MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

April 28, 1966

ACUTE TUBULAR NECROSIS

Case 1 - [redacted]

This 31-year-old woman was first seen in this hospital in 1953 at age 18 with a normal pregnancy complicated by measles. Then blood pressure 120/80 and urinalysis disclosed 1+ protein and specific gravity 1.020.

Next seen with premature labor in fourth pregnancy. Two previous pregnancies had been complicated by toxemia and hypertension was known between pregnancies. Had elevated blood pressure throughout current pregnancy. No blood chemistries drawn.

At time of admission was probably anuric. Blood pressure always high (200/103-180/110). Found to have small abruptio (less than 500 cc) and had immediate blood replacement.

During course of oliguria developed pyelonephritis (was catheterized on admission) with positive blood cultures (aerobactor).

Had both peritoneal and hemodialysis by means of shunt.

Biopsy - Acute tubular necrosis and sclerosing chronic glomerulonephritis.

Day	1	2	3	4	5	6	7	8	9
Urine Vol.	18	0	0	65	80	365	250	0	400
BUN	22	36			70			56	
Creatinine		4.0			10			10.3	

Day	10	11	12	13	14	15	16	----	32
Urine Vol.	540	300	800	1955	1850	3160	3350		
BUN			80				69		23
Creatinine			11				77		3.1

Ccr = 40 ml/min

Continues (3 months) to have mild azotemia (BUN 26, Creat. 1.8), proteinuria, and cylinduria. Maximum concentration = 532 mOsM/Kg.

(See Ref. 9, 10 and 19)

Case 2 - [redacted]

At the time of admission, the patient was 23 years old. She had had three normal deliveries at this hospital. One month prior to this admission she was admitted with a stab wound which resulted in a hemopneumothora. Received one unit of blood; made rapid recovery and sent home.

Was seen in EOR 10 days before this admission with "FUO". Tem. 103^{8}, BP 120/60. Chest X-ray not remarkable. WBC 5400. No therapy.

For three days prior to admission she noted marked decrease in urine volume (maybe voided 3 times in 3 days). Developed nausea and some vomiting, and for this returned to hospital. Fever had subsided shortly after EOR visit.

On admission, hemoglobin 10.8 gm% (had been 12.0 at time of discharge). Urinalysis disclosed many hyaline and granular casts with many small round epithelial cells. Urine negative for heavy metals. No history of exposure to toxins.

She was normotensive throughout admission. Appeared to have only minor fluid deficit on admission.

Renal biopsy 13 days post admission - Acute tubular necrosis with some dystrophic calcification.

Day	1	2	3	4	5	6	12
Urine Vol.	320	675	1350	1790	2700	1600	1500
BUN	180		160			69	15
Creatinine	24.5		15.6			6.8	1.4
$(CO_2)_s$	20						
$(Na^+)_s$	130						

Case 3 - [redacted]

This 51-year-old man was admitted after the abrupt onset of coma. There was no history of hypertension, heart or renal disease.

BP 180/96; remained high normal. Patient remained comatose throughout. Found to have grossly bloody spinal fluid.

Sometime after admission a history of exposure to CCl_4 fumes 6 days prior to admission was obtained.

Liver function studies were within normal limits except for an SGOT of 78 three days after admission.

He lived 10 days. Autopsy revealed massive brain hemorrhage and acute tubular necrosis.

Urine contained many granular casts with RBC inclusions.

Day	1	2	3	4	5	6	7	8	9	10
Urine Vol.	188	185	133	98	287	810	860	700	900	--
BUN	146	160	135	110	80	64	62	84	105	165
Creatinine	-	-	12.2	15.2	13.3	11.0	9.6	12.4	13.4	12.2

Case 4 - [redacted]

In the eighth month of pregnancy this 40-year-old woman experienced the sudden onset of lower abdominal cramping pain. After 3 or 4 hours of continued severe pain she arrived at the EOR with no detectable blood pressure. Diagnosis: Placenta abruptio.

She immediately received whole blood with quick restoration of blood pressure to 120/90 (she continued mildly hypertensive throughout). She delivered a stillborn and otherwise made an uneventful recovery.

On the eighth day a renal biopsy disclosed acute tubular necrosis.

Day	1	2	3	4	5	6	7	8	+60
Urine Vol.	40	2450	2650	1600	4050	2850	2400	2650	-
BUN	22	35	47	42				27	13
Creatinine	-	4.3	-	3.5				1.9	1.0

(See Ref. 22,23)

Case 5 - [redacted]

Without much in the way of medical history, this 50-year-old man arrived from the [redacted] in a comatose state. He was known to take large amounts of barbiturate. There was no history of convulsions.

He was cyanotic, exhibited extracellular fluid deficit, and had a blood pressure of 95/0.

Replacement of extraceullar fluid by means of I.V. salt solutions did not increase urine flow although blood pressure quickly returned to 120/80-130/90. Two test doses of I.V. mannitol failed to increase urine flow.

Thirty days after admission a renal biopsy revealed acute tubular necrosis.

					↓ Start Peritoneal Dialysis					
Day	1	2	3	4	5	6	7	8	9	10
Urine Vol.	270	86	62	41	0	100	120	150	325	200
BUN	61	66	116	149	150	135	134	120	119	123
Creatinine		5.3	6.7	11.9	12.6	13.2	11.6	13.0	12.0	11.8

				↓ End Peritoneal Dialysis					
Day	11	12	13	14	15	16	17	18	+60
Urine Vol.	100	798	1125	1250	1450	1500	1750	1850	--
BUN	110	77	100	117	119	118		79	18
Creatinine	11.5	8.2	10		12.3	12.7		10.7	1.6

Note - Hemoglobin concentration fell from 15.4 to 7.8 in 20 days (no blood loss). He had a weight loss of 8 Kg in 30 days.

