PYELONEPHRITIS

MYTH OR MISDIAGNOSIS

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September 28, 1978

"It is the failure to recognize that the kidney has a limited number of ways in which to respond to a large number of stimuli that has caused so much confusion over the diagnosis of chronic pyelonephritis."

Robert Heptinstall

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PROBLEMS

	Diagnosis	Treatment and/ or workup	Long term prognosis
1. Child - age 3 enuresis recurrent abd upset small for age			
2. Female - age 16 1st U.T.I.			
3. Female - age 25 recurrent U.T.I. pyelonephritis at term 2nd pregnancy with septicemia			
4. Female - age 35 asymptomatic bacilluria 2 normal pregnancies, no complications			
5. Male - age 41 1st U.T.I.			
6. Male - age 71 poor stream G.F.R. 80 urine culture positive x 3			

WHATEVER HAPPENED TO PYELONEPHRITIS?

The Great Crusade (or Will the Real Pyelonephritis Please Stand Up)

"There was a time in the beginning of the second half of the 20th century when nephrologists led a crusade to enshrine pyelonephritis as their fiercest and most destructive god. Led by a gentle though dedicated saint, they swept all opposition before them with frightening phrases like "20% of the population", "leading cause of uremia", "important cause of hypertension, premature labor, preeclampsia and baldness". Heretics, particularly among the urologists, were diligently hunted and properly humbled for keeping their hats on in the presence of the pyelonephritologists. Those caught with catheters in their hands were forced to run the gauntlet midst jeering medical students. Worse punishments were dealt to the skeptics, i.e., those who wondered if bacilluria should really be treated for six months or more.

The Great Kidney in the sky was sorely vexed at these follies and sent down among his children a warrior named KIM-EL-STEEL (whom he had previously sent to discover diabetic glomerulosclerosis). Kim roared mightily, and all the interstitial and ischemic invaders dropped their pyelonephritic flags and ran. Soon other voices were heard. The dialyzer armies said they could find only a few victims of pyelonephritis, and their influence was great, for they had the keys to the treasury. Finally, it came to pass that reason, truth, and beauty were once more restored to the

land. The gentle saint retreated to his room and stared from the window of his study, listening to silent trumpets. Urologists could once more walk the streets with safety and dignity, and a measure of reason guided the treatment of patients with genitourinary tract infections.

Thus, we once again learned the hard lessons that are forgotten, learned, and forgotten again, in a rhythm like that of the ocean's tides.

One: The voice of authority is sometimes the voice of foolishness.

Two: Crusades are very bad things.

Three: Saints are even worse.

Four: Those who oppose popular ideas are national treasures.

So say we nephrons here below.

Leonard B. Berman, M.D.
St. Joseph Hospital
Orange California
Editorial JAMA

I. History of PYELONEPHRITIS

"Chronic and healed pyelonephritis occurs more frequently than chronic glomerulonephritis."

Weiss and Parker. Pyelonephritis. Medicine (Balt) 18:221, 1939.

"It seems safe to say that subacute and and chronic glomerulonephritis as defined here are second in frequency only to pyelonephritis as a cause of serious renal disease."

Arnold Relmon, Chapter 15, p. 486. Strauss and Welt, 1971, Little and Brown & Company.

While such material still appeared in text books, as late as the 1970's, three authors, Kimmelstiel, Hepinstall and Freedman, began as early as the mid 1960's to question if pyelonephritis was as common as Weiss and Parker had stated.

In 1966 Kimmelstiel, in the New England Journal Case Records, made the following statement, *"I stopped making the diagnosis of chronic pyelonephritis in humans on purely morphological grounds and refer to the process in such cases as Interstitial Nephritis unless I have corroborative clinical and bacteriological evidence. Bacteriuria isn't all I want because it can occur without pyelonephritis".*

In 1967, in the Annals of Internal Medicine, Freedman (1) reviewed the findings for the Yale New Haven Hospital in regard to pyelonephritis. This study excluded diabetes mellitus, and patients with septicemia and bacteremia during their terminal illness. In addition, obstructive disease of the urinary tract was also excluded (essentially tumors, prostatic enlargement and stones). A total of 4,686 consecutive autopsies were looked at between 1957 and 1964. The results showed a total of 64 cases that met the criteria of uncomplicated chronic pyelonephritis. Of this number 15 (10 female and 5 male) clearly died because of renal insufficiency. A detailed review of these 15 cases is shown in Table I on the following page.

Even this study was not selective enough in regard to pathology because no gross scaring or asymetry was found. In addition, 8 of 12 who had papilla examined showed scaring compatible with analgesic abuse. One could summarize this study using only histological criteria as showing that all 15 cases could be explained as having an etiology other than pyelonephritis.

Table 1

Autopsy Findings	Number
Previous U.T.I.	1 (during pregnancy)
Positive Urine Cultures	
Before Renal Failure	2
After development of Renal Failure	1
Hypertension	
Marked	12
Moderate	3
Toxemia of pregnancy	5
Peptic Ulcer Disease	5
Hx Analogesic Abuse	4
Sickle Cell Trait	2
Proteinuria >3gm/24 hrs	6

In 1970 Heptinstall (2,3) reviewed 3,584 consecutive autopsies at Johns Hopkins. In this series diabetics and patients with obstruction were also excluded. These authors correctly demanded at least one dilated calyx with an overlying parenchymal scar in addition to histological cellular findings. In the 8 patients they found that met these criteria, 5 were female and in only 3 of the 8 was renal failure the cause of death. This study probably best represents the true incidence of chronic pyelonephritis and its relationship to end stage renal disease.

If obstructive cases were included in the Johns Hopkins study the incidence of chronic pyelonephritis rose from .23% to 1.4%. This compares closely with Cotans (2) figure of 1.85 from the Boston City Hospital reported in 1974.

Summary: If careful analysis is done demanding either radiological and/or rigid pathological criteria the incidence of pyelonephritis is very low and correlates poorly with a history of urinary tract infections of bacilluria.

1. Freedman, L.R. Chronic pyelonephritis at autopsy. Ann. of Int. Med. 66:697, 1967.

A good review that shows in retrospect that criteria used at that time were inadequate to diagnose chronic pyelonephritis.

2. Farmer, E.R., and Hepinstall, R.H. Chronic non-obstructive pyelonephritis a reappraisal in Kincaid. Smith, P., and Fairley, K.F. (eds) Renal Infection and Renal Scarring, Melbourne Mercedes p. 233, 1970.

Probably the best concept of what is chronic non-obstructive pyelonephritis in the adult and what one can expect prognosis-wise.

