheter with ease through the involved segment of ureter and into the pelvis. It thus appears likely that in most cases the obstruction is only relative and may involve failure of the normal peristaltic propagation of ureteral contraction through the involved segment.

Surgical relief of the obstruction is often successful and involves dissection of the ureters free of their fibrous encasement, bringing them out onto the anterior surface or the fibrotic mass. The results of this procedure have generally been satisfactory, although occassional cases of recurrence of ureteral entrapment have been reported. There have been occassional reports of successful treatment with corticosteroids alone (11), but there have been no controlled studies, and most authors have found steroids ineffective (12,13). In those cases associated with methysergide administration, withdrawal of the drug has occassionally been associated with regression of the process and relief of obstruction (14).

In most cases, surgical relief has not led to a complete return of normal renal function, however the increase in GFR is generally striking and of sufficient degree to sustain life adequately without the need for dialysis. The results of surgical relief of obstruction on subsequent renal function are shown in six recently reported cases (15) in Table V. It is imperative that long-term follow-up of patients after surgery be instituted in order to detect cases of recurrent obstruction.

TABLE V

EFFECT OF SURGICAL RELIEF OF OBSTRUCTION FROM RETROPERITONEAL FIBROSIS ON RENAL FUNCTION (FROM REFERENCE NUMBER 15)

Case	Pre-Op BUN (mg %)	Last Post-Op BUN
1	186	35
2	250	33
3	189	34
4	33	34
5	190	84
6	169	42

7. Comings, D.E., Skubi, K.B., Van Eyes, J., and Motulsky, A.G.: Familial multifocal sclerosis. Ann. Intern. Med. 66:884, 1967.

8. Gelford, G.J., Wilets, A.J., Nelson, D., and Kroll, L.L.: Retroperitoneal fibrosis and methysergide: Report of three cases. Radiology 88:976, 1967.

9. Lipman, R.L., Johnson, B., Berg, G., and Shapiro, A.P.: Idiopathic retroperitoneal fibrosis and probable systemic lupus erythematosus. J.A.M.A. 196:1022, 1966.

10. Arger, P.H., Stolz, J.L., and Miller, W.T.: Retroperitoneal fibrosis: An analysis of the clinical spectrum and roentgenographic signs. Am. J. Roentgenol., Rad. Therapy Nucl. Med. 119: 812, 1973.

11. O'Regan, R., Trealry, P.A., and Prior, I.A.M.: Idiopathic retroperitoneal fibrosis. A case presenting with renal failure, treated effectively with adrenal steroids. New. Zeal. Med. J. 60:518, 1961.

12. Bartholomew, L.G., Cain, J.C., Woolner, L.B., Utz, D.C., and Ferris, D.O.: Sclerosing cholangitis: Its possible association with Riedel's struma and fibrosing retroperitonitis. New. Eng. J. Med. 269:8, 1963.

13. Stueber, P.J.: Primary retroperitoneal inflammatory process with ureteral obstruction. J. Urol. 82:41, 1959.

14. Gelford, G.J., and Cromwell, D.K.: Methysergide, retroperitoneal fibrosis and rectosigmoid stricture. Am. J. Roentgenol., Rad. Therapy Nucl. Med. 104:566, 1968.

15. Jones, J.H., Ross, E.J., Matz, L.R., Edwards, D. and Davies, D.R.: Retroperitoneal fibrosis. Am. J. Med. 48:203, 1970.

C. Periureteritis Plastica

This entity was first reported in 1953 by Vest and Barelare (16). It is characterized by ureteral obstruction secondary to a periureteral inflammatory fibrous mass which forms a hose-like sheath encasing the ureter. It may occur unilaterally or bilaterally, although unilateral involvement, especially of the right ureter, is more common. Most cases have been associated with prior lower urinary tract infection (16), although one case developed after staphyloccal sepsis and hematogenous pyelonephritis (17). The pathology of the stricturing lesion is that of a fibrosis with chronic inflammatory reaction, and in some cases bacterial organisms have been identified within the mass (16). It thus appears that this disorder is related to chronic suppurative infection of the lower urinary tract and may represent extension of the inflammatory response thru the ureteral wall, producing a periureteritis with eventual development of fibrous proliferation. Alternatively, it has been postulated that chronic cystitis is the initial lesion. Because the lymphatic drainage of the bladder communicates with that of both ureters, and on the right side there are numerous anastomoses between lymphatics draining the lower ureter and bladder with those draining the upper ureter, it is possible that chronic suppurative cystitis may result in extension of the infection to the periureteral lymphatics, and eventually lead to a fibrotic encasement of the ureters (16). This hypothesis could also account for the propensity for involvement of the right ureter.

In most cases of this rare syndrome, the ureters can be surgically freed from their entrapment, although temporary urinary diversion may be necessary.

16. Vest, S.A., and Boulare, B., Jr.: Peri-ureteritis plastica: A report of four cases. J. Urol. 70:38, 1953.

17. Behrens, M.M., and Holland, J.M.: Peri-ureteritis plastica: Report of a case following staphylococcal infection. J. Urol. 97:829, 1967.

D. Granulomatous Bowel Disease

It remains poorly appreciated that regional enteritis with or without colonic involvement is frequently associated with hydronephrosis. In the

series reported by Schofield, et al, (obviously a highly selected group) 50% of patients with severe involvement with regional enteritis had some evidence of ureteral stasis when studies by radioisotope enography (18). While this certainly is an overestimate of the frequency of obstructive uropathy in this disorder, it underscores the need for diagnostic awareness.

Although urolithiasis is common in patients with inflammatory small bowel disease (usually oxalate stones) and accounts for most cases of hydronephrosis, it is less well appreciated that ureteral encasement by retroperitoneal extension of the intestinal inflammatory process may occur. Present, et al, (19) found this complication in 7% of 150 consecutive patients with granulomatous bowel disease.

Although either ureter may be involved, the right side is most commonly affected. The patient is usually free of urinary tract symptoms and the only clue to the presence of this complication is pain either in the hip, anterior aspect of the thigh, or flank, presumably reflecting psoas involvement with compression or irritation of the innervation of the hip and thigh. Because of the paucity of symptoms, however, an IVP should probably be part of the routine work-up of all patients with granulomatous bowel disease.

Treatment of the urinary obstruction is difficult and fraught with all of the complications associated with abdominal surgery in this disease. The inflammatory mass is usually so dense, often with adherent bowel loops, that any attempt to mechanically free the ureter is probably unjustified. Present, et al, indicate that the initial surgical procedure should be a bypass of the diseased bowel segment. In many cases the inflammatory process will subside and the obstruction will be relieved or at least diminished. If hydronephrosis persists, an attempt should then be made to excise the diseased bowel segment. Only if the latter procedure is also unsuccessful should a direct attempt to free the ureter be made. One would expect that attempts at urinary diversion in this clinical setting would be fraught with a high incidence of fistula formation between bowel and urinary tract. In cases where surgical attempts to relieve the obstruction, as outlined above, have failed, one is faced with a decision as to the advisability of nephrectomy. If there has been recurrent infection of the obstructed kidney, nephrectomy should probably be done at this point, if the contralateral kidney is uninvolved. If, however, the patient has been free of infection, it is probably wisest not to further intervene, and simply to follow the patient carefully.

The differentiation of this complication from that due to calculous disease, which is a relatively simple surgical problem, is usually not difficult. In the former case the IVP shows a gradual, smooth tapering of the dye column at the level of ureter obstruction, whereas with blockage due to stone there is usually an abrupt cut-off of the dye column, often with a relatively concave termination (19).

18. Schofield, P.F., Staff, W.G., and Moore, T.: Ureteral involvement in regional ileitis (Crohn's disease). J. Urol. 99:412, 1968.

19. Present, D.H., Rabinowitz, J.B., Banks, P.A., and Janowitz, H.D.: Obstructive hydronephrosis, a frequent but seldom recognized complication of granulomatous disease of the bowel. N.E.J.M. 280:523, 1969.

E. Intratubular Obstruction

There is reasonably good evidence that intratubular obstruction is of pathophysiologic significance, and plays a major role in the etiology of renal failure in only two disorders - uric acid nephropathy and renal failure associated with multiple myeloma. A recent report suggests that, in addition, obstruction of the collecting ducts by casts of mucoproteinaceous material may rarely result in renal failure in patients with adenocarcinoma of the pancreas (20) and possibly, by inference, in patients with other mucus-secreting adenocarcinomas.

"Uric acid nephropathy" results from massive precipitation of uric acid in the distal tubules and collecting ducts in the clinical setting of massive elevations of the plasma uric acid concentration. The latter situation is usually encountered in patients with myeloproliferative disorders or multiple myeloma, especially when in relapse and receiving cytolytic drugs (21). Histologically, intratubular obstruction secondary to uric acid crystals in the distal tubules and collecting ducts, with intact proximal tubular epithelium, is characteristic. The alterations in renal function also more closely resemble those of obstruction than those of the usual types of nephrotoxic renal failure (22).

Although controversy still ranges about the extent to which intratubular proteinaceous casts cause physiologic obstruction in multiple myeloma, most authorities agree that, in the setting of myeloma kidney, as well as after dehydration preparatory for intravenous pyelography, obstruction of the distal nephron by eosinohillic, lamellated proteinaceous casts plays a major role in the deterioration of renal function (23). The presence of Bence Janes proteinuria greatly increases the incidence of renal failure. These proteins, dimers of L-chains with a molecular weight of 22,000 are easily filterable at the glomerulus in their monomer form. In the distal tubule and collecting duct, where tubular fluid pH progressively falls to the range of 4.5-6.0, and with increased concentration of these monomers as a result of water abstraction, dimerization, precipitation, and cast formation likely occur, resulting in tubular obstruction (23).

There has been a single recent case report of renal failure in a patient with adenocarcinoma of the pancreas (20). The kidneys at post-mortem were

of normal size, with patent vessels and normal glomeruli, but showed distention and plugging of distal and collecting tubules by casts which stained positively for mucoproteins. The urine on electrophoresis showed prominent bands of B and γ mobilities which stained with PAS, and identical PAS-staining bands were found in an extract of the tumor. Serum electrophoresis and immunoelectrophoresis showed normal immunoglobulins, no L-chains, and α 1 and α 2 globulin peaks. Thus it appears that, in association with mucin-producing adenocarcinomas, under rare circumstances certain mucoproteins or fragments thereof can accumulate in serum and urine to an extent sufficient to result in precipitation, cast formation, and obstruction.

20. Hobbs, J.R., Evans, D.J., and Wrong, O.M.: Renal tubular obstruction by mucoproteins from adenocarcinoma of pancreas. Brit. Med. J. 2:87, 1974.

21. Weinman, E.J.: Uric acid and the kidney, In The Kidney in Systemic Disease, Suki, W.N. and Eknoyan, G. (Eds), John Wiely & Sons, New York, 1976.

22. Rieselbach, R.E., Benzel, C.J., Cotlove, E., Frei, E., and Freireich, E.J.: Uric acid excretion and renal function in the acute hyperuricemia of leukemia. Am. J. Med. 37:872, 1964.

23. Martinez-Maldonado, M.: The kidney in sickle-cell disease and multiple myeloma. In The Kidney in Systemic Disease, Suki, W.N. and Eknoyon, G. (Eds), John Wiley & Sons, New York, 1976.

F. Miscellaneous

Space does not allow a discussion of each of the numerous other causes of obstruction; the list is extensive (see Table IV). However, a few points should be made about certain often neglected or poorly appreciated sources of obstruction.

1) Endometriosis. Although an uncommon cause of ureteral obstruction, this possibly is often overlooked in young and middle-aged females. The obstruction is usually unilateral and caused by extrinsic compression of the ureter by ectopic endometrial tissue plus fibrosis (24). Medical therapy is generally unsuccessful; therefore a surgical approach to the problem should be sought early, in order to avoid irreversible renal damage.

2) The gravid uterus. Although pregnancy is frequently associated with a dilated ureter and some degree of hydronephrosis, especially involving the right kidney, high-grade obstruction to urine flow is unusual. In fact, most investigators agree that the relative "hydroureter" of pregnancy is primarily related to "ureteral atony"

resulting from the effect of hormonal changes on ureteral peristalsis. However, especially in dextrorotated uteri, occassional cases of high grade obstruction of the right ureter are encountered. Even more rarely, severe bilateral ureteral compression has been reported in late pregnancy, resulting in oliguric renal failure (25). The clue to the diagnosis is the finding of marked changes in urine output with changes in position of the patient.

3) Renal cysts. Evans and Coughlin analyzed radiographs from 125 patients with solitary intrarenal cysts, and found evidence for pelvic or calyceal obstruction in about 75% of the cases (26). In most cases this involved infundibular obstruction of only one calyx and thus would not be expected to affect overall renal function, although increasing the risk of infection associated with localized urinary stasis. 16%, however, had high grade pelvic or ureteral compression. The size of the cyst bore little relation to the degree of obstruction; rather the position of the cyst is the critical factor, namely, a central, perihilar location. Peripheral cysts do not cause obstruction.

4) Congenital ureteral strictures. This term includes a group of congenital disorders characterized by a short segment of ureter which permits passage of catheters and probes but is obstructive to the normal peristaltic transmission of urine (27). Synonymous terms appearing in the literature are: achalasia of the ureter, congenital megaureter, and congenital ureteropelvic junction obstruction, depending on their location. The study by Allen (27) indicates that such lesions are limited to three ureteric sites: the U-P junction, the mid-ureter at the pelvic brim, and the lower ureter at the bladder wall. At the stenotic area no circular muscle fibers or sphincters could be identified (which are also absent from the normal ureter). The involved segment had a reduced diameter, and although longitudimal smooth muscle fibers persisted throughout the diseased segment, the extent of muscularization was markedly reduced, suggesting developmental arrest. The author has thus postulated that localized compression of the ureter during fetal developmental, either by aberrant vessels at the U-P junction, the iliac vessels at the pelvic brim, or the umbilical artery near the base of the bladder, results in arrest in the normal development of the ureter, which subsequently produces a relative obstruction by inferring with transmission of the normal peristaltic wave of ureteric contraction. Such an idea is compatable with the high association of U-P junction strictures with aberrant vessels at this level. Lack of total concordance may be due to subsequent atrophy and fibrosis of obstructing vessels in later life.

This cause of ureteric obstruction is not uncommon and usually presents clinically in the first or second decade of life.

5) Infection. Infection of the urinary tract may cause obstruction in two settings: a) when associated with papillary necrosis, and b) rarely, in Candidal infections of the kidney resulting information of a fungus ball, with pelvic obstruction (28).