ACUTE TUBULAR NECROSIS

1960 - 1965

Survivals	-	19	- (5 Biopsies)
Deaths	-	10	- (6 Autopsies)

Survivals

Male	Female
9	10
	(5 Obstetrical)

Nephrotoxins

2 - (Both Obstetrical)
5 - Not documented
(All questionable)

Hemolysis

1 - Clostridia (Obstetrical)
1 - Cold Agglutinins

Illness with Shock

5 - (2 Obstetrical)

Barbiturate Addiction

3 - (Includes 1 possible)

Deaths

Male	Female
6	4
	(3 Obstetrical)

Nephrotoxins

3 - Heavy Metals
2 - CCl_4
1 - Gall Bladder Dye

Hemolysis

None

Illness with Shock

4 - (3 Obstetrical - shock <u>not</u> documented)

Barbiturate Addiction

None

CLINICAL PROFILE

I. Inciting Incident

A. Crushing injury - (Classical)

1. Trauma with extensive tissue injury, especially muscle.

B. Vascular collapse*

1. Salt depletion

a. Gastrointestinal loss (vomiting and diarrhea)
b. Sequestration

1) Burns, thermal
2) Gastrointestinal

a) Pancreatitis
b) Chemical peritonitis
c) Infectious peritonitis

2. Anoxia (perhaps requires salt depletion)

a. Primary pulmonary
b. Primary CNS dysfunction

3. Central or cardiac shock†

a. Congestive heart failure
b. Myocardial infarction
c. CNS injury

4. Endotoxic shock‡

C. Nephrotoxins

1. Drugs

a. Antimicrobials

1) Sulfa (Classical)
2) Streptomycin, etc.

b. Quinine, etc.

2. Poisons

a. Heavy metals

1) Mercury salts

b. Single-bonded chlorinated hydrocarbons (CCl_4)
c. Radio-opaque dyes
d. Animal toxins (Pit viper toxin)

CLINICAL PROFILE (Continued)

3. Respiratory pigments (Perhaps requires decreased renal perfusion)

   a. Hemoglobin

      1) Transfusion reaction
      2) Cold agglutinins
      3) Intravenous water
      4) Barbiturate and Doriden intoxication
      5) Quinine and other drugs

   b. Myoglobin

      1) Muscle injury
      2) McArdles syndrome
      3) Ethanol induced
      4) Barbiturate induced

* Note that simple hemorrhagic shock is not included. (Ref. 12 and 75)

† Frequently accompanied by anoxia.

‡ Endotoxin may be nephrotoxic.

II. Oliguric Phase

A. Defined as a period during which 24 hour urine volumes are 300-500 cc or less (7 to 14 days duration)

   1. Urine flow of 15 ml per hour or less is a good definition.
   2. Anuria defined as less than 100 ml/24 hours.

B. Water requirement

   1. The algebraic sum of insensible loss and endogenous water production = + 300 to 400 ml per 24 hours for 70 Kilo man.

   2. Water requirement increased by high ambient temperature, to a slight extent by fever, and by low ambient relative humidity.

   3. Best followed by noting daily body weight (optimum: loss of 200 to 250 gms per day) and by evaluating serum sodium concentration (should remain in 130 to 145 mEq/L range).

C. Caloric requirement

   1. At least 100 gms carbohydrate daily

      a. Increase amount as tolerated

   2. Oral intake poorly tolerated - give CHO in daily water intake as 20 to 25%. Glucose I.V.

   3. NO PROTEIN - fat offers no advantage

CLINICAL PROFILE (Continued)

D. Salt - Usually not required after initial replacement

1. Urine Na^+ concentration usually less than 70 mEq/L

a. Body weight loss in excess of 300 gms per 24 hours with a continued normal serum Na^+ concentration should be replaced ml for gm with physiologic salt solution.

2. GI suction, diarrhea, and continued sequestration must be replaced.

3. If acidosis exists, salt loss should be replaced by alkalinizing salts ($NaHCO_3$-Na Lactate).

E. Potassium - Small deficits should not be replaced. No K^+ INTAKE.

1. Except in the presence of necrotic tissue, infection, or continued hemolysis, usually not a problem.

F. All phases of treatment during oliguric phase are simplified by early dialysis either by means of A-V shunt and hemodialysis or by peritoneal dialysis or both (See Ref. 17 and 18).

III. Diuretic Phase

A. By definition begins with a 24 hour urine volume of something over 350 cc per day.

1. Classically at this point urine volume doubles on successive days until volume of 2000 to 3000 cc is reached.

B. Increased urine volume generally accompanied by continued increase in azotemia for several days.

1. At present over 30% of deaths occur in diuretic phase.
2. Usually, dialysis must be continued into the diuretic phase.

C. Previously described massive urine volumes during this phase were the result of:

1. Formation of edema during oliguric phase (fluid overload), and
2. "Pushing" I.V. fluid during early diuretic phase.

D. Sodium and potassium balance must be followed closely by means of body weight and daily serum concentrations of sodium and potassium.

1. Urine Na^+ concentration seldom over 70 mEq/L and usually less.
2. Urine K^+ concentration about equal to Na^+ concentration, but may be slightly higher.

E. Important to note that many drugs are still poorly excreted during the early (7-10 days) portion of diuretic phase.

CLINICAL PROFILE (Continued)

IV. Late Phase

A. Ability to elaborate a maximally concentrated urine will return, but may take 3 months or longer.

1. Usually patients' only renal symptom during this phase is nocturia which gradually disappears as ability to concentrate improves.

B. BUN and creatinine concentrations are usually in normal range from 5 to 60 days after onset of diuretic phase.

1. Measured glomerular filtration usually slowly increases and is 70 to 80% of normal within 2 years.

C. Although urinary tract infection is common during oliguric phase, evidence for chronic infection in the late phase is rare.

D. There is no evidence of progressive renal disease in recovered patients.

PATHOLOGY - ACUTE TUBULAR NECROSIS

1. The most remarkable point is the paucity of histologic findings even in fatal cases. (See Ref. 42 and 47)

2. Glomeruli - Most authors believe there is no significant lesion. Protein deposits in Bowman's space are frequently described.

   a. Sevitt (44,45) and Price and Palmer (46) present data that glomerular lesions are present and although morphologically minor are functionally important in producing oliguria.

3. Proximal tubules - Are selectively injured by nephrotoxins, e.g., Hg^{++}. Spotty necrosis of tubular cells together with swelling and vacuolation of non-necrotic cells seen.

   a. In ischemic necrosis very rare lesions are seen.
   b. Clinical shock resulting from nephrotoxins may give rise to typical distal tubule lesions.

4. Ascending limb (thick portion) and distal tubules - Here the classical lesions of ischemic necrosis are most often seen. Include tubule cell necrosis, disruption of tubular basement membrane and more minor changes in remaining tubular epithelium.

   a. Pigmented casts are found in many tubules but rarely as many as 50%.

   b. Necrosis of cells with basement membrane destruction is Oliver's tubulorhexis lesion (40,41). Its functional significance was overrated by him since it involves so few tubules, even in fatal cases.

