EXPERIMENTAL LOCAL BLADDER EDEMA CAUSING URINE REFLUX INTO URETER AND KIDNEY*

By JOHN AUER, M.D., AND LLOYD D. SEAGER, M.D.

(From the Department of Pharmacology of St. Louis University School of Medicine, St. Louis)

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A number of facts and theories have been published to explain the reflux of urine from the bladder into the ureters and a general view of our present knowledge will be found in the literature—surveys and experimental work of Graves and Davidoff (1–3) and of Gruber (4, 5). Among the factors that may produce this reflux, there is one that has not been experimentally investigated in the living animal, as far as we know, although its theoretical significance has been mentioned by Sexton (6) and by Gruber (5). This factor is an edema of the ureterovesical valve. In the following pages, we shall submit evidence that an acute, experimental, non-inflammatory, non-obstructive edema of the ureteral valve region in the living animal causes a temporary reflux of vesical contents into the ureters and kidneys. It will further be shown that this experimental reflux may occur when the driving force is merely the hydrostatic pressure of the urine in the bladder of a recumbent animal (2 to 3 mm. of Hg in dog).

Technique.—Our material consists of guinea pigs, rabbits and dogs. The guinea pigs were narcotized by the subcutaneous injection of 300 mg. of sodium barbital per kilo; rabbits received subcutaneously per kilo 1 gm. of magnesium sulfate and 150 mg. of sodium barbital; in dogs ether only was employed.

The bladder and ureters were exposed through an incision extending from the sternum to the pubis; when necessary, the recti muscles were cut near the pubis. This procedure gave a satisfactory exposure of the bladder and the ureters could be inspected through most of their course by gently shifting the intestines. The apex of the bladder was incised and a flanged cannula tied into position. After injecting 0.5 to 4 cc. of India ink through the cannula, the amount depending upon the species of animal, the bladder was filled to capacity by pouring in warm

Ringer solution and the cannula was then connected either to a water or a mercury manometer. A large rubber bulb filled with water formed part of the manometer circuit, and screw-compression of this bulb permitted accurate variations in bladder pressure by air transmission. The initial pressure in the bladder under these conditions was only the hydrostatic pressure of the bladder contents itself; this varied from 20 mm. of water in the guinea pig to 40 mm. of water (3 mm. of mercury) in the dog. The amount of fluid in the bladder varied with its tonus and ranged roughly from less than 50 to less than 150 cc. in the dog. The urethra was not ligated in most experiments; in a few guinea pigs and dogs, however, this became necessary because the slightest rise in vesical pressure evoked urination. No catheter was tied into the urethra because we wished to avoid any irritation near the ureteral orifices.

No part of the intestinal tract was resected. The viscera were kept moist with warm Ringer-blood solution. Cooling of the animal was reduced by keeping the room at approximately 29.0°C.

After completion of the manometer circuit, the peristaltic rate and character of contraction of each ureter were observed and recorded throughout most of the experiments.

At the beginning of an experiment, the vesical pressure was slowly raised to determine whether or not a moderate pressure would cause a spontaneous reflux of urine into the ureters; if micturition occurred, the bladder was refilled with ink-Ringer solution. These pressures served as base lines and were not exceeded in general when the effect of a local edema was tested. An abbreviated protocol (page 743) will illustrate the routine of an experiment.

Localized edema about the ureteral orifices was produced by infiltrating an intravesical ureter with physiological salt solution. The injection was made through a 23 gauge needle inserted in line with the intravesical course of the ureter. In fat animals and in those with tonically contracted bladders, some difficulty was encountered in determining the proper slant of the needle when it was inserted at the ureterovesical junction. In our early experiments, a 25 per cent solution of magnesium sulfate was used under the assumption that a hypertonic solution would produce a better local edema; experience, however, demonstrated that physiological salt solution was more satisfactory and this was used exclusively in our later work. The amount injected varied from 0.2 cc. in the guinea pig to 0.5 to 2.0 cc. in the dog. These infiltrations were made repeatedly; in some dogs for example more than six infiltrations were carried out on both ureters. India ink proved to be an excellent indicator and its presence could be easily detected in the relatively thick walled ureter of the dog.