6) Vesico-ureteral reflux. That reflux may cause relative obstruction to urine flow remains undisputed. In cases of severe reflux the entire ureter and renal pelvis are grossly dilated. What is unclear is whether the progressive decline in renal function usually observed with severe reflux results primarily from obstruction to urine flow or from the almost universally coexistent chronic infection. The studies of Lenaghan, et al, (29,30) suggest that high-grade reflux without infection in dogs dilates the ureter but results in no loss of renal mass, scarring, etc. When infection is superimposed, the result is a shrunken, fibrotic kidney. Others, however, have found that reflux alone may result in a scarred contracted kidney, especially when the condition is induced in newborn animals. Thus at present there is no definitive answer regarding the relative roles of pressure and infection in determining the functional consequences of this lesion.

There is similar controversy as to the etiology of V-U reflux. It appears likely, however, that the causation is varied. Clearly, mechanical distortion by tumors and mass lesions at the U-V junction can produce reflux, as can high-grade bladder-outlet obstruction. There is also evidence that chronic infection alone can also result in reflux, although it is unlikely that infection alone can account for severe degrees ureteral dilation and wide-mouthed ureteral orifices.

Despite these controversies it is clear that clinically, high-grade V-U reflux is almost always associated with chronic infection and that despite various attempts to free the urine of bacteria, renal function will progressively decline in the absence of surgical intervention. On the other hand, small degrees of reflux, commonly seen in patients with chronic urinary tract infection, do not appear to adversely affect renal function. In a recent study by Aperia, et al, (31), the functional damage associated with high-grade V-U reflux was examined in 22 children with recurrent urinary tract infection. The results were compared to those in children with small-to-moderate degrees of reflux as well as those with recurrent infection alone. In individuals free of reflux or with mild-to-moderate degrees of it plus recurrent infection, renal function was stable over a period of several years (It should be noted that most patients received both acute and chronic suppressive anti-microbial therapy). In individuals with high grade reflux (ureteral dilatation) there was a gradual deterioration of renal function that accelerated after age six despite vigorous treatment

of associated bacteriuria. By puberty more than 50% deterioration in GFR had occurred on the affected side. The results of this study have led these authors to recommend that children with recurrent UTI's and high grade V-U reflux be subjected to corrective surgery, preferably before age six.

In individuals with lesser degrees of reflux, conservative management, including vigorous treatment of urinary infection, is probably justified. This is especially important in cases where the only apparent cause for backflux of urine is chronic infection. In such cases, eradication of bacteruiria is often associated with disappearance of radiographic evidence of reflux.

7) Renal homotransplantation. The reported incidence of major urologic complications of renal transplantation varies from 3% to 20% in the available literature (32). The most common of these have been necrosis of the distal ureter within its newly created submucosal tunnel (or just proximal to its bladder insertion) and obstruction of the intravesical portion of the transplanted ureter. It is thus important to consider and rule-out these possibilities with appropriate studies in any patient with either initially poor function or subsequent deterioration of renal function in the immediate post-transplant period (32).

III. CLINICAL MANIFESTATIONS OF OBSTRUCTION

The clinical, as well as physiologic manifestations of urinary tract obstruction obviously will vary with the extent and type of obstruction: whether it is complete or partial, unilateral or bilateral, acute or chronic. In addition, various patterns of renal functional disturbances have been observed, depending on whether the observations are made while obstruction is still present, or after the relief of obstruction. Moreover, the functional abnormalities and clinical manifestations may vary widely from day-to-day in any individual, due to the frequently intermittent nature of the obstruction, with periods of anuria and virtual cessation of glomerular filtration alternating with partial relief of obstruction, massive diuresis, a fall in tubular hydrostatic pressure, and a resumption of some degree of glomerular filtration. Much apparent controversy exists in the literature as a result of the influence of these factors on the clinical and physiologic findings, and failure to consider these factors when comparing different studies.

A. Symptomatology

It is important to make the distinction between symptoms of intravesical obstruction and those of obstruction at the ureteral level or higher.

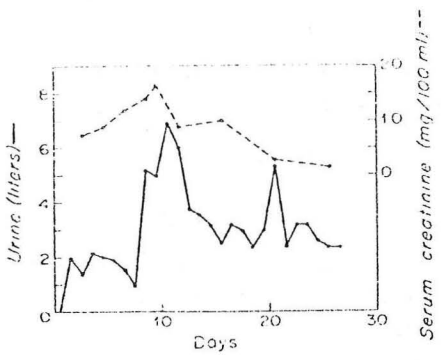
Urgency, intermittency, and frequency are not necessarily indicative of infravesical obstruction but may reflect only the inability to empty the bladder completely (as in cystocele or functional bladder disturbances). On the other hand, hesitancy, decrease in the size and force of the urinary stream, post-void dripping, and nocturia are all symptoms of infravesical obstruction. It should be cautioned, however, that hesitancy, when the sole symptom, may be on a purely psychological basis. Flank pain during micturition is essentially pathognomonic of vesicoureteral reflux. Gross hematuia is an occassional finding in obstructive disease, most commonly associated with urolithiasis.

With ureteral obstruction, pain is the symptom which most often brings the patient to medical attention. Pain is most severe when obstruction is acute, and relates the rate of distension of the collecting system rather than degree of dilatation. Thus with acute ureteral obstruction pain is usually excruciating, often radiating to the lower quadrant, testes or labia, and the patient is characteristically restless, unable to remain motionless. It is continuous, with minor fluctuations, rather than truly colicy, and generally lasts several hours to a day. Chronic ureteral obstruction is associated with much milder pain, often vague in location and intermittent. It usually is located in the costovertebral angle or flank and may be exacerbated or precipitated by ingestion of large volumes of fluid or vigorous diuresis.

Periumbilical pain does not result from obstruction of the collecting system, but may develop secondary to paralytic ileus, which frequently occurs in response to acute obstructive uropathy.

Oliguria is characteristic of bilateral acute obstruction. In contrast, when bilateral obstruction is long-standing, polyuria, associated with a urinary concentrating defect is a frequent finding. It is important in evaluating polyuria to determine whether the voidings are of normal or diminished volume. The latter findings are typical of incomplete bladder emptying, whereas frequent voidings of normal or increased volume are seen in some patients with chronic hydronephrosis exhibiting a diabetes inspidius-like state. Thus, frequent voidings of normal (rather than diminished) volume by no means rules out obstructive disease.

An important clue to the presence of obstructive disease is the observation of large day-to-day fluctuations in urine volume. This is most typically seen in patients with high-grade bilateral obstruction in whom the nature of the lesion (or of the surrounding inflammatory edema) allows fluctuation in the degree of obstruction. Shown in Figure 1 is the record from a patient with bilateral ureteral obstruction due to netroperitoneal fibrosis exhibiting this phenomenon. In this case the fluctuations in urine output and serum creatinine simulated recurrent acute renal failure (33).



1. First admission (July 4, 1968). Serum creatinine (dashed line) *and urine volumes* (solid line) *of patient with recurrent acute renal failure.*

2. Second admission (Aug 21, 1968). Serum creatinine (dashed line) *and urine volumes* (solid line) *of patient with recurrent acute renal failure.*

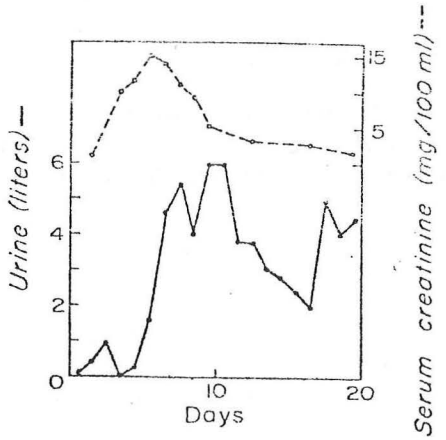


Figure 1. Serum creatinine and urine volumes in a patient with fluctuating urinary tract obstruction. (From Reference Number 33)

It is obvious that advanced degrees of obstruction lead to the uremic syndrome. Furthermore, it is not unusual for patients with obstructive uropathy to be asymptomatic until severe azotemia has ensued. It is therefore imperative that obstructive uropathy be considered and ruled out in all patients with unexplained renal failure.

One should always require as to a history of malignancy, previous abdominal, pelvic, or genito-urinary surgery as well as radiotherapy. A history of extensive endometriosis, pelvic inflammatory disease, and regional enteritis should be specifically sought.

B. Physical Examination

There are few findings which would lead one to suspect obstructive disease of the urinary tract. The abdomen may be distended and silent if paralytic ileus has complicated the obstruction. Careful palpation for the presence of a renal or subrapubic mass should be done. The foreskin and urethral meatus should be carefully examined and the urethra palpated in order to detect induration. A rectal examination is important for evaluation of sphincter lone (as regards the possibility of neurogenic bladder),

pelvic masses, and status of the prostate in males. Pelvic examination in the female is important in order to evaluate the possibility of cervical, uterine or ovarian disease.

C. Laboratory Findings

Aside from the laboratory findings common to renal failure, there are several specific findings which should always alert the physician to the possibility of obstructive disease. These are summarized in Table VI.

TABLE VI

DISTINGUISHING FEATURES OF RENAL FUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE UROPATHY

I. Polyuria Associated with Vasopressin-Resistant Urinary Concentrating Defect

II. Salt Wastage

III. Tendency Toward Potassium Wastage

IV. Distal Acidification Defect

If one contrasts patients with chronic hydronephrosis with those having various forms of generalized, chronic glomerular disease (e.g., chronic glomerulonephsitis, nephrosclerosis, etc.) there is a pattern which emerges which clearly separates patients in the former category from the usual forms of chronic glomerular disease. Not all patients with chronic bilateral obstructive disease will manifest all of these features, but it is very common for patients to exhibit one or more of the following features:

1) Polyuria associated with a urinary concentrating defect. Although polyuria is usually mild to moderate (2-4 liters/day) occasional patients have massive polyuria simulating diabetes insipidus and which is unresponsive to administration of vasopressin. Some of these cases have been reported in the literature under the moniker "water-losing nephritis" (34). Many patients exhibit urine osmolalities essentially isotonic with plasma, but occasional patients

have hypotonic urines despite dehydration. If patients do not have adequate access to oral fluids, severe dehydration and hyponatremia may ensue (35). Thus chronic bilateral hydronephrosis should be included in the differential diagnosis of hypernatremia. Although several factors appear to play a role in the pathogenesis of the concentrating defect (as will be discussed in detail in a later section) it is clear that washout of solutes from the normally hypertonic medulla and papilla plays a major role. This washout phenomenon is a predictable, reproducible consequence of high grade obstruction to urine flow and is probably brought about by the combination of the reduced GFR and relatively increased medullary blood flow characteristic of ureteral obstruction. Loss of medullary hypertonicity would then prevent the normal degree of water abstraction from tubular fluid across the medullary collecting duct, leading to reduced urinary osmolality and polyuria. It is obvious that such abnormality does not respond to vasopressin.

2) Salt-losing state. Varying degrees of inappropriate salt loss have been described in chronic obstructive uropathy. Although usually mild and requiring minimal dietary NaCl supplementation, an occasional patient may have urinary sodium loses of such magnitude (up to 40 gms/day) that circulatory collapse ensues unless very high NaCl intake is maintained (36,37). Most experimental studies of chronic obstruction, including micropuncture models (to be discussed later) support the contention that the salt-loss reflects damage to medullary structures including deep loops of Henle and collecting ducts. It is not clear to what extent filtration still occurs in deep nephrons of the distorted, compressed medulla of chronic hydronephrosis, but there is some evidence that some degree of filtration does occur prior to the complete destruction of the medulla. It is likely that sodium reabsorption in these nephrons is impaired. In addition there is a large body of inferential evidence as well as some direct observations that indicates that ureteral obstruction impairs sodium reabsorption in the collecting duct. Although it has been suggested that hyperfiltration and/or depression of proximal reabsorption leading to distal overperfusion of remaining cortical nephrons, as a consequence of medullary destruction, accounts for the renal salt wastage, micropuncture studies have in fact found reduced fluid and sodium delivery out of the proximal tubule of cortical nephrons in animal models of chronic hydronephrosis.

3) A tendency toward potassium wastage. This finding is quite variable, and in most cases the potassium wastage is mild. The pathogenesis has not been established, but it may be related to disproportionate damage to juxtamedullary nephrons, leading to depressed sodium reabsorption in the loop and/or proximal nephron, thereby increasing

sodium delivery to the more distal potassium secretory sites where Na^+/K^+ exchange occurs. Again there is little evidence that a similar phenomenon of increased sodium delivery occurs in superficial nephrons. It should be emphasized, however, that potassium wastage is a highly variable feature of chronic obstructive uropathy.

4) Acidification defects. Many patients with chronic hydronephrosis have a distal acidification defect which simulates distal RTA. The most characteristic feature is the inability to maximally lower urine pH (below about 6.0) in response to systemic acidosis. Although NH_3 excretion and titratable acidity are usually depressed, these findings usually reflect only a reduction in GFR and the high urine pH. In six of seven patients with chronic bilateral hydronephrosis, Berlyne found an inability to maximally lower urine pH (38). Similar findings have been reported in patients after relief of chronic hydronephrosis (39) as well as in experimental animals (40,41).

It appears that the site of the acidification defect is localized to the collecting duct, again providing further evidence for various functional derangements localized to this nephron segment in obstructive disease.

Of course, none of these features is pathognemonic of obstructive uropathy. Rather, these features are all shared by those diseases which appear to affect disporportionately medullary structures, such as analgesic abuse, some cases of chronic pyelonephritis, medullary cystic disease, milk-alkali syndrome, polycystic kidney disease, etc.

Finally, it should be pointed out that the typical urinary findings of a hypoperfused kidney (or per-renal azotemia) have been observed in some patients with acute, bilateral partial urinary obstruction, such as that produced by lesions involving the lower ureters as they insert into the bladder. Under circumstances of acute, bilateral, partial obstruction, the kidney responds in a fashion similar to that produced by acute constriction of the aorta above the renal artery (as will be discussed later). Thus, hydrostatic pressure in the tubules suddenly rises and the driving forces for glomerular filtration are reduced, leading to diminished GFR and underperfused nephrons with slowed rates of flow of tubular fluid. The urine will have a low sodium concentration, a high osmolilty, and a high U/P creatinine ratio--i.e., all the findings of an underperfused kidney. Thus it is important to recognize that occasional cases of acute obstructive disease may masquerade as "pre-renal azotemia" (42).

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D. Complications of Urinary Tract Obstruction

1) Infection. It is clear that complete or partial urinary obstruction does not invariably lead to urinary infection. In fact, the majority of patients with obstructive disease, in the absence of instrumentation, remain free of infection (4). Nevertheless, the incidence of infection is increased in the presence of urinary obstruction. Hasner found an infection rate of 8.6% in 221 men with BPH, no history of prior instrumentation, and post-void residual urine volumes greater than 50 ml (43). Similarly, Kelalis, et al, found infection in about 16% of 109 children with clinically significant ureteropelvic junction obstruction (44).