5. Blood vessels - Aside from rare micro-venous thrombi in the medulla, blood vessels are not involved.

6. Interstitial tissue may be more obvious than normal due to edema, but there is rarely a cellular infiltrate.

MECHANISM - ACUTE TUBULAR NECROSIS

A. Several simultaneous factors must prevail:

1. Renal ischemia - By itself, does not produce acute tubular necrosis. However, if great enough, and sufficiently prolonged may produce renal infarcts or cortical necrosis. (See Ref. 66)

2. Low urine flow - Usually present during renal ischemia.

3. Concentrated urine - Normally present during renal ischemia. It is of interest that the inability to elaborate a concentrated urine may protect against tubular necrosis. (See Ref. 9, 10 and 19)

4. Presence of endogenous nephrotoxin. Endogenous nephrotoxins include products of cell death only 2 of which are certainly identified; hemoglobin and myoglobin. (See Ref. 4,71,72 and 81)

5. Certain exogenous nephrotoxins can produce clinical acute tubular necrosis without apparent renal ischemia and during diuresis of a dilute urine. Inhaled CCl_4 is a good example.

MECHANISM - OLIGURIC PHASE IN ACUTE TUBULAR NECROSIS

A. Possible mechanisms

1. Back-diffusion of tubular fluid through damaged tubular epithelium (See Ref. 38,57,58 and 68).

   a. This concept includes the leakage of fluid from tubular lumen into interstitial tissues through tubulorhexic lesions of Oliver (40,41), but these are not quantitatively important.

2. Interstitial edema with raised interstitial pressure

   a. If interstitial pressure is raised, it is apparently not sufficiently raised to collapse either tubules or blood vessels. (Ref. 79 - No change in interstitial pressure noted in necrotic kidney, and Ref. 70).

3. Intrarenal shunting of blood. Trueta shunt. If operative in man, perhaps more clearly related to the pathogenesis of acute cortical necrosis. (See Ref. 51, 53,55 and 56)

4. Obstruction of tubules by cellular and pigmented casts. Although casts are always present, sufficient numbers of tubules do not appear to be obstructed to result in oliguria (Ref. 53 and 62).

5. Decreased renal blood flow - By direct measurement (experimental disease, and by means of Fick principle in human disease, renal blood flow is decreased, but even in severe oliguria remains significant; 40% of normal. (See Ref. 49, 51-54, and 59)

6. Decreased glomerular filtration - If back diffusion is significant, then no clearance measure of filtration rate is reliable.

MECHANISM - OLIGURIC PHASE IN ACUTE TUBULAR NECROSIS (Continued)

a. Oldest micropuncture studies and glomerular tagging experiments suggest filtration continues even during severe oliguria (Ref. 40,58 and 68).

b. More recent micropuncture studies suggest that glomerular failure is the primary lesion (Ref. 69 and 70). However, massive back-diffusion was not ruled out by these studies.

B. Proposed mechanism

1. Renal ischemia, oliguria, and "nephrotoxin" result in tubular epithelium damage.

   a. Includes tubular cells of entire nephron - most significant in proximal tubule.

   b. Degree of dysfunction not correlated with morphologic change, although necrosis of cells may be seen, especially in distal nephron.

   c. Destruction of tubular basement membrane may not be reversible, but small numbers of such lesions make them insignificant.

2. Damaged tubular epithelium allows massive back diffusion as evidenced by Lissamine green injection studies.

   a. Back diffusion is so great that it might be interpreted as glomerular failure in micropuncture studies.

3. Cast formation in the distal nephron obstructs some nephrons by cellular and pigmented casts.

4. Renal blood flow and glomerular filtration continue at modestly reduced rates.

5. Excess interstitial fluid from back-diffusion accomodated without increased intrarenal pressure by increased lymph flow from kidney (See Ref. 78).

6. Diuretic phase begins with repair of tubular epithelium.

   a. Most lesions repaired in 7 to 14 day period.

   b. Nephrotoxin may delay regeneration of tubular epithelium for periods in excess of 30 days.

7. Bladder urine in oliguric and early diuretic phase is derived from a few undamaged and newly repaired nephrons, respectively, and has most of the characteristics of urine from patients with chronic renal disease (See Ref. 61,87,88,89 and 98).

REFERENCES

Clinical

1. Merrill, J.P. The Treatment of Renal Failure. 2nd Ed., Grune and Stratton, New York, 1965.

In this book the clinical management of patients with acute tubular necrosis is carefully and completely outlined. In addition, most of the important contributions to the subject are cited.

2. Report of the Study Group on Acute Renal Failure Convened by the U.S. Army Surgical Research Unit, 1957. Unpublished.

As of October 1957:

Diagnosis	Patients	Fatalities	Fatalities Per Cent
Post traumatic	242	160	66
Transfusion reaction	142	56	39
Nephrotoxins	137	44	32
Post partum	270	82	30
Other	253	170	67
Totals	1044	512	Mean 49

3. Bywaters, E.G.L. and D. Beall. Crush injuries with impairment of renal function. Brit. Med. J. 1:427, 1941.

The initial description of crush nephropathy. The renal morphology described was that of tubular necrosis and cast formation (mainly pigmented). The authors felt strongly that the renal damage was related directly to toxic products from necrotic muscle in the limbs of the crush victims. It appears that this syndrome was described during World War I, but forgotten between wars.

4. Bywaters, E.G.L. Ischemic muscle necrosis, crushing injury, traumatic edema, crush syndrome, traumatic anuria. Compression syndrome: A type of injury seen in air raid casualties following burial beneath debris. J. Am. Med. Assoc. 124:1103, 1944.

A good review presenting this group's concept of the "crush syndrome". Here even stronger evidence is given that myoglobin arising from crushed muscles is the nephrotoxic agent. Stresses that many patients did not show clinical shock at any time. Advocated the early establishment of an alkaline diuresis in a effort to prevent renal injury.

5. Bull, G.M., Joekes, A.M. and K.G. Lowe. Conservative treatment of anuric uremia. Lancet 2:229, 1949.

Clinical (Continued)

Clinical results suggested the importance of adequate daily carbohydrate intake during the oliguric phase. Suggested that large amounts may be more helpful than the usually recommended 100 gms per day. However, there seems now to be little evidence that there is much difference between 100 and several hundred grams intake per day.

6. Burnett, C.H., Shapiro, S.L., Simeone, F.A., Beecher, H.K., Mallory, T.B. and E.R. Sullivan. Recent advances in surgery. III. Post traumatic renal insufficiency. Surg. 22:994, 1947.