At the end of most experiments the bladder was opened and the mucosa of the valve area carefully examined. No histological sections were prepared because the edema we produced was transitory and non-inflammatory and therefore probably unsatisfactory for microscopic demonstration. The biopsies also showed ink in the pelvis and calyx of the kidney in some animals of all three species.
The following abbreviated protocol will show the general course of an experiment.

Dog X 12-92 ♀ 6800 gm.; not pregnant.

9:25. Etherized in box; tracheotomy; connect with ether bottle; belly opened m.l.; not pregnant. Room temperature 27.0°C. Cannula in apex of bladder; connect with manometer system; urethra not ligated.

9:50. 30 cc. warm saline + 3 cc. Higgins' waterproof ink into bladder; pressure rose to 4 mm. Hg.

9:52. Right ureter: 14 waves in 1 minute; strong.
Left ureter: 6 waves in 1 minute.

9:54. Pressure now 2 mm. Hg.

9:55. Right ureter: (no note).
Left ureter: 8 waves in 1 minute; strong.

9:58. Raise pressure to 40 mm. Hg.
No ink in ureters.

9:59. Pressure now 20 mm. Hg; no ink in ureters; reduce pressure to 0 (hydrostatic pressure only).

10:00. Suddenly ink seen in left ureter, extending 1 to 2 cm. above bladder; no ink higher up.
Right ureter: no ink.
Pressure 0 mm. Hg.

10:02. No urination so far.

10:03. Right ureter: 4 in 1 minute; weak.
Left ureter: 2 in 1 minute; moderately strong; no ink in either ureter.

10:04. Pressure 0 mm. Hg.

10:06. 0.5 cc. saline along left vesical ureter: during injection left ureter filled with ink; rose ½ way; no peristaltic wave started.

10:08. Ink column stationary; no peristalsis.
Inject 15 cc. saline into bladder: pressure rose to 10 mm. Hg.
Black column rose in left ureter; then swept clear by peristaltic wave.

10:09. Pressure has sunk to 5 mm. Hg.

10:12. Both ureters clear of ink; no peristalsis in left ureter.

10:13. Right ureter: 3 strong waves in 1 minute.

10:16. Infiltrate right vesical ureter slowly with 2 cc. saline; after 0.5 cc.: black to column rose in right ureter, 2 to 3 cm. above bladder; swept back by strong peristaltic wave; ureter became pink; continue infiltration up to 2 cc.; black column rose ½ way, remained 1 minute, swept into bladder by peristaltic wave; column again rose ½ way; bladder pressure 4 mm. Hg.

10:19. Bladder pressure = 0 mm. Hg; right ureter now clear, pink; no ink in left ureter; resp. 41 per ½; heart 70 per ½; gut pink. Room temperature 29.0°C.
10:21. 0.25 cc. saline into left vesical ureter; during injection black column rose in left ureter 3 cm. above bladder; 0.5 cc. more; column rose ½ way to kidney; 1.5 cc. stop, ink column now apparently at hilus of kidney; one weak peristaltic wave seen, no effect on column.

10:24. Left ureter distended, black; no waves; right ureter pink. Pressure = 4 mm. Hg.


11:30. Biopsy of bladder: both ureteral entrances edematous; no hemorrhage.

EXPERIMENTAL RESULTS

Guinea Pig.—In 14 guinea pigs (9♂, 5♀), 6 (5♂, 1♀) showed reflux of bladder contents after infiltration of either one or both intravesical ureters; the vesical pressures ranged between 50 and 280 mm. of water (4 to 21 mm. Hg).

In 4 non-pregnant females, spontaneous reflux without a preceding infiltration, occurred with vesical pressures ranging between 20 and 120 mm. of water (2 to 9 mm. Hg). In one of these spontaneous regurgitations (X 10-12) both ureters filled with ink under mere hydrostatic pressure of the bladder contents (30 mm. of water, 2 mm. Hg). Unfortunately the bladders of the guinea pigs with spontaneous regurgitation were not examined for edema of the ureteral orifices; it will be noted later that several rabbits with spontaneous regurgitation but without any infiltration exhibited definite edema of the ureterovesical area.

