



# Hematuria

*Richard E. Scammon*

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COURTESY OF CITIZENS AID SOCIETY

## I. ABSTRACT

HEMATURIA

A. K. Doss

The abnormal appearance of blood from any part of the body is probably second only to pain in causing the laity to seek medical attention. Kretschmer found, however, in reviewing 933 consecutive cases of hematuria, the average time lapsing between the onset of hematuria and the time at which examination was undertaken was 2.39 years.

A. Incidence

Approximately 3.9% of the patients admitted to the Pennsylvania Hospital of Philadelphia give a history of having passed bloody urine, or are found on examination to have microscopic hematuria. Patients seen strictly in urology clinics present a much higher incidence.

<u>Cases seen in urology clinics</u>		<u>Percentage with Hematuria</u>
MacKenzie	3,800	21.6
Lower	2,922	26.0
Rathbun	1,500	13.5

B. Classification of Hematuria (Hinman)1. General Causes (extraordinary)

(a) Blood dyscrasias:  
hemophilia, erythremia,  
scurvy, morbus maculosus,  
purpura, jaundice, leukemia,  
Hodgkin's disease, etc.

(b) Infections:

(1) Infectious fevers:  
typhoid, malaria,  
smallpox, scarlet fever.

(2) Local infections adjacent to the tract:

appendicitis, pelvic abscess, perinephritis.

(c) Medicinal or toxic: cantharides, turpentine, urotropin.

(d) Nervous: tabes dorsalis, vicarious menstruation, hysteria.

2. Local Causes (urogenital)

(a) Lower tract:

(1) Urethra (initial hematuria is the rule, i.e. blood at the beginning of urination).

Particularly post-urethral infections

Stricture

Foreign bodies or trauma

Prostatic conditions

Tumors

(2) Trigone and neck of bladder (terminal hematuria is the rule, i.e. at the end of urination).

(b) Mid-tract

(1) Bladder

Stone,

Tumors of bladder cause at least 50% of all massive hematurias.

(c) Upper tract

(1) Ureter

Stone

Stricture

Tumor

(2) Kidney

The five most frequent are:

Stone, renal tumor, tuberculosis, infection, glomerulonephritis.

But any disease of the kidney may cause hematuria.

C. Problems

What is the origin or source of the hematuria? What is the cause of the bleeding? What line of treatment should be pursued? These are questions which one is likely to turn in his mind

when confronted with a case of hematuria.

#### D. Determination of Source

##### 1. History

The above classification emphasizes the fact that one should question the patient in detail when the complaint is hematuria and especially is this true in that case which seems to be symptomless at the start.

Consider that one is reasonably certain that the condition responsible for the hematuria is primary in the genito-urinary system and not due to cardiac decompensation, one of the various blood dyscrasias, some medication, etc., then what is the importance of pain? What is the importance of the type of hematuria? What significance has the character of the hemorrhage? What are the possibilities in symptomless hematuria?

##### (a) The importance of Pain

"Severe pain in a kidney usually, but not always, locates the hemorrhage to that kidney, but occasionally the pain is referred to the opposite healthy side. Again, unilateral renal pain and hematuria may be due, not to a renal lesion, but to a growth at the vesical orifice of the ureter. Severe renal pain and hematuria are generally due to calculi, to oxaluria and uric acid, or to the passage of clots and pieces of growths. Vesical pain and hemorrhage are due to cystitis of all varieties, such as stone, foreign bodies and extensive malignant growths. Pain at the end of the penis with hematuria indicates a lesion of the prostatic urethra or base of the bladder, a vesical calculus, or a stone in the lower end of the ureter. Rectal and perineal pain with hematuria usually point to the prostate and seminal vesicles. Hematuria with frequent micturition indicates that the bladder is inflamed or irritated, and may also be the source of the hemorrhage. The commonest causes are Bacillus coli cystitis; tuberculous cystitis secondary to renal or genital tuberculosis, for primary tuberculous cystitis is

practically unknown; cystitis due to foreign bodies and calculi; oxaluria and uric acid (usually sudden in onset and often accompanied by renal and ureteric pain)". (Nitch)

##### (b) The importance of the Type of the Hematuria

The hematuria may be initial, terminal, or thoroughly mixed with the urine. "If the hematuria is initial, i. e., at the beginning of micturition, it probably comes from the prostatic urethra, or possibly from the anterior urethra. Blood issuing from the urethra independently of micturition comes from a source distal to the compressor urethra muscle. A small quantity may lie in the urethra and form a cast of the canal, which is swept out by the next act of micturition."