This is a review of a large number of World War II patients from which 2 interesting points can be made: 1) The severity of the renal lesion was not related to the degree of shock - some patients had no documented shock. 2) All patients had hypertension (135/90 or above); 23% had edema; in those measured all had increased plasma volume. The dichotomy between shock and renal failure is apparent, although not so clearly as seen later in the Korean event. Although volume expansion was detailed, it was not identified as a cause of hypertension.

7. Strauss, M.B. Acute renal insufficiency due to lower nephron nephrosis. New Eng. J. Med. 239:693, 1948.

8. Strauss, M.B. Therapeutic considerations in acute renal impairment. Bull. New Eng. Med. Cen. 11:247, 1949.

These two papers emphasize the dange of fluid excess in the conservative management of the oliguric phase of tubular necrosis. Suggested that perhaps only 500 cc of water a day were needed plus 100 gms of glucose. However, here as in the papers as late as 1955 it was not clearly pointed out that most hypertension and most "heart failure" seen in these patients was due to volume over-expansion.

9. Welt, L.G. and J.P. Peters. Acute renal failure; lower nephron nephrosis. Yale J. Biol. and Med. 24:221, 1951.

These authors point out that most cases of tubular necrosis occur during periods of dehydration and/or hypertonicity - both of which would serve as stimuli to maximum urine concentration. They note that adequately hydrated patients and patients who cannot ordinarily elaborate a concentrated urine (i.e., chronic renal disease) are protected and seldom manifest acute tubular necrosis.

10. Swan, R.C. and J.P. Merrill. The clinical course of acute renal failure. Med. 32:215, 1953.

A comprehensive report of 85 patients with acute tubular necrosis. Many characteristic features of the disease described in this report.

Oliguric Phase

Urine volume (24 hour) usually continues to fall for 2 or 3 days after insult. Thereafter tends to rise very slowly until a volume of 350-400 ml/day is reached. Thereafter urine volume tends to increase daily by 50 to 100% over previous days volume.

Clinical (Continued)

With nephrotoxin, oliguria is delayed several days after ingestion.

During first few days of renal failure urine may be grossly bloody. To start with there is usually intense proteinuria. The sediment usually contains RBC, WBC, granular and pigmented casts (after nephrotoxins especially, may contain RBC casts).

Diuretic Phase

Even though urine volume increases, azotemia, acidosis, and hyperkalemia may worsen for several days after the start of diuresis. About 1/4 of the deaths occur in this phase. Interesting that shock during this period does not appear to re-injure kidneys (See Ref. 9).

At the time of this writing, the major cause of death in this illness was thought to be cardiac failure (volume overload).

11. Meroney, W.H. and R.F. Heindon. The management of acute renal insufficiency. J. Amer. Med. Assoc. 155:877, 1954.

A review of the methods of treatment used and results in Korean war casualties in particular. It is of interest that although fluid balance was carefully followed, it appears that volumes of fluid given were too large as evidenced by the massive diuresis described during the diuretic stage.

12. Teschan, P.E., Post, R.S., Smith, L.H. Jr., Abernathy, R.S., Davis, J.H., Gray, D.M., Howard, J.M., Johnson, K.E., Klopp, E., Mundi, R.L., O'Meara, M.P. and B.F. Rush, Jr. Post traumatic renal insufficiency in military casualties. I. Amer. J. Med. 18:172, 1955.

13. Smith, L.H. Jr., Post, R.S., Teschan, P.E., Abernathy, R.S., Davis, J.H., Gray, D.M., Howard, J.M., Johnson, K.E., Klopp, E., Mundy, R.L., O'Meara, M.P. and B.F. Rush, Jr. Post traumatic renal insufficiency in military casualties. II. Am. J. Med. 18:187, 1955.

These two papers characterize the clinical picture of acute tubular necrosis in severely traumatized individuals. Several important points are brought out: 1) Etiology - Duration and depth of shock (systolic) BP below 100 mm) was not significantly different in the tubular necrosis group from a control group having equal injury and no renal failure. Serum blood pigment levels were the same in both groups. Muscle pigments not measured. 2) High catabolic rate - BUN rose 20-25 mg% per day. Serum K^+ often difficult to control. 3) Period of oliguria about the same length as in non-trauma patients. Decline in azotemia did not occur until urine volume over 1000 ml per 24 hours.

14. Iseri, L.T., Batchelor, T.M., Boyle, A.J. and G.B. Myers. Studies of fluid, electrolyte and nitrogen balance in acute renal insufficiency. Arch. Int. Med. 89:188, 1952.

One of the first careful balance studies on 4 patients with acute tubular necrosis. Although the data presented look good, for the most part, the conclusions of the authors are not reasonable, particularly with regard to the development of hyponatremia. In this case the wrong conclusion was reached primarily as the result of an overestimation of insensible water loss.

Clinical (Continued)

15. Bluemle, L.W. Jr.,Potter, H.P. and J.R. Elkinton. Changes in body composition in acute renal failure. J. Clin. Invest. 35:1094, 1956.

In this study, balance data are presented from 8 female patients. The suggestion is made that protein metabolism is uninfluenced by exogenous factors (7 of 8 patients dialyzed once). Of perhaps more importance it was concluded that water requirement during the oliguric phase was 330 ml/meter^2/day or approximately 550 ml per day.

16. Keleman, W.A. and W.J. Kolff. Survey of dialysis for acute renal failure at Cleveland Clinic Hospital in 1958. Cleveland Cl. Quart. 26:227, 1959.

Twenty-seven cases treated with 73 hemodialyses with an overall recovery of 44%. (Only 19 were diagnosed as acute tubular necrosis).

Noted that if at the onset of renal failure, the initial urine volumes were less than 100 ml/24 hours that the oliguric phase would be over 10 days in length. Two patients recovered after 30 and 34 days of oliguria.

17. Teschan, P.E., O'Brien, T.F. and C.R. Baxter. Prophylactic daily hemodialysis in the treatment of acute renal failure. Surg. Forum 10:362, 1959.

18. Teschan, P.E., Baxter, C.R., O'Brien, T.F., Freyhof, J.N. and W.H. Hall. Prophylactic hemodialysis in the treatment of acute renal failure. Ann. Int. Med. 53:992, 1960.

This is the first description of the use of indwelling vessel cannulars and repeated dialysis through these cannulas.

The authors propose that prophylactic dialysis may reduce the very high overall mortality of acute renal failure.