The guinea pig is not satisfactory on the whole for this type of work: the bladder is small, thick and muscular, quite sensitive to manipulation, difficult to cannulate and the direction of the intravesical ureter was often impossible to determine with accuracy.

Rabbit.—In 27 rabbits (16♂, 11♀) reflux after infiltration was observed in 22 (14♂, 8♀; 2 in early pregnancy); in one female no reflux was obtained after repeated infiltration. The vesical pressure at which reflux occurred ranged between 30 and 120 mm. of water (3- to 9 mm. Hg). The average control pressure was 110 mm. of water (9 mm. of Hg).

Spontaneous reflux without a preceding infiltration was noted in 4 rabbits (1♂, 3♀; one in early pregnancy). Further details will be given on page 750.

Dog.—In 17 dogs (8♂, 9♀) reflux of ink after infiltration of the
corresponding ureter was observed in 14 (6♂, 8♀, one in early pregnancy). The bladder pressures necessary to produce reflux varied between 3 and 12 mm. of mercury. The control pressures tested with negative results before infiltration ranged between 8 and 40 mm. of mercury.

Spontaneous regurgitation without a preceding infiltration of the intravesical ureter was seen in 2 females, one of them in early pregnancy. These 2 dogs are discussed in some detail on page 750.

In 3 dogs (2♂, 1♀ early pregnancy) repeated infiltrations of each intravesical ureter yielded no reflux. Biopsy of the bladder in one male and in the female revealed definite edema of the ureteral valve region; no notes were recorded on the bladder condition of the 2nd male.

It must be emphasized that all infiltrations of the intravesical ureter were not successful in producing reflux of bladder contents. Thus in 4 dogs (2♂, 2♀ not pregnant) infiltrations of the right ureter only were successful, while all attempts on the left side failed. In 3 other dogs however, (1♂, 2♀ non-pregnant) infiltrations on the right side were uniformly negative, while infiltrations of the left ureter were successful. In 7 other dogs (3♂, 4♀, one in early pregnancy) infiltrations were successful on both sides; and finally in the 3 remaining dogs (2♂, 1♀ pregnant) all attempts to produce experimental reflux in either ureter were failures. It should also be noted that an unsuccessful infiltration may be followed by a successful one, or vice versa.

The results to be reported now are derived largely from the dog, for this animal was studied most carefully in our work.

The onset of experimental reflux was rapid; in the majority of instances ink was detected in the ureter during the process of infiltration (see protocol page 744). In some dogs ink appeared within 1 minute after completion of the infiltration. In 2 dogs reflux occurred immediately after the bladder had been allowed to fall back; here apparently the dislocation of the bladder necessary for infiltration had kinked the ureter at its vesical junction.

The width of the ink column flowing into a ureter varied. In some dogs, a ribbon of ink 2 to 3 mm. wide appeared; in others a thin, black thread of ink was seen in the ureter after the lapse of some time.

The degree of reflux varied. In 26 successful infiltrations of either right or left ureters in the dog, 9 filled the lower third of the ureter (6
right, 3 left); 4 reached approximately the midpoint of the ureter (2 right, 2 left); and in 13 the ink column appeared to reach the kidney pelvis (4 right, 9 left). These results indicate no definite difference between right and left ureters after separate infiltration: reflux occurred 14 times on the left side and 12 times on the right side.

Urine secretion strongly affected the degree of reflux. If an ascending column of ink from the bladder met a column of urine being driven down by a peristaltic wave, the column of ink in some cases became practically stationary while the peristaltic contraction wave passed on to the bladder weakly indenting the ink-filled section during its passage, but subsequent peristaltic waves almost always, sooner or later, cleared the ureter of ink. In other instances, the column of regurgitating ink oscillated up and down, some 5 mm. being driven down by a peristaltic wave and returning more or less to same level between peristaltic waves; here again the ureter cleared itself of ink after the lapse of some minutes. In still other instances, no ink entered the ureter until the peristaltic wave had completely emptied it of urine, when upon relaxation ink swiftly rose in the ureter, reaching the pelvis at times. The bladder pressure under these conditions varied from 4 to 12 mm. of mercury.

