A STUDY OF THE PHYSIOLOGY AND PHARMACOLOGY OF THE URETER

by

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INTRODUCTION

Structure

The structure of the ureter in dogs is treated in such a cursory fashion by Bradley[1] and by Ellenburger and Baum[2] that recourse has had to be made to studies on the human. However, the embryology and neurology of this organ has been largely demonstrated in the dog.

Embryology:

The ureter makes its first appearance in the development of the ovum as a bud on the posterior aspect of the Wolffian duct. This is shown diagrammatically in figure 1. Later the cloaca becomes divided into a dorsal and a ventral cavity by the downward growth of the uro-rectal septum. The dorsal portion becomes the rectal end of the bowel while the ventral portion becomes the urogenital sinus or allantois. The Wolffian duct stays ventral to this fission and opens as a consequence on the dorsolateral aspect of the urogenital sinus. This process is illustrated in figure 2. While the fission is progressing, the opening of the primitive ureteral canal rotates on the long axis of the Wolffian duct traveling in a semicircle around the outer side until it assumes a ventral and lateral position. While this is going on, the orifice of the Wolffian duct appears to be absorbed into the growth of the lateral portion of the allantois from which the bladder is ultimately to be formed. As this progresses, the ureter eventually gains its own independent implantation and orifice. The kidneys in their ascent behind the Wolffian bodies and developing sex glands rotate on their vertical axes so that the pelves occupy a mesial position in relation to the renal mass. After the ascent of the kidneys the ureters become lengthened as a result of (1) changes in the

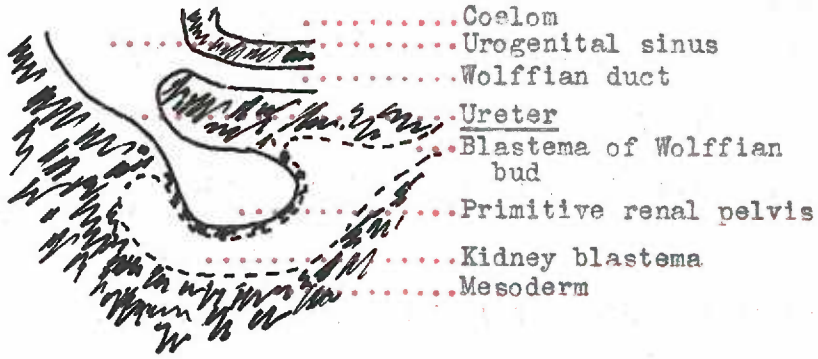


Figure I
(after Kelly-Burnam)

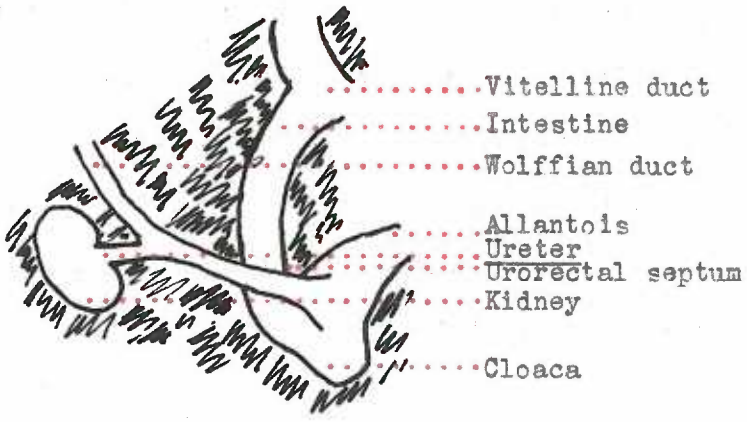


Figure 2
(after Kelly-Burnam)

lumbar and sacral vertebrae, (2) descent of the pelvic organs, (3) development of the psoas muscle, and (4) straightening out of the renal mass.

Anatomy:

The ureter is a muscular tube of a few millimeters diameter which extends from the kidney pelvis to the bladder. It courses downward and slightly medialward on the ventral aspect of the psoas sheath behind the spermatic (or ovarian) vessels for about one-half of its length. It is then in close relation to the peritoneum anteriorly and curves over the common iliac artery near its bifurcation to enter the bony pelvis. Here it curves laterally and posteriorly hugging the wall in close proximity to the hypogastric vessels. Finally it curves medially, anterior to all of the vessels in the pelvis except the vesical (also the uterine in the female), and dips under the vas or round ligament to enter the bladder obliquely.

Along its course the ureter presents narrowings at sites which are more-or-less constant, and which represent normal thickenings of the circular muscle coat. These are accentuated in figure 3 for the purpose of demonstration.(*)

The arterial supply of the ureter is as follows:

Upper 1/3:- branches from the renal artery

Middle 1/3:-branches from the aorta, common iliac artery, inferior mesenteric artery, uterine or spermatic artery, and the deep hypogastric artery

Lower 1/3:- branches from the vesical artery and from the artery to the vas.

(*) Abstracted. See bibliography (3).

The venous circulation of the ureter parallels the arterial for all practical purposes.

The lymphatic drainage from the lower portion of the ureter flows downward into the vesical lymphatics. That from the pelvic and abdominal portions courses medially to the pelvic and lumbar lymph nodes while the upper portion is drained by the renal lymphatics.

Data concerning the innervation of the ureter is controversial and will be presented in a separate section of this paper.

Histology:

The outer sheath of the ureter consists of loosely constructed fibrous tissue in which the major vessels run. The middle sheath is composed of an inner and an outer longitudinal muscle coat with an interposed circular muscle coat. The inner sheath consists of a tunica propria (submucosa) of fibroelastic tissue and a lining membrane of stratified transitional epithelium.

The major vessels in the outer coat form a plexus consisting of longitudinal tortuous branches from which at short intervals many smaller tributaries arise, anastomosing freely and penetrating the muscle coats of the ureter in many places. This arrangement makes possible periodic contractions and distention without injury to the blood supply. There is also a delicate plexus in the submucosa whose meshes are elongated in the long axis of the ureter. From this plexus capillaries take origin and supply the musculature, submucosa, and epithelium(*).

(*) Abstracted. See bibliography (4).

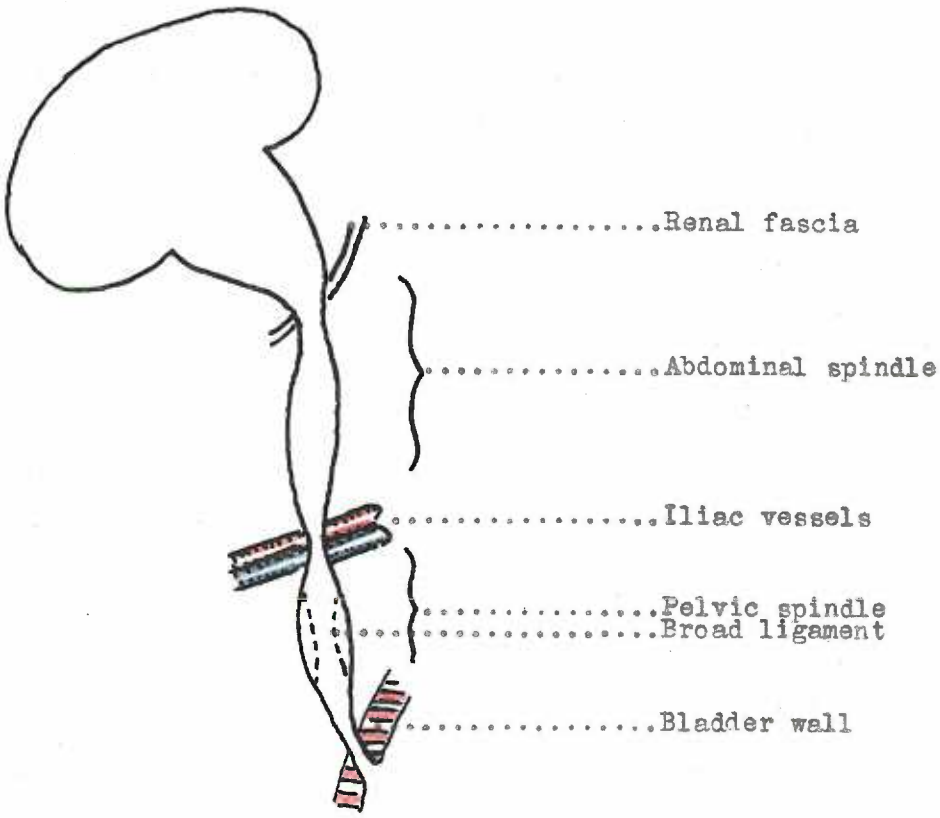


Figure 3
(after Kelly-Burnam)