They describe the treatment in 12 patients. Only 3 deaths. Three patients with 3 or more weeks of oliguria survived.

19. Bluemle, L.W., Webster, G.D. and J.R. Elkinton. Acute tubular necrosis: Analysis of 100 cases with respect to mortality, complications and treatment with and without dialysis. Arch. Int. Med. 104:180, 1959.

The overall mortality in these patients was 50%. This figure could be broken down as follows:

Transfusion reaction - 29% Obstetrical Complication - 25%

Surgery and Trauma - 72%

Eighty per cent of all patients developed some form of infection and in one-third infection was primarily responsible for death.

20. Maher, J.F. and G.E. Schreiner. Cause of death in acute renal failure. Arch. Int. Med. 110:493, 1962.

Clinical (Continued)

Report covers 70 autopsied cases of acute tubular necrosis. Twenty-two patients (1/3) died of infection (in 8 of these septicemia was thought to be the cause of renal failure). Twenty-nine died of their underlying disease (trauma, acute poisoning, perforated viscus, etc.). In only 13 patients could death be ascribed to uremia, hyperkalemia and/or fluid excess.

21. Holmes, J.H. Acute tubular necrosis and its management. Surg. Clin. N. Amer. 43:555, 1963.

A clinical review of 110 patients covering the years 1953-1963. During this period an improvement in overall mortality was noted:

1953 - 1958	1959 - 1963
58 patients	52 patients
53% mortality	22% mortality

In both groups, infection was the most frequent complication.

22. Sevitt, S. Distal tubular necrosis with little or no oliguria. J. Clin. Path. 9:12, 1956.

Reported 8 patients dying of uremia who pathologically had acute tubular necrosis. None of these patients had a period of oliguria.

23. Perlmutter, M. Unusual cases of acute tubular necrosis. Ann. Int. Med. 47:81, 1957.

Report of a case with only 1 day of oliguria, but showing marked rise in BUN during the diuretic phase. Report of another case that had very low urine sodium concentration (21-48 mEq/L) during the diuretic phase, a perhaps not too unusual circumstance if salt infusions are not "pushed" during diuretic phase.

24. Waugh, W.H. Functional types of acute renal failure and their early diagnosis. Arch. Int. Med. 103:686, 1959.

Early Urinary Features

Type of Renal Failure	Vol.	Sp. Gr.	Na mEq/L
Extrinsic renal failure	Low	Above 1.018	20 or less
Intrinsic renal failure - diffuse glomerular nephritis	Low	Above 1.018	20 or less
Intrinsic renal failure - tubular necrosis	Low	Below 1.018	30 or more

This table given by the authors predicts a high Na concentration in urine in ATN. However, many authors have noted low values particularly early in the disease course.

Clinical (Continued)

25. Perlmutter, M., Grossman, S.L., Rothberg, S. and G. Dobkin. Urine-serum urea nitrogen ratio (simple test of renal function in acute azotemic oliguria). J. Amer. Med. Assoc. 170:1533, 1959.

In oliguric patients, urine (urea N_2/blood urea N_2) concentration ratios of 14 indicate renal damage, and ratios below 10 are usually associated with acute organic renal failure.

26. Sporn, N., Lancestremere, R.G. and S. Papper. Differential diagnosis of oliguria in aged patients. New Eng. J. Med. 267:130, 1962.

These authors point out that, particularly, in elderly patients total urine solutes (mOsM/Kg) may not help in differentiating salt depletion oliguria from oliguria due to acute tubular necrosis. However, even in these patients, urine sodium concentration tends to be low (> 30 mEq/L) in salt depletion oliguria and much higher in tubular necrosis.

Five Examples

Tubular Necrosis	Urine Vol ml/24 hr	Urine Concentration mOsM/Kg	Urine Na^+ mEq/L
1	300	310	72
2	185	230	70
Salt Depletion			
3	140	480	6
4	210	373	6
5	288	400	8

27. Lowe, K.G. The late prognosis in acute tubular necrosis: An interim follow-up on 14 patients. Lancet 1:1086, 1952.

Clearance studies in 14 patients recovered from severe acute tubular necrosis (oliguria 1 to 3 weeks) showed gradual improvement throughout the first post illness year. In the second year recovery was complete and generally reached the lower limits of normal for RBF and GFR. In general, all patients were in good health; no mention of pyelonephritis.

28. Finkenstaedt, J.T. and J.P. Merrill. Renal function after recovery from acute renal failure. New Eng. J. Med. 254:1023, 1956.

This is a study of 16 post tubular necrosis patients selected for study because of the absence of any cardiovascular-renal disease prior to their acute illness. One patient subsequently developed periarteritis nodosa, but the other 15 patients made a complete recovery and were in good health. Within 6 months PSP excretion and urine concentration tests were normal. Clearance values (GFR $_{inulin}$ and RPF $_{PAH}$) remained in the low normal range. There was no evidence of progressive renal disease.

Clinical (Continued)

29. Meroney, W.H. Phosphorus to nonprotein nitrogen ratio in plasma as an index of muscle devitalization during oliguria. Surg. Gynec. and Obstet. 100:309, 1955.

A plasma phosphorus: Nonprotein nitrogen ratio above 0.05 suggests muscle damage and a ratio above 0.06 is indicative of a large, perhaps lethal, mass of necrotic muscle. (Thus, a danger of malignant hyperkalemia). (See next reference).

30. Doolan, R.D., Theil, G.B., Wiggins, R.A., Lee, K.J. and E. Martinez. Acute renal insufficiency following aortic surgery: Discussion of pathogenesis and consideration of gangrene of extremity as a complication. Am. J. Med. 28:895, 1960.

Authors were unable to confirm value of Meroney's P/NPN ratio. Obvious muscle necrosis with severe hyperkalemia occurred with ratios below 0.05.

31. Morrin, P.A.F., Gedney, W.B., Barth, W. and R.H. Heptinstall. Acute tubular necrosis. Report of a case with failure to recover after 67 days of oliguria. Ann. Int. Med. 56:925, 1962.

Most authors imply that time will heal all lesions of tubular necrosis. This report of a patient with CCl_4 intoxication (without significant liver damage) is supported by 2 renal biopsies and post mortem findings all of which suggested regeneration of tubular epithelium. However, the patient never had over 320 cc of urine/24 hours and became progressively oliguric after the 25th day. No adequate explanation of the failure to recover is given.

32. Powers, S.R., Kiley, J. and A. Boba. Management of acute renal failure complicating massive trauma. Bull. N.Y. Acad. Med. 35:131, 1959.