3. Hepinstall, R.H. The enigma of chronic pyelonephritis. J. Inf. Dis. 120:104, 1069.

An excellent review of the problems in diagnosing this disease.

II. The Etiology and Cause of Acute Pyelonephritis, Bacilluria and Chronic Pyelonephritis

If the sixties had raised questions regarding the previous high incidence of pyelonephritis as a cause of end stage renal disease then the 1970's raised questions regarding the interrelationship between acute pyelonephritis, bacilluria and chronic pyelonephritis.

A. Acute pyelonephritis can be best defined as a complex of symptoms associated with certain laboratory findings, e.g., the sudden onset of chills and fever, accompanied by flank or abdominal pain usually associated with severe dysuria and frequency.

The urine may be cloudy or even have mild gross hematuria. On microscopic examination an unspun drop should show many bacteria. A spun sample should have greater than 5 WBC/h.p.f.

A leukecytosis with a left shift may be present. Urine concentrating ability is decreased. However, except in pregnancy, there is little, if any, decrease in GFR that cannot be accounted for on a volume basis.

The application of such a symptom complex diagnosis was compared to urine culture by a group in New Zealand (4). In this study 8 M.D.'s saw patients and made a diagnosis. The patient was then visited within hours and catheterized by a trained nurse. The urine was placed on ice, looked at microscopically and cultured within one hour. Unfortunately, microscopic examination of the urine is not described in detail, but only 7 patients showed >5 WBC/HPF.

Table II shows their culture results:

Table II

NEW ZEALAND STUDY OF URINE CULTURES IN ACUTE PYELONEPHRITIS
(130 patients)

Bacterial Count/ml		Number of Patients with infection	Number of Patients without infection
>100,000		56	-0-
10-100,000		8	-0-
<10,000		-0-	12
sterile		-0-	41
Urine not done	13		
Total	117	64 (54%)	53 (46%)

When the doctors were asked to mark their certainty in diagnosis we fine the following results.

Table III

CONFIDENCE OF CLINICAL DIAGNOSIS IN THE NEW ZEALAND STUDY

Clinical Assessment	#	Patients with Infection	Patients without Infection
Certain	37	73%	27%
Highly probable	56	61%	39%
Probable	25	52%	48%
Doubtful	12	25%	75%

The major problem with this study was that most of the patients had a history of recurrent urinary tract infection and many who were not infected at this time became infected within the next 3 months.

4. Gallager, D.J.A., Montgomerie, J.Z., and North, J.D.K. Acute infections of the urinary tract and the ureathral syndrome in General Practice. Brit. Med. J. 1:622, 1965.

A good attempt to ascertain accuracy of clinical judgement.

Because of the problems in such studies, Dr. Bob Munford, in the Infectious Disease Division here at the Medical School, undertook a related study at Southwestern/Parkland Memorial Hospital.

Table IV shows the criteria for entry and the results with clean catch mid stream urines. In this study the per cent of patients with antibody coating (ABC) was high. The coating of bacteria with antibody is said to demonstrate upper urinary tract involvement and be due to the immune response of the host against the bacteria. Many workers feel this is the best non-invasive test to recognize infection in the kidney itself (5,6). It appears to have few false positive results in women, but is probably less reliable in men and children. Regardless of the reliability of the test, women with antibody coated bacteria have more relapses post-treatment.

Table IV

103 WOMEN WITH SYMPTOMS OF CYSTITIS --
PMH EMERGENCY ROOM, 1977-1978

CRITERIA FOR ENTRY:
- 18-50 years old
- 5 or more WBCs/HPF in urine sediment
- Temp. 100^5 po
- No complicating illness or history of urinary tract surgery

RESULTS:

Urine culture with 10^5 organisms/ml: 48 (46%)

E. coli	36	(75%)
Proteus	7	(14%)
Klebsiella	1	(02%)
Other GN	2	(04%)
S. Aureus	2	(04%)

Antibody-coated bacteria test: positive (upper tract infection) in 66%

An additional finding in Dr. Munford's study is shown in Table V. There are a number of conditions that mimic cystitis and a good number of these could be picked up by a simple examination of the genitalia without a complete pelvic. In regard to his last condition 4) in the table, please refer to definitions (uretheral syndrome).

Table V

CONDITIONS WHICH MAY MIMIC CYSTITIS:

(dysuria, frequency, suprapubic pain,
+/- flank pain, +/- pyruia)

1)	Genital Herpes simplex infection
2)	Vulvo Vaginitis -- caused by N. gonorrhoeae, Trichomonas vaginalis, Candida albicans, others
3)	Infections of the periurethral area -- Bartholin's gland abscess
4)	"Urethral syndrome" - probably many etiologies

5. Jones, S.R., Smith, J.W., and Sanford, J.P. Localization of urinary tract infections by detection of antibody coated bacteria in the urine sediment. N. Eng. J. Med. 290:591, 1974.

6. Harding, G.K.M., Morrie, T.J., Ronald, A.R., et al. Urinary tract localization in women. JAMA 240:1147, 1978.

Because of the problem in clinical medicine of localizing the site of infections; in this grand rounds, the less specific term, Urinary Tract Infection (U.T.I.) will be used hereafter. The more specific terms, pyelonephritis, cystitis, or urethral syndrome are given in the definitions. At the present time the "Gold Standard" for localization would be the bladder washout technique as described by Fairley (7).

7. Fairley, K.F., Bond, A.G., Brown, R.B., et al. Simple test to determine the site of urinary tract infection. Lancet 2:427, 1967.

Still probably the "gold standard" for localization of infection in the urinary tract.

If only 50% of patients with the symptoms of "acute pyelonephritis" or U.T.I. are truly shown to be infected at the time of study, what happens to such patients long term? Generally, one can divide patients who have had one attack of U.T.I. into two groups.

A. Those who will not have another attack for what ever reason.

B. Those who will have recurrent attacks of U.T.I. This group tends to have asymptomatic bacilluria.

Remember, however, that the opposite is not true. Most patients with asymptomatic bacilluria do not have recurrent U.T.I.

Note: If one had to depend on ONE test or finding to make the diagnosis of U.T.I., it should probably be bacteria in the urine. This test, in conjunction with any degree of symptomatology, will give the highest diagnostic yield. Below in Table VI is data from Dr. Munford using gram stain of the urine and its correlation with positive urine cultures.