The pelvis and calyces, though thinner, are identical with the ureter histologically with but one exception. In the minor calyces the circular muscle coat is modified such that the fibers run in a spiral direction; this structure has been termed musculus spiralis papillae by Muschat[5]. Figure 4 is a sketch of a reconstruction from serial sections.

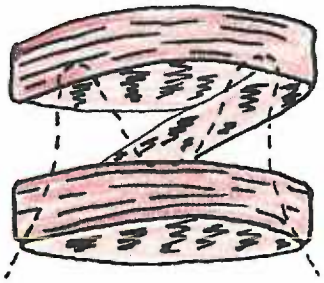


Figure 4
(after Muschat)

Physiology

Since Engelmann's classical description of the motion of the ureter in 1869[6], the organ has been studied by many workers and by almost as many methods.

Motility:

Engelmann studied the ureter visually in the anesthetized dog, cat, rabbit, and rat and observed peristaltic activity which, for the most part, proceeded from the kidney pelvis to the bladder. However, on occasion the wave might travel in a retrograde fashion, i.e., antiperistalsis. He noted further that, for no apparent reason, any point

along the course of the organ could initiate motion either spontaneously or upon direct stimulation, and that in these instances the contractions spread in both directions. Moreover, he observed that nerve stimulation affected motility. To explain the origin of muscular activity in the ureter Engelmann likens it to the heart the contractions of which are automatic but influenced by nerve impulses.

Lucas employing a graphic technique(7) contributed a great deal toward the exposition of ureteral kinetics. His method was that of cannulating the ureter with a modified Ludwig-Spengler artery cannula which was connected to a water manometer containing an Emerson float(8) by means of a rubber tube. The urine was allowed to flow into the bladder unimpeded or through a vertical tube the height of which delineated a measured resistance to flow. In addition to recording from the ureter he obtained records from the renal pelvis by inserting a trocar into it through the renal parenchyma. All of his experiments were performed under morphine narcosis except when the effects of other anesthetic agents were to be tested on the ureter. Under the conditions of his experiments Lucas found that the middle part of the ureter which comprised two-thirds of the total length of the organ shows comparatively large contractions which recur at intervals varying from six to twenty seconds when the urine is allowed to flow unimpeded into the bladder. In contrast to this he noted that the renal pelvis and uppermost portion of the ureter exhibit small oscillations which recur much more frequently than the large ones.

A singularly unique method of investigating the kinetics of the ureter was introduced by Trattner(9). Briefly, it consisted of diverting

the urinary stream through a cannula to a water tambour to which was affixed an outlet with a screw valve so that a resistance to the flow of urine or complete obstruction to that flow could be achieved. A water manometer incorporated in the system enabled him to take pressure readings whenever he desired. In order to interpret the records obtained by this method Sollman(10) with Trattner and others took composite moving pictures showing the perfused, motile ureter in a water bath and the writing lever in the same phase of time. With his apparatus Trattner was able to detect two types of waves, one of which represented segmental or pendulum type of movements (small waves with a frequency of from six to twelve per minute) and the other which represented propulsion or peristaltic waves (large waves with a frequency of from one to eight per minute). Peristalsis is represented by a longitudinal contraction which shortens and narrows but does not obliterate the lumen, and a circular contraction which momentarily obliterates the lumen in successive segments of the organ as the wave advances. Pendulum type of movement (swaying movement) occurs only during relaxation. His observations concerning the relationship between contractions and the flow or urine are as follows:

1. Continuous flow with no contractions
2. No flow with intra-ureteral pressures at zero or negative(*)
3. Contractions with no urine flow
4. Propulsion of urine with contractions only
5. Flow independent of contractions (pendulum type of movement)

(*) Lucas(12) concludes that under normal conditions the intra-ureteral pressure remains at zero and that the amount of urine that ordinarily is necessary to call forth peristalsis is probably so slight as to cause scarcely any pressure.

A clinical test of function of the ureter at routine cystoscopy with ureteral catheters in place grew out of Trattner's work with the "hydrophorograph"(11). It consisted of obstructing the flow of urine through the apparatus so as to increase the intra-ureteral tension. The pattern of motility was recorded at pressure levels of 5, 10, and 15 cm. of water.

The relationship of pressure within the ureteral lumen and the contractility of the organ is quite constant for the same ureter but varies in different ureters even from the same animal. Trattner delineates four pressure levels from experiments on excised and intact ureters of dogs. They are as follows:

	Cm. of water pressure
Appearance level	0 - 12
Best contraction level	3 - 18
Crucial level	3 - 18 (usually)
Disappearance level	38 - 70

A similar phenomenon has been observed in the human by Kreutzmann(13) and in dogs by Wislocki and O'Conner(14), Sokoloff and Luchsinger(15), and Henderson(16). A vivid description of effects of increasing ureteral pressures is given by Lucas(17).

"In experiments on the ureter in situ, in which it was suddenly occluded below the distal cannula, the contractions of the middle portion became more and more frequent and of larger size. The urine accumulated, and the pressure became greater. The peristalsis increased until a point was reached when apparently, from fatigue, the ureter relaxed; the pressure fell, and the waves disappeared for a short time

from the middle portion and appeared in the pelvis, after which the record was repeated, the whole phenomenon taking place in a manner very suggestive of clinical renal colic due to calculi or other obstruction, in which the pain, moderate at first, steadily increases to an almost intolerable degree, then suddenly ceases, shortly to recur."

An interesting corollary to the work of Lucas on intra-ureteral pressure and urine flow is an hypothesis which he prefers concerning the possible role of the ureter in the mechanism of diuresis(18). When the ureter is normally acting, the pressure in the pelvis of the kidney remains constantly negative; this is borne out by the fact that simultaneous records from the straight portion of the ureter and from the renal pelvis show reciprocal wave patterns. It is accounted for by the anatomic arrangement of the kidney pelvis which prevents it from collapsing under such conditions. The negative pressure is produced and sustained by considering a volume of urine acting as a piston as it is propelled toward the bladder creating, thereby, a wake of decreased pressure localized in the pelvis of the kidney; not in the ureter because it is a collapsible structure.

In an attempt to prove this concept he eliminated the ureter on one side in a dog by inserting a widely-flanged cannula into the pelvis, mobilized the ureter on the contralateral side in order to collect urine from it, and compared the urinary output after establishing a diuresis. Prior to the above described experiment he ran a control to determine the response of each kidney to diuresis of the same degree so as to qualify his results. He observed that (1) the output from the intact side was about two-hundred percent greater than that from the other and

that (2) an increased flow of urine calls forth an increased peristalsis and therefore does not result in an increased pressure in the kidney pelvis.