"When blood is intimately mixed with the urine, it is probable that the source of the hemorrhage is the kidney. When the blood-stained urine is dark in color, the evidence is still more strongly in favor of a renal source. Yet, these tests are utterly misleading. All we can say with certainty is that blood has been shed in small or moderate quantity, allowing intimate mixture with the urine before clotting has had time to take place. The size and shape of clots may be of assistance in diagnosis. A long cast of the ureter is sometimes passed; its length and thickness indicate its origin. More frequently, shorter lengths are passed. Casts formed in the urethra are thicker and often show constrictions corresponding to those normally present in the canal. Massive clotting suggests bleeding from the bladder or prostate, but primary or secondary hemorrhage from the kidney after gunshot wounds may be so profuse as to fill the bladder with blood which rapidly clots. Frequent micturition suggests that the site of the hematuria is the bladder or prostate, but I have several times seen renal hematuria due to new growths or other cause when I have expected to see an enlarged prostate, cystitis or a bladder tumor." (Fullerton)

Terminal hematuria for the most part, is associated with conditions common to the posterior urethra: vesiculitis, prostatitis, prostatic stone, etc. Infrequently, however, terminal hematuria may be a symptom of disease located in some other part of the urinary tract.

### (c) The Character of the Hemorrhage

"Hemorrhage may be profuse or slight, constant or intermittent. Profuse hematuria is generally vesical, but may be renal, for sometimes it is impossible to differentiate between them. If vesical, it may come from benign enlargement of the prostate, a ruptured vessel in the wall of a vesical diverticulum; ulceration produced by a foreign body; a growth, generally sarcoma, for profuse hemorrhage is unusual with carcinoma or papilloma. If renal, the most likely causes are as follows: hemangioma, papilloma of the renal pelvis. In both the hemorrhage is sometimes so profuse as to endanger life, and may require a hurried nephrectomy, preceded by a transfusion. Chronic nephritis and renal tuberculosis give rise to both sudden and profuse hemorrhage and may be the initial symptom, and may precede the appearance of either casts or calculi by several days."

The kidney may further be the source of sudden and profuse hemorrhage in hypertension and arteriosclerosis, malignant growths, chiefly papilliferous carcinoma and the very vascular hypernephroma; purpura, particularly the form known as thrombocytopenic purpura hemorrhagica with or without the characteristic eruption of hemorrhages from the various mucous membranes; aneurysm of the renal artery. Slight vesical hemorrhage in patients over 50 may be due to enlarged prostate, carcinoma of the prostate, and carcinoma of the bladder, and at most ages to papilloma and calculus. Hemorrhage may also be caused by ulceration secondary to extravescical lesions, such as adherent diverticulitis of the colon, and adherent pyosalpinx or inflamed appendix; by stitches and foreign bodies sloughing into the bladder some years after a pelvic operation; and by direct extension of malignant growths of

the colon, rectum, uterus and vagina. Another cause which may be overlooked is involvement of the bladder in an inguinal or femoral herniation leading to congestion and occasional slight hemorrhage.

"Slight renal hemorrhage is generally caused by stone, chronic nephritis and various growths. It is occasionally associated with nephroptosis and hydronephrosis, and is not uncommon in the late stage of polycystic kidney. In nephroptosis, it is probably due to congestion, and in hydronephrosis and polycystic kidney to rupture of vessels in the thin septa between the cysts."

"Constant slight hemorrhage is almost invariably due to a malignant growth of the kidney or bladder, and intermittent hemorrhage to a papilloma."

### (d) Symptomless Hematuria

"Burgess analyzed 100 personal cases of symptomless hematuria, and found that the hematuria was of vesical origin in 65 (the commonest single cause being villous papilloma, 41 cases), and of renal origin in 35 (malignant growths, including hypernephroma, being the most frequent cause). Of the 86 cases in which the pathological lesion responsible for the hematuria was identified, 71 or 82.5% were due to neoplasm." (Roche)

"Almost every lesion of the kidney and bladder may manifest itself symptomless, but over 70% consist of some form of new growth, especially villous papilloma. Other causes are diverticulum; a small angioma of the renal papilla (the large ones generally cause profuse hemorrhage with renal pain); large fixed renal calculus causing ulceration; chronic nephritis; polycystic kidney; and the condition termed 'essential hematuria'."