Table VI

URINE GRAM STAIN AND CULTURE RESULTS:

Gram stain	Culture: > 10^5/ml
> 1 organism/oil field	95%
Negative microscopy	5%

(C.L. Hall and R.S. Munford, 1977 - 1978)

High-dry microscopy on unspun urine and culture results:

	Culture: > 10^5/ml
Non-adherent bacteria, 1 or more per HPF	96%
Negative microscopy	4%

(from Barbin et al., J. Clin. Microbiol. 7:286-291, 1978)

B. Asymptomatic Bacilluria, Recurrent U.T.I. and Progression to End Stage Renal Disease

Figure 1 gives a schematic outline taken from many authors of the relationship of bacilluria to age. Note that males only led during early life when congenital anomolies are life shortening.

/12/

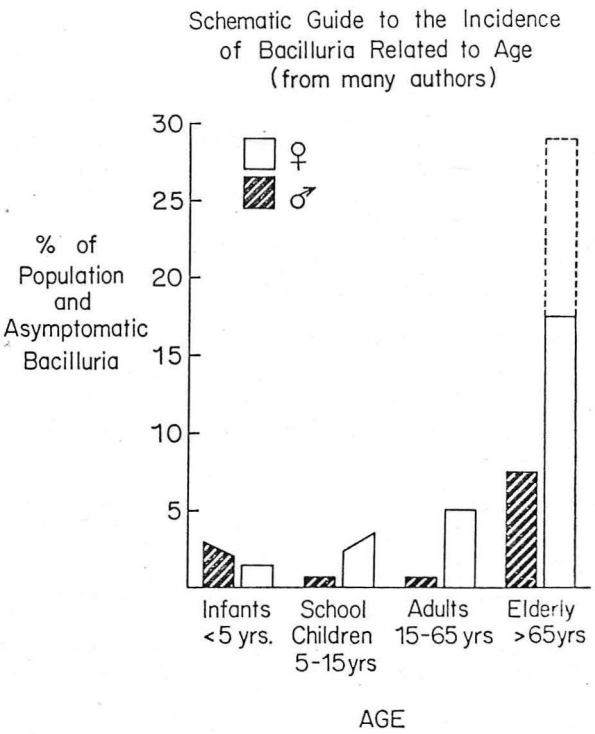


Figure 1

A number of studies have tried to determine if either the presence of bacturia in the urine or recurrent symptomatic attacks of urinary tract symptoms effect renal function. Most studies do not have enough patients followed for a long enough period of time. The results of such studies for relatively short periods in pregnant and nonpregnant groups can be summarized as follows:

1. Acute attacks of true pyelonephritis (often severe) are seen during pregnancy if asymptomatic bacilluria is not treated (15).

2. Most patients with bacilluria have had one or more previous attacks of U.T. symptoms, sometimes going back to childhood (14).

3. Renal function appears to be stable but some studies (12) show a borderline significant difference for B.U.N. as compared with non-bacilluria controls.

4. Blood pressure again tends to be slightly increased in such patients either as mean disatotic (14) or as systotic pressure.

5. Concentrating ability was significantly decreased in a subgroup who had infectious symptoms in childhood when these were compared to nonbacilluric controls (14).

6. Abnormal pyelograms were found in up to 20% of patients with bacilluria and tended to be highest in those who had pyelonephritis late in pregnancy (10,15) and/or were difficult to treat (8).

7. Treatment during pregnancy or afterwards appeared to have little, if any, long term effect (9).

8. There was a signficantly higher incidence of stones and differences in kidney size in the bacilluric group (18%) versus control group (4%) (14).

9. About 5% of the nonbacilluric control group selected during pregnancy developed asymptomatic bacilluria in long term follow-up (9).

10. There appears to be little, if any, progression to end stage renal disease at least up to 15 years in Kass's study (9).

11. The major complication of asymptomatic bacilluria is in that small group that get recurrent pyelonephritis and SEPTICEMIA.

8. Gower, P.E., Hoswell, B., Sidoway, M.D., and de Wardner, N.E. Follow-up of 164 patients with bacteruria of pregnancy. Lancet 1:990, 1968.

9. Zinner, S.H., and Kass, E.H. Long term (10-14 years) follow-up of bacteruria of pregnancy. N. Eng. J. Med. 285:820, 1971.

10. Leigh, D.A., Gruneberg, R.N., and Brumfitt, W. Long term follow-up of bacilluria in pregnancy. Lancet 1:603, 1968.

11. Sussman, M., Asscher, A.W., Watus, W.E., Evans, J.A.S., Campbell, H., Evans, K.T., and Williams, J.E. Asymptomatic significant bacteruria in non-pregnant women: I Description of a population. Brit. Med. J. 1:799, 1969.

12. Asscher, A.W., Zussmon, M., Watus, W.E., Evans, J.A.S., Campbell, H., Evans, T.K., and Williams, J.E. The clinical significance of asymptomatic bacteruria in the non-pregnant woman: II Response to Tx and follow-up. Br. Med. J. 1:804, 1969.

13. Freedman, L.R., and Andriole, V.T. A long term study of women with urinary tract infection. Proceedings of the 4th International Congress of Nephrology, Basel Kroger, p. 386, 1969.

14. Watus, W.E., Elwood, P.C., Asscher, A.W., and Abernathey, M. Clinical significance of dysuria in women. Brit. Med. J. 2:754, 1970.

15. Whalley, P.J. Bacilluria of pregnancy. Am. J. Obstet. Gyn. 97:723, 1967.

The above 8 references each give a slightly different view of the overall problem. They should be looked at in concert.

C. Chronic Pyelonephritis is an uncommon entity that has been frequently diagnosed incorrectly.

In the historical review section, it can be seen that a histological finding of an interstitial cellular reaction with fibrous tissue formation was mistaken for pyelonephritis.

If, as has just been discussed, either recurrent U.T.I. or asymptomatic bacilluria do not progress to chronic pyelonephritis, then is chronic pyelonephritis a misdiagnosis?

Chronic pyelonephritis must be thought of as being made up of 2 groups.