Sex was not a significant factor, for successful infiltrations were obtained in 6 males and in 8 females. In our 3 failures to obtain experimental reflux, 2 were males and the 3rd a pregnant female. The degree of reflux perhaps was influenced by sex: 6 out of 9 females exhibited refluxes that reached the kidney, while only 2 of 8 males revealed a reflux of this extent. It must be recorded, however, that our later experiments were carried out with females and that our technical skill had improved by that time.

No conclusions about the effect of pregnancy are permissible because only 2 of our series were in this state; in one, the experimental reflux reached the kidney, and in the other all infiltrations of the intravesical ureters failed.

The speed with which the regurgitant ink traveled up the ureters after a successful infiltration varied in the different dogs. In some, a ribbon of ink, 2 to 3 mm. wide, fairly shot up the ureter to the kidney, the rate of travel being much faster than that of a peristaltic wave. In others, a similar broad band of ink ascended rapidly to a varying
distance and then slowed and stopped, its progress being apparently
impeded by a descending column of urine. In still others, a mere
black thread of ink moved slowly up the ureter until removed by
peristaltic waves.

The duration of urine reflux in dog varied from less than 1 minute
to more than 18 minutes; it seemed to depend chiefly upon the strength
and frequency of ureteral peristaltic waves and upon urine secretion.

Peristaltic activity of the ureters bore no definite relation to the
ultimate occurrence of reflux after infiltration: ink entered the ureters
when peristalsis was strong, weak or absent. It may be noted that
in our 4 failures to obtain reflux after infiltration, ureteral peristalsis
was strong in 1, fair in 2, and entirely absent in 1 dog. Antiperistalsis
was never seen, that is the rising column of ink was never driven up
by a visible antiperistaltic wave of contraction.

The tonus of the bladder in dog adjusted itself readily to the slow
injection of moderate amount of warm ink-Ringer solution when the
entire manometer circuit was closed, and the vesical pressure rose
only a few millimeters of mercury or not at all. Rapid injections
raised the pressure to 20 to 40 mm. Hg temporarily without urine
escape (see protocol page 743). The total amount of vesical fluid
rarely reached 150 cc. in our experiments.

Reflux into the ureters after infiltration occurred when the bladder
wall was firm, moderately soft or well relaxed. It has already been
noted that the vesical pressure necessary for an experimental reflux
ranged between 3 mm. (hydrostatic pressure) and 12 mm. of Hg.

After an experimental reflux it was noted numerous times both in
rabbit and dog, that an increase of vesical pressure failed to cause any
change in the level of the regurgitant ink column. The significance of
this observation will be discussed later.

Biopsy showed the following bladder conditions: in 8 dogs (4♂, 4♀
non-pregnant) the ureteral orifices and their neighborhood were edem-
atos; there were no hemorrhages and no inflammation or injection
of the mucosa; experimental reflux occurred in all.

Three dogs (2♂, 1♀ not pregnant) showed reddening and pouting
of the ureteral orifices associated with edema of adjacent areas and
general congestion of the mucosa but without hemorrhages; experi-
mental reflux occurred in all except 1 male.
Three dogs (3♀, 2 pregnant) showed hemorrhages of greater or less degree and edema of the ureteral orifices, but no injection of the bladder mucosa; experimental reflux was obtained in 2, 1 of them pregnant; no reflux was secured in the remaining pregnant female.

One pregnant female (X 12-52) with ink in the kidney pelvis after an infiltration, showed no definite edema of the ureteral orifice. In this animal, the biopsy was made more than 45 minutes after the infiltration of 1 cc. of saline solution.

In 2 males, 1 showing experimental reflux, no notes on the bladder condition were recorded.