An article attempting a clinical correlation of the authors' experimental work on acute tubular necrosis. (See Reference 67).

33. Barry, K.G., Cohen, A. and P. LeBlanc. Preliminary report: mannitolization. I. Prevention and therapy of oliguria associated with cross-clamping of abdominal aorta. Surg. 50:335, 1961.

34. Barry, K.G., Cohen, A., Knochel, J.P., Whelan, T.J., Beisel, W.R., Vargas, C.A. and P.C. LeBlanc. Mannitol infusion: II. Prevention of acute renal failure during resection of an aneurysm of the abdominal aorta. New Eng. J. Med. 264:967, 1961.

35. Barry, K.G. and A.R. Berman. Mannitol infusion. III. Acute effect of the intravenous infusion of mannitol on blood and plasma volumes. New Eng. J. Med. 264:1085, 1961.

36. Barry, K.G. and J.P. Malloy. Oliguric renal failure: Evaluation and therapy by intravenous infusion of mannitol. J. Amer. Med. Assoc. 179:134, 1962.

Although not the first to suggest that an osmotic load might alter the course of a nephrotoxic injury, to Barry and his group must go the credit for its first systematic clinical application. Most importantly, they stressed the safe limits of use of mannitol. The plan as outlined in Reference 36 appears safe and beneficial: 12.5 gms of mannitol as a 25% solution (1 ampule) are given over a 3 minute period. If urine flow rate does not increase within 3 hours no further mannitol is given. If urine flow increases to

Clinical (Continued)

40 cc per hour or above, a sustaining I.V. drip is given to keep urine flow at about 100 cc per hour. (See References 63,75,80 and 81).

37. Luke, R.G., Linton, A.L., Briggs, J.D. and A.C. Kennedy. Mannitol therapy in acute renal failure. Lancet 1:980, 1965.

A recent clinical report of 35 patients (25 responded to mannitol injection) which tends to confirm Barry's observations.

The data suggest that mannitol infusion is worth trying even up to 48 hours of severe oliguria.

REFERENCES (Continued)

Pathology

38. Bywaters, E.G.L. and J.H. Dible. The renal lesion in traumatic anuria. J. Path. and Bact. 54:111, 1942.

Material examined from 22 cases of "crush injury".

Changes: Glomeruli - Protein material in Bowman's space. "Tubulization" of the cells lining Bowman's capsule.

Tubules - Lumen of proximal tubules filled with the remains of necrotic epithelial cells.

Thin limb of loop - No changes.

Thick limb of loop and distal tubules show the most extensive changes - Some areas of complete necrosis; areas of tubular rupture with cast material in interstitum; many pigmented casts.

On the basis of pathology, authors concluded that oliguria was the result of back-diffusion of urine through damaged tubules.

39. Lucki, B. Lower nephron nephrosis. The renal lesions of the crush syndrome, of burns, transfusion, and other conditions affecting the lower segments of the nephrons. Mil. Surg. 99:371, 1946.

This paper is the origin of the term "Lower Nephron Nephrosis". It is a report of 538 fatal cases seen at the AIP during World War II. The clinical data is now of little value; the morphologic data concerns us most. Lucki noted necrotic lesions primarily in the ascending limb (thick portion) and distal tubule with few necrotic areas in collecting ducts. Noted that except for protein deposits in Bowman's space, glomeruli were normal. Proximal cells exhibited increased granularity and cloudy swelling only. Mentioned the spotty nature of the lesions but did not stress it.

Pathology (Continued)

40. Oliver, J., MacDowell, M. and A. Tracy. The pathogenesis of acute renal failure associated with traumatic and toxic injury. Renal ischemia, nephrotoxic damage and the ischemuric episode. J. Clin. Invest. 30:1307, 1951.

In this very long paper Oliver describes 2 basic lesions; 1) Nephrotoxic - involving changes (necrosis?) in all the proximal tubular cells; 2) Ischemic lesion involving any part of the nephron characterized by spotty destruction of the basement membrane (his term - tubulorhexis).

Discounts the importance of casts as an etiology of oliguria. Likewise, does not believe that blood or muscle pigment are toxic to the nephron.

At most, tubulorhexis lesion manifest in only 50% of nephrons - usually far less. This last point not emphasized by Oliver.

Although morphologic data presented are important, the functional correlations made are not well founded.

41. Oliver, J. Correlations of structure and function and mechanisms of recovery in acute tubular necrosis. Am. J. Med. 15:535, 1953.

A further long paper reaching conclusions similar to the foregoing paper. Of interest is that Oliver finds it necessary to have decreased RBF and GFR together with increased interstitial pressure in order to maintain the oliguric phase.

Restates that tubulorhexic lesions are irreparable despite the unmentioned fact that renal function (RBF and GFR) returns at least to 75 to 80% of normal in most patients that recover.

42. Brun, C. and O. Munck. Lesion of the kidney in acute renal failure following shock. Lancet. 1:603, 1957.

Kidney for histologic examination was obtained from 33 patients. Both biopsy and necropsy material was used. The lesions described were not significantly different from previous pathological reports. The outstanding feature is the lack of marked morphologic changes.

Findings: 1) Dilatation and flattening of epithelium of distal convoluted tubules - found to some extent in 26 of 33 cases.

2) Casts - primarily in distal tubules - mostly pigmented - found in 32 cases.

3) Dilatation and flattening of epithelium of proximal convolutions. Found in only 4 cases.

4) Hydropic changes in proximal epithelium—Twenty-two of 33 cases.

5) Interstitial edema - twelve of 33 cases.

6) Tubular necrosis - five of 33 cases.

7) Mitosis of tubular cells - seven of 33 cases.

Pathology (Continued)

43. Dalgaard, O.Z. and K.J. Pedersen. Renal tubular degeneration. Electron microscopy in ischemic anuria. Lancet 2:484, 1959.

Renal biopsy in a single patient with acute renal failure following a suicide attempt with barbiturates. No light microscopy glomeruli available. On EM and phase microscopy of the EM sections, the glomeruli are reported as normal. Both spotty proximal and distal tubular changes were seen on EM. Mostly cloudy swelling and hydropic degeneration.