1) obstructive

2) non-obstructive

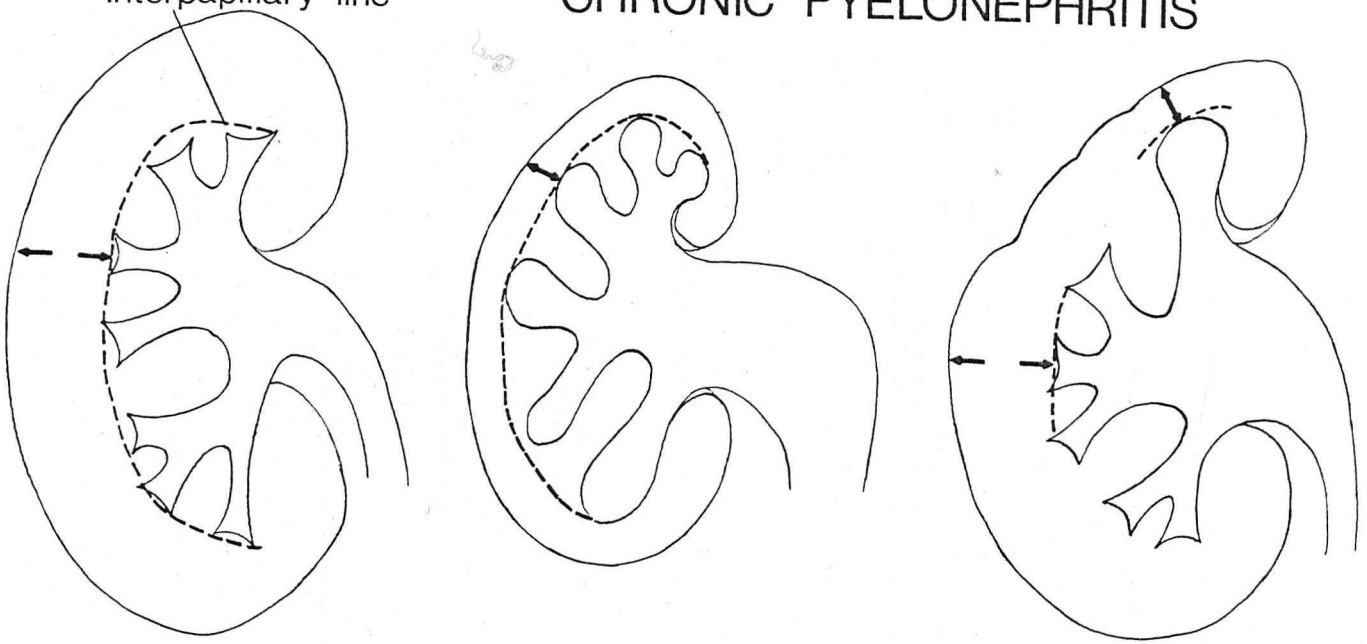
The diagnosis of either of these two entities is now made by radiological procedures. Since it has been shown repeatedly (16,17) that the presence of organisms in the urine do not correlate well with chronic pyelonephritis. Figure 2 shows Hodson's observations schematically.

1) Chronic OBSTRUCTIVE pyelonephritis will show a dilated pelvis and calyceal system that generally effects the whole kidney equally. Usually a cause and/or location of the obstruction can be located and surgically repaired with a good response. THIS FORM OF CHRONIC PYELONEPHRITIS PROGRESSES TO END STAGE RENAL DISEASE IF IT IS BILATTERAL AND REMAINS UNTREATED. Therefore, the obstructive form of chronic pyelonephritis is treatable if found early enough before pressure damage and/or infection cause tissue destruction or atrophy.

2) Chronic NON-OBSTRUCTIVE pyelonephritis will show no obstruction radiographically but a scar is usually present in the upper and/or lower polar regions, in one or both kidneys. The lesion does not appear to be progressive, at least in the older adult population. There may or may not be infected urine. Hypertension appears to be increased in this population and the increased blood pressure in adults is probably the major concern.

Figure 2

RADIOLOGICAL DIAGNOSIS OF CHRONIC PYELONEPHRITIS



Normal

Chronic Obstructive Pyelonephritis

1. Uniform decrease in size
2. All calacies effected

Chronic Atrophic Pyelonephritis

1. Polar calyx only
2. Deformed outline

16. Hodson, C.J. The radiological diagnosis of pyelonephritis. Proc. Royal Soc. Med. 52:669, 1959.

An excellent early review of the radiological diagnosis of chronic pyelonephritis.

17. Hodson, C.J. Natural history of chronic pyelonephritic scarring. Brit. Med. J. 2:191, 1965.

A good review of current diagnostic technique.

It would seem fair if we are to use radiological criteria to clinically diagnose chronic pyelonephritis either obstructive or non-obstructive, then we must comment briefly regarding the histology. This has been beautifully outlined by Heptinstall (18) in his 1976 paper on "Interstitial Nephritis" in the American Journel of Pathology. Table VI is perhaps a useful listing of the various causes of chronic interstitial nephritis. Chronic pyelonephritis is merely one category of this group.

INTERSTITIAL NEPHRITIS:

I. Pyelonephritis

- A. Bacilluria
- B. Reflux
  1. Vesicoureteral
  2. Intra-renal
- C. Obstruction
  1. With Infection
  2. Without Infection
- D. Immunological
  1. Antibody Complexes
  2. Anti-tubular Basement Membrane

II. Drugs

- A. Acute - e.g., Methicillin
- B. Chronic - e.g., Analgesics

III. Toxins

- A. Heavy Metals
- B. Balkan Nephritis

IV. Hereditary

A. Alports

B. Medullary Cystic

C. Sickle Cell

V. Metabolic

A. Gout

B. Nephocalcinosis

C. Hypokalemia

VI. Iatrogenic

A. Irradiation

B. Transplant Rejections

18. Hepinstall, R.H. Interstitial nephritis: A brief review. Am. J. Path. 83:214, 1976.

Excellent review plus he probably gives the best classification for where pyelonephritis really belongs, from a pathological viewpoint.

Hypertension and chronic non-obstructive pyelonephritis, major authors on this subject from Longscope 1937 and Weiss and Parker, 1939, up to Kincaid Smith in 1959 have estimated a 65% or greater incidence of hypertension in patients with chronic phyelonephritis. In the face of recent more restrictive criteria for pyelonephritis, hypertension may be less common. A review of the more recent literature seems to disclose two camps almost equally divided regarding the relationship of pyelonephritis and elevated blood pressure. The studies quoted previously regarding suggestive increases in blood pressure with bacilluria do not apply here. Most of the new studies, whether pro or con, lack specificity regarding the diagnosis of pyelonephritis. The only suggestive clinical evidence is that up to 50% of patients with a unilaterally infected kidney improved their blood pressure at least transiently with unilateral nephrectomy (19). The best study regarding the possible etiology of the hypertension was undertaken by Heptinstall and Michaels (20) with careful examination of 28 kidneys with a confirmed diagnosis of pyelonephritis on clinical as well as pathological grounds. This careful work compared vessel (arteriolar and arterial) changes in both scarred and unscarred areas of these kidneys. It was the authors' assumption that any vessel changes in the non-scarred area were probably

due to hypertension. Whereas changes in the scarred areas could be due to blood pressure, the inflammatory process or a combination of these two. The findings were compared with the level of blood pressure. The results can be summarized as follows:

1. Vascular changes in the non-scarred areas occurred only in cases with elevated blood pressure.

2. Vascular changes are greater in scarred than non-scarred areas and worse in those with hypertension.

3. Severe vascular changes are only found in scarred areas of hypertensive kidneys compared with, at worst, moderate changes in scars of non-hypertensive kidneys.