Further evidence that the mechanism of diuresis or at least its facilitation and perpetuation does not reside wholly in the kidney per se but also upon muscular elements distinct from the vascular tree is suggested by the work of Muschat[19] on the musculus spiralis papillae. His in vitro studies revealed a rhythmic contraction rate of about two per minute and a drop of urine from each papillae with each contraction.

In vitro studies of ureteral motility are optimal in a slightly acid media such as that afforded by a 1:10 dilution of fresh urine or a 0.2 to 0.4 percent solution of urea added to oxygenated Locke's solution at about 37 degrees centigrade[20]. The longitudinal musculature can best be observed when ureteral strips are employed whereas rings two to three mm. wide suffice to demonstrate activity in the circular muscle coat. In contrast to ring preparations Macht[21] discovered that strips of ureter showed no rhythmic contractions and responded to drugs for the most part only by an increase or decrease in tone. In addition he found that a lack of oxygen diminished activity and that the range of temperature for sustained kinetics was between 32 and 41 degrees centigrade. The observation of Lucas that greater amplitude and frequency of contractions exist in the middle portion of the ureter in corpore has also been shown by Satani[22] in vitro. He ascribes this to the difference in thickness of the muscular coat at various levels along the course of the ureter--the middle section being the thickest. Wu[23], on the

contrary, as a result of his in vitro study suggests that a gradient of motility may exist in the ureter with the pelvic end showing the greatest excitability; however, his results are not conclusive.

Innervation:

Fagge[24], utilizing a graphic method of recording from the ureter, studied the motor effect of nerve stimulation. His technique was to insert into the lumen of one ureter a very fine silver cannula over the perforated end of which was fixed a small rubber capsule. The catheter was introduced after opening the bladder and was connected by a rubber tube to a water manometer. The manometer in turn was connected with a piston recorder; the height of the water in the manometer could be regulated so as to produce an adequate distension of the balloon in the ureter. The hypogastric nerves were isolated just below the inferior mesenteric ganglion and were placed together on Ludwig electrodes. The dogs used in these experiments were anesthetized with A.C.E. mixture (alcohol, chloroform, and ether) preceded by a dose of morphine. Fagge noted that ureteral contractions varied considerably from the standpoint of amplitude, occurrence, frequency, and wave pattern, but never failed to observe some sort of increased motor activity after stimulating the hypogastric nerves. He was unable to confirm Protopopow's experiments in which stimulation of the splanchnic nerves excited the ureter; he also found that the pelvic visceral nerves were equally without effect. From the foregoing he concluded that the ureters were innervated solely by the hypogastric nerves.

Satani[22] expresses a distinctly different view derived from visual observations on the excised and intact ureter. From the finding that various autonomic drugs showed anatomic localization he postulated that the upper end is innervated chiefly by the sympathetics and the lower chiefly by the parasympathetics while the middle is probably innervated about equally from the two sets of fibers. Contrary to Fagge and corroboratory to Protopopow he found that stimulation of the splachnic nerves was motor to the ureter as was also stimulation of the pelvic nerves. He further states that inhibitory fibers reach the ureter by way of the communicating branches to the inferior mesenteric ganglion. His observations on the histology of the ureter[25] relevant to its innervation reveal that ganglia and nerve cells vary a great deal in size and form with the large ganglia being observed in the outer fibrous and mucous coats. There are highly developed plexuses between the fibrous and muscular coats.

Another contention[26] is that the ureter derives its parasympathetic supply from the vagus for the most part but at its lower end from the sacral outflow via the vesical plexus and, therefore, is analogous to the alimentary canal in this latter respect. The sympathetic supply is said to be from the celiac and hypogastric plexuses. It is claimed that the afferent fibers from the ureter are probably more numerous than the efferents and that they enter the cord at T 11 & 12 and L 1. Some non-sensory afferents are said to be in the vagus.

Wharton[27] carefully removed the ureter and adjacent tissues en bloc from various animal and human cadavers and examined them under the microscope after staining by a special technique. He concluded that the

ureter receives a nerve supply which is independent of the innervation of the kidney and bladder. These nerves come from the lowest renal ganglion at the upper end of the spermatic plexus and from the abdominal sympathetics (aortic, hypogastric, and pelvic plexuses). Clinically, it was found that cutting these nerves does not interfere with the function of the ureter and specifically does not cause atony, hydro-ureter, stricture, or any other ureteral disturbance. Similar results from experimental denervation on animals have been shown by Andler[28] and Frommolt[29].

Smith and Strasberg[30] using the microdissection and staining methods of Wharton state that the middle 3/5 of the ureter is relatively free of nerve fibers.

Aptly illustrating the confusion concerning this question of the innervation of the ureter is the work of Hrynschak[31, 32, 33], who in 3,564 serial sections of the pelvis, ureters, and ureteral orifices of man, pig, dog, and cat found no ganglion cells in the mucosa or muscularis and none in the tissue adjacent to the upper 2/3 of the ureter; he found a few isolated in the lower 1/3.

Reflexes:

Cross reflexes involving the ureters are seen not uncommonly in patients with unilateral renal or ureteral disease. Contralateral spasm is the most frequent manifestation[34]. Irritation of the ureter by calculus may cause reflex anuria lasting for days[26].

Farrell[35] has demonstrated that when the pelvis of one kidney was distended with saline, the urine flow from the opposite kidney ceased but began again after the pressure was reduced. The reduction in urine volume was considered to beon the basis of vasoconstriction, for concomitant with the decreased urine output a decrease in kidney volume was recorded. The experiments were done under morphine-ether anesthesia on dogs, the abdomens of which were opened from ensiform to pubis. It was noted further that there was an inhibition of urine flow during the active phase of micturition.

Similar experiments performed by Burton-Opitz and Lucas[36] revealed that sudden increases in the pressure in the renal pelvis were more effective in checking the circulation homolaterally as measured by the stromuhr than were gradual increases, and that contralateral effects were absent! It is a moot question whether the stromuhr is as sensitive as the oncograph in this situation.

Using dogs under chloral narcosis Bariety and Kohler[37, 38] correlated stimulation of the kidney pelvis and ureter with oncographic studies of the homo- and contralateral kidneys and the general arterial blood pressure. Stimulation was done with dilute HCl in saline or by pressure (expressed in cc.) and was increasingly effective the nearer it was applied to the kidney. Changes consisted usually of a diminution in volume, but sometimes it was increased. The volume changes in the kidney were independent, for the most part, of the changes in the general arterial blood pressure. This, they felt, spoke for the existence (among the various vasomotor regulators of the kidney) of a proper factor for the vessels of this region alone, giving it a separate

control as far as automatic regulators of vascular control is concerned. The volume of the contralateral kidney was found, as a general rule, to follow the general arterial blood pressure. Renal denervation did not affect the response. The response was inhibited by yohimbine, cocaine, and eserine and was augmented by atropine.

The effects of ureteral occlusion on kidney function of unanesthetized, trained dogs prepared with bilateral cutaneous ureterostomies was investigated by Pilcher, Bollman, and Mann[39]. The kidney on one side was made to work against definite pressures for periods too short to injure the organ permanently, and the quantity and composition of the urine thus excreted was compared with the urine excreted from the opposite kidney which was under normal conditions of pressure. They found that urine, normal in quantity and composition, was excreted against pressures up to and including 30 cm. of water. At pressures of 40, 50, and 60 cm. there was a regular diminution in the volume of urine, and often proportionately greater diminution in the total amount of chloride. There was no change in the total amount of creatinine or urea eliminated at pressures less than 60 cm. Causing the kidney to work against pressures up to and including 60 cm. of water for one hour did not affect the function of the opposite kidney, nor was significant anuria or polyuria from either kidney ever observed.