44. Sevitt, S. Pathogenesis of traumatic uremia: Revised concept. Lancet 2:135, 1959.

Makes a strong case, on the basis of renal tissue examination, that tubular necrosis cannot be the cause of oliguria. Not only is very little necrosis seen in some fatal cases, but non-oliguric renal failure may have significant tubular necrosis. The author concludes that the oliguric state is the result of depressed GFR - depressed greater than the known reductions in RBF shown to be present in these cases. Believes that there may indeed be a morphologic glomerular lesion characterized primarily by lipid droplets in glomeruli epithelial cells.

45. Graber, I.G. and S. Sevitt. Renal function in burned patients and its relationship to morphological changes. J. Clin. Path. 12:25, 1959.

Here more complete data are presented in an attempt to show that:

1) Considerable "tubular function" still exists even in the oliguric patient.

2) GFR, as measured by endogenous creatinine clearance is always markedly reduced and increases only slowly during the diuretic phase; and

3) The primary lesion may well be a glomerular lesion characterized by only minor morphologic changes.

46. Price, J.D.E. and R.A. Palmer. A functional and morphological follow-up of acute renal failure. Arch. Int. Med. 105:90, 1960.

Some 14 patients were studied from 4 weeks (1 case) to 7 years (1 case) after acute tubular necrosis. Again found continued slight depression in renal clearance studies. In 8 patients renal biopsies were done, and the authors attempt to show persistent glomerular and tubular lesions. They feel that the glomerular lesions, in ischemic renal failure, may be the cause of oliguria. Tubular lesions alone are the cause in nephrotoxic nephritis.

47. Finckh, E.S., Jeremy, D. and H.M. Whyte. Structural renal damage and its relation to clinical features in acute oliguric renal failure. Quart. J. Med. 31:429, 1962.

This paper stresses the paucity of morphologic findings in the kidneys of patients dying of acute tubular necrosis. They state that very similar findings are seen in kidneys from routine autopsy material and thus believe that the lesions may have nothing to do with renal failure. (From transplant studies using cadaver kidneys it appears that death itself may often produce tubular necrosis both histologically and clinically).

REFERENCES (Continued)

Physiology

48. Selkurt, E.E. Renal blood flow and renal clearance during hemorrhagic shock. Am. J. Physiol. 145:699, 1946.

Renal blood flow was directly measured in one kidney during hemorrhage and shock and in some dogs after recovery. When blood pressure was 60 mm Hg RBF was about 40% of normal. When blood pressure was 40 mm Hg direct measured RBF was about 11% of control. At this point clearances (creatinine and PAH) were zero as the dog was anuric. With re-infusion of blood, direct RBF rather quickly returned but clearance returned slowly or not at all suggesting to the author that a tubular lesion had occurred allowing back-diffusion.

49. Sirota, J.H. Carbon tetrachloride poisoning in man. I. The mechanism of renal failure and recovery. J. Clin. Invest. 28:1412, 1949.

Measurements in humans disclosed RBF and GFR extending well into the diuretic phase. The author believed that a large part of the oliguria, however, was due to back-diffusion of filtrate. The use of PAH clearance to measure RBF is open to considerable question. See following references.

50. Bull, G.M., Joekes, A.M. and K.G. Lowe. Renal function studies in acute tubular necrosis. Clin. Sci. 9:379, 1950.

This important paper presents data on 34 patients. Renal plasma flows were measured daily during the oliguric phase by means of the Fick principle using PAH. All were low (about 10% of normal); moreover, O_2 saturation in the renal venous blood was low (65-75%). These data lead the authors to conclude that there was no significant intrarenal shunting of blood, i.e., no Trueta shunts. However, the blood flow measurements are open to question; too low.

It was in this paper that the term "Acute Tubular Necrosis" was first used.

51. Conn, H.L., Jr., Wilds, L. and J. Helwig. Study of renal circulation, tubular function and morphology, and urinary volume and composition in dogs following mercury poisoning and transfusion of human blood. J. Clin. Invest. 33:732, 1954.

From arteriography studies in dogs with damaged renal function as a result of mercury or human blood, these authors could not see any intrarenal shunts. This is used by many as one of the key points against the theory of juxtamedullary shunting in the kidney.

By means of a N_2O method, renal blood flow was measured in these dogs and found decreased (by 50%) only in the two anuric dogs (was normal in the oliguric dogs). These measurements more reliable than PAH clearance.

52. Brun, C., Crone, C., Davidsen, H.G., Fabricius, J.T., Hansen, A., Lassen, N.A. and O. Munch. Renal blood flow in anuric human subject determined by use of radioactive Kryptom 85. Proc. Soc. Exp. Biol. and Med. 89:687, 1955.

Physiology (Continued)

Using K_r^{85} and the Fick principle, renal blood flows were estimated in 4 anuric patients (biopsy confirmed tubular necrosis). By this method blood flow varied from 60 to 360 cc/100 gm/min. Normal 200 to 400 cc/100 gm/min. Thus, RBF is not necessarily reduced to the very low values found by PAH clearances.

53. Goldberg, M. Studies of the acute renal effects of hemolyzed red blood cells in dogs including estimations of renal blood flow with Krypton 85. J. Clin. Invest. 41:2112, 1962.

In these studies oliguria was produced acutely by means of intra-aortic injections of hemolyzed RBC without a measured decrease in the Krypton measured renal blood flow. Shunts were ruled out by the failure to observe A-V O_2 changes across the kidney. Concluded that the oliguria was the result of pigment and/or cellular casts within the tubule.

54. Walker, J.G., Silva, H., Lawson, T.R., Ryder, J.A. and S. Sheldon. Renal blood flow in acute renal failure measured by renal arterial infusion of indocyanine green. Proc. Soc. Exp. Biol. and Med. 112:932, 1963.

Renal blood flow was measured in 8 patients with acute tubular necrosis. There was an average reduction to 40% of normal. Renal O_2 uptake was not significantly altered from normal.

55. Trueta, J., Barclay, A.E., Daniel, P.M., Franklin, K.G. and M.M.L. Prichard. Studies of the Renal Circulation, Oxford, Blackwell, 1947.

In this book evidence for a shunt circulation in the mammalian kidney (rabbit and man) is given. The suggestion was made that this cortical to medullary shunt might be important in the genesis of tubular necrosis. Modern evidence suggests that it is not but also suggests that it may play a role in bilateral acute cortical necrosis and that the juxtamedullary glomeruli (nephrons) described by this group may have important roles in regulating normal renal function, e.g., sodium reabsorption and excretion-volume control.

56. Clark, J.K., Barker, H.G. and A/P. Crosley, Jr. Evidence against renal vascular shunts in a case of lower nephron nephrosis. Amer. J. Med. 9:268, 1950.