## 2. Physical Examination

One must do a thorough examination keeping in mind the etiological factors, both systemic and local, and seek to rule out each as far as it is possible on physical examination.

Glass test (Wolbarst): At best, this procedure is little more than an estimate of the source of bleeding when employed during the course of bleeding but it is of no value at all in the absence of hematuria.

Examination of the male patient:

The patient lying on the table has a full bladder. The anterior urethra is thoroughly irrigated with a bland solution until the washings come out entirely clear of blood or other foreign elements; all foreign matter in washings originate in the anterior urethra. Lavage fluid is poured into a clear glass (glass I); This represents the anterior urethra. Further irrigation is continued for a few moments into glass II, as a control, this glass proving that the anterior urethra has been thoroughly cleansed. A sterile soft catheter of fine caliber is now introduced into the bladder and some of the contents allowed to enter a third glass, which represents the bladder urine. If the urine thus drawn into glass III is free from blood, this is supposedly absolute proof that the blood does not originate either in the bladder or in the upper urinary tract. In this event, the catheter is withdrawn and the patient voids urine into glass IV. If the bladder urine has been found free from blood and the anterior urethra has been thoroughly cleansed, it is evident that any blood found in the urine just voided into glass IV, must necessarily originate in the posterior urethra. At this point, both portions of the urethra have been isolated and one proceeds to investigate the prostate and seminal vesicles. With some urine still in the bladder, the prostate is gently yet firmly massaged after which the patient voids the remainder of the urine into glass V. Blood found in this glass is positive evidence of prostate as the site of bleeding. The vesicles may be stripped individually and separate urines voided in glass VI and VII, for each of the vesicles.

If one assumes that a catheter was introduced into the bladder, the urine instead of being devoid of blood, actually contained more or less blood. This blood must have had its origin somewhere in the urinary system except the

anterior urethra because blood from this part of the tract always gravitates to the meatus. The anterior urethra has been rested and cleansed. One now proceeds with catheter in situ, to empty the bladder and thoroughly irrigate with bland solution until no visible trace of blood is noted. There is then deposited 5 or 6 ounces of clear irrigating fluid in the bladder and the catheter is withdrawn. If the bladder contents are clear and bloodless, the test proceeds as though the bladder urine were perfectly clear (as above described). On the contrary, if blood is found in the voided fluid, then it must come from the posterior urethra. At this point, one learns whether the bleeding originates in the posterior urethra, prostate or seminal vesicles in addition to the anterior urethra. If the bleeding has not been found, the test is carried further.

In either sex, if the search has proved unsuccessful, the next thing is cystoscopy. Usually if the bladder is cleansed quickly, the fact is strongly suggestive of the upper tract as the source of blood. On the other hand, if considerable irrigation is required to cleanse the bladder of accumulated blood, it is quite evident that the bleeding originates in that viscus. A careful cystoscopic examination is done including thorough study of the ureteral orifices. The next step is to put ureteral catheters up into the pelvis of the kidney on either side. If blood is found, then one will have to use other means for study, pyelograms, etc. Should the urine be found free of blood, the catheters should be withdrawn until the bleeding is noted from the catheters and then concentrated study devoted to determine the cause of the hematuria.

### 3. Laboratory procedures

K.U.B.: A flat plate of the urinary system should be taken to demonstrate the presence of foreign bodies and give some idea of the general configuration of the urinary tract.

Pyelography: The flat plate should be followed with a pyelogram,

either intravenous or retrograde as the condition seems to indicate.

Urine: Urine culture together with pig inoculations should be matters of routine. Microscopic study of the urine sediment should be done on frequent occasions to determine the presence of infection.

Kidney function: At least one, if not more functional tests, is absolutely essential in each urological case and especially one of hematuria.

#### E. Cause of Hematuria

Walther, Kretschmer, Van Duzen and MacKenzie have each reported series of cases of hematuria. In so far as it has been possible, these reports have been combined with an attempt to learn the relative frequency of hematuria. Those cases reported in which the diagnosis was in doubt were excluded from the study.