Campbell and Patterson[40] prepared dogs as had Pilcher et al with, in addition, a gastric fistula for recording the effects of ureteral and pelvic distention upon hunger contractions of the stomach. They found that pressures less than 35 mm. of mercury were without effect, but that with greater pressures one or combinations of the

following would occur: (1) inhibition (partial or complete, (2) changed type of contraction, (3) hypermotility, (4) changes in tonus, (5) vomiting movements. The pathways of this reflex were not studied.

Satani[22] suggests that the chemical composition of the urine may also affect the development of ureteral contractions by means of reflex action.

Pharmacology

Autonomic drugs:

The original contributions in this field were by Macht[21, 42]. A summary of this work is presented in table 1. The findings have been corroborated by Satani[22].

Using Trattner's hydropherograph on dogs Greene and Essex[43] were able to demonstrate the action of adrenalin in situ and found it to be stimulatory as was the cholinomimetic compound mecholyl (acetyl-betamethyl-choline). The action of the latter compound on the ureter persisted after the blood pressure had returned to normal. They noted that ergotoxine intravenously diminished ureteral tone considerably, and that atropine gave variable, inconclusive results. Samaan[44] states that atropine relaxes the bull's and the human ureter if they are already rendered in a state of spasm through parasympathetic stimulation whereas it fails to relax these organs if the cause is directly muscular.

TABLE I

Summary of the Actions of Autonomic Drugs on the Ureter
(Macht)

Drug	Concentration	Response
Epinephrine	1:5,000,000	Increased frequency, amplitude, & tone
	Larger (?)	Tetany
Ergotoxin	1:50,000	Immediate-increased tone & frequency Delayed-decreased tone & frequency
Ergotoxin followed by epinephrine	(?)	None or further decrease in tone(*)
Pilocarpin	1:25,000	Increased frequency, amplitude & tone
	1:2,500	Inhibition of motility
Physostigmin & Muscarin	(?) (?)	Increased frequency, amplitude & tone
	Larger (?)	No inhibition
Choline & "Synthetic Muscarin"	1:25,000 1:25,000 1:2,000	None None Increased frequency, amplitude, & tone
Atropine	1:25,000 to 1:5,000 0.01%	Immediate-variable Delayed-inhibition Inhibition
Atropine followed by:		
Pilocarpin	(?)	:
Physostigmin	(?)	: None
Muscarin	(?)	:
Epinephrine	(?)	:
Nicotine	Small (?)	Increased motility
	Large (?)	Decreased motility Adrenalin action is inhibited

(*) This represents the first demonstration of reversal of the effect of adrenalin in an organ which has peristaltic movements.

Other drugs:

Anesthetics such as nembutal, sodium amytal, ether and chloralose are held not to alter the response of the ureter to drugs(43). Chloroform renders the organ relatively refractory(10). Avertin (tri-brom ethanol) has been shown to depress the musculature of the ureter when excised or in situ; in the latter instance it is effective by intravenous, rectal, or intra-ureteral administration(45).

The opium alkaloids, in respect to their action on the ureter, may be divided into two groups according to their chemical structure--the pyridine-phenanthrene group (morphine and codeine) and the benzyl-isoquinoline group (papaverine and narcotin)(46). Morphine and its allied alkaloids increase the contractions and produce a greater tonicity whereas papaverine and its allied alkaloids produce a slowing or total inhibition of the contractions and relaxation of the tonus. The benzyl iso-quinoline effects predominate when the two groups are given in combination. The effect of morphine on the human ureter has been shown to be excitatory by Carlson and Ockerblad(47).

In 1843 Cruveilhier first described dilatation and elongation of the ureter as a frequent accompaniment of the gravid state(48). That hormones play a part in the production of this condition has been ably demonstrated by Handley et al(49). Using the hydrophorograph to measure ureteral activity in both gravida and non-gravida, they have demonstrated that estrogenic substances tend to activate the ureter

whereas progestogenic substances tend to allay contractions of the organ and produce the muscular hypertrophy and the hyperemia found during pregnancy.

The pharmacology of the musculus spiralis papillae is essentially the same as that of the ureter[50] except that the cholinomimetic compound pilocarpine hydrochloride in a dilution of 1:20,000 is depressant.

EXPERIMENTAL WORK AND DISCUSSION

A Photographic Method of Recording Ureteral Kinetics in Situ (51)

Introduction:

The most feasible method to study the ureter at the onset of this work was felt to be that of Trattner(9) since in principle it involved the least operative interference and hence the most physiologic means to investigate this organ. However, during a series of experiments on dogs it was found that the water tambour has several undesirable features which made records obtained difficult, if not impossible, to interpret. A membrane tambour because of its elasticity yields a tracing which is approximately a logarithmic function of the pressure applied; therefore, the sensitivity is reduced appreciably when working with increasing pressures. This is demonstrated in figure 5 the data for which was obtained from the same membrane used in securing the kymographic records to be presented later. The membrane exerts a similar effect on fluid displacements so that successive increments and decrements of liquid are not recorded isometrically. The fling of the lever arm--a result of its inertia and momentum--further adds to the inaccuracy of the method. Friction of the writing style on a smoked drum became perceptible when working with small animals.

Description:

The essential features of the unit designed to replace the water tambour are apparent in figure 6. Hypodermic needles of various gauge (20 to 25) were used as resistance to the flow of urine. Alternate