When acute infection does complicate obstruction it is generally severe and ravaging, and if untreated, can rapidly destroy the kidney and produce systemic sepsis. It is thus imperative that infection be searched for in patients presenting with obstruction and vigorously treatment with systemic antibiotics.

There is insufficient data at present to indicate whether routine long-term proplylactic antimicrobial suppression therapy is of any benefit in patients with urinary obstruction (4). Similarly, the data are equivocal as to the efficacy of suppressive therapy in patients with obstruction complicated by chronic bacteriuria. In children, however, with recurrent urinary tract infections with or without obstruction, proplylactic antibiotics do reduce the indicence of acute infections (45,46,47).

2) Hypertension. In the dog, acute elevation of ureteral and pelvic pressure results in hypertension associated with increased renin release from the ipsilateral kidney (48,49). The hypertension is not sustained, however, and both renin levels and blood pressure generally return to normal within six weeks (49). Clinical cases of hypertension produced by a similar mechanism in man are rare, and in

those reported the obstruction has been of an acute or subacute nature (50,51). Chronic, sustained hypertension in man on the basis of accelerated renin release resulting from hydronephrosis has not been clearly documented. The mechanism whereby tubular obstruction results in renin release has not been delineated.

In patients with bilateral obstruction, of course, volume-related hypertension is common. Under these circumstances, relief of the obstruction will also cure the hypertension, but pre-operative plasma renin levels are low, distinguishing these cases from the very few instances of acute or subacute renin-mediated hypertension (52).

3) Polycythemia. This is also a rare complication of hydronephrosis. There have been only a few reported cases in the literature, and the only well studied case has been that reported by Jaworski and Wolan, who found and increased packed cell volume, erythroid hyperplasia of the bone marrow, and complete remission of the erythrocytosis following relief of the ureteral obstruction (53). It was postulated that the changes were secondary to increased erythropoietin release by the obstructed kidney.

4) Neonatal ascites. Urinary obstruction is a common cause of both ascites and abdominal masses in the neonatal period. The ascites results from urinary extravasation, and the majority of cases have occurred in male infants with posterior urethral valves (54). It has rarely also been observed in adults with high grade bilateral obstruction (4).

5) Interstitial Nephritis. The intrarenal pathologic changes accompanying obstruction have been well defined (55). Early on, the interstitium is edematous and infiltrated with PMN's and round cells. With time fibrosis develops, first in the papilla and medulla, around collecting ducts, and later in the cortical interstitium. The glomeruli are generally spared. In the pelvis the ducts of Bellini are lost and the papilla becomes flattened. In the latest stages the papillae completely degenerate and are replaced by a fibrous tissue-lined cavity.

6) Post-Obstructive Anuria. There is at least one instance of anuria occurring for a period of several days after relief of ureteral obstruction. In this patient with a single, obstructed kidney passage of a retrograde catheter into the pelvis past the point of obstruction failed to produce urine flow despite spontaneous drainage of contrast material around the catheter into the bladder (56). This was followed by a period of increasing urine output, up to 3,500 cc/day, with urine osmolalities of ∿170 mosm and urine [Na] 11 mEq/L. The hyposthenuria and low urinary [Na] argue against ATN

as the cause of the anuria. A renal arteriogram showed patent renal artery and veins, but revealed marked cortical vasoconstriction. Thus, the development of severe vasoconstriction, even after release of the obstruction, was postulated to account for the transient period of anuria. Experimental animal studies have also shown that severe progressive vasoconstriction develops after 24 hours of ureteral obstriction. Moreover, after release of obstruction renal blood flow and glomerular hydrostatic pressure remain subnormal. Thus in the reported case vasoconstriction may have been so severe that inadequate filtration pressure could be generated to maintain significant urine flow.

7) Post-Obstructive Diuresis. The phenomenon of massive diuresis of water and solute after relief of high-grade urinary tract obstruction has been well documented in the literature (57-61). Several features are worth noting. Most patients have had high-grade bilateral obstruction, while many have had total obstruction for several days. It is probable that acute obstruction in this setting is often superimposed on a background of chronic obstruction. BUN and creatinine values are generally markedly elevated, and often all of the clinical features of acute renal failure are present. After release of the obstruction, the diuresis generally ensues within a few hours and generally lasts 2-7 days. Although urine volumes are often massive, it is clear that this is not just a water diuresis; large amounts of solute are also excreted. In the study reported by Persky, negative balances during the period of diuresis amounted to 50-470 mEq for sodium and 50-525 mEq for potassium (57). An osmotic diuresis consisting of urea, and non-reabsorbable solutes and as sulfate also occurs. In a series of patients studied by Bricker's group, relief of virtually complete bilateral obstruction was associated with daily urine volumes ranging from 4.5 to 15.0 liters and daily sodium excretion of 250 mEq to 1900 mEq, representing 15-31% of filtered water and 6.2 to 20.0% of filtered sodium) (59). Moreover, two-thirds of the urine osmolality could be accounted for by the excreted electrolytes, suggesting that tubular rejection of sodium is primarily responsible for this form of "osmotic diuresis." Although accelerated urea excretion (resulting from the high plasma levels and the sudden increase in GFR) may account, in part, for the diuresis, when urea alone is the source of an osmotic diuresis, it generally constitutes about 2/3 of the urinary solutes. Table VII depicts the typical urinary findings in post-obstructive diuresis.

It is generally true that relief of unilateral obstruction, in the presence of a normal contralateral kidney, is not associated with post-obstructive diuresis. Either bilateral severe obstruction, or unilateral obstruction with a non-functional or absent

TABLE VII

URINE AND BLOOD FINDINGS IN THE FIRST 24 HOURS AFTER THE RELIEF OF URINARY-TRACT OBSTRUCTION (FROM REFERENCE NUMBER 60)

Time*	Urine†										C_{Cr}‡	U/P§	Blood		
	UV	C_{osm}		Osmolality	Urea		Sodium		Potassium				Sodium	Osmolality	Cr‡
hr	*ml/min*	*ml/min%*	C_{Cr}	*mOsm/liter*	*μmoles/min*	*% FL*	*μEq/min*	*% FL*	*μEq/min*	*% FL*	*ml/min*	*Cr*	*mEq/liter*	*mOsm/liter*	*mg/100 ml*
2.0–4.0	18.3	19.5	27.6	352	2,360	91.3	1,555	15.6	320	88	70.6	3.8	140	328	10.10
4.0–5.0	13.3	15.0	18.0	363	1,689	67.2	1,157	9.5	259	67	83.1	6.2	145	321	8.80
5.0–6.0	11.3	13.9	14.6	395	1,808	75.5	1,074	7.9	259	66	95.5	8.4	145	320	6.90
Normal saline infusion (500 ml/hr)															
6.0–7.0	11.0	13.5	14.3	395	1,551	72.7	1,155	8.2	275	69	94.5	8.5	148	320	6.50
7.0–8.0	11.0	13.8	13.9	398	1,276	68.0	1,232	8.4	286	73	99.2	9.0	146	316	5.10
Intravenous d-aldosterone (1.0 mg) and normal saline infusion (500 ml/hr)															
8.0–8.5	12.0	14.8	14.0	390	1,392	73.8	1,320	8.5	312	70	105.5	8.8	147	316	4.70
8.5–9.0	10.0	12.3	12.3	398	1,240	72.2	1,100	7.5	270	62	100.0	9.9	147	315	4.30
9.0–9.5	8.0	9.4	9.3	370	824	52.9	800	5.3	264	60	101.0	12.6	147	315	2.80
9.5–10.0	8.3	7.7	7.1	290	764	49.4	623	4.1	216	50	107.2	12.9	142	318	2.40
10.0–11.0	7.7	6.5	6.3	263	708	49.3	500	3.4	154	42	102.0	13.9	143	319	1.90
0.5 normal saline in 5% dextrose infusion (450 ml/hr)															
11.0–19.0	6.6	8.2	7.2	375	766	60.9	660	4.2	198	34	113.7	18.6	140	299	1.50
19.0–21.0	6.6	7.9	6.9	355	429	60.6	719	4.4	205	36	114.8	17.4	141	295	0.90
Intravenous fluids discontinued															
21.0–22.0	4.1	4.9	4.7	352	185	38.6	437	2.9	131	26	103.5	25.0	143	295	0.84
22.0–23.0	3.8	4.7	4.4	364	179	38.8	448	3.0	118	23	105.3	27.7	142	295	0.83
23.0–24.0	4.0	4.9	4.7	363	220	40.0	480	3.2	132	26	103.4	25.8	145	290	0.89

* After catheterization.
† UV = urine volume, FL = filtered load.
‡ Cr = creatinine, C_{Cr} = endogenous creatinine clearance.
§ U/P = urine/plasma.

contralateral kidney is generally the clinical setting in which post-obstructive diuresis is to be expected. The protective effect of a normal contralateral kidney suggests that retention of some substance or substances (Na, urea, natriuretic humoral substances) is necessary for full expression of this syndrome. Although both urea retention and expansion of the ECF volume during the period of oliguria have been shown to greatly exagerate the magnitude of the subsequent post-obstructive diuresis, the relative quantative roles of each of these factors in the magnitude of the diuresis observed clinically remains to be established. Micropuncture studies in rats have shown that some degree of natruiresis and diuresis can occur after release of bilateral obstruction when either urea retention (62) or ECF volume expansion are prevented (63). What remains to be established, however, is whether excessive solute and water excretion occurs when both ECF expansion and urea (plus other non-reabsorbable solutes) retention are prevented during the period of obstruction. Although there is inferential evidence suggesting both sodium transport and acidification defects in the collecting duct and possibly in juxtamedullary nephrons, the unequivocal demonstration of intrinsic tubular damage has yet to be made. The best evidence generated to date indicating intrinic defects in sodium reabsorption are the studies by Sonnenberg (64), McDougall and Wright (63), and Thirakomen, et al, (40).

It is clear that in most patients the diuresis observed is not life-threatened and reflects excretion of sodium retained during the period of obstruction, osmotic diuresis, and transient excretion of non-reabsorbable anions. Such an explanation is compatable with the transient nature of the diuresis as well as with the observation that rapid rates of parenteral fluid administration augment and perpetuate the diuresis. The usually benign nature of the phenomenon was confirmed in the studies by Persky, et al, (57) and Muldowney, et al, (58). The latter investigators measured changes in total exchangeable body sodium in several patients with post-obstructive diuresis. Total exchangeable sodium was elevated in these patients and fell to within normal limits concomitant with the abatement of the diuresis.

There are, nevertheless, a few reports in the literature of massive negative sodium and water balance after release of urinary tract obstruction, which has persisted after osmotic diuresis had subsided and which required NaCl supplementation to maintain ECF volume (59,65,66). Most nephrologists have also observed this phenomenon in rare instances. Thus while most patients with post-obstructive diuresis represent a transient, benign syndrome, it appears that this is not always the case and in rare instances transient but nonetheless serious sodium wastage develops.

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IV. DIAGNOSTIC EVALUATION OF OBSTRUCTIVE UROPATHY

A. Standard Techniques

Initially a flat plate film of the abdomen should be obtained, which may reveal enlargement of one or both kidneys or a discrepancy in size between the two kidneys in the presence of obstruction.

In most patients intravenous pyelography will provide useful information. If renal function is not seriously impaired, standard techniques are usually adequate. In the presence of renal failure, however, high dose pyelography with tomography will be required. If the latter does not provide adequate visualization and the patient is uremic and in need of dialysis, intravenous pyelography should be repeated after the patient has been dialyzed and the BUN has fallen toward normal. Under these circumstances adequate visualization can often be achieved, presumably as a result of removal of non-reabsorbable osmotic solutes from the blood, thus allowing more complete water abstraction by the tubules and concentration of the contrast medium (67).

In the presence of obstruction, if there is a marked reduction in GFR, the nephrogram may be delayed. In an acutely obstructed kidney the nephrogram, although delayed may be especially dense (Fig. 2); the latter finding is a useful clue to duration of the obstruction. In an acutely obstructed kidney, the calyces, pelvis and ureter above the level of obstruction, will all be dilated. The ureter, however, is not tortuous, as is the case with chronic obstruction. The pyelographic phase may be extremely faint, due to dilution of the contrast medium in the grossly dilated pelvis. Delayed films, however, may provide much better definition, and will often demonstrate the level of obstruction. A delay as long as 24-36 hours may be necessary. Thus, the study should be continued until the site of obstruction is identified or the contrast material has been excreted. The value of delayed films is seen in Figure 3.

In the chronically obstructed kidney, the ureter is often very tortuous as well as dilated, the kidney is often huge, and a "rim sign", indicating a small residual rim of remaining cortex, may be visible (4). In infants and children with obstructive hydronephrosis, a series of crescent-shaped shadows of increased density appear in the first 20-30 minutes of the examination. This has been termed the "calyceal crescent sign" (68) and is thought to represent dye-filled collecting tubules that are stretched and displaced in relation to the distended calyx, rather than perpendicular to it (the normal relationship). This "sign" disappears in the later films, as the pelvis fills with contrast material. It is thought to be a reliable sign of chronic obstructive hydronephrosis. These are shown in Figure 4.

Some patients have only intermittent ureteropelvic junction obstruction. In such cases, pyelography should be done when patients are in pain, since dilatation of the collecting system can be expected at this time; it may be normal when patients are asymptomatic. Oral hydration or mannitol infusion sufficient to result in pain often produces sufficient dilatation in the collecting system to allow a diagnosis to be made (4). Such an example is depicted in Figure 5.