19. Pickering, G.W., and Heptinstall, R.H. Nephrectomy and other treatment for hypertension in pyelonephritis. Quart. J. Med. 22:1, 1953.

Very small series and highly selective.

20. Michaels, L. and Heptinstall, R.H. Pyelonephritis in Pathology of the kidney. 2nd ed. Little Brown & Co. p. 914, 1974.

A reasonable attempt to explain the causes of hypertension.

In summary, there does seem to be an increased incidence of hypertension in perhaps 20% of patients with well documented chronic pyelonephritis. The etiology is uncertain, but it would fit with localized intra-kidney vascular changes and a renin mechanism.

A review of what we have covered to date seems to indicate the following:

THE INCIDENCE OF TRUE CHRONIC PYELONEPHRITIS IN ADULTS IS LOW AND IN THE ABSENCE OF OBSTRUCTION RARELY SEEMS TO PROGRESS TO END STAGE RENAL DISEASE.

If this is true we still do not know the etiology of this entity. Before we look at that aspect I would like to review the urinary tract with you so we will be able to better understand the later presentation.

III. The Urinary Tract

A. Lower Urinary Tract

1. The Urethra

a. Proximal - normally sterile
- said to antimicrobiol

b. Distal - normally contains organisms.

NOTE: THIS DISTAL SITE IS THE MAJOR SOURCE OF CONTAMINATION WITH INSTRUMENTATION.

Organisms beyond the distal urethra are abnormal and indicate a failure of the normal protective mechanisms.

Major Associated Causes of Bacilluria

1. Instrumentation - good correlation particularly in males.

2. Sexual - Between ages 15-40, bacilluria is 8 times more common in females. A number of reasons have been given.

   A. Anatomy - the very short female urethra is said to offer less protection

   B. Absence of prostatic fluid: this fluid is believed by some workers to have an antimicrobial action. Evidence for this is weak.

   C. Trauma during intercourse - probably related to A.

   D. Hygiene

2. The Bladder

Normally sterile and if organisms are induced experimentally into a normal bladder they will be cleared in three or four days. This antimicrobial action is probably important and is thought to depend on at least three mechanisms.

a. Bacterostatic effect of normal urine:

While urine will support bacterial growth both in vivo and in vitro there are certain conditions that will inhibit growth.

(1) Osmolality greater than 600 milliosmols.

(2) Ph less than 6.0

These conditions are found more commonly in male urines and this probably explains the "magical powers" some authors have attributed to such urine. One can readily see that if bacilluria and/or previous infection effect the kidney's concentrating ability it could promote bacterial survival. This would be potentiated if the bacteria are urea splitters and raise pH.

b. Voiding with complete emptying

This probably only dilutes the number of organisms present. Normally a thin layer of urine containing organisms would be left on the bladder wall. However, if the residue is small it could allow c. below to exert its effect.

c. Mucosal factor:

If this factor exists it relates to neutrophil migration and appears to be abolished by outflow obstruction and/or increased bladder pressure.

Therefore, normally most of the lower urinary tract is sterile and perhaps has mechanisms to eradicate or at least decrease bacterial multiplication. However, even if all the above mechanisms fail, a normal person can have an infected bladder urine forever without causing upper tract infection.

It should be emphasized that the most important protection to the kidneys is at the ureterovesical junction.

The Ureterovesical Junction:

Belman (21), in an excellent review, has outlined the various problems that effect this "valve" and allow reflux.

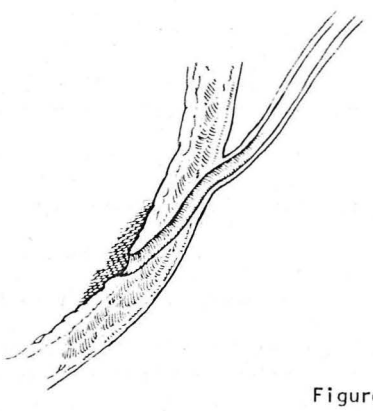


Figure 3

During normal voiding the bladder essentially contracts around the urethra and prevents urine from reflexing up to the kidney.

21. Belman, A.B. The clinical significance of vesicoureteral reflux. Ped. Cl. of N. Am. 23:707, Nov. 1976.

An excellent review of the nephrological and urological problems related to children.

Important known causes of bladder infection:

1. Residual Urine:

   This not only leaves more organisms to multiply but such remaining bacteria will have less direct contact with the bladder mucosal surface.

2. Increased pressure in the bladder:

   1) At high levels this may cause reflux

   2) May inhibit normal antimicrobial mechanisms

   3) Hypertrophy changes bladder wall surface

3. Inadequate micturition is probably a combination of 1 and 2 above.

4. Foreign body: i.e. stones

5. Previous inflamatory process - negates mucosal defense mechanisms
   - can cause reflux.

B. The Upper Urinary Tract

Bacteria can move from the bladder or elsewhere to the kidney by three possible routes.

1. Lymphatic Spread

   At present, there is little evidence to support this as a major route from the bladder to the kidney.

2. Hematogenous Route

   In clinical experience probably only significant for

   a. Group A streptococci

   b. Coagulase positive staphylococci

   The hematogenous route may be more significant in patients with already damaged kidneys from whatever cause (22).

3. Ascending Infection

   This is the major route of kidney infection. The theory is that organisms from our own G.I. tract infect the urine and can then ascend to the kidney. As has been shown in normals various defence mechanisms prevent this. The major deterant to such a route of

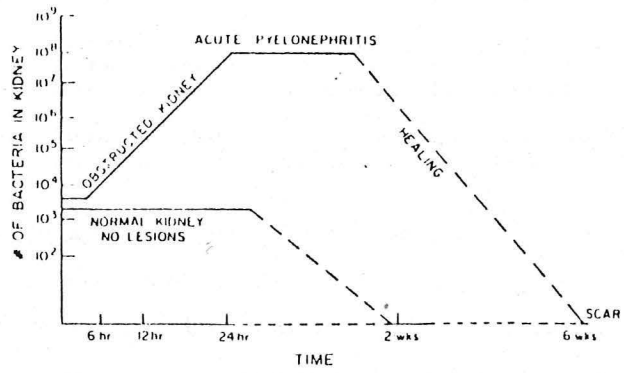
infection is a competent vesicoureteral orifice. If this system is competent there is probably a negligable incidence of ascending infection. It must be remembered that cystitis itself can cause mild reflux and thus allow bacteria to ascend. There are controversial reports with sulphur granules suggesting a few organisms may get up to the kidney even in a competent system. However, as will be seen in the next section, the kidney has a significant defense mechanism as well and such a small innoculation of bacteria from time to time probably cause little problem in the normal.