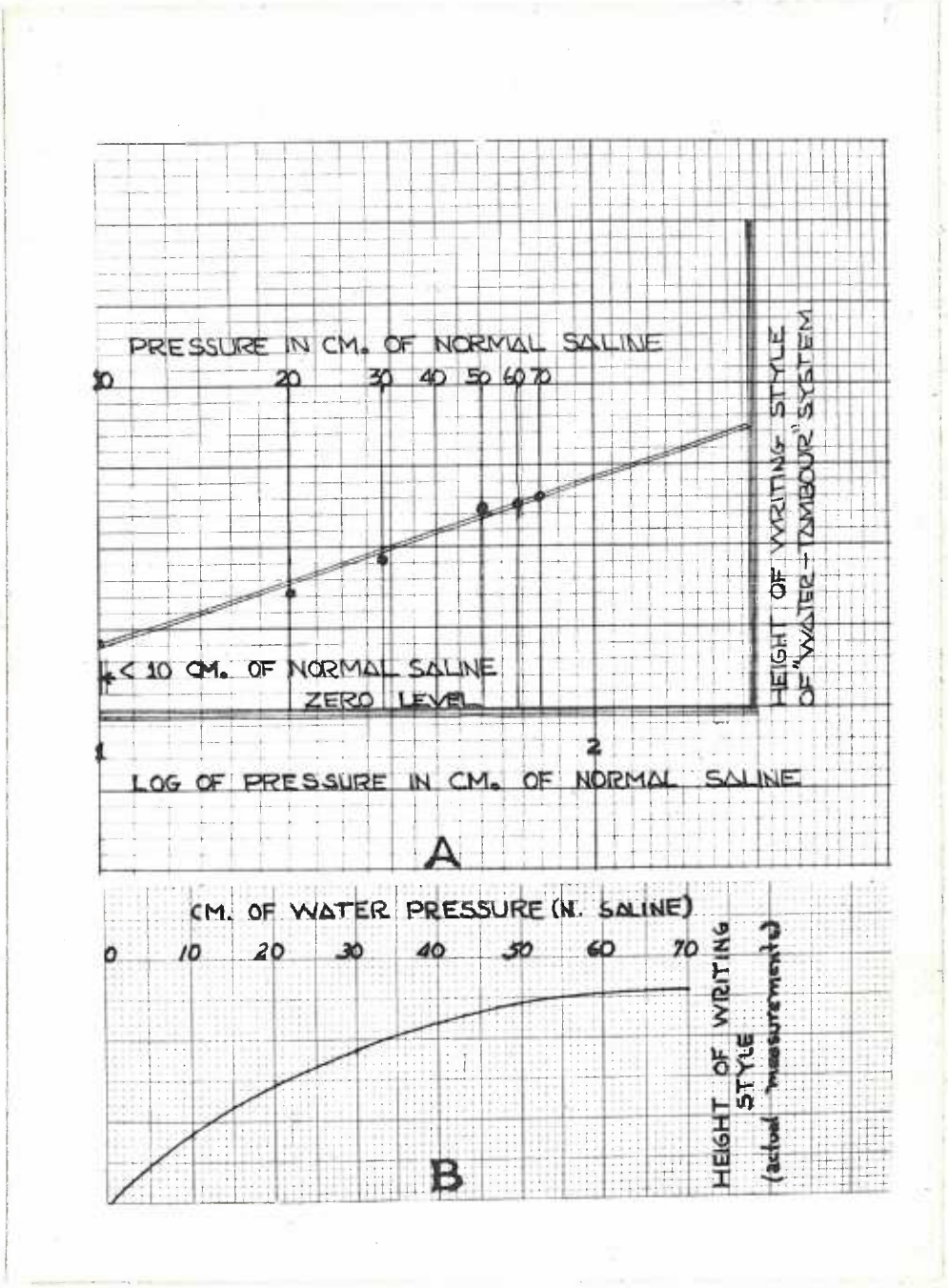

PRESSURE IN CM. OF NORMAL SALINE
10
20
30
40
50
60
70
< 10 CM. OF NORMAL SALINE
ZERO LEVEL
HEIGHT OF WRITING STYLE OF "WATER-TAMBOUR" SYSTEM
1
2
LOG OF PRESSURE IN CM. OF NORMAL SALINE
A
CM. OF WATER PRESSURE (N. SALINE)
0
10
20
30
40
50
60
70
HEIGHT OF WRITING STYLE
(actual measurements)
B

Figure 5

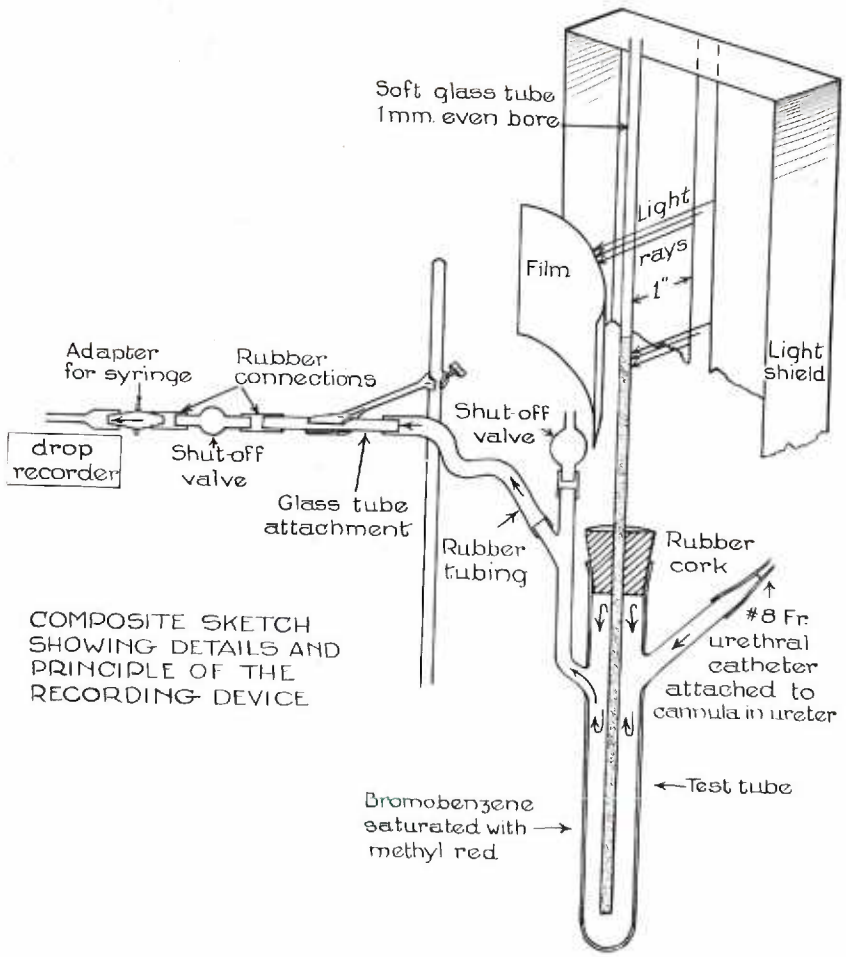

Soft glass tube
1mm. even bore
Light
rays
1"
Film
Light
shield
Adapter
for syringe
Rubber
connections
drop
recorder
Shut-off
valve
Glass tube
attachment
Shut-off
valve
Rubber
tubing
Rubber
cork
#8 Fr.
urethral
catheter
attached to
cannula in ureter
COMPOSITE SKETCH
SHOWING DETAILS AND
PRINCIPLE OF THE
RECORDING DEVICE
Test tube
Bromobenzene
saturated with
methyl red

Figure 6

methods are the incorporation of a screw valve at the outflow of the use of a constant-bore aperture connected with the outflow by a rubber tube so that it can be raised or lowered to provide the desired resistance.

The principle of the unit is based on Pascal's Law which states that pressure exerted at any point upon a confined liquid is transmitted undiminished in all directions. Bromobenzene was chosen because it has a density of 1.4991(52) and a surface tension about 1/3 that of water; furthermore, it is immiscible with water (0.0446 grams are soluble in 100 cc. of water at room temperature). The manometer tube is of small caliber so that small amounts of liquid displacement can be readily detected.

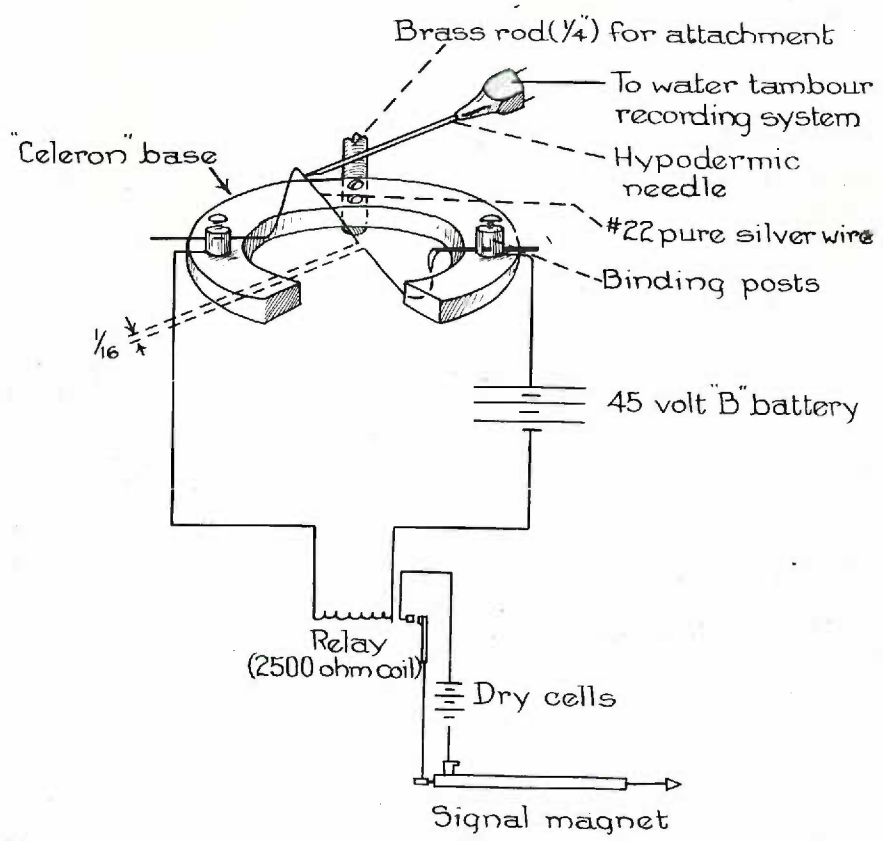
An excellent method for recording the excursions of a liquid column photographically has been reported by Kirchhof and David(53). However, the scheme shown in figure 6 is satisfactory. Illumination is provided by a clear, 500-watt, tungsten-filament, projection bulb. The film (bromide paper) is fastened to the drum of a kymograph with scotch tape and placed within a light-tight box with a thin slit to which the manometer tube is juxtaposed.