If intravenous pyelography proves inadequate, retrograde ureteropyelography should be carried out by an experienced urologist. Although some

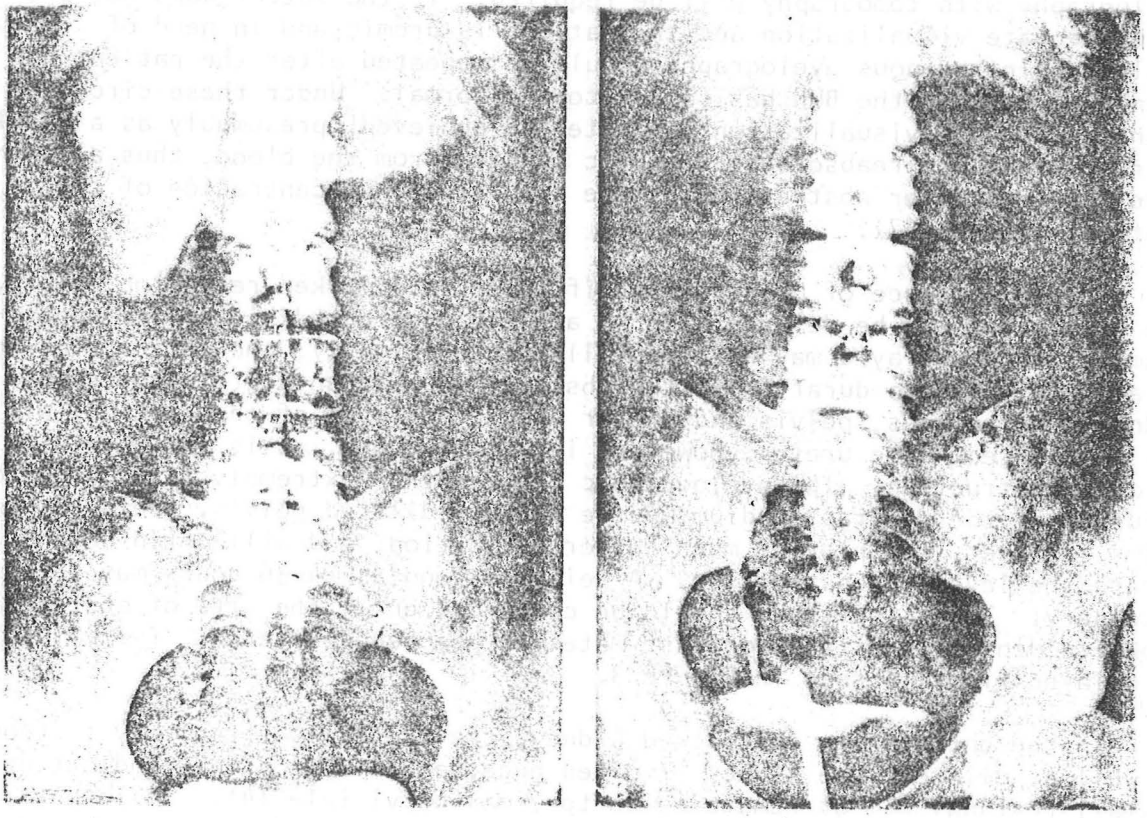


Figure 2. A, Intravenous pyelogram obtained in a 31-year-old female with right and flank pain for five hours. Radiogram was taken two hours after injection of contrast material and shows a very dense nephrogram. A clear right pyelogram was never seen.

B, Bulb retrograde ureterogram. This technique permitted localization of the obstruction in the ureter and demonstrated that the ureter was dilated above the obstruction. A ureteral catheter passed directly to the renal pelvis may bypass a site of obstruction, allowing a partially obstructing lesion to remain undetected. The bulb retrograde ureterogram avoids this problem and is invaluable in demonstrating small, radiolucent or multiple ureteral lesions. (From Reference Number 4).

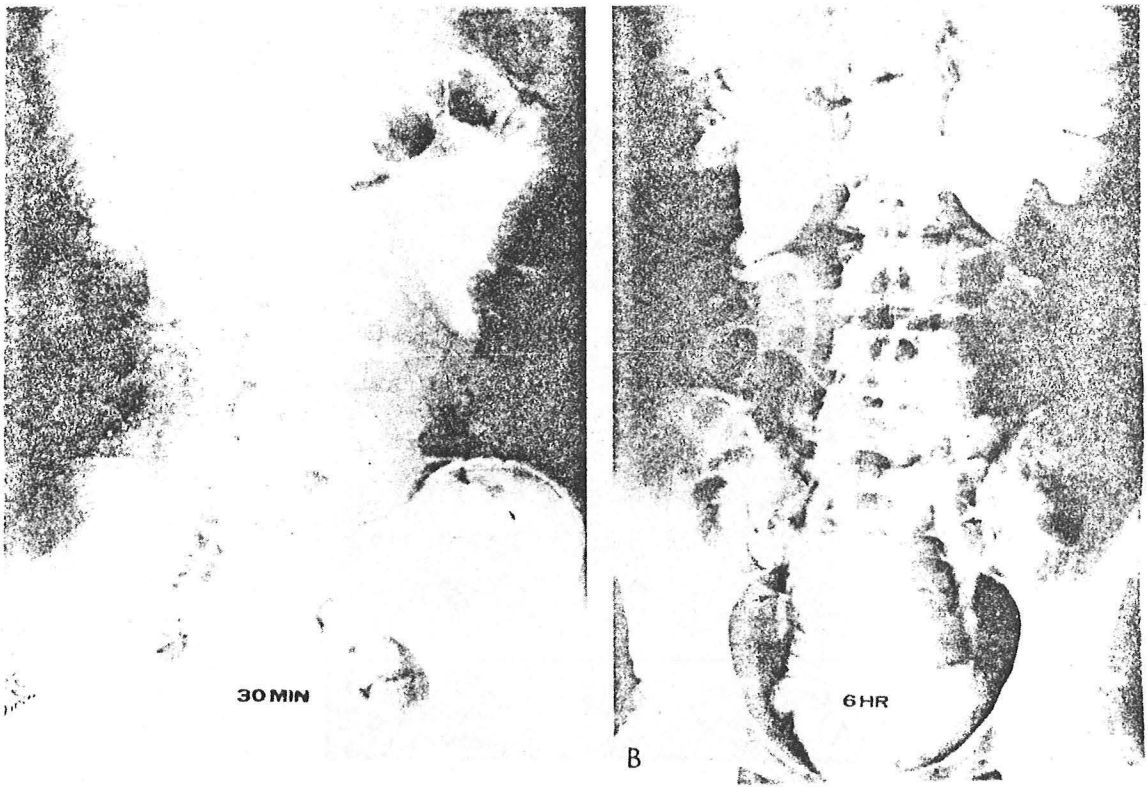


Figure 3. A, Pyelogram from a patient with a functional obstruction due to a neurogenic bladder. Notice the additional information available on the delayed film (B) which defines the level of obstruction and suggests the underlying pathological process. (From Reference Number 4).

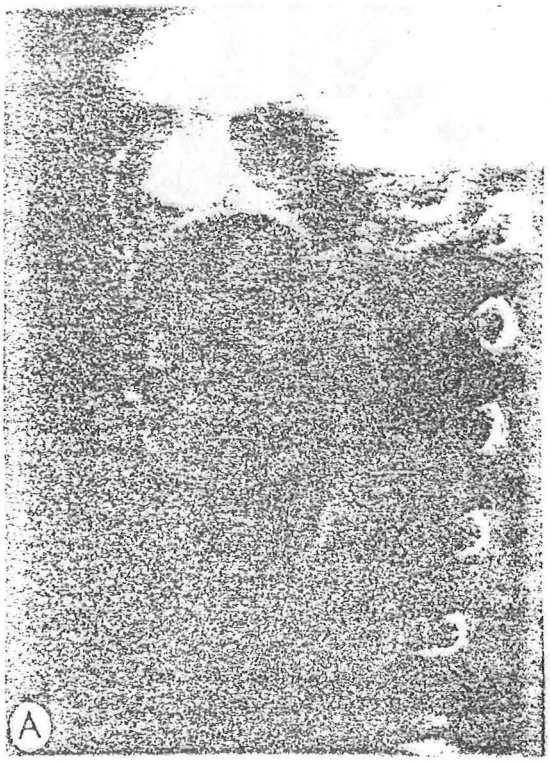


Figure 4 . Typical crescents during urography. (From Reference Number 68).

Figure 5. Intravenous pyelograms from two patients with intermittent hydronephrosis. A and C, Pyelograms made at a time when the patients were dehydrated and without pain. B and D, Pyelograms made after hydration when the patients experienced pain. Notice the marked difference in the renal pelvis and calices on the two studies. In patients with suspected intermittent obstruction, the discomfort can be elicited and the relative obstruction documented with a hydration or mannitol-infusion pyelogram. (From Reference Number 4).

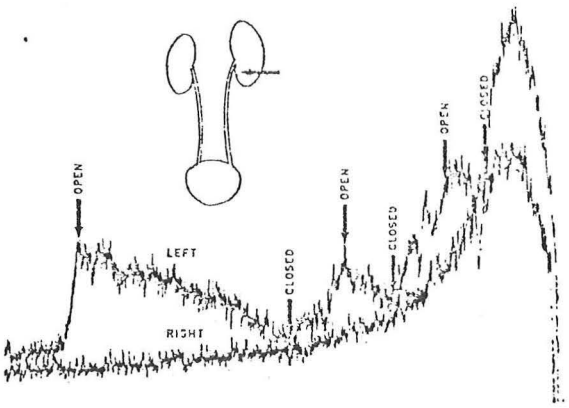
risk of introducing or disseminating infection in the instrumented collecting system is appreciated, it is nonetheless imperative that the presence, nature, and site of obstruction be elucidated when obstruction is suspected; if intravenous pyelography has proved inadequate, further delays in diagnosis and appropriate therapy may irreversibly sacrifice renal function. A bulb ureteropyelogram should first be obtained (4). This technique allows visualization of the ureter and pelvis and can often demonstrate small ureteral lesions. If the bulb ureterogram does not visualize the obstruction, a catheter can be passed into the renal pelvis. From this site urine can be obtained for appropriate cultures, electrolyte and creatinine determinations, and determination of unilateral renal function, when indicated. Dye can then be injected, the catheters removed, and pyelograms obtained. Anuria after bilateral retrograde pyelograms is usually due to edema or the ureteral orifices and is transient.

Evaluation of infravesical obstruction, neurogenic bladder, and vesicoureteral reflux is best done by voiding cystourethrography, including cine studies when functional abnormalities in either ureteral peristalsis or bladder function are suspected. A retrograde urethrogram should be performed prior to instrumentation in any patient suspected of having a urethral stricture or injury (4).

B. Special Techniques

These basically consist of techniques which evaluate urodynamics, including radioisotope renograms, various techniques for dynamic quantification of urine flow ("uroflowmetry"), and measurements of intravesical and rectal pressures during voiding.

Radioisotope renography has been utilized to detect urinary tract obstruction. This has been based on the fact that the renogram has two visible phases--uptake of the isotope by the kidney, and subsequent washout and excretion. Thus in the presence of an obstructed kidney, with a markedly increased volume of pelvic urine, the washout phase will be prolonged and the slope of its curve altered (69,70), as shown in Figure 6. One group of investigators has suggested that the technique can be extended further by comparing the appearance of the renogram curves before and after a drug-induced diuresis (69). It is claimed that this procedure will differentiate a hydronephrotic kidney which is no longer obstructed from one which is both dilated and obstructed. In the former case the delay in excretion is solely a function of the increased volume of pelvic urine, allowing relative pooling of the isotope (such as ^{131}I-Hippuran) after its excretion. In this case a rapid diuresis will produce a normal renogram when the study is repeated during the diuresis. When obstruction is also present, despite administration of diuretics, drainage of pelvic urine is prolonged, and the renogram will not be "normalized." Typical renograms demonstrating this principle are shown in Figure 7.



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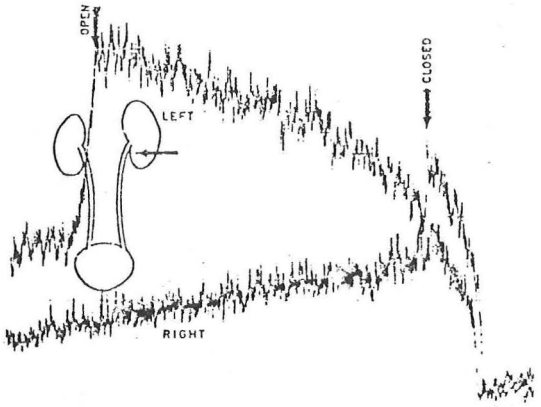

b

Figure 6. Renography in a dog. a) Clamping was made at the ureteropelvic junction. b) The curve for the left kidney shows the effect of clamping during a longer period of time. (From Reference Number 70).

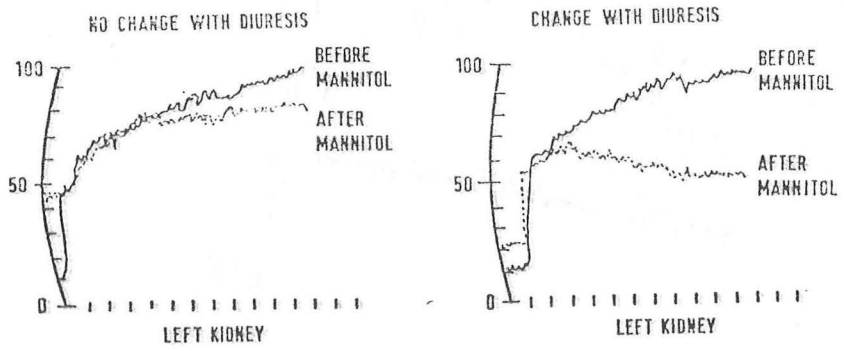

Figure 7. Effect of osmotic diuresis on the renogram in an unobstructed, hydronephrotic kidney (right), and in an obstructed, hydronephrotic kidney. (From Reference Number 69.)

When renal function is severely impaired, however, as is often the case in obstructive uropathy, the uptake of isotope by the kidney is reduced, and interpretation of the curves is unreliable. Moreover, in the presence of bilateral obstruction, it is not possible to compare the contour of the renogram on the affected side with the contralateral normal kidney, and under these circumstances, isotope renography cannot be considered reliable. In the final analysis, although this technique may have some value for screening purposes, as well as in the initial evaluation and detection of unilateral hydronephrosis, it cannot provide the detailed information required in the evaluation of urinary tract obstruction and provided by intravenous pyclography and/or retrograde studies.

On the other hand, the measurement of urinary flow rates by a number of available techniques (71-74) has proved useful in the evaluation of infravesical obstruction. For example, Shoukry, et al, has evaluated the degree of bladder outlet obstruction associated with symptoms of prostatism in a large series of patients, utilizing urine flowmetry (73). It was found that the most reliable indicator of the presence and degree of obstruction was the maximum urinary flow rate. They have also emphasized that maximum urinary flow rates are only meaningful when related to the volume voided. Such a comparison allows differentiation between low flow secondary to inadequate bladder contractions (in which case voided volume will be small but flow relatively normal) and true outlet obstruction (in which flow rate for any volume will be diminished). Others have compared urine flow rates with simultaneously-measured intravesical pressures, as well as intrarectal pressures (74). These simultaneous measurements have allowed the delineation of distinctive patterns resulting from obstruction of the prostatic urethra, atonic and neurogenic bladder, so called "detrusor instability" associated with certain neurological lesions, and psychological inhibition of urine flow (74). Examples are shown in Figures 8-10. Although these techniques remain primarily an investigative tool, it is clear that in many centers they are proving very useful in the differential diagnosis of bladder dysfunction as well as in the quantitative assessment of infravesical obstruction.