The "Hematogenous Spread" model of kidney infection:

Even though E coli is almost never spread by a hematogenous route it has been used experimentally to study kidney infection: It should be realized that once infection starts in the kidney the process is the same for hematogenous or ascending infections(25).

Figure 4

"HEMATOGENOUS SPREAD MODEL"



Comparison of the time sequence of bacterial proliferation in the normal and obstructed kidney after intravenous injection of approximately 5×10^8 *E coli*. The diagram is a schematic representation of data from different studies, and values for each curve are highly approximate

Numerous studies using this model and/or similar manipulations allow one to make a number of comments on inducing infection into the kidney.

Please note that obstruction is required or the organisms will not seed the kidney. It is of interest that this obstruction can be for as short a period as 15 minutes.

Without treatment the normal kidney is free of organisms in 2 weeks. The infected kidney has eliminated the majority of organisms by 6 weeks and scar formation has occurred. However, subsequent obstruction can cause an exacubation of infection in some cases (22).

If one reviews the various models certain facts regarding kidney parenchymal infections are repeatedly observed.

1. The medulla is more vulnerable to infection than the cortex, e.g. with direct infection of either E coli or coagulose positive staphlococci 10 organisms can initiate infection in the medulla, yet 10^4 are required to infect the renal cortex.

2. Except for pseudomonas, infection always starts in the medulla and spreads to the cortex.

3. Previous medullary injuries in a non-obstructed model became reinfected 85% of the time with experimental hematogenous infection whereas cortical injuries do not become reinfected.

4. It should be realized that once an infection becomes established in the medulla that regardless if the source is from the blood stream or below the progression is essentially the same.

5. Bacteria do not appear in the urine in the hematogenous model until reproduction occurs and tissue damage developes.

Reasons for Medullary Cortical Difference

1. Lower blood supply to the medulla

2. Higher concentration of ammonia (NH^3) in the medulla:

   This is said to interfere with complement activity.

3. Hypertonicity:

   This is said to interfere with phagocytocis of bacteria by polymorphonuclear leukocytes. This effect can be negated by water diruesis.

4. Granulocyte Emigration:

In the renal cortex following thermal injury WBC's begin to migrate to the area in two hours and become maximal at 8 hours. In apparently similar medullary injuries such exudation could not be detected for 12 hours and at 24 hours still did not equal the 8 hour cortical response.

22. Heptinstall, R.H., and Brumfitt, W. Experimental pyelonephritis: Reactivation of the healing lesion by ureteric occlusion. Br. J. Exper. Path. 41:381, 1960.

An important paper that may explain terminal undiagnosed pyelonephritis in autopsy specimens.

23. Leaf, A, and Cotran, R.S. Pyelonephritis and other interstitial diseases. in Renal Pathology, Oxford University Press, Chapter 14, 1976.

The best recent overview.

24. Cotran, R.S. Experimental pyelonephritis. in C. Roueller and A.F. Muller (eds), The Kidney Academic Press, New York, 269:361, 1969.

An absolutely exhaustive review of various experimental models. Most of the information regarding the defense mechanisms was summarized from this excellent chapter.

25. Heptinstall, R.H. Experimental pyelonephritis: a comparison of blood born and ascending patterns of infection. J. Path. Bact. 89:71, 1965.

A good study that confirms that the hematogenous spread model produces infection like ascending infections in humans.

In Summary:

The kidney and urinary tract have many defense mechanisms and except for anatomical abnormalities or obstructions pyelonephritis should not occur. This is true in adults but it must be realized that the major damage to the kidney by bacteria probably occurs before the age of five years.

IV. The Etiology of Chronic Non-Obstructive Pyelonephritis

This apparently stable disease in adults that we have discussed must start sometime. Recent work by Hodson and others would seem to now be able to pin point that time. The major question has always been, when do these scars seen at autopsy and portrayed by radiological studies (26) develop. Hodson has termed these findings PRIMARY ATROPHIC PYELONEPHRITIS. It would appear that such scarring develops in early childhood, probably before the age of 5 years and is always associated at some time with marked reflux. Recently Hodson (26) and Rolliston (32), in conjunction, have utilized the minature pig to produce a lesion indistinguishable from that lesion seen in children. They found the following factors to be important:

1. Reflux - as in children, the more severe the reflux the greater the likelihood of producing kidney damage.

2. Pressure - both in studies in children and in experimental animals, this appears to correlate with damage.

3. Infection - there is still considerable debate on this point. However, in the minature pig, sterile reflux can produce renal damage providing 1 and 2 above are severe.

Over the past 20 years Hodson, in his various writings, has gradually been putting together what he believes occurs. His theories are now generally supported by most workers in the field.

Children, because of some congenital problems or perhaps anatomically slow maturation, develop reflux. Since 50% of refluxing is gone by age 6, and 70% by age 14, reflux itself is not the only problem. The degree of refluxing is important and this probably relates to pressure. An easy system of grading reflux is as follows:

1. Into the lower 3rd of the ureter

2. Up to the kidney without dilation

3. Up to the kidney with dilation at the height of reflux

4. Gross reflux up a permanently dilated tract.

It is in the last 2 categories that one generally sees the major marker of potential scarring, i.e. INTRARENAL reflux. This has also been referred to as pyelotubular back flow. In Hodson's terminology this means that in a study where dye is placed in the bladder, on voiding, dye refluxes right up into the kidney parenchyma.

It is of interest that this intrarenal reflux only occurs in the polar regions. This gives the lesion radiologically a marker since it is the one disease where the central area of the kidney is spared. The reason for this anatomical localization has recently been described by Ronsley and Risdon (29) in the pig. (This animal is used because anatomically and physiologically it

is closest to the human.) Their one page communication in Lancet points out an anatomical difference found with the dissecting microscope. The mid zone papillae have a simple conical structure that is easily occluded when pressure increases. By contrast, the polar papillae have a different type of opening, are often compounded and cannot close when pressure rises. Hence the polar areas cannot prevent refluxed material from going up into the tubules themselves. If such refluxed fluid contains organisms, then infection and inflamation will destroy these areas of the kidney producing the classic scars seen in later life and called chronic pyelonephritis. Often these scars are seen in people without reflux and with sterile urine.