Prior to recording, the optical system is aligned and adjusted by trial and error. The distance between the light source and the manometer as well as the distance between the manometer and the paper must be regulated so as to achieve sharp contrast. The unit is filled with physiological saline solution so as to realize an all-liquid system. Hydrostatic pressure from the liquid in the inflow and outflow arms forces bromobenzene into the manometer, the meniscus of which establishes a base of zero pressure line.

Small strands of thread fixed across the slit 1 cm. apart enables one to read pressure directly and continuously in linear terms on the photographic record. In Trattner's apparatus a water column manometer had to be shunted into the system to ascertain the pressure at any given instant.

Though the apparatus described is more bulky than the one it was designed to replace, it is felt that its advantages more than compensate for this fault. This defect, too, could be eliminated but at greater expense.

A valuable adjunct to the interpretation of the records obtained by this method is a simultaneous record of the outflow in drops. Figure 7 shows the one used in the experiments to be described subsequently. Though not original in principle, it has some merits in its construction which are unique. It is cheap and easy to construct. Moreover, the nidus of drop formation is always the same so that the results can be compared from one experiment to the next. Never once, even with considerable diuresis, was the urine found to be so dilute that this instrument would not function. Occasionally, when the urine contained a relatively large proportion of solids, a deposit would form on one silver wire. This was eliminated by simply changing the polarity of the B-battery circuit between experiments. A signal magnet was used to trace a record of drops when working with the water tambour and a kymograph. It is more convenient to replace this with a small light bulb such as is used in pocket flashlights, a pinhole, and a small positive lens when working with the optical system so that a "dot" record of urine in drops is realized on the final recording.



DETAILS OF AUTOMATIC DROP RECORDER (CUTAWAY SKETCH) WITH CIRCUIT

Figure 7

The Action of Dibutoline on the Ureter of the Dog

Introduction:

In the quest for an improved drug for use in refraction and internal examination of the eye, Swan and White were prompted to explore the possibility of synthesizing surface-active derivatives of a choline compound by replacing the hydrophilic NH_2 group of carbaminoylcholine with water insoluble amines. The research culminated in the synthesis of a new class of autonomic drugs; a series of choline esters with mydriatic and cycloplegic actions(54 - 58). The addition of non-polar groups to carbaminoylcholine effected a spectacular reversal of action--"an event unparalleled in autonomic pharmacology." A number of preparations were synthesized. Of these, dibutylurethane of dimethyl-ethyl-B-hydroxyethyl ammonium sulfate (Dibutoline*) was found to be the most suitable for clinical ophthalmogic use.

Subsequently, studies on the systemic pharmacology of dibutoline were reported by Featherstone and White(59, 60) and by Peterson and Peterson(61, 62). It is beyond the scope of this presentation to do more than indicate its pharmacodynamics. There is good evidence to point to the site and mode of action of dibutoline as qualitatively similar to that of atropine, i.e., blocking nerve impulses at cholinergic neuro-effector junctions. Clinically, therefore, it would be classed as a spasmolytic. In dose for dose comparison dibutoline is a much shorter-acting compound than is atropine. Its therapeutic index is considered to be high and side effects are, in the main, minimal.

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* Merck and Company

Apparently, too, there is specific organ and tissue susceptibility to the compound, for there was noted a varied dosage threshold depending upon the one studied. The jejunum is the most sensitive since complete inhibition is produced with as little as 0.01 mgm. per kg. The foregoing suggested a study of its action on the ureter.

Methods:

All the animals used in these experiments were anesthetized by injection into a radial vein of one grain of veterinary nembutal per five pounds of body weight. During the course of the experiments one to two grains, depending upon the size of the dog, were injected intravenously as indicated to maintain suitable anesthesia. Six dogs were used.

The bladder was delivered through a two-inch, midline, suprapubic incision in the female dogs and through a similar incision just lateral to the base of the penis in the males. A small glass cannula was inserted into the ureter just proximal to the intramural portion and held in position by carefully placed ligatures. Because of its convenience the right ureter was used exclusively. Before the bladder and the cannulated ureter were placed within the animal, the site of cannulation was inspected for leakage or obstruction. Ligation of the distal ureteral stump was not deemed necessary. The incision was closed with hemostats; within about one hour the wound would be sealed by fibrin deposition. The operation was usually accomplished in less than 15 minutes. The left radial vein was cannulated, and the cannula attached

to a Murphy drip apparatus so that physiological saline solution or 5% dextrose in water could be administered at room temperature at any desired rate to maintain diuresis and, consequently, ureteral motility.

The recording apparatus was essentially that devised by Trattner consisting of a No. 8, Fr. urethral catheter leading from the cannula in the ureter to a water tambour system; care was taken to align the membrane of the tambour on approximately the same level as the ureter. A drop recorder as previously described was used to record urine output.

Drugs used in this study were injected into the right femoral vein. Respirations were recorded on several occasions by means of a partially inflated rubber bladder bound to the animal's thorax and connected with an air tambour. Blood pressure tracings were taken in the conventional manner using a mercury manometer with a Ludwig float; the left femoral artery was cannulated for these records.

A few in vitro studies were made utilizing the perfusion method described by Trattner(63).

The dibutoline used was a 5% stock solution obtained from Dr. Kenneth C. Swan; suitable dilutions were made fresh for each experiment and tested for decomposition with litmus paper.

Results:

Thirty-one injections of dibutoline were administered in doses ranging from 0.1 to 5.0 mgms. per kg. An analysis of the response of the ureter to the drug are summarized in table II. Had the photographic recording method been employed in all cases perhaps these results would present a slightly different picture. However, it can be suggested, at least, that the ureter is not affected by dibutoline to the same extent

TABLE II

Analysis of Responses to Dibutoline

Experiment	Mgm/Kg of Dibutoline 0.1	1.0	5.0	Sex of Dog
1.	-	*	*	Male
2.	--*-	*****-		Female
3.	--*	***--		Male
4.	-	*	*	Female
5.		----		Female (pregnant)
6.	-	-	*	Male
	Responses in Percent of Trials			
	22	71	100	

* Unquestionable response
\- No or questionable response
#5 Excluded in calculation of percent

as the gut since it rarely responded to less than 1.0 mgm. per kg. If this is taken as the minimal effective dose for the ureter, it seems unlikely that the compound can be used clinically to relieve ureteral spasm since the degree of tachycardia, visual disturbances, and asyalosis would constitute untoward side reactions. Notwithstanding, experiments on the human subject employing the photographic method are planned, for it is conceivable that the human ureter may be more sensitive to the action of dibutoline.

Proof that true relaxation of the organ was obtained is evident from figure 8. Perfusion of the excised ureter showed a depressant effect with dibutoline in a 1:1,000,000 dilution (figure 9).