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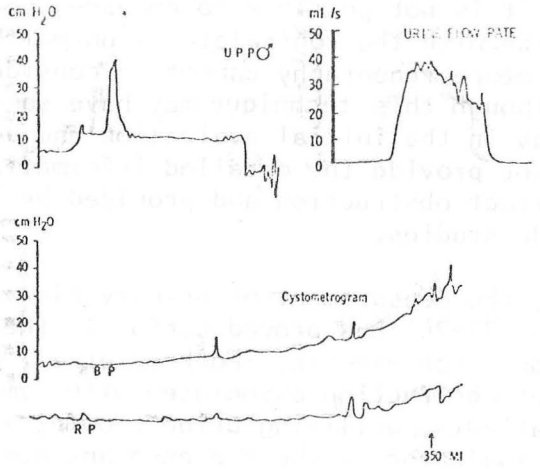

Figure 8. Normal urodynamic study. The urethral pressure profile (UPP) shows a low pressure in the region of the bladder neck and prostatic urethra. The peak represents the external sphincter. The peak flow rate is the highest point of the flow curve (normal range 15-40 ml/s). The cystometrogram shows an initial fla. phase with a terminal rise in pressure towards the end of filling. Simultaneous recording of rectal pressure is used as a subtraction factor to deduce the intrinsic bladder pressure (BP, bladder pressure; RP, rectal pressure). (From Reference Number 74).

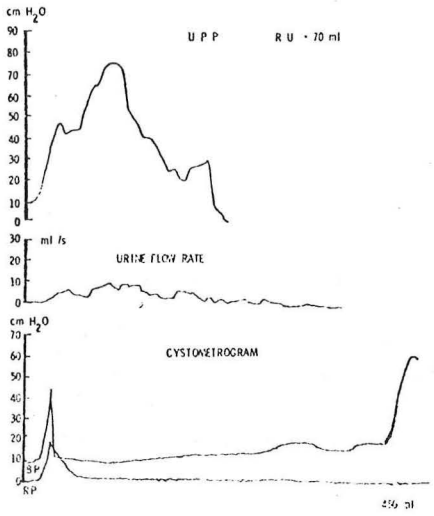

Figure 9. The urethral pressure profile (UPP) shows an abnormal curve with a high pressure in the prostatic urethra. Large residual urine volume. Obstructed flow curve with low peak flow rate. Cystometrogram shows a spontaneous contraction towards the end of filling (From Reference Number 74).

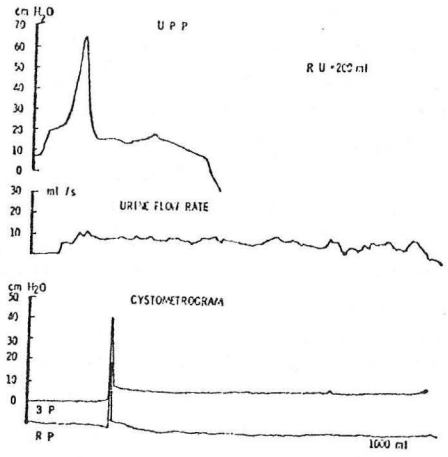

Figure 10. Lumbar disc prolapse, chronic retention of urine. Urethral pressure profile (UPP) normal. Residual urine (RU)--200 ml. Low urine flow rate with protracted curve. Cystometrogram--flat curve, capacity 1000 ml, absent sensation. These findings indicate an atonic bladder due to caude equina compression. (From Reference Number 74).

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V. THERAPEUTIC CONSIDERATIONS

Since appropriate therapy has already been alluded to frequently in previous sections dealing with specific disease processes, this discussion will address only a few important therapeutic principles.

A. Is There a Role for the Medical Management of Benign Prostatic Enlargement?

Although trials with testosterone and estrogenic compounds (75) have claimed therapeutic success in treating prostatic hypertrophy, these studies have been uncontrolled and difficult to evaluate, not to mention the potential side effects of such therapy. These have been several well-controlled studies, however, of the use of progestational agents in selected patients with symptoms of bladder outlet obstruction secondary to BPH (76,77,78). Aubrey, et al, (76) studied 24 patients in a double-blind, crossover fashion. Treatment consisted of 17-, 19- norprogesterone caproate, 200 mgm I.M. weekly for three months. There was marked to moderate improvement in symptoms of obstruction, decrease in prostate size, and reduction in residual bladder volume in 22 of 24. Geller (77) treated 11 patients with an unstated dose of hydroxyprogesterone caproate for 3-16 months. Ten of the eleven required chronic catheter drainage before treatment. Within three months 6/11 had spontaneous voidings without catheter drainage and less than 50 ml residual urine volumes. By five months two additional patients noted similar improvement. Histologic evidence of involution of the hyperplastic charges typical of BPH was also noted. Ragno, et al, (78) also studied 24 patients utilizing a random, double-blind, crossover design. Medrogestone, 50 mgm BID for 24 weeks, was administered. Compared to the control group there was marked improvement in prostate size, symptoms, and reduction in residual urine volumes. Involutional changes in response to treatment were also noted on prostate biopsies, when compared to the placebo group.

It would thus appear that in certain patients with complicating illnesses (or advanced age), a trial of progestational agents may be justified. It appears likely that a significant fraction of patients so treated will have sufficient improvement in symptoms to obviate the need either for surgery or for chronic catheter drainage.

B. When is Surgical Intervention Advisable in Obstructive Uropathy?

The mere presence of post-voiding residual urine, vesico-ureteral reflux, or dilatation of the collecting system is not an indication for surgical intervention. In the presence, however, of recurrent urinary tract infection, persistent pain, recurrent bleeding, severe obstructive symptoms, or progressive deterioration in renal function, elective surgery is indicated.

Once the level of obstruction has been determined and intervention is deemed necessary, it is often advisable to provide temporary relief of the obstruction, allowing the patient's condition to improve while awaiting definitive surgery. This can be accomplished by either catheter drainage of the bladder or a ureteral catheter, depending upon the level of the obstruction. When the latter is ineffective in bypassing the obstruction or deemed inadvisable, one of several diverting procedures, such as nephrostomy, pyelostomy, cutaneous ureterostomy, can usually be accomplished. This will often allow time for adequate assessment of renal function in the affected kidney, and thus the advisability of nephrectomy versus definitive surgical relief of the obstruction. Of course, temporary diversion of the urinary stream is often necessary to successful surgical repair of more distal ureteral or bladder lesions. Permanent diversion of the urinary stream, as is often necessary with carcinoma of the bladder, or neurogenic bladder with refractory, recurrent urinary infection, is best accomplished by means of uretero-ileal anastomosis, with the creation of an ileal conduit. This procedure has superceded that of ureterosigmoidostomy, with a resultant reduction in the incidence of ascending urinary infection and hyperchloremic acidosis.

Calculi in the renal pelvis which are too large to pass spontaneously should generally be removed surgically, especially when complicated by infection or obstruction (4). Considerable controversy exists, however, regarding non obstructive, branched calculi. Significant risk attends both operative and non-operative management (4). It would appear, therefore, that decision regarding management should be dictated by the particular circumstances associated with each individual case.

Eighty-five to ninety percent of ureteral stones pass spontaneously, and this is especially the case with those under 5 mm diameter. If, however, a large stone completely obstructs the ureter, surgical removal should be accomplished within a few days if there is no evidence of passage distally. Many urologists are of the opinion that if the obstruction is incomplete,

the urine is sterile, and the pain manageable, the patient can be observed over a period of several weeks. Most stones lodged in the lower ureter will eventually pass in this interval. Those which do not can usually be removed by transurethral basket extraction (4). However, stones which obstruct the upper ureter, and which do not progress distally in several weeks (assuming the obstruction is incomplete and the urine sterile) should be removed by an open surgical procedure. Blood clots, fungus balls, and pieces of papillary tissue obstructing the ureter can generally be managed in a fashion similar to that described for stones. Ureteral obstruction secondary to neoplastic or inflammatory disease is unlikely to remit spontaneously and will require either definitive surgery or a diverting procedure.

C. How Should Patients with Post-Obstructive Diuresis be Managed?

It is clear that the majority of patients with this syndrome experience an osmotic diuresis and excrete sodium in a fashion which is generally appropriate to the preceding degree of overexpansion of the ECF volume. If intravenous salt solutions are administered in amounts approaching the magnitude of the urinary volume, the diuresis will only be perpetuated. Nonetheless, as previously mentioned, it is likely that in rare instances, diuresis and negative-sodium balance may persist despite normal or even contracted ECF and vascular volume, and if urinary losses are not replaced, hypovolemia and vascular collapse may ensue. In addition, post-obstructive diuresis often occurs in a clinical setting of symptomatic renal failure prior to release of obstruction.

In view of these considerations, the following recommendations seem appropriate. The patient should be kept under close observation in an intensive-care setting with frequent and careful monitoring of fluid and electrolyte intake and output, pulse, supine and upright blood pressure, plasma creatinine and electrolytes, etc. Replacement of one half to two-thirds of hourly urine volumes by an intravenous electrolyte solution, the composition of which can be largely dictated by measurement of urinary electrolytes, should prevent perpetuation of the diuresis. In most cases urine output will gradually diminish without signs of hypovolemia. If, however, evidence of hypovolemia does develop, the rate of intravenous fluid administration can be appropriately increased. It should be pointed out that the rapid infusion of glucose-containing solutions under these circumstances may produce glycosuria and pertertuate the osmotic diuresis. Indeed, iatrogenic massive glycosuria can, of itself, produce severe volume depletion. Since proximal Tm for glucose is depressed by in the post-obstructed kidney (79), it is important that the urine be checked regularly for the presence of glucose if glucose-containing intravenous fluids are being administered.

D. What is the Likelihood of Recovery of Renal Function in a Completely Obstructed kidney?

This remains a difficult question to answer. Studies in dogs after release of complete ureteral obstruction have shown GFR returns to normal after one week of obstruction, after four weeks of obstruction GFR returns to 20-30% of normal, after about 40 days of obstruction there is minimal residual function, and after eight weeks little or no return of GFR is observed (80,81,82). Similar findings of no return in renal function beyond four weeks of total ureteral occlusion have been made in the rat and rabbit (83,84).

In a general sense a similar prediction can be made in man. However, there are a number of reports of some return of renal function after periods of obstruction varying between 50 and 90 days (85-87). Many other reported cases have not been adequately documented by adequate renal function tests, the criteron of renal function being the IVP or a renal scan. The case reported by Better, et al, was well studied and showed return of glomerular filtration to the level of 10 cc/min after relief of three months' of complete unilateral obstruction.

Thus, if complete ureteral obstruction has been present for less than one month, there appears to be a reasonable chance for a significant degree of recovery of renal function after surgical relief of obstruction. In kidneys obstructed for 1-3 months, there still appears to be a possibility of some residual function adequate to sustain life. In such situations a temporary diverting procedure might be advisable, allowing adequate assessment of recovery of function of the affected kidney. Kidneys totally obstructed for periods greater than three months appear very unlikely to regain significant function. Under such circumstances, especially in the presence of repeated infection and a contralateral normal kidney, nephrectomy might be the wisest choice. Partially obstructed kidneys have a much greater likelihood of recovering function and nephrectomy should be avoided unless it is clear that the continued presence of an infected kidney or a complex surgical repair constitute a clear threat to the life of the patient.

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VI. PATHOPHYSIOLOGY OF OBSTRUCTIVE DISEASE

A. General Physiologic Considerations

With cessation of urine flow by obstruction, tubular hydrostatic pressure throughout the nephron rapidly rises. Under these circumstances, the driving pressure for glomerular ultrafiltration, namely the balance between glomerular mean hydrostatic pressure and tubular hydrostatic pressure and between glomerular and tubular oncotic pressures, given by the equation

(EFP = $P_G - P_T - \pi_G + \pi_T$ where EFP = effective filtration pressure, P_G = glomerular hydrostatic pressure, P_T = tubular hydrostatic pressure, π_G = mean glomerular oncotic pressure, and π_T = tubular oncotic pressure) is rapidly reduced to zero. Thus filtration stops completely. If there is subsequent reabsorption of water and solutes beyond the point of obstruction, or even if the obstructed segment, and there is some evidence for this (88), then hydrostatic pressure will fall, and some degree of filtration will resume until hydrostatic pressure again rises to previous levels. Thus some glomerular filtration may intermittently exist, but it serves no useful function in the total absence of urinary excretion.

In the absence of flow of tubular fluid (as with complete obstruction), the pressures within the entire nephron should eventually equalize and the only determinant of tubular pressure would be glomerular hydrostatic pressure. Even though subsequent further tubular or pelvic dilatation might transiently reduce intratubular pressure, this would result in a pressure gradient from glomerulus to tubule, filtration would resume until tubular hydrostatic pressure returned to control values, and then stop. Therefore the net result of progressive tubular dilatation would be no change in tubular hydrostatic pressure. Thus after total tubular obstruction, the progressive fall in tubular pressure with time which has been observed (89, 90), would have to be secondary to a fall in glomerular hydrostatic pressure. That this is, in fact, the case has recently been confirmed in studies reported by Safirstein and Wright (90), as will be discussed in some detail later.

So long as there is flow of tubular fluid through the nephron, intratubular pressure, like pressure in any fluid flowing through a series of tubes, is determined both by the tubular resistance, which is directly related to tubular diameter (as well as fluid viscosity), and by tubular fluid flow rate which is in turn determined both by tubular resistance and by forward driving pressure, i.e., glomerular hydrostatic pressure. Recent studies have indicated that the major resistance drop (with respect to flow of tubular fluid) along the nephron occurs across the terminal 750 μ of the collecting duct (91). Normally, hydrostatic pressures average about 10 mmHg for the proximal tubule, and 8 mmHg for the distal segments during hydropenia. During diuresis pressures in all segments of the nephron (proximal to the terminal portion of papillary collecting duct) equalize and average about 14 mmHg. Pelvic and ureteral pressures are 0-5 mmHg. Thus, after ureteral obstruction, pressure in the pelvis has to rise above the prexisting 10-14 mmHg level in proximal collecting duct before the increased ureteral and pelvic pressures are transmitted throughout the nephron. Once ureteral and pelvic pressures rise above this point, proximal tubular pressure will also rise. It also follows that the greater the rate of flow of tubular fluid prior to ureteral occlusion, the greater the subsequent rise in tubular pressures for any given degree of ureteral constriction. Thus, during an osmotic diuresis, Goltschalk, et al, (92) found proximal tubular pressures as

high as 80-90 mmHg after ureteral occlusion. Under these circumstances the balance of passive driving forces across the glomerular capillary would actually be reversed and it is at least theorectically possible that "reverse filtration" might transiently occur. This process would necessarily be very transient since tubular hydrostatic pressure, with reversal of filtration, would rapidly fall, and glomerular hydrostatic pressure would rise. In addition, the latter might rise further, due to changes in afferent or efferent arteriolar resistance. Thus tubular hydrostatic and glomerular pressures would rapidly come into balance, and there would be no filtration in either direction. If ureteral obstruction is partial, tubular hydrostatic pressure would eventually fall below glomerular pressure, and filtration would resume at some level. This further drop in hydrostatic pressure would result from: a) gravity drainage of fluid out of collecting ducts; b) progressive tubular and/or pelvic dilatation; and c) whatever level of continued fluid reabsorption persists during elevated tubular pressures.

