Chapter II

Background Information

Physiological function of the ureter.

The ureter are small, smooth muscle tubes that originate in the pelves of the two kidneys and pass downward to enter the bladder. Each ureter is innervated by both sympathetic and parasympathetic nerves, and each also has an intramural plexus of neurons and nerve fibers that extends along its entire length. The rich innervation of the ureter suggests that normal ureteral function is neurally regulated and detailed microscopic studies have indicated the presence of both afferent and efferent components of the autonomic nervous system (Notley, 1968). Recent histochemical studies suggest that the ureter, like other viscera, is innervated by both divisions of the autonomic nervous system Duarte-Escalante, 1969). The relative role that play is not known and it may well be that it is the sympathetic division which predominates. It has been shown that blocking the parasympathetic nerves do not influence ureteral colic (Kiil, 1957; Weinberg and Maletta, 1961; Sierp and Draper, 1964), but studies of blockade of the sympathetic nervous system in ureteral colic do not seem to have been made. It has been reported that there are 2 types of receptors, alpha and beta, which are susceptible to catecholamine stimulation (Ahlquist, 1948). It has been shown that the ureter has both such receptor sites Malin et al, 1968; Boyarsky et al, 1968; Malin et al, 1970) and the question arises whether blockade of either or both types

of receptors will relieve ureteral colic. As urine collects in the pelvis, the pressure in the pelvis increases and initiates a peristaltic contraction beginning in the pelvis and spreading downward along the ureter to force urine toward the bladder. A peristaltic wave, traveling at a velocity of about 3 cm./sec, occurs from once every 10 seconds to once every 2 to 3 minutes. The peristaltic wave can move urine against an obstruction with a pressure as high as 25 to 50 mm.Hg. Parasympathetic stimulation increases and sympathetic stimulation decreases the frequency. Transmission of the peristaltic wave is probably caused mainly by nerve impulses passing along the intramural plexus in the same manner that the intramural plexus functions inthe gut. At the lower end, the ureter penetrates the bladder obliquely through the trigone. The ureter courses for several centimeters under the bladder epithelium so that pressure in the bladder compresses the ureter, thereby preventing backflow of urine when pressure builds up in the bladder during micturition.

Pain sensations from the ureters, and the ureterorenal reflex.

The ureters are well supplied with pain nerve fibers. When the ureter becomes blocked, such as by a ureteral stone, intense reflex constriction associated with very severe pain occurs. In addition, the pain impulses probably cause a sympathetic reflex back to the kidney to constrict the renal arterioles, thereby decreasing urinary output from that kidney. This effect is called the ureterorenal reflex; it obviously is important to prevent excessive flow of fluid into the pelvis of a kidney with a blocked ureter. Ureteral stones originate

in the kidney. Gravity and peristalsis both contribute to spontaneous passage into and down the ureter. Ureteral stones are seldom completely obstructive; they are usually spiculated, so that urine can flow around them. Occasionally, a stone will remain lodged in a ureter for many months without harming the kidney. Partial obstruction is usually present, however, and causes dilatation of the ureter and renal pelvis proximal to the stone. In the early phase, this dilatation is due more to distention than to "hydronephrosis", which implies definite renal damage (Ganong, 1981). If the stone passes within a few days, no evidence of renal injury can be shown. However, if the stone is definitely obstructive and is allowed to remain for weeks or months, irreparable damage to the renal parenchyma can occur. A stone is apt to be arrested at the narrowest points in the ureter. If infection complicates the urinary stasis, further renal damage results.