An incidental observation on contraction of the bladder may be placed on record. In 4 dogs (1♂, 3♀ all pregnant) ligation of the urethra became necessary because urination followed the slightest rise in intravesical pressure. 2 of these dogs (1♂, 1♀) showed a marked constriction of the bladder at the junction of upper and middle thirds and this girdle effect was especially striking in the female. The bladders of these 2 dogs had not been cannulated and the ink-Ringer solution had been injected through the apex of the bladder with a hypodermic needle. None of the other dogs showed a similar type of contraction.

**DISCUSSION**

The work described in this paper was based on the hypothesis that an experimental, acute, non-obstructive edema of the ureterovesical valve was a vital factor in producing a reflux of urine from the bladder into the ureter. The mechanism was pictured as follows: Largely on the basis of Gruber’s studies (7, 4, 5) it became evident that the terminal portion of the intravesical ureter acts chiefly as an ordinary flap-valve, the flap being formed by the thinning inner wall of the ureter as it plunges diagonally through the bladder musculature. When the bladder fills, the vesical pressure pushes this membranous flap against the firmly anchored parietal wall of the ureter and closes the ureteral lumen, thus preventing the entry of urine. In a valve of this type, any decrease in passive motility should decrease its efficiency. If the valve became slightly edematous for example, a formerly effective, low vesical pressure might not then suffice to press this edematous and therefore more rigid flap against the parietal wall and urine in the bladder could then enter the ureter; a higher vesical pressure could perhaps overcome this decreased motility, press the flap back and again effectively close the ureteral orifice.
Our basic experimental observations fit this theoretical framework without any mutilation of the facts. It is clear that a causal relationship exists in our experiments between infiltration of the intravesical ureter and the appearance of bladder contents in the ureter: the reflux occurred during or shortly after the infiltration; it occurred only on the side infiltrated; it occurred at pressure levels (3 to 12 mm. Hg) that had been ineffective before infiltration. Biopsy of the bladder readily demonstrated that the infiltration had produced an edema of the valve flap and adjacent bladder mucosa. The edema, however, had to be slight, because too much edema occluded the ureteral lumen. Evidence for this is furnished by the widths of the regurgitant ink columns which varied from 3 mm. to about 0.5 mm. in diameter. Some of our failures were probably caused by too much edema. It deserves emphasis that 0.5 cc. of saline infiltrated for the first time in the dog, has produced a prompt reflux of bladder contents that reached the kidney. It is difficult to conceive of any other valid effect that a few drops of saline could exert under these conditions, beyond that already noted, namely a non-stenotic edema of the valve flap.

The short duration of experimental reflux indicates that absorption of the saline reestablished competency of the valve. Since the ureteral valve is a simple flap-valve, it is legitimate to assume that a moderate, non-occluding edema of the flap renders it incompetent by decreasing its pliability. This view that the valve flap became more rigid because of edema, is supported again by the following observation made in a number of rabbits and dogs and seen best in a relaxed motionless ureter. It was noted repeatedly that the level of a regurgitant ink column in the ureter was not altered appreciably by increasing the vesical pressure. Here apparently a valve that was incompetent at a low vesical pressure, became competent at a higher pressure. This action is readily explained by assuming that the increased vesical pressure was able to seat the valve by overcoming its increased rigidity.

Spontaneous reflux without a preceding infiltration was seen a few times in all species of animals. It occurred in 4 non-pregnant female guinea pigs under vesical pressures ranging between 2 and 9 mm. Hg; unfortunately the bladder findings were not recorded.
In rabbits, spontaneous reflux was seen in 1 male and 3 females, 1 of them in early pregnancy; the effective vesical pressure was 3 mm. of Hg in 2, and in the other 2, the pressure was not noted. The bladder condition of only 3 (1 o, 2 g, 1 in early pregnancy) was recorded. They showed pouting edematous lips of the ureterovesical orifices and in the male there was also a marked congestion of the mucosa. In these 3 rabbits at least, we feel that a pathological process accomplished the same results by the same changes that we produced by infiltrating the ureterovesical region.