B. Studies of the Direct Effect of Hydrostatic Pressure on Tubular Function.

There have been very few investigations which have allowed a direct examination of the effect of hydrostatic pressure on tubular function in various segments of the nephron. Most of the data which does exist has come from studies of isolated tubules perfused *in vitro*, and includes the studies of Burg and Orloff (93), those of Helman, *et al*, (94) and those from our own laboratory (95,96). In addition, Wilson and Sonnenberg, using microcatheterization techniques, studied the influence of release of bilateral ureteral obstruction on the reabsorption capacity of the medullary collecting duct (64).

In the study of Burg and Orloff, the influence of increased hydrostatic pressure on absolute and fractional reabsorption was examined in proximal convoluted tubules, using the *in vitro* isolated, perfused tubule technique, as shown in Figure 11. In this technique, physiological solutions are perfused through one end of the tubule by means of a small pipette inserted into the tubular lumen; this pipette also serves as a microelectrode. Fluid is collected from the other end of the tubule segment by means of a collection pipette. Changes in fractional reabsorption can be calculated by changes in a volume marker, and absolute reabsorption calculated from the changes in fractional reabsorption and the perfusion rate. In the above study, when hydrostatic pressure was increased in the proximal convoluted tubule, resulting in marked tubular dilatation, while perfusion rate was kept constant, there was no significant change in either fractional or absolute reabsorption in the proximal convoluted tubule. A similar inference could be made regarding the lack of effect of hydrostatic pressure when the proximal straight tubule was examined.

In studies from our own laboratory (95), it was noted that below perfusion rates of 10 nanoliters per minute, the electrical potential difference

in isolated, perfused proximal convoluted tubules, using the same technique as above, showed a dependence on tubular flow rate. That this variation in the potential difference was related to tubular fluid flow rate, and not to concomitant changes in transtubular hydrostatic pressure was shown by the ability to dissociate PD from hydrostatic pressure at different flow rates, while PD and flow rate changed in a similar fashion. Thus this study also provided evidence that hydrostatic pressure has no influence on proximal tubular function.

In contrast to the lack of evidence of any direct effect of hydrostatic pressure in the proximal tubule, studies from our laboratory have recently shown an inverse relationship between tubular fluid flow rate and transtubular potential difference (an index of active electrolyte transport) in the isolated, perfused cortical collecting tubule and in the distal convoluted tubule (96). This is shown in Figure 12. This data is similar to that reported for the collecting tubule by Helman, et al, (94). However, as mentioned above, the change in PD could have been due to either a change in flow rate or a change in hydrostatic pressure (perfusion rate was varied by means of changing the height of an open hydrostatic fluid column). Therefore, the tubular lumen was occluded at the collection site so that flow rate fell to zero while hydrostatic pressure rose, and the tubule became distended (Fig. 13). When this was done, potential difference fell as hydrostatic pressure rose and flow rate decreased. Thus the variation in PD was due to the influence of hydrostatic pressure and not flow rate.

In the collecting tubule, the fall in transtubular potential difference with increased hydrostatic pressure could be a result of either of two primary events. Since the potential difference in this segment, ordinarily -15 to -45 millivolts (lumen negative) is generated by active sodium transport (96,97), a reduction in the PD could result either from inhibition of active sodium transport, or of increased back diffusion of sodium, due to an increase in tubular permeability. This latter mechanism would effectively shunt the sodium current and reduce the voltage toward zero. Increased hydrostatic pressure could theoretically act in either manner. Dilatation of the tubule could alter its passive permeability and increase solute backflux. On the other hand, the marked flattening of the tubular epithelial cells associated with increased hydrostatic pressure and tubular dilatation could somehow inhibit the active transport mechanism. In the studies of Helman, et al, transtubular electrical resistance was unchanged when tubular hydrostatic pressure was increased, even though PD fell. This would favor the hypothesis that inhibition of active transport, rather than increased passive back flux, is responsible for the inhibitory effects of hydrostatic pressure on the potential difference. Regardless of the mechanism, however, it seems likely that net transport under these circumstances falls concomitant with an inhibition of the PD.

Even more recently, studies utilizing microcatheterization of the medullary collecting duct suggest that increased intratubular hydrostatic pressure is

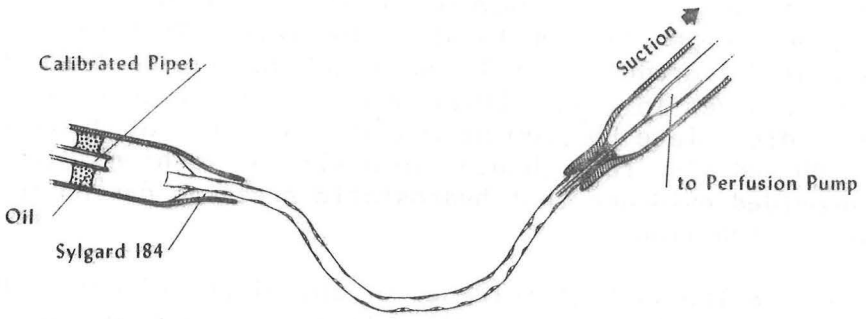

Figure 11. In vitro microperfusion technique. Reprinted from Kokko. Tubules are held at each end by pipets. Third pipet of smaller diameter is advanced into tubular lumen and serves as perfusing pipet and exploring electrode. Fluid collected in holding pipet at distal end of tubule can be collected and electrolyte content, perfusion rate and absolute volume reabsorption can be measured.

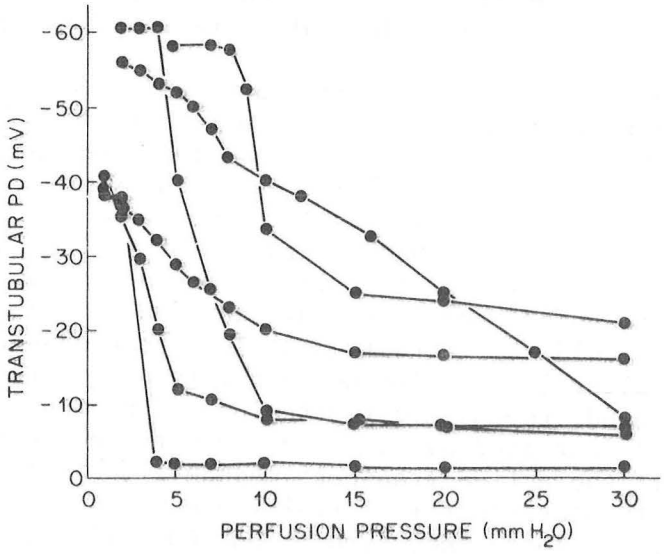

Figure 12. Relationship of hydrostatic pressure to transtubular potential difference in distal convoluted tubule. Similar relationship holds for cortical collecting tubule. Reprinted from Gross and associates.

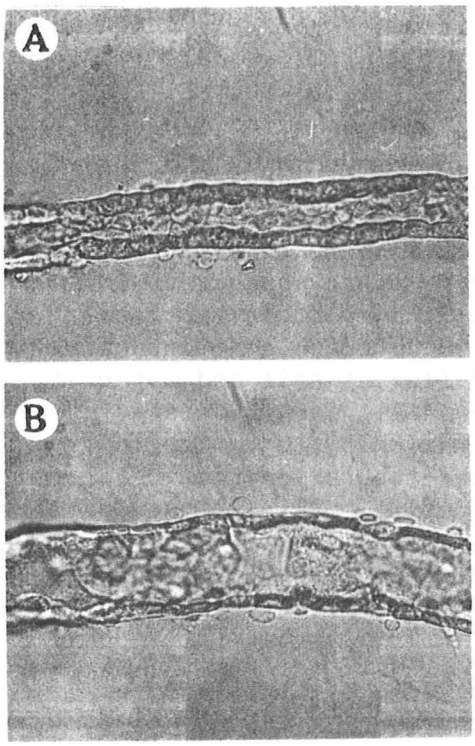

Figure 13. Effect of increased hydrostatic pressure on morphology of collecting tubule. A, appearance of collecting tubule at normal hydrostatic pressure. B, markedly increased hydrostatic pressure is associated with tubular dilatation and flattening of tubular epithelial cells.

indeed associated with net inhibition of transport in this segment (64). These studies were done in rats undergoing a post-obstructive diuresis after relief of 24 hours of bilateral ureteral ligation. Under these circumstances, delivery of filtrate to the collecting duct was reduced, but reabsorption in this segment was inhibited, and in fact, there was net secretion of salt and water into the lumen. Thus the natriuresis was entirely attributable to the changes occurring in the medullary collecting duct, and amounted to about 12% of the filtered load, a figure very similar to that found in the study of Yarger, et al (89). The net secretion of salt and water into the medullary collecting duct could have resulted either from an inhibition of active transport in the face of unaltered back diffusion (a transtubular sodium chloride gradient existing in this segment) or from an increase in back-flux of salt and water in the absence of any change in active sodium flux. Although hydrostatic pressure per se may have been responsible for the inhibition of collecting duct function observed in this study, changes in peritubular physical factors or release of some natriuretic agent are alternative possibilities.

With respect to the direct influence of tubular hydrostatic pressure on other nephron segments, there is currently insufficient data to allow any definitive statement.

C. Partial Tubular Obstruction (Acute)

There have been several important studies of either partial ureteral obstruction or increased ureteral pressure, including those of Gottschalk and Mylle (92), Share (98), Selkurt, et al (99), and Suki, et al (100). In those studies in which observations were made shortly after onset of obstruction, the rise in intratubular pressure was associated with varying degrees of diminutionin glomerular filtration, depending on the magnitude of rise in tubular hydrostatic pressure. In the study of Gottschalk and Mylle (92), the level of pre-existing urine flow rate greatly influenced tubular pressures subsequent to ureteral occlusion. Tubular pressure did not rise unless ureteral pressure approached tubular pressure. In hydropenic animals, brief ureteral occlusion increased ureteral pressure toward pre-existing tubular pressure, but the latter rose only slightly. In animals undergoing an osmotic diuresis, there was a rapid, greater rise of both ureteral and tubular pressures. Peritubular capillary pressures were found to approximate intratubular pressures, and tubular fluid flow rate was markedly decreased. In the studies of Share (98), Selkurt (99), and Suki, et al (100), there was a decrease in urinary flow rate and sodium excretion on the partially obstructed side. In the latter study urinary sodium concentration, fractional sodium excretion, and fractional free water clearance were also reduced. Urine osmolality was higher on the partially obstructed side than on the control side during water diuresis and fell to below that of the control side during hypotonic saline diuresis (100). These findings are depicted in Figures 14-16. This pattern was strikingly similar to that associated with acute renal arterial constriction, and was therefore interpreted as representing underperfusion of the nephron distal to the proximal

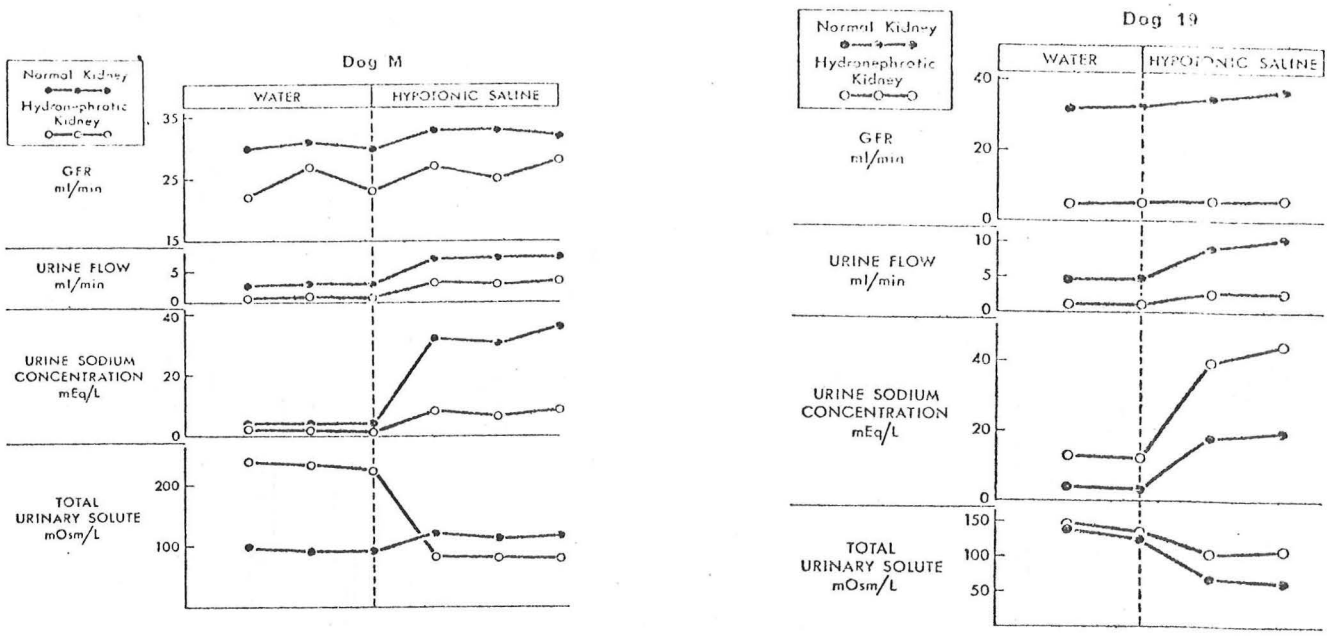

Figure 14. Effect of acute (right) and chronic (left) hydronephrosis on water and electrolyte excretion during water and hypotonic saline diuresis. (From Reference Number 100).