The effect of indomethacin on ureteral colic

Above an obstructing ureteral stone the pressure of urine tends to increase, causing an increase in tension in the ureteral and pelvic walls, which elicits pain (ureteral colic) (Kiil, 1957; Risholm, 1954). The increase in renal blood flow, which is seen in an acutely obstructed kidney (Vaughan et al, 1971), is caused by a decrease of the resistance in the preglomerular renal vessels (Canton, 1977). Therefore, the glomerular pressure will increase, which may cause a further increase in the intrapelvic pressure. These vascular events depend on the synthesis of prostaglandins. Olsen et al (1976) found an increased efflux of prostaglandin E_2 in urine from a partially

obstructed kidney in dogs. Allen et al (1978) showed that the increased renal blood flow in an acutely obstructed kidney was abolished when the dogs were pre-treated with indomethacin, a prostaglandin synthesis inhibitor. The increase in pelvic pressure also was attenuated in the indomethacin pre-treated dogs. Prostaglandin E_2 also might increase diuresis (Feigen et al, 1976) and, together with the increase of pressure, this will contribute further to the increase in wall tension and pain. Infusion of indomethacin decreased the glomerular filtration pressure and the intrapelvic pressure in pigs (Sjodin and Holmlund, 1982) as well as rats (Sjodin et al, 1982) with acute unilateral obstruction. The diuresis from a partially acutely obstructed kidney in pigs was diminished significantly after administration of indomethacin. In both of these species these effects of indomethacin were found only in non-volume loaded animals. No decrease in the glomerular and pelvic pressure or urine excretion was found following infusion of indomethacin in animals subjected to a saline load. Intravenous indomethacin has been used successfully in the treatment of patients with ureteral colic (Holmlund and Sjodin, 1978; Sjodin and Holmlund, 1982). Relief of pain was obtained in 78 to 84 per cent of the patients.

The effect of indomethacin on renal function

Many investigators have examined the role of prostaglandins in the regulation of renal function. Some have implicated the prostaglandins in renal autoregulation (Chang et al, 1975; Herbaczynska-Cedro and Vane, 1973), although recent reports have failed to confirm this action (Varkarakis et al, 1974; Anderson et al, 1975). Prostaglandins have been shown to be capable of altering renal blood flow

(Bailie et al, 1975; Needleman et al, 1974; Owen et al, 1975) and intrarenal hemodynamics (Bailie et al, 1975; Chang et al, 1975; Kirchenbaum et al, 1974), as well as water and/or electrolyte excretion (Fulgraff et al, 1974; Gross and Bartter, 1973; Johnston et al, 1967; Tannenbaum et al, 1975). However, the importance of endogenously formed prostaglandins in the maintenance of renal function remains unclear. Some of this uncertainty centers on the methods that have been employed to alter prostaglandin levels in the kidney, since different methods of changing intrarenal prostaglandin concentration can elicit variable results. Several investigators have infused prostaglandins directly into the renal artery (Zins, 1975). Others have stimulated prostaglandin (PG) synthesis in the kidney by infusing arachidonic acid, the substrate for synthesis of PGA_2, PGE_2 and PGF_2 (Chang et al, 1975; Tannenbaum et al, 1975). Still others have examined the role of renal prostaglandins by administering drugs, such as indomethacin and meclofenamate, which inhibit prostaglandin synthesis by inhibiting arachidonic acid change to be prostaglandin (Venuto et al, 1975; Anderson et al, 1975; Kirschenbaum et al, 1974). Each of these techniques has its limitations.

Infusion of prostaglandins into the renal artery cannot produce the same distribution of these acidic lipids within the kidney as the distribution produced by endogenous synthesis, since synthesis of prostaglandins occurs primarily in the medulla (Crowshaw, 1973; Larsson and Anggard, 1973). The prostaglandins are thought to be transported from the medulla to the cortex by the renal venous system (vasa recta) or renal tubules (Zins, 1975). Therefore, both the route

of administration of prostaglandins and the local concentrations in the renal cortex may be nonphysiological when these substances are infused into the renal artery. Thus, stimulation of endogenous prostaglandin synthesis by arachidonic acid has been proposed by Tannenbaum et al. (1975) to be a more physiological method of altering prostaglandin levels in the kidney. This technique also may not prove to be entirely satisfactory, since Larsson and Anggard (1973) have demonstrated that a greater proportion of prostaglandins are synthesized in the renal cortex, as compared to the medulla, in response to arachidonate infusion than is observed when synthesis is dependent on endogenous substrates in the kidney. Thus, arachidonate infusion may also produce a nonphysiological distribution of prostaglandins within the kidney.