If one reviews the literature, the following general groups appear to emerge at various ages:

1. Children who loose all renal function before the age of 10. This group has a very high incidence of congenital abnormalities, e.g. duplication of the ureters is 100 times more common (21).

2. Children who develop renal failure with their growth spurt. Renal function may be borderline until adolesence, however, as they suddenly grow the damaged kidneys cannot undergo the necessary hypertrophy. Therefore, what was adequate function for a 50 pound child is no longer adequate for a 120 pound adolescent. It should be noted that some of these children (usually girls) may no longer reflux but they do have the classic polar scars.

3. There appears to be a group that get through the growth spurt but still have impaired renal function. Many of these get into trouble in their late teens and twenties because of uncontrolled hypertension, stones with obstruction, pregnancy and recurrent infection.

4. The last group are the ones we see in adult medicine as "chronic non-obstructive pyelonephritis". They have the scars but generally have not had as severe a renal damage and now often do not reflux or have infected urine. These people are probably at greater risk for kidney seeding, particularly with a gram positive septicemia from any source. The great majority of these show, as has been stated, no progression to end stage renal disease.

If group 4 has only minor problems, the other 3 have major ones. The emphasis must be on the prevention and treatment of the childhood problems, particularly before the age of 5 years.

26. Hodson, C.J., Mailing, T.M.J., McManamon, P.J., and Lewis, M.G. The pathogenesis of reflux nephropathy (Chronic atrophic pyelonephritis). British J. of Radiology. Supplement 13, 1975.

The definitive paper on the etiology of chronic pyelonephritis, with experimental models and data.

27. Rolleston, G.L., Shannon, F.T., and Utley, W.L.F. Relationships of infantile vesico-ureteric reflux to renal damage. Brit. Med. J. 1:460, 1970.

28. Smellie, L.M., and Normand, I.C.S. Experience of follow-up of children with urinary tract infection in Urinary Tract Infections. F. O'Grady and W. Brumfitt (eds), Oxford Univ. Press London. p. 123, 1968.

Good follow-up of children with renal problems.

29. Ransley, P.C., and Risdon, R.A. Renal papillae and intrarenal reflux in the pig. Lancet 2:1114, 1974.

30. Asscher, A.W., and Chick, S. Increased susceptibility of the kidney to ascending E coli infection following unilateral nephrectomy. Brit. J. Urol. 44:202, 1972.

Reviews subject of infection and its inhibition of renal growth.

31. Miller, T.E., Layzell, D., and Stewart, D. Experimental pyelonephritis: The effect of chronic active pyelonephritis on renal function. Kidney Int. 9:23, 1976

This paper demonstrates the ability of antibiotics to reverse the concentrating defect and growth inhibition produced by infection.

32. Rolleston, G.L., Mailing, T.M.J., and Hodson, C.J. Intrarenal reflux and scarred kidneys. Arch. Dis. Childh. 49:531, 1974.

Companion clinical article to Reference 23.

V. Investigation, Therapy and Long Term Management of U.T.I.

If investigative workups were done on all patients who have U.T.I. then the cost of medical care would rise significantly. However, certain cases should be investigated.

U.T.I. requiring workup:

1. Recurrent attacks in females
2. All children
3. Males - 1st attack
4. Pregnancy - if develops pyelonephritis (40% do if bacilluria is not irradicated).
   - if treatment does not irradicate bacilluria even if no U.T.I.

A. Workup of U.T.I. or Bacilluria:

1. Treat acute U.T.I. (if patient presents as such)

2. Intravenous Pyelogram (I.V.P.) - for kidney size and shape
   - for appearance of ureters
   - for signs of obstruction and/or stones

   Note: Cystitis can cause transient reflux.

3. Voiding Cysto Ureathrogram (V.C.U.G.) - if ureters not well visualized.
   - if any question regarding reflux
   - in all children

4. Retrogrades - reserve for specific problems, e.g. stones, non-visualizing kidney, abnormality in ureters.

   Note: Sonography is replacing the retrograde study as the first line study for investigation of obstruction. It may not be as accurate but it is less invasive.

5. Aortography - reserved for non-visualizing kidneys
   - looking for a specific renal abnormality.

6. Localization studies - at present mostly a research tool.

   a. selective catheterization - bladder washout (7)

   b. antibody coating of bacteria - still in question in females

   c. phage typing

   d. immunological studies

7. Glofil clearance for baseline renal function

8. Repeat cultures off antibiotics and with any exacerbation of symptoms

B. Aids in Selecting Which Patients to Workup:

1. Infants - often do not present with fever or usual signs of a U.T.I. All infants with "failure to thrive" or vomiting and/or diarrhea should have their urine cultured.

2. Fever 102° - in older children and adults with U.T.I., this has been shown to correlate with reflux in 2 studies. Govan (35) showed that in young children 60% of those with reflux will have significant fever whereas only 8% without reflux will have an elevated temperature. In a second study of 350 older children, Woodard and Holden (34) show that 90% of patients with reflux who had U.T.I. had temperatures greater than 101° versus 40% of those without reflux. If these authors had only investigated U.T.I. with temperatures > 101° they would have 51% incidence of reflux in those studied but would have missed 10% of the refluxers. Unfortunately, the authors do not correlate the findings with degree of reflux.

33. Fairley, K.F. The investigation and treatment of urinary tract infection. Med. J. Aust. 2:305, 1976.

A thorough review from a good center of their approach to investigation and treatment.

34. Woodard, J.R., and Holden, S. The prognostic significance of fever in childhood urinary infections. Clinical Pediatrics. 15:1051, 1976.

35. Govan, D.E., Fair, W.R., and Freedland, G.W., et.al. Management of children with urinary tract infection. Urol. 6:273, 1975.

Hospital Treatment of Patients with U.T.I.

Table VII shows complicating conditions that make hospitalization advisable, if not mandatory. (Courtesy of Dr. Bob Munford)

Table VII

INDICATIONS FOR HOSPITALIZATION

Pregnancy

Diabetes mellitus

Prior pyelonephritis

Immunocompromised host
(Organ transplantation, neutropenia, etc.)