Reflexes Involving the Ureter

Lucas[12] observed that stimulation of the nares of a morphinized dog with ether vapor altered the motility pattern of the ureter. His is the only account of such a somato-ureteral reflex found in the literature that was reviewed. Figure 10 shows a similar phenomenon provoked by tugging on the exposed left femoral nerve of a nembutalized dog. In other experiments faradization of the nerve elicited the same response in several instances; the depth of anesthesia probably accounted for some of the failures to elicit the reflex, for no attempt was made to control this factor. Seven experiments were successful.

A uretero-respiratory reflex was elicited each time the flow of urine from the ureter was completely obstructed. It was manifested by fixation of the thorax in inspiration and decreased amplitude of the respiratory excursions, and it lasted until the pressure was released. Figure 11 demonstrates the reflex; the period of latency was 35 seconds.

Figure 8. 8 kg. nembutalized male dog. Right ureter. 50 mgm. dibutoline i.v. at arrow.

A. period of active dilatation
B. period of isotonic filling) no urine flow
C. period of tonic reflux filling)
D. period of compensatory contractility

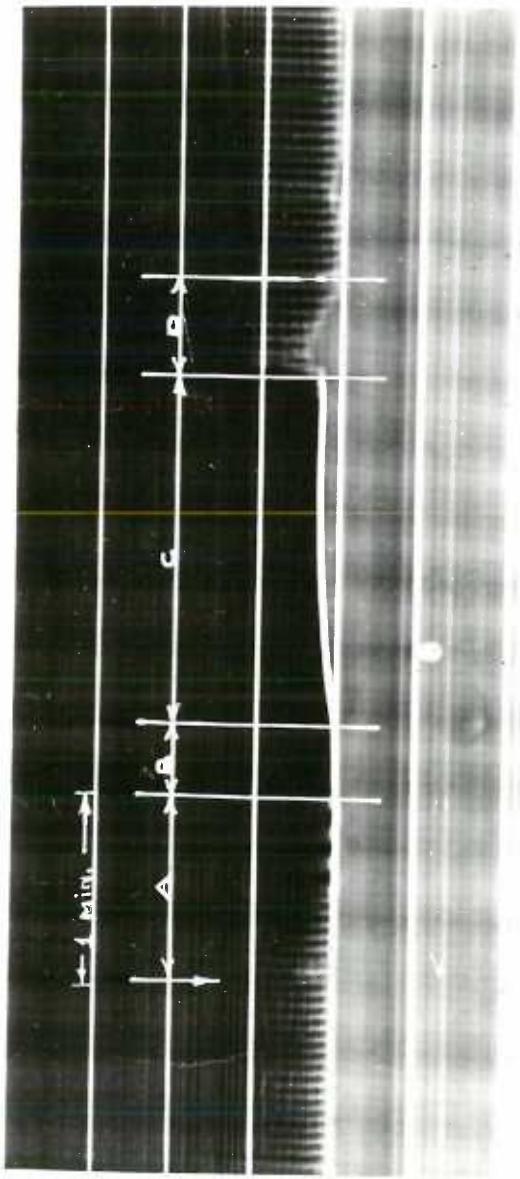

1 min.
A
B
C
D

Figure 9. Trattner's perfusion (dog ureter) in Loche's solution at 37° C. with 0.3% urea hydrochloride.

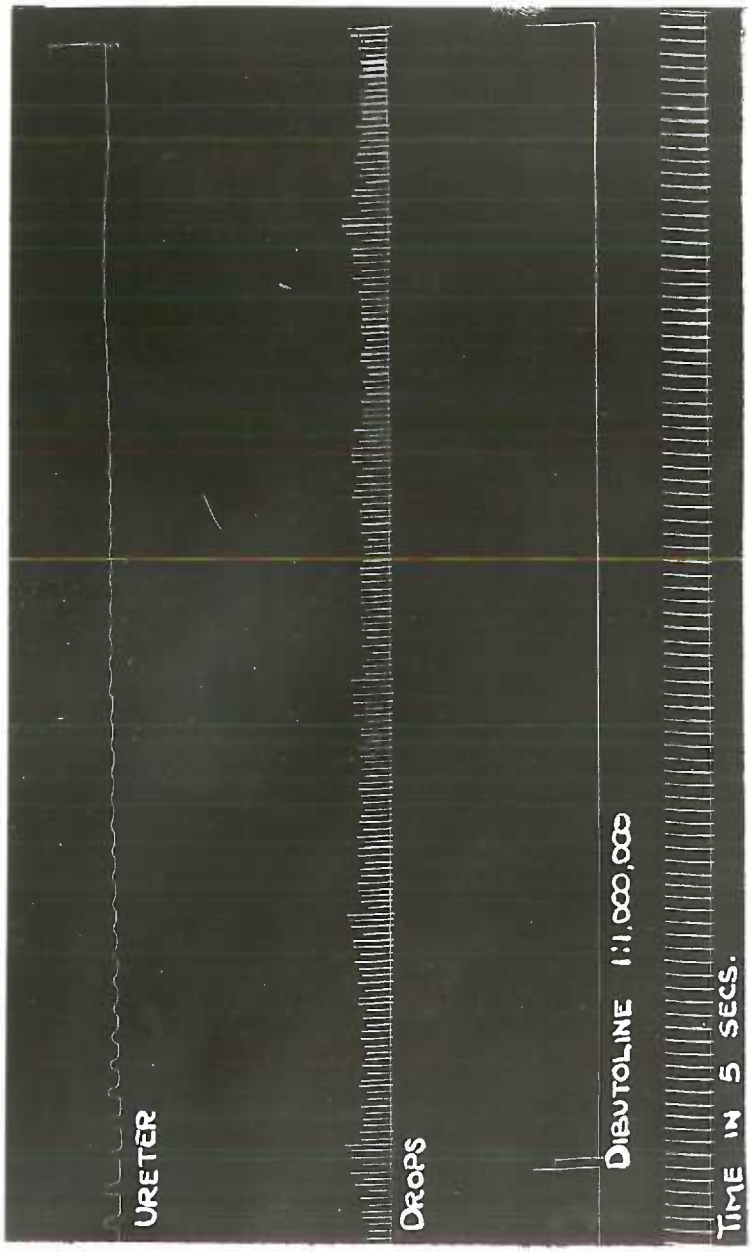
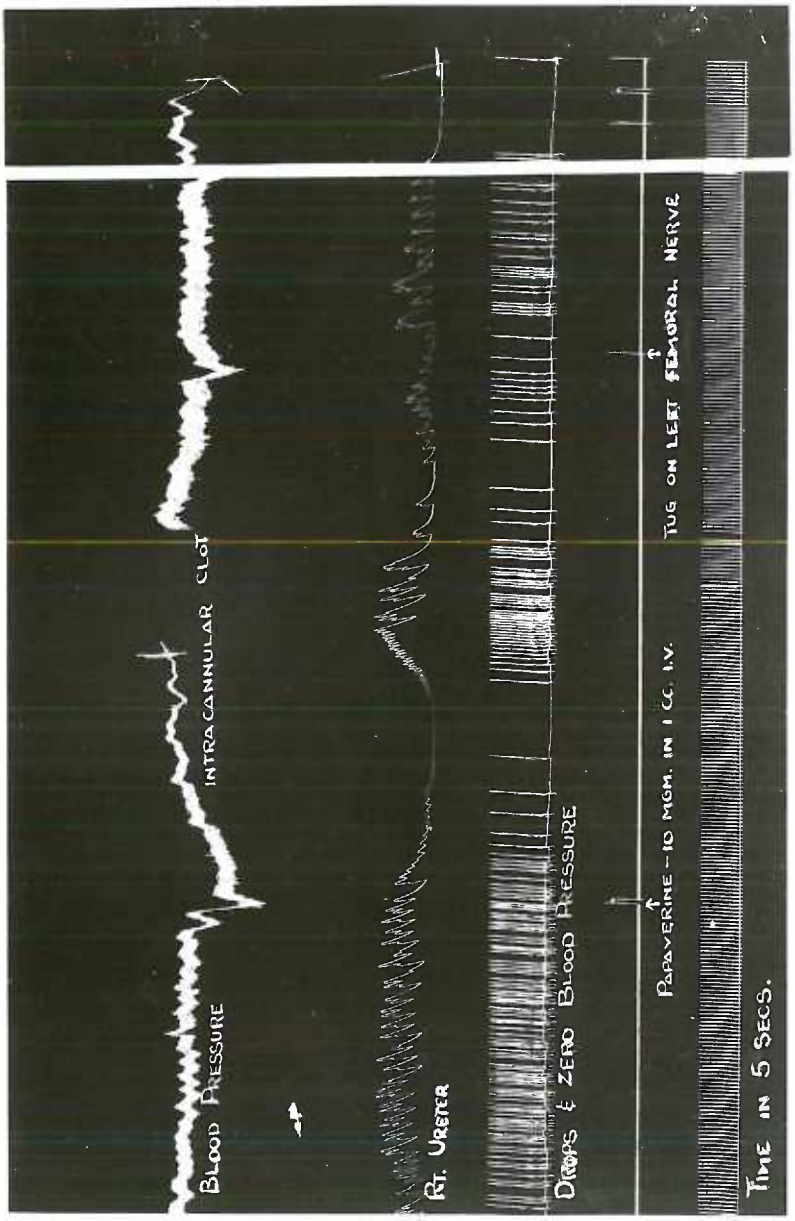