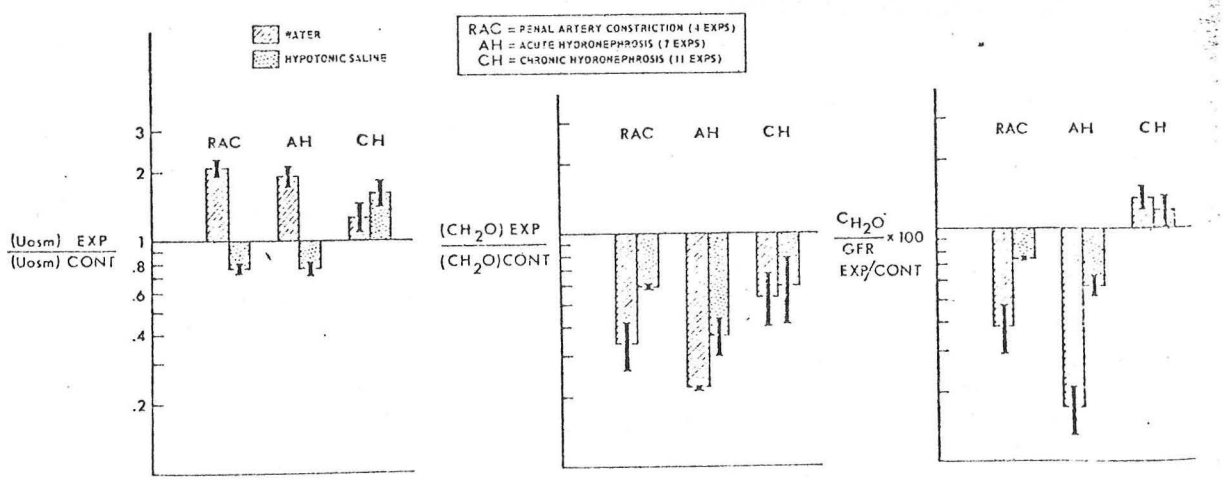

Figure 15. The effects of renal arterial constriction and acute and chronic hydronephrosis on urinary solute concentration (U osm), absolute solute-free water clearance (C_{H_2O}), and fractional free water clearance (C_{H_2O} x 100/GFR). The vertical bars represent the mean of the ratios of the experimental to the control side ± standard error. (From Reference Number 100).

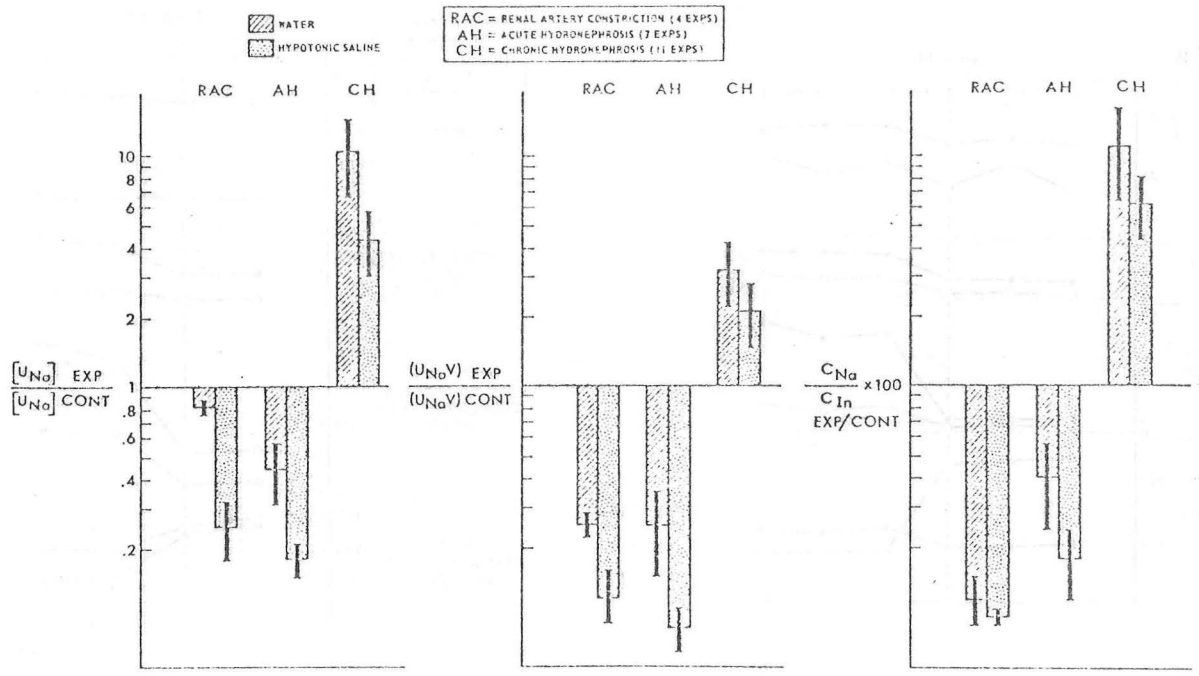

Figure 16. The effects of renal arterial constriction and acute and chronic hydronephrosis on urinary sodium concentration (U_{Na}), and absolute (U_{Na} V) and fractional (C_{Na} x 100/inulin clearance) rates of sodium excretion. The vertical bars represent the mean of the ratios of the experimental to the control side ± standard error. (From Reference Number 100).

tubule. Thus it would appear that the functional changes attending partial ureteral obstruction and those associated with acute reductions in arterial perfusion pressure, sufficient to reduce GFR, are similar. This is of interest since intratubular pressure is increased in the former circumstance and reduced in the latter. Thus, acute changes in tubular hydrostatic pressure per se would seem unlikely to play a major pathogenetic role. Since glomerulotubular balance is maintained during aortic constriction (100) as well as during acute partial ureteral occlusion (101), the reduction in distal delivery reflects only a reduction in GFR, and not a change in fractional reabsorption in the proximal tubule. Also, since the changes attending partial tubular obstruction mimic those of aortic constriction, it would appear that in this latter setting also, the reduction in perfusion of more distal nephron segments is the sole result of a reduction in GFR.

D. Partial Tubular Obstruction (Chronic).

In contrast to the changes associated with partial acute obstruction, Suki, et al (100), found a markedly different pattern after partial chronic ureteral obstruction (see Figs. 14-16). In this setting, urine volume and free water clearance were decreased, while urinary sodium concentration, sodium excretion, and fractional free water clearance were increased. This pattern was best explained on the basis of a combination of reduced nephron mass and overperfusion of residual nephrons. It was felt that in this chronic model, tubular hydrostatic pressure fell with time, as has been previously shown (102), but that since some nephrons had been destroyed, filtration was resumed in a fewer number of functioning nephrons. Compensatory changes in these remaining nephrons could then lead to an increased GFR per nephron. The only evidence for this was inferential, however, namely an observed fall in Tm PAH greater than the fall in GFR, giving an increased GFR/Tm PAH ratio. Such inferentential evidence is subjected to other interpretations and there is no direct evidence supporting an increased GFR/nephron in chronic partial urinary tract obstruction. The overperfusion of the distal nephron was felt to be due to decreased fractional reabsorption in the proximal nephron (100). Since these same authors subsequently documented in this chronic model medullary washout, i.e., reduced medullary and papillary osmolality (20), a more likely alternative explanation for the observed pattern in chronic hydronephrosis can be given. The observed reduction in GFR would be expected to lead to reduced delivery of filtrate distally, even if glomerulotubular balance is maintained (which appears to be the case with increased tubular hydrostatic pressure). If, however, in this chronic situation there has been washout of the solutes of the medulla, as has been documented (103), then water abstraction of filtrate along the descending limb of Henle's loop would be severely reduced, if not completely eliminated, and this could not only normalize, but actually increase delivery of filtrate distally. Since the integrity of the thick ascending limb of Henle's loop would remain intact, increased delivery of filtrate would generate increased amounts of free water, and the relationship between delivery of filtrate, given by the

urine volume under conditions of water loading, and free water clearance, would be unaltered. This was indeed what was observed in the study of Suki, et al (100). When V/100 ml GFR was plotted against C_{H_2O}/100 ml GFR, the relationship was the same as in the control kidney. Since the osmolality of the papilla is markedly reduced, under hydropenic conditions, back diffusion of water out of the collecting ducts, even in the presence of maximal amounts of ADH, would be reduced, accounting for the observed reduction in U_{max} and $T^c_{H_2O}$, as well as the clinical observation of vasopressin-resistent polyuria, which frequently accompanies chronic hydronephrosis, especially when bilateral.

In summary, then, the findings in acute partial ureteral obstruction are compatable with that of a reduced GFR, secondary to increased tubular hydrostatic pressure, without a change in fractional absorption by the proximal tubule. This would lead to underperfusion of the distal nephron, a reduction in urine volume and sodium excretion. In the studies reported by Suki, et al (105), acute ureteral occlusion failed to produce medullo-papillary washout. This may have been related to the fact that GFR was reduced in only one-third of the animals; in fact in those animals in which GFR fell markedly, U_{max} was also impaired (105). In the chronic setting, however, medullo-papillary washout clearly occurs (103). Such a development probably explains the increased urine volume and sodium excretion and reduced U_{max} observed in the chronic setting. The reason for the development of medullary washout is not entirely clear, but the following explanation seems most plausible. With acute ureteral obstruction there is an increase in renal blood flow and a shift in the relative distribution of flow toward the medulla, with medullary flow showing an absolute increase (89,104,105). With chronic obstruction, after the initial rise in blood flow, GFR and blood flow fall in concert (106,107), though there is still a relative increase in medullary flow (108). The latter change, in combination with a reduction in GFR, could lead to progressive washout of the medulla. In addition, scarring and distortion of the medullary architecture, typical of chronic, severe hydronephrosis probably contributes to the reduction in medullary tonicity.

Because of the marked anatomic compression of medullary structures, it would be expected that reabsorptive function might be impaired in deep nephrons. Indeed, most studies of chronic hydronephrosis suggest that the observed salt-losing state results from damage to deep nephrons and/or collecting ducts, since both GFR and sodium delivery out of proximal superficial nephrons is actually reduced (109-111). In deep nephrons, it is likely that some degree of filtration persists, especially since tubular hydrostatic pressure tends to fall with time, as previously mentioned. Moreover, there is direct evidence to suggest that several weeks of partial ureteral obstruction reduce filtration in, but do not completely destroy juxtamedullary nephrons (110,111). Persistence of filtration in these deep nephrons probably leads to the following events. As filtrate travels down

the descending limb of Henle's loop into the washed-out medullary environment, water abstraction of descending limb fluid is reduced, which results in delivery of a greater volume of filtrate with a lower sodium concentration to the ascending limb of Henle and the distal nephron. The combination of a) such overperfusion of the distal nephron, and b) the effects of chronic elevated hydrostatic pressure on the transport function of these deep loops and/or collecting ducts, likely results in excessive sodium excretion. In addition, the excessive volume of filtrate which enters the collecting ducts of these deep nephrons experiences reduced water abstraction as it tranverses the length of this segment, because of the washed-out, virtually isotonic medulla. Thus, both the polyuria and the salt losing state probably result from the damage to deep nephrons and collecting ducts in association with medullo-papillary washout. The frequently observed acidification defects would also be predicted on the basis of the morphologic and physiologic evidence of collecting duct damage. Finally, additional support for collecting transport abnormalities comes from the recent report of reduced Na-K ATP'ase activity in the outer medulla of chronically obstructed rats (112). Enzyme activity in this zone is primarily localized within collecting ducts, and probably plays a role in sodium reabsorption by this segment.

E. Complete Tubular Obstruction

As mentioned above, with complete ureteral obstruction, acutely there is an increase in total renal blood flow, primarily due to an increase in medullary blood flow, associated with marked vasodilatation within the kidney. Within 24 hours, however, renal blood flow has fallen to or below normal, and progressively falls thereafter, finally stabilizing at a low value after about 4 weeks (106). Glomerular filtration ceases abruptly, probably within one minute (113). Any small degree of resumption of glomerular filtration would be transient and due either to a rise in glomerular capillary pressure, creating a transient driving force for filtration, or a fall in tubular hydrostatic pressure due to further dilatation of the renal pelvis. Despite the virtually complete cessation of filtration and tubular flow, data from stop-flow studies provide at least some evidence for persistence of certain tubular processes (88). These include continued transport of glucose, PAH, sodium, potasium, calcium and magnesium. The studies of Kerr would suggest that release of complete obstruction, if it has been maintained for one week or longer, is not associated with a complete return of renal function. Although GFR progressively increased in the post-obstructed kidney, it never returned to control values, and there was a persistence of at least some diminution in urine concentrating ability (114).

Why GFR remains persistently low after release of obstruction of more than a few days' duration is not clear. Obviously, nephrons which are severely and irreversably damaged may drop-out entirely. It is also possible that GFR remains low in surviving nephrons after release of obstruction. Recently, Blantz, et al (115), have demonstrated that acute rises in

ureteral pressure in the rat cause a reduction in the glomerular hydraulic permeability coefficient (L_pA, an index of the water permeability of the glomerulus in response to a given hydraulic pressure gradient) even after release of the partial obstruction. Thus it is conceivable that chronic obstruction produces irreversible permeability changes in glomeruli of affected tubules, and contributes to the persistently low total kidney filtration rate after release of obstruction.

F. Post-Obstructive Diuresis

The most extensive examination to date of the mechanisms involved in the diuresis occurring after release of total ureteral obstruction has been that of Yarger and associates (89). Since a number of important observations were made in that study the findings will be reviewed in some detail. Clearance and micropuncture observations were carried out in rats 24 hours after release of either bilateral or unilateral ligation. Release of unilateral obstruction was not associated with a diuresis. In fact, urine flow and sodium excretion were lower on the post-obstructed side than on the control side. Release of bilateral obstruction was associated with a striking diuresis and natriuresis. These changes were not influenced by administration of either vasopressin or d-aldosterone. Total kidney inulin clearance was 10 per cent of control values after unilateral release of obstruction model and similarly though less severely depressed after release of obstruction in the unilateral model. Superficial single nephron glomerular filtration rate was depressed to only 40 per cent of control. This fact strongly suggested that after release of obstruction juxtamedullary glomerular filtration rate was much more severely depressed than that in superficial nephrons and may have ceased entirely. Indeed, if extrapolations are made based on the estimated number of juxtamedullary nephrons, the total number of nephrons per kidney and the observed superficial single nephron glomerular filtration rate, it can be calculated that in order for total kidney glomerular filtration rate to have decreased to 10 per cent of normal while superficial glomerular filtration rate was 40 per cent of normal, juxtamedullary filtration would virtually have had to cease. After the unilateral release of bilateral obstruction, although total renal blood flow decreased sharply to 20 per cent of control, medullary renal plasma flow remained relatively increased. Tubular fluid/plasma (TF/P) inulin values in the late proximal tubule were unchanged from control after release of obstruction, indicating that fractional reabsorption in the proximal tubule was unaltered (and, in fact, glomerulotubular balance was maintained). TF/P inulin ratios in the distal tubule and in final urine decreased dramatically from 8.0 to 2.9 and from 263 to 5.6, respectively. Thus, the major sites of impaired salt and water reabsorption appear to be distal to the proximal tubule. These findings are summarized in Tables VIII and IX.