In dog, spontaneous reflux was seen only in 2 adult females, 1 of them being pregnant. In the pregnant female (X 12-52) the urethra had been ligated because the slightest bladder manipulation caused urination; no cannula for pressure readings was inserted. The history of the second female is recorded in the protocol page 743. In both dogs vesical pressures of at least 40 mm. Hg existed or had existed before spontaneous reflux occurred. It must be added that the first female (X 12-52) received 87 cc. of ink-Ringer solution into a tonically contracted bladder so that our pressure estimate of 40 mm. Hg is conservative. In both females, spontaneous reflux was observed only in one ureter: in X 12-52 into the right and in X 12-92 into the left. In the pregnant female (X 12-52), the right ureteral orifice appeared normal, and the bladder mucosa was pale; the right side had not been infiltrated at any time; in X 12-92 experimental infiltrations of both ureters had been made so that the bladder condition was of no value in interpreting the spontaneous reflux. We therefore believe that high vesical pressures played a dominant rôle and that our examples of spontaneous reflux in the dog are comparable to those obtained in the same animal by Graves and Davidoff (3) and by Barksdale (8). These investigators used high pressures and strong vesical distension in order to obtain ureteral reflux. Graves and Davidoff reported reflux in 9 dogs out of 33; the average bladder pressure was 85 mm. Hg at the time of reflux and the average bladder content 488 cc. Barksdale saw bilateral reflux in 5 out of 6 pregnant dogs when cystograms were taken after the bladder had been filled with 120 to 480 cc. of 12 per cent sodium iodide under a pressure of 40 to 50 mm. Hg. Barksdale also adds the interesting observation that 3 of these 5 dogs failed to develop reflux when the same procedure was tried 2 to 3 days after the uterus had been emptied. Gruber (4) has analyzed the results of Graves and Davidoff and explains them by stating that overdistension of the bladder and high vesical pressures shorten the ureteral valves and render them incompetent. We agree with this interpretation.

Since the human ureterovesical valve is qualitatively similar in structure and function to that of dog (Gruber, 7) we may legitimately assume that a slight, non-obstructive edema of this valve will also render it incompetent at low pressures thus permitting a reflux of

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1 Gruber (7), pages 575, 579; fig. 10.
urine into the affected ureter. Such an edema of the valves may readily occur as the result of any pelvic congestion caused by physiological or pathological processes; menstruation, pregnancy, cystitis, operations on the pelvic floor may be mentioned as examples.

When urine regurgitates, the consequent distension of the ureter generally evokes peristaltic waves that attempt to drive the urine back into the bladder. This struggle between opposing forces has been well described by Wislocki and O'Connor (9) and anyone who has ever seen it, readily understands that the local ureteral distension must cause afferent sensory impulses. The strength of these impulses will depend on the degree of distension and this in turn is dependent upon the force of the ureteral peristaltic waves and the opposing vesical pressure. Under ordinary conditions, the micturition reflex will be stimulated, the bladder and ureters emptied and the symptoms produced need not exceed a more or less vague discomfort. If, however, the vesical pressure is abruptly raised by coughing or sneezing for example, the ureteral peristaltic waves suddenly meet this additional opposing force and an increased distension of the ureter occurs with an increase in painful sensations. If the increased vesical pressure drives still more urine into the ureter, though this need not necessarily occur (see page 749), the ureter must exert still more force with an aggravation of the symptoms. The pressure that a ureter may record in normal human beings when straining has been measured by Kreutzmann (10): with catheter in the kidney pelvis: 32 mm. Hg; 20 cm. in ureter: 50 mm. Hg; 10 cm. in ureter: 66 mm. Hg.

It is conceivable that the feeling of discomfort occasionally noted in normal persons at the beginning of micturition may be the result of a ureteral distension that occurred when the ureter was propelling some urine to the bladder at a time when the vesical pressure was suddenly raised.

That reflux of urine into a ureter may produce pain is not a new idea. Lewis (11) has described a number of cases in both men and women where symptoms indistinguishable from renal colic caused by calculi were produced by urinary reflux alone; prompt and permanent abolition of pain was given by relieving urethral obstruction.