URETER
DROPS
DIBUTOLINE 1:1,000,000
TIME IN 5 SECS.

Figure 10. 9 kg. nembutalized female dog. Blood pressure from left femoral artery.

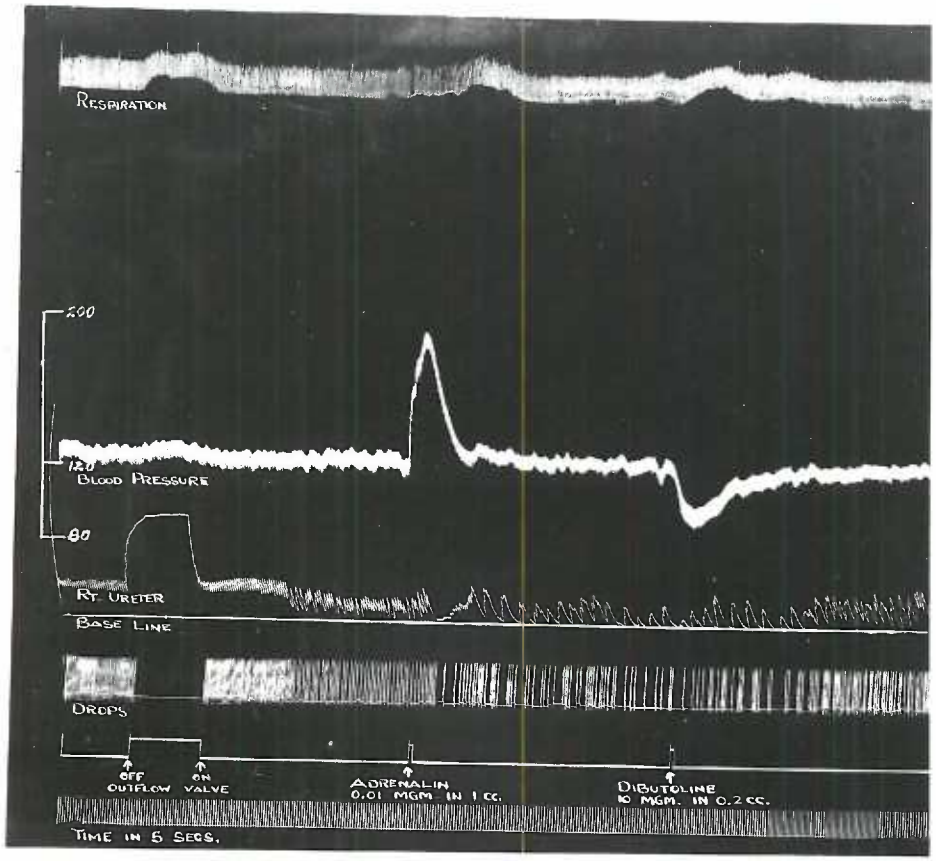

BLOOD PRESSURE
INTRACANNULAR CLOT
RT. URETER
DROPS & ZERO BLOOD PRESSURE
PAPAVERINE - 10 MGM. IN 1 CC. I.V.
TUG ON LEFT FEMORAL NERVE
TIME IN 5 SECS.

coincident with the time it took for the intra-ureteral pressure to reach a plateau at about 70 cm. of water (50 mm. mercury). In the same record it is evident that the respiratory effect is quite similar to that produced by the intravenous injection of adrenalin. This reflex was observed each time it was tried in three experiments.

Action of Various Drugs on Ureteral Motility

The action of adrenalin, ergotoxine ("Gynergen"), papaverine, morphine, acetyl-betamethyl choline, pilocarpin, and atropine, all of which have been reported, were tested in an attempt to compare and therefore evaluate the action of dibutoline. In every instance the results were in accord with published accounts. In addition to these a few other compounds were tried. Acetylcholine, 0.5 mgm., injected intravenously, using precautions to prevent hydrolysis prior to injection, was found to augment peristaltic contractions for a few seconds in 5 experiments. Nembutal was depressant to the ureter and rendered the musculature somewhat refractory to the effect of excitatory influences and drugs.

Figure 11. 9 kg. nembutalised female dog. Blood pressure from left femoral artery.


RESPIRATION
200
120
BLOOD PRESSURE
80
RT. URETER
BASE LINE
DROPS
OFF OUTFLOW
ON VALVE
ADRENALIN 0.01 MGM. IN 1 CC.
DIBUTOLINE 10 MGM. IN 0.2 CC.
TIME IN 5 SECS.

SUMMARY AND CONCLUSIONS

Literature is reviewed pursuant to the structure, physiology, and pharmacology of the ureter. No attempt has been made to present a critical review but rather to summarize certain papers pertinent to the experimental work performed.

A new method for recording ureteral motility is described. This method enables the investigator to obtain isometric measurement of liquid displacements and pressure changes linearly and continuously with a minimum of artefact from the friction, inertia, and momentum of a writing style. It is sensitive to liquid displacements of 1 cubic millimeter.

Dibutoline, a choline ester with atropine-like pharmacological effects, was found to have a depressant action both on the intact and excised ureter of the dog. Six dogs were used in this study; on five the method of Trattner was used, and on the other the method described in the preceding paragraph was used. In thirty-one experiments the compound was administered intravenously in doses ranging from 0.1 to 5.0 mgm. per kg. of body weight. The ureter was found to be unresponsive to dibutoline in doses less than 1.0 mgm. per kg. whereas it has been shown that the small bowel reacts to 1/100 of this amount.

In seven experiments tugging on the left femoral nerve or faradization of it resulted in an altered motility pattern of the right ureter.

Complete obstruction to the flow of urine induced a reflex fixation of the chest in inspiration with decreased amplitude of breathing movements in three experiments. The threshold for the production of the

respiratory reflex appears to be the point at which the increasing intra-ureteral pressure reaches a plateau which is about 50 mm. of mercury in each case.

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