#### The Cause of Bleeding in 5,965 Cases of Hematuria

	<u>Uretbra</u>		<u>Prostate</u>		<u>Bladder</u>		<u>Ureter</u>		<u>Kidney</u>	
	No.	%	No.	%	No.	%	No.	%	No.	%
Neoplasm	67	24.0	582	68.7	840	47.0	2	0.4	175	6.8
Inflammation	142	51.0	199	23.0	528	29.8	32	6.0	970	38.0
Foreign Body	8	2.9	11	1.0	240	13.5	467	90.5	469	18.0
Trauma	45	16.0			74	4.0			106	4.0
Tuberculosis						*			562	22.0
Other causes	14	5.0	54	6.0	89	5.0	19	3.6	270	10.0
Total	<u>276</u>		<u>846</u>		<u>1,771</u>		<u>520</u>		<u>2,552</u>	

The total number of cases with the cause of hematuria in the lower tract was 2,893 or 48%; in the upper tract, 3,072 or 51%.

\* All cases of tuberculosis are assumed to be primary in kidney.

#### Summary of Above Table

	<u>Cases</u>	<u>%</u>
Neoplasm	1,666	28.0
Inflammation	1,871	31.0
Foreign body	1,195	20.0
Trauma	225	4.0
Tuberculosis	562	9.0
Other causes	<u>446</u>	<u>7.0</u>
	5,965	

It should be remembered that these cases have been studied not from the point of view of frequency of hematuria in any particular pathological condition but merely on the basis of hematuria as a symptom. MacKenzie reviewed 11,035 urological cases with reference to the frequency of hematuria in various diseases. A summary of this study has been compiled.

% of Hematuria in Various Urogenital Diseases

	<u>No. of Cases</u>	<u>Cases of Hematuria</u>	<u>%</u>
<u>Kidney</u>			
Neoplasm	98	66	67.3
Trauma	46	38	82.6
Inflammation	3,027	428	14.1
Tuberculosis	334	200	59.0
Foreign body	5,481	168	31.0
Other causes	83	11	13.0
<u>Ureter</u>			
Neoplasm	2	1	50.0
Inflammation	6	4	66.6
Foreign bodies	673	266	39.5
Other causes	17	3	17.6
<u>Bladder</u>			
Neoplasm	407	255	62.6
Inflammation	410	95	23.7
Foreign bodies	305	92	30.6
Trauma	13	10	76.9
Other causes	245	14	5.7
<u>Prostate</u>			
Neoplasm	1,897	220	11.5
Inflammation	800	134	16.8
Foreign bodies	35	5	14.2
Other causes	47	42	89.3
<u>Urethra</u>			
Neoplasm	128	25	19.5
Inflammation	486	83	17.0
Foreign bodies	20	3	15.0
Trauma	15	13	86.6

Summary of above Table

	<u>No. of cases</u>	<u>Cases of Hematuria</u>	<u>%</u>
Neoplasm	2,532	567	22.3
Trauma	74	61	82.4
Inflammation	4,729	744	15.7
Foreign bodies	6,514	534	8.1
Tuberculosis	334	200	59.8
Other causes	392	70	18.9

(Note: Compare this table with previous one)

1. Age and Sex

Kretschmer, in studying 933 consecutive cases of hematuria, found the greatest incidence between the ages of 30 and 60.

Age

1 - 10	5
10 - 20	24
20 - 30	129
30 - 40	179
40 - 50	140
50 - 60	194
60 - 70	147
70 - 80	62
Over 80	11
Not stated	42
Male	690
Female	241
Not stated	2

Debenham studied 742 consecutive patients with hematuria who attended the Genito-Urinary Department of the London Hospital in the years of 1924-30. The most frequent causes of hematuria together with the decades in which they appear in each instance is listed (in order of frequency).

First decade: 1 - 10

Calculi, pyelitis, cystitis.

Second decade: 11 - 20

Boys: Inflammatory conditions (pyelitis and cystitis), tuberculosis, calculi.

Girls: Rare at this age. Stone, tuberculosis, pyelitis and foreign body.

Third decade: 21 - 30

Men: Pyelitis, cystitis, tuberculosis, stone, papilloma, and neoplasms only very rarely.

Women: Pyelitis, cystitis, tuberculosis and stone.

Fourth decade: 31 - 40

Men: Cystitis, pyelitis, stone, papilloma of the bladder, tuberculosis, malignant diseases.