TABLE VIII

RENAL HEMODYNAMICS AFTER RELEASE OF BILATERAL URETERAL OBSTRUCTION IN RATS

	Control	Experimental
Glomerular Filtration Rate (ml/min/kg)	6.6	0.8
Renal Plasma Flow (ml/min/kg)	21.5	7.4
Medullary Plasma Flow (ml/min/kg)	3.7	4.2
Filtration Fraction	0.41	0.28

TABLE IX

HYDROSTATIC PRESSURE IN TUBULES AND EFFERENT ARTERIOLES BEFORE AND AFTER RELEASE OF BILATERAL AND UNILATERAL OBSTRUCTION IN RATS

	Proximal Tubular Pressure (mmHg)		Distal Tubular Pressure (mmHg)		Efferent Arteriolar Pressure (mmHg)	
	Before Release	After Release	Before Release	After Release	Before Release	After Release
Bilat.	30.1 (nl. = ∿13)	14.5	27.7 (nl. = ∿8)	10.0	19.0 (nl. = ∿15)	13.9
Unilat.	9.2	--	6.5	--	5.5	--

Hydrostatic pressures in proximal and distal tubules and efferent arteriols were measured after 24 hours of tubular obstruction and shortly after release of obstruction in the unilateral and bilateral models. Of note is the fact that in the bilaterally obstructed animals, proximal and distal, as well as efferent arteriolar pressures were elevated just prior to release of obstruction at 24 hours, proximal tubule pressure averaging 30 mm. Hg. In sharp contrast, in the unilaterally obstructed model tubular and efferent

arteriolar pressures were less than normal prior to release of obstruction, proximal tubular pressure averaging 9 mm. Hg. After release of obstruction in the bilateral model tubular pressures decreased but remain slightly more than normal, while efferent arteriolar pressure decreased to slightly less than normal. Thus, the only significant difference between the bilaterally obstructed and unilaterally obstructed animals, which might serve to explain the absence of diuresis or natriuresis in the latter, is the marked difference between tubular hydrostatic pressures in these two groups.

With respect to the issue of hydrostatic pressure recent studies of Safirstein and Wright have examined this issue in more detail (90). They measured arterial pressure, proximal stop-flow pressure (an index of glomerular hydrostatic pressure) and proximal tubular pressures at different intervals during the first 24 hours after complete ureteral obstruction in unilaterally and bilaterally obstructed rats (Table X). During the first few hours of obstruction tubular and glomerular pressure increased, although the magnitude of increase was much greater in the bilaterally obstructed animals. These findings were suggestive of a progressive increase in renal blood flow during the first few hours after obstruction, as has been documented, associated with efferent arteriolar dilatation and increasing glomerular hydrostatic pressure. During the remainder of this 24-hour period there was a progressive decrease in glomerular pressure and, thus, in tubular pressure, reflecting progressive efferent arteriolar constriction and a marked decrease in total renal blood flow by 24 hours. By this point glomerular hydrostatic pressure was less than normal and proximal tubular pressure was normal in the unilateral model but both remained more than normal in the bilaterally obstructed animals. Thus, in the unilaterally obstructed animals vasodilatation and an increase in renal blood flow were not nearly as marked as in the bilateral group and the subsequent vasoconstriction and diminished renal blood flow were more severe in these animals. This more marked decrease in renal blood flow and in glomerular hydrostatic pressure in the unilaterally obstructed rats, therefore, explains the normal or even subnormal (as in the study of Yarger and associates [89]) tubular pressures at 24 hours, prior to the release of obstruction.

G. A Proposed Model of the Mechanism of Post-Obstructive Diuresis.

Based on the data discussed in the section on post-obstructive diuresis, as well as the direct studies just reviewed, we wish to propose a model that offers an adequate explanation for most, if not all, features of post-obstruction diuresis. This model is summarized in schematic form in Figure 17 (116).

Subsequent to acute complete bilateral ureteral obstruction the following sequence of events may occur. There is initially a marked increase in renal blood flow, associated with renal vasodilatation. The mechanism underlying this established observation is not clear but several possibilities exist, including the local release of various vasodilators, such as prostaglandins

TABLE X

PROXIMAL TUBULAR AND GLOMERULAR HYDROSTATIC PRESSURES BEFORE AND AFTER RELEASE OF BILATERAL AND UNILATERAL OBSTRUCTION IN RATS*

	Stop Flow (Glomerular Hydrostatic) Pressure (mm. Hg)		Proximal Tubular Pressure (mm. Hg)	
	Unilat.	Bilat.	Unilat.	Bilat.
Pre-Obstruction	36	35	13	13
0 to 8 Hours	43	60	30	46
24 Hours	23	37	14	32
Release	24	28	13	18

*Modified from data of Safirstein and Wright (90).

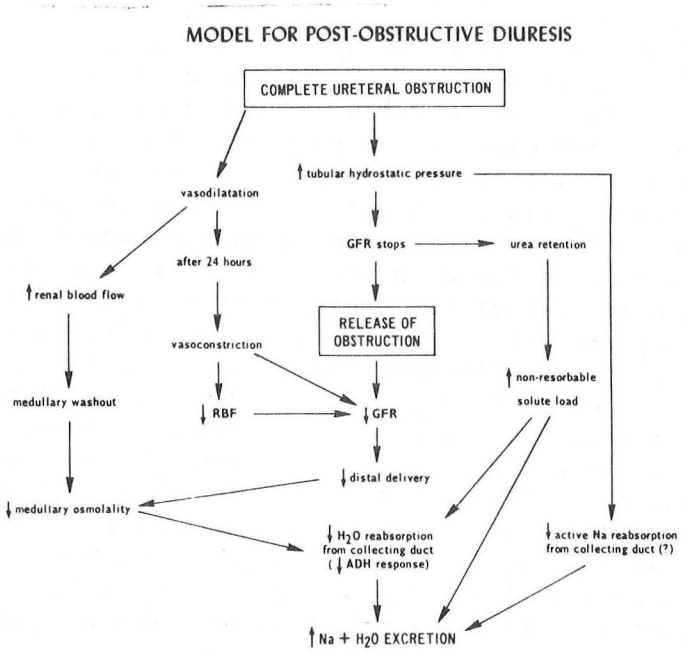

Figure 17. Schematic representation of major physiological alterations associated with post-obstructive diuresis.

or kinins, or possibly vasodilatation secondary to changes in interstitial fluid pressure, as has been suggested (117). In any event, the combination of cessation of glomerular filtration because of complete tubular obstruction plus an initial marked increase in renal blood flow owing in large part to augmented medullary flow would result in progressive medullary washout. As suggested by Yarger and associates, papillary washout could result in a marked decrease in the viscosity of blood flowing through the vasa recta, since the high viscosity is probably caused by the normally high medullary tonicity, which results in crenation of red cells and a 3-fold increase in protein concentration in vasa recta blood (9). A washout of the medullary hypertonicity would, therefore, reduce the viscosity of vasa recta blood. Since viscosity is a major determinant of resistance to blood flow, it is possible that the latter decreases, resulting in an increase in vasa recta blood flow. This would contribute to if not entirely explain the progressive increase in medullary blood flow in the first few hours after complete tubular obstruction. It has been suggested that resistance to blood flow through the vasa recta provides most of the resistance to flow through juxtamedullary efferent arterioles, which connect with the vasa recta (118). Thus, a decrease in resistance and increase in blood flow in the vasa recta would be expected to decrease efferent arteriolar resistance in juxtamedullary nephrons, a major determinant of filtration pressure.

In the remainder of the first 24 hours after onset of obstruction there is a progressive decrease in renal blood flow associated with increasing afferent arteriolar resistance, as is strongly suggested by the experimental evidence (89,90). Thus, by 24 hours in juxtamedullary nephrons medullary blood flow has returned essentially to normal levels, reflecting increased afferent arteriolar resistance. Efferent arteriolar resistance remains reduced, reflecting persistent medullary washout and its effect on vasa recta resistance. This combination of a marked reduction in efferent arteriolar resistance and an increase in afferent arteriolar resistance would likely so reduce glomerular hydrostatic pressure that, despite the relief of tubular obstruction, glomerular filtration rate in juxtamedullary nephrons would either remain zero or be extremely low. In contrast, in superficial nephrons, as suggested by the data of Safirstein and Wright at 24 hours, afferent arteriolar resistance, while higher than initial values, is still somewhat less than control values, resulting in somewhat higher than normal glomerular hydrostatic pressure, which in turn is reflected in slightly elevated proximal tubular pressures (90). With release of obstruction proximal tubular pressure decreases, as does glomerular hydrostatic pressure allowing for some filtration but over-all filtration would be moderately to markedly reduced. This would account for the prolonged lissamine green transit time in surface nephrons (89).

Thus, after release of total bilateral ureteral obstruction total kidney glomerular filtration rate would remain markedly reduced because of a combination of moderate depression of filtration in surface nephrons and severe depression or complete cessation of filtration in juxtamedullary glomeruli.

In superficial nephrons normal fractional reabsorption in the proximal tubule in combination with reduced filtration would lead to reduced distal delivery in surface nephrons. In juxtamedullary nephrons persistence of medullary washout would be maintained after release of obstruction by persistence of medullary blood flow at or slightly above normal and filtration rates close to zero. To the extent that some filtration was occurring in deep nephrons medullary washout would result in a marked decrease in water abstraction of descending limb fluid and a fall in the TF/P inulin ratio of fluid reaching the distal tubule. Even if filtration ceased entirely in deep nephrons, the urine/plasma inulin ratio would be expected to be low since the final urine would now reflect only that delivered from superficial nephrons, which do not have long loops and, therefore, do not possess a mechanism for further water abstraction, which would increase the TF/P inulin ratio above that existing at the late proximal straight tubule. Indeed, in the study of Yarger and associates TF/P inulin in superficial punctured distal tubules was about 2.9 after release of obstruction, while that in proximal superficial nephrons was about 2.2. This further rise in TF/P inulin could reflect subsequent volume resorption in the proximal straight tubule, in which case the observed urine/plasma inulin ratio could be entirely explained on the basis of complete dropout of the contribution of juxtamedullary nephrons plus inhibition of collecting duct fluid reabsorption.

According to the model delivery of fluid to the collecting ducts would likely be reduced, as was observed in the study of Sonnenberg and Wilson (64). In the face of persistent loss of medullary hypertonicity water abstraction along the collecting duct would be reduced, and urine flow would be increased and concentrating ability impaired under hydropenic conditions.

The period of marked elevation of tubular hydrostatic pressures also could directly inhibit the reabsorptive capacity of the collecting duct, as suggested by our potential difference studies as well as the direct observations of Sonnenberg and Wilson. Thus, the final result would be natriuresis and a diuresis (Fig. 18).

To the extent that urea retention occurred during the period of total obstruction, release of obstruction, with resumption of glomerular filtration, albeit reduced, could add an osmotic diuretic component to the other mechanisms acting to produce a post-obstructive diuresis.

It also should be emphasized that in most patients the continued intake of salt and water during the period of total obstruction, either inadvertently by the patient or iatrogenically, would lead to progressive volume expansion and also could contribute to the diuresis after relief of the obstruction.

The reason for the absence of diuresis or natriuresis after relief of unilateral obstruction is not entirely clear. The studies by Harris, et al, (119) suggest that the explanation is related to a) lower plasma urea levels,

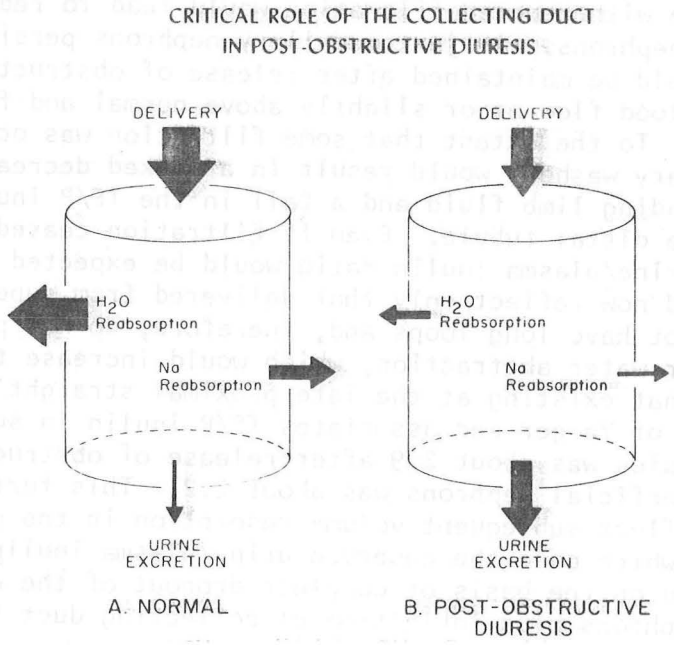

Figure 18. Schematic representation of central role of collecting duct in post-obstructive diuresis.

b) a more severe reduction in distal delivery of filtrate in surface nephrons, resulting both from a reduction in single-nephron GFR and the fact that 60% of superficial tubules are collapsed (compared with only 16% after release of bilateral obstruction), and c) a more severe reduction in filtration in deep nephrons (only 12% of deep nephrons were observed to be filtering in the unilateral post-obstructive model, compared to 60% in the bilateral model).

In summary then it would appear that the critical events associated with relief of bilateral obstruction are: 1) a moderate reduction in superficial nephron glomerular filtration rate and distal delivery resulting from a reduction in glomerular hydrostatic pressure as well as persistence of a mild increase in tubular hydrostatic pressure, 2) a more severe depression or virtual absence of filtration in juxtamedullary nephrons, associated with medullary washout and 3) a marked reduction in the intrinsic reabsorptive capacity of the collecting duct, possibly reflecting the direct inhibitory effect of increased hydrostatic pressure. In any individual case two additional mechanisms may become superimposed on this basic process and contribute

to the diuresis: 1) osmotic urea diuresis resulting from progressive urea retention during the period of obstruction and 2) progressive volume expansion resulting from continued intake of salt and water during the period of anuria.

Although it has been suggested recently that some circulating natriuretic factor may play a role in post-obstructive diuresis (120), such a natriuretic hormone has yet to be unequivocally identified in any diuretic state. Furthermore, the complex nature of the experimental technique used in this study makes interpretation difficult.

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