Hydrostatic pressure in the bladder is a more important factor for
regurgitation in the human subject than in the dog, and its effect illustrates one of the several evils following the assumption of an upright posture. In the normal horizontal position of dog, the ureters enter at or near the highest level of the bladder and hydrostatic pressure of the urine has little or no effect on the ureteral valves, no matter how full the bladder becomes. An upright posture, however, alters this condition profoundly, for the ureters now enter at or near the base of the bladder and consequently hydrostatic pressure upon the ureteral valves will increase with filling of the bladder. If the valves are moderately edematous, the same cycle of events that has been described in dog may occur in the recumbent human subject: mere hydrostatic pressure in the bladder may suffice to drive urine into the affected ureter or ureters and even into the kidney hilus; in the upright position, the same pressure would only be sufficient to force urine as far as the middle third of the ureter. An increase in vesical pressure through any cause will increase the driving force and the reflux may reach the kidney provided that this increased pressure does not render the incompetent valve competent.

Reentry of urine into the pelvis of the kidney may cause further pathological consequences. If the recurrent column is under sufficient pressure the pelvis of the kidney may be damaged as Marcus (12) showed both in rabbit and dog. If the urine contains infectious organisms excreted by the normal kidney (13) the foundation for a pyelitis or pyelonephritis has been laid. Furthermore the traumatizing force of a regurgitant column of urine that reaches the kidney may possibly be aided by contraction of Muschat’s muscle (14). This structure is a spiral ribbon of smooth muscle in the calyceal wall and encircles each papilla of the kidney. One of its functions seems to be a milking action upon each papilla and this action according to the author is possibly great enough to explain the enormously dilated veins found in the papillae of a case of chronic nephritis with bleeding papillae. In pig kidneys, Muschat demonstrated (15) that this muscle may exert a force of 10 cm. of saline (8 mm. Hg); in the same article he also publishes a human pyelogram where the calyceal shadows are cut off from the main pelvic shadow, apparently by a contraction of a peripheral portion of the spiral muscle.
SUMMARY

Experimental infiltration of the intravesical ureter of the normal bladder in the living, anesthetized animal with magnesium sulfate or physiological salt solution caused a reflux of urine into the ureter in 6 out of 18 guinea pigs (33 per cent); in 22 out of 27 rabbits (81 per cent), and in 14 out of 17 dogs (82 per cent).

The vesical pressure necessary to produce this experimental reflux is low and ranges between 2 and 12 mm. of Hg; hydrostatic pressure of the bladder contents often sufficed to drive urine into the kidney pelvis.

After an experimental reflux had occurred, increased vesical pressure often failed to raise the level of the regurgitant column in the ureters of rabbit and dog: these higher pressures had rendered an incompetent valve competent.

Control pressures ranging between 8 and 40 mm. of Hg without a preceding infiltration, caused no reflux in the great majority of dogs.

The amount of infiltrated fluid necessary to produce reflux varied from 0.2 cc. in the guinea pig to 0.5 to 2 cc. in dog.

Spontaneous regurgitation, that is regurgitation without a preceding infiltration, was seen in 4 guinea pigs, 4 rabbits and 2 dogs.

Antiperistalsis of the ureters, that is a wave of contraction passing from the bladder to the kidney, was never seen in our animals with experimental reflux.

Biopsy of the bladder in rabbit and dog showed edema of the ureterovesical valves after infiltration in most of our animals. Hemorrhages into the submucosa in the neighborhood of the ureteral valves were observed in some. The bladders of 3 rabbits, exhibiting spontaneous reflux without infiltration showed pouting, edematous lips of the ureterovesical orifices.

The cause of experimental regurgitation is a non-obstructive edema of the vesical valve; this edema renders the valve flap more rigid and therefore incompetent at relatively low intravesical pressures. Higher intravesical pressures may again render the incompetent valve competent.

The experimental results are applied to the human subject because the urinary bladder of dog and of man are quite similar in structure.
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and function. Reasons are presented suggesting that the described type of reflux may cause pyelitis and pyelonephritis.

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