Women: Inflammatory conditions (pyelitis and cystitis), stone, malignancy rarely found.

Fifth decade: 41 - 50

Men: Papilloma and carcinoma of bladder, stone, inflammatory conditions (pyelitis and cystitis), tuberculosis rarely found.

Women: Inflammatory conditions (pyelitis and cystitis), stone and malignancy rarely.

Sixth decade: 51 - 60

Men: Neoplasms, especially papilloma of bladder, commonest cause; prostate, inflammatory conditions (pyelitis and cystitis).

Women: Neoplasms (especially papilloma of bladder), inflammatory conditions (cystitis and pyelitis), stone; all 3 of these about same frequency.

Seventh and Eighth Decades: 61 - 80

Men: enlarged prostate and carcinoma of bladder are by far commonest causes, papilloma of bladder, carcinoma of prostate, carcinoma of kidney, stricture of urethra with secondary infection in like order.

Women: Papilloma and carcinoma of bladder are commonest causes; condition is much less common in women than in men.

Summary, in general:

Inflammatory conditions and calculi of the urinary tract are common-

est causes of hematuria in women. Hematuria, as a presenting symptom in men, has a 50% chance of being due to papilloma or carcinoma of the bladder. In women, the cause is as likely to be inflammatory as neoplastic. Over the age of 50, the prostate is a common cause of hematuria. In 130 cases of hematuria in men over 60 years of age, 43% were suffering from papilloma or carcinoma of the bladder, and 37% from simple or malignant enlargement of the prostate.

Hematuria is a rare finding in the first two decades of life. In the second and third decades, inflammatory conditions and calculi are the commonest causes in both sexes. Neoplasm becomes the commonest cause of hematuria in the fifth decade in men and in the sixth in women.

#### F. Idiopathic or "Essential" Hematuria

Rathbun is of the opinion that many of these cases, in fact, most of them, are to be explained on the basis of scar formation. Such scar formation is suggested to be the result of one of several causes.

1. Those cases in which there has been a more or less violent acute inflammatory process recognized as pyelitis or pyelonephritis and which have responded more or less quickly to the well recognized methods of treatment, only to result in diffuse scarring of the kidney.

2. Rupture of a renal abscess into a neighboring calyx or renal pelvis, later being replaced by scar tissue and leaving one or more areas of scar tissue.

3. Infarcts which may occur from remote foci of infection, which do not go on to suppuration but which do bring about histological changes; tissue degeneration, round cell infiltration, fibrosis and scar tissue following.

Such scar formation may very likely have as a complicating factor the development of small varicosities, impaired circulation resulting in degenerative

changes in the vessel walls themselves, with rupture in the former and disintegration in the latter being responsible for the presenting symptom.

Bumpus concludes: "It would seem from this clinical study that essential hematuria is not the early manifestation of an impending disease but is caused by a minor local lesion, as described by Braasch in 1913."

"I am under the impression that it would be difficult to assign any one cause to the variety of conditions which are grouped under the term 'Essential Hematuria'." (Braasch)

Hunner bases the etiology of essential hematuria on ureteral stricture, having found 174 cases on examining 178 cases complaining of hematuria.

"Essential hematuria, etc. are but expressions of our inability to determine the cause of bleeding, and are generally used to 'gloss over the neglect of giving the patient the benefit of a complete genito-urinary examination'." (Kretschmer)

Hagner, while discussing a paper presented by Rathbun states, "While infection unquestionably bears some importance in these things, I believe undoubtedly the bleeding is an early arterial renal change in the kidney, not a distinct nephritis; possibly a change in the blood vessels of the kidney causes this bleeding."

"Up to within a short time ago, it was the exception rather than the rule to excise specimens from the kidney at operation for microscopic study; no gross lesions being found, it was assumed that there were no organic changes. Later on, sections of the kidneys or the extirpated organ itself were subjected to careful microscopic examinations with the result that changes in the cortex indicative of true nephritis were frequently found. Thus, in time, essential hematuria came to be considered a manifestation of chronic nephritis." (Hyman)

## Summary

Rathbun:	"scar tissue"
Bumpus:	"minor local lesions"
Braasch:	"variety of conditions"
Hagner:	"change in blood vessels of kidney"
Hyman:	"manifestation of chronic nephritis"
Kretschmer:	"expression of our inability to find cause?"
Hunner:	"ureteral strictures"