Elderly

History of obstruction or of a stone

Recent instrumentation (likelihood of resistant organism)

Sickel Cell disease

Results of Workup

An investigation as outlined above should disclose the following groups:

1. Normals - No infection
   - Normal I.V.P.
   - Normal GRF for size.

2. Bacilluria - but normal radiological and functional workup

3. Anatomical abnormalities

   a. Congenital

   b. Reflux

   c. Scarring

   d. Stones or obstruction

Kunin (38) has retrospectively done such a study and his findings were 54% normal, 18% bacilluric and 28% with abnormalities in I.V.P.

C. Principals of Treatment

1. Acute infections

   grantrisin

2. Recurrent infections

   appropriate agent obtained from culture and sensitivity data.

3. If there is no correctable lesion and recurrent infections are either debilitating or , more important, producing septicemia, then suppressive agents should be considered. However, before going to suppression, localization studies with bladder washout and ureteric cultures should be undertaken and a prolonged course (4-6 weeks) of appropriated antibiotics should be initiated. If this fails then suppression should be utilized. The choice of a selective agent probably does not matter because such patients will have break through infections on any agent. At present trimethoprim sulfa seems to be the favored choice in low doses.

4. Reflux

   Mild reflux can probably be observed and not treated surgically since 50% of children studied stopped refluxing by age 6 and 68% by age 14. However, certain children are at risk even though observation is continued. Children with any of the following will probably not resolve with age and will require surgical repair.

a. Severely dilated ureters

b. Shortened mucosal tunnel

c. Laterally placed orifices on cystoscopy

d. Any patient with intrarenal reflux

e. Recurrent infections in the presence of reflux

5. Surgical repair including reimplantation

Reimplantation in selected children is 95% successful in stopping reflux. However, scarring may develop or progress and renal failure may develop despite a successful repair.

Reasons for progression of disease following reimplantation:

a. Scars (one measure of progression) may take up to 2 years to form.

b. Continued reflux with or without increased pressure

c. Protoplasts or L forms present

d. Secondary hypertension

e. Occult infections

f. Immunological mechanisms

Note: Antireflux surgery will almost certainly fail in stopping progression to end stage renal disease if severe scarring and/or hypertension and/or impaired function is already present.

36. Devine, P.C., Davis, C.S., and Devine, D.C., Jr., et.al. Vesicoureteral reflux in children. Urol. 3:315, 1974.

Excellent results with selection.

37. Tanagho, E.A. Surgical revision of the incompetent ureterovesical junction. A critical analysis of techniques and requirements. Brit. J. Urol. 42:410, 1970.

An excellent review for anyone interested in the surgical technique and its application to the prevention of reflux.

38. Parker, J., and Kunin, C. Pyelonephritis in young women - a 10-20 year followup. JAMA 224:585, 1973.

A good retrospective review of what workup would show in women with "pyelonephritis".

In Summary:

Pyelonephritis should now be thought of as 3 entities.

1. ACUTE PYELONEPHRITIS - a hard to diagnois constellation of symptoms and findings that may be more correctly called Urinary Tract Infection (U.T.I.). In the absence of obstruction this is a self limited disease.

2. CHRONIC PYELONEPHRITIS - without obstruction over the age of 20, this form of interstitial nephritis remains either stable or is very slowly progressive. If obstruction is present it must be corrected or infection and progression to end stage renal disease will result.

3. PRIMARY ATROPHIC PYELONEPHRITIS - this must be diagnosed early (probably before age 5). If intrarenal reflux is present the treatment is surgical. Medical treatment alone in this entity is not sufficient below 5 years of age.

DEFINITIONS:

ACUTE PYELONEPHRITIS - Inflamation of the kidney parenchyma initiated by bacteria. Clinically it is portrayed by a variety of symptoms (none of which are in themselves essential for the diagnosis) associated with bacteria and/or white blood cells in the urine.

PYURIA - More than 5 white blood cells with high power field on a spun urine.

BACILLURIA - The presence of bacteria in the urine greater than 100,000 ($>10^5$) bacteria/ml is said to denote infection. However, 10,000 - 100,000 ($>10^4$) may well be significant infection particularly in males.

URINE COLLECTION - Males - A "clean catch mid-stream" urines are a satisfactory method providing proper cleansing has been done before collection. Females - "Clean catch mid-stream" urines are always suspect if they are positive. If there is a real question regarding the presence of infection and treatment is to be decided on the result a CAREFUL in and out catheterization should be done.

"URETHRAL SYNDROME" - Usually designated by the presence of symptoms compatible with pyelonephritis or cystitis but with a negative urine culture. It is believed by many authors to be a localized chronic infection of the urethral glands.

PRIMARY ATROPHIC PYELONEPHRITIS - A term used by Hodson to define the process that scars the kidney in early life. This entity has 3 distinct findings:

1) It always occurs before 5 years of age
2) It is always associated with intrarenal reflux
3) It is marked by large polar scars

INTRARENAL REFLUX - The refluxing of urine from below on voiding into the renal parenchyma. This phenomena is demonstrated by placing dye in the bladder and recording the subsequent voiding by taking X-rays of the kidneys.

URINARY TRACT INFECTION (U.T.I) - A symptom complex (dysuria, fever, flank or abdominal pain, etc.) associated with bacteria and often pus in the urine. This term deliberatly attempts no localization between the upper and lower urinary tracts.

END STAGE RENAL DISEASE (ESRD) - A term demanded by the federal government to entitle patients to treatment. It is defined as that point when the patient would become uremic and die if dialysis and/or transplantation were not undertaken.

CYSTITIS - Generally refers to infection of the lower urinary tract. The symptoms are usually thought of as less severe and more localized than acute pyelonephritis. Studies show considerable overlap in clinical diagnosis.

PROBLEMS

		Diagnosis	Treatment and/ or workup	Long term prognosis
1.	Child - age 3 enuresis recurrent abd upset small for age	U.T.I.	urine culture V.C.U.G. Surg. if severe	Worrisome
2.	Female - age 16 1st U.T.I.	"Honeymoon cystitis"	gantrisin observe	probably good
3.	Female - age 25 recurrent U.T.I. pyelonephritis at term 2nd pregnancy with septicemia	Bacilluria rule out obstruction	gantrisin I.V.P creatinine clearance	good if no obstruction may need surpression
4.	Female - age 35 asymptomatic bacilluria 2 normal pregnancies, no complications	asymptomatic bacilluria	observe	good
5.	Male - age 41 1st U.T.I.	pyelonephritis rule out prostrate	gantrisin I.V.P. culture	probably OK
6.	Male - age 71 poor stream G.F.R. 80 urine culture positive x 3	probably BPH with obstruction GFR probably normal for age	urology consult T.U.R.	Good