Levy, in studying 30 cases of unexplained hematuria seemingly presents the view accepted by most of those who are interested in this field. "Essential or idiopathic hematuria is a condition of renal bleeding the etiology of which cannot be determined. It is a clinical diagnosis which is offered when all the present known urological methods have been employed with negative results. It is quite evident that there is no one accepted explanation for a hematuria with negative urological findings. From a study of the kidneys removed at operation, a single pathological entity cannot be made to apply in all cases; it is quite possible that different factors are responsible. If there is no agreement as to the etiology of essential hematuria, clinically, however, we deal with this condition as a definite disease the diagnosis of which is always arrived at by exclusion."

## G. Treatment

"The interests of the patient are not best served when hematuria is treated by drugs and rest in bed. Especially important is it to avoid such blind therapy with symptomless hematuria, since a neoplasm may thus be overlooked, and possibly allowed to progress to an inoperable stage, before hematuria recurs or before it recurs copiously enough to compel serious attention. With hematuria of unknown origin, investigation should always precede treatment. An exception is provided by clot retention. This condition, in which the bleeding nearly always comes from the bladder, calls for removal of the clots either by lavage through a large urethral catheter, or by aspiration with an

evacuating bulb, or finally by means of cystotomy." (Roche)

The treatment of essential hematuria is as confused as the theories concerning etiology are numerous. Lavage of the renal pelvis with styptics, simply the mere dilation of the pelvis, dilation of the ureter, nephrostomy, decapsulation of the kidney, simple exploration of the involved kidney have all resulted in cures according to the literature at hand. Only rarely does one seem justified in the removal of a kidney on the basis of "essential hematuria." In comparing cases studied, it seems that about as much is to be accomplished in use of conservative measures as with the use of the more radical procedures.

## H. Impressions

1. Hematuria patients constitute approximately 4% of general admissions and 20% of admissions to urological services.
2. On the average, hematuria exists 2 years before medical attention is sought (or adequate examination done?).
3. A classification of hematuria is given. (Hinman)
4. It is essential to determine the source and then the cause of hematuria.
5. Often, the history is of little aid in establishing a diagnosis.
6. Inflammation, neoplasm and foreign body comprise 79% of causes of hematuria. On the other hand, hematuria as a sign is most frequently noted in cases of trauma, tuberculosis and neoplasm.
7. In 51% of all cases of hematuria the origin is in upper genito-urinary tract. The majority of bleeding in upper urinary tract is due to foreign bodies of the ureter (calculi).
8. Hematuria, as a presenting symptom in men, has a 50% chance of being due to papilloma or carcinoma of the bladder.

9. Inflammatory conditions and calculi of the urinary tract are the commonest causes of hematuria in women.

10. The diagnosis "essential" hematuria does not seem justified but instead one should be stimulated to make a more thorough search for the etiology of hematuria at repeated intervals.

11. Treatment of hematuria should in each instance be preceded by the determination of its etiology whenever possible.

12. Diagnostic tables on incidence in various urogenital diseases are included.

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## II. LAST WEEK

Date: February 20, 1936

Place: Recreation Room,  
Nurses' Hall

Time: 12:15 - 1:07

Program: Movie: Whaling  
Perinephritic Abscess

Present: 107

Discussion: L. G. Rigler  
M. H. Mansen  
C. D. Creevy  
Theo. Sweetser  
H. A. Reimann

Gertrude Gunn,  
Record Librarian.

## III. MOVIE

Title: Energy and Its  
Transformation

Owned by: Visual Education Department,  
University of  
Minnesota

## IV. BOOK FUND BENEFIT

The Pediatric Nursing Staff is sponsoring a Benefit at the Campus Theatre, Wednesday, March 4, 1936. Picture: "I Dream Too Much" - with Lily Pons. Tickets are 25¢ each, and may be purchased from any of the Pediatric nurses.

## V. PITUITARY EXTRACT IN PYURIA

B. A. Watson calls our attention to the use of pituitary extract in pyuria for the purpose of draining the pelvis and ureter during the height of the attack. The patients admitted with high temperature, chills, pain, and a small amount of pus in the urine are often relieved by the injection of six doses of pituitary extract given at 4-hour intervals. It is not contra-indicated in pregnancy up to the 8th month.

Thank you, Dr. Watson.