In a single patient, oliguria following a blood transfusion, these authors measured the arterial and renal venous oxygen contents (as well as creatinine, PAH, mannitol). Since there appeared to be no arterialization of the renal venous blood they concluded that the Trueta juxtamedullary shunt was not operative in producing oliguria. (See Ref. 51).

57. Dunn, J.S., Haworth, A. and N.A. Jones. The pathology of oxalate nephritis. J. Path. and Bact. 27:299, 1924.

These authors, on the basis of studies in rabbits, concluded that the oliguria incident to proximal tubule injury caused by oxalate injection was due to the back-diffusion of tubular fluid and the formation of high interstitial pressure which could collapse blood vessels.

Physiology (Continued)

58. Richards, A.N. Direct observations of change in function of the renal tubule caused by certain poisons. Trans. Assoc. Amer. Phys. 44:64, 1929.

From direct micropuncture studies in the frog single tubule it was found that filtration continues after $HgCl_2$ poisoning, but that the fluid diffused out of injured tubules. Thus, oliguria was caused by back-diffusion of tubule contents.

59. Marshall, D. and W.S. Hoffman. The nature of the altered renal function in lower nephron nephrosis. J. Lab. and Clin. Med. 34:31, 1949.

On the basis of clearance studies in patients with acute tubular necrosis these authors concluded that blood flow is markedly decreased during the oliguric phase and that the low urine volume was the result of back-diffusion from the lumen of the "damaged lower nephron". Although their conclusion may still be nearly correct, their data appears overinterpreted. PAH clearances are certainly open to question.

60. Chesley, L.C. and W.H. McCaw. A physiologic study of acute renal failure with follow-up observations. Am. J. Obstet. and Gynec. 62:1187, 1951.

Report of 25 cases, 11 of which were associated with placenta abruptio. From clearances of urea and inulin or creatinine measured simultaneously the authors conclude that early in the course there is evidence for some back-diffusion through damaged tubules. After about 10 days, however, oliguria cannot be explained on this basis alone and is the result of continued low renal blood flow and glomerular filtration.

61. Meroney, W.H. and M.E. Rubini. Kidney function during acute tubular necrosis: Clinical studies and theory. Metabol. 8:1, 1959.

On the basis of urine Na, K, and Na concentration in 7 patients during early and late oliguria these authors propose that urine produced during the oliguric periods is coming from a few normally functioning nephrons. Unlike so often is stated, the urine does not represent an ultrafiltrate of plasma but rather contains less Na^+, more K^+ and N_2. They further believe that oliguria is the result of blockage of tubules by cellular debris and interstitial edema. They doubt the back-diffusion hypothesis mainly on the basis of divergent healing times.

62. Baker, S.L. and E.C. Dodds. Obstruction of the renal tubules during the excretion of hemoglobin. Brit. J. Expt. Path. 6:247, 1925.

First presentation of the concept of toxic casts causing renal failure. (See Ref. 53).

63. Eggleton, M.G., Richardson, K.C., Schild, H.C. and Winton, F.R. Renal damage due to crush injury and ischemia of the limbs of the anesthetized dogs. Quart. J. Expt. Physiol. 32:89, 1943.

Studied crush injury nephrosis in dogs subjected to traumatic muscle necrosis.

1) Few histologic lesions in the kidney were identified by the authors.

2) Could maintain urine flow by I.V. injections of hypertonic NaCl, $NaHCO_3$,

Physiology (Continued)

and Na_2SO_4 if begun before crush injury.

Perhaps the first mention of diuretic phophylactic therapy.

64. Van Slyke, D.D., Phillips, R.A., Hamilton, P.B., Archibald, R.M., Dole, V.P. and K. Emerson, Jr. Effect of shock on the kidney. Trans. Assoc. Amer. Phys. 58:119, 1944.

Describes experiments in dogs:

1) Momentary clamping of the renal artery results in cessation of urine flow with immediate resumption of urine flow when artery is released.

2) Clamped renal artery for 2-3 hours produces renal insufficiency of 2-4 days duration.

3) Clamping over 4 hours results in death (uremia) in 7 to 8 days.

Concludes: Shock of any kind reduces renal blood flow. Therefore, the development of renal failure is dependent on the length of time of shock.

65. Phillips, R.A., Dole, V.P., Hamilton, P.B., Emerson, K. Jr., Archibald, R.M. and D.D. Van Slyke. Effects of acute hemorrhage and traumatic shock on renal function of dogs. Am. J. Physiol. 145:314, 1945.

The hemorrhagic shock produced in these dogs was for the most part not reversible. It is doubtful that the renal impairment produced had much in common with clinical tubular necrosis. It is also apparent that clamping the renal artery for 2-4 hours produced cortical necrosis, not tubular necrosis.

66. Murphy, G.P. and J.A. Gagnon. Renal alterations in dogs during renal arterial constriction, hemorrhagic hypotension and osmotic diuresis. J. Surg. Res. 5:11, 1965.

No morphologic changes in the kidneys of dogs subjected to hemorrhagic shock sufficient to reduce GFR by 80% for a prolonged period (5 hours).

67. Powers, S.R. Jr., Baba, A., Shioya, N. and A.A. Stein. Experimental studies on acute renal tubular degeneration following crush injury. Surg. Forum 9:62, 1959.

Produced graded trauma to leg of dogs sufficient to change renal blood flow without any change in systemic blood pressure. Renal blood flow was measured by a direct method. Trauma resulted in a fall of renal blood flow with an increased O_2 extraction which was sufficient to keep O_2 consumption normal. Dogs subjected to trauma showed "extreme but patchy" hydropic degeneration of tubular epithelium, most marked in the distal nephron. Prolonged oliguria with recovery in some dogs suggests that a true clinical tubular necrosis was produced.

68. Sims, E.A.H., Goldberg, H.I., Kelly, J.R. and B. Sisco. Glomerular profusion during acute renal insufficiency from mercury poisoning in rat. J. Lab. Clin. Med. 54:440, 1959.

Physiology (Continued)

Rats were given subcutaneous mercuric chloride which produced oliguria or anuria in the majority of rats. These were studied by means of the Schlegel technic (injection of a fluorescent dye) in order to see glomerular blood flow. Flow in glomeruli in these animals appeared similar to that seen in normal control animals thus suggesting continued RBF and GF during oliguria and anuria.

69. Flanigan, W.J. and D.E. Oken. Renal micropuncture study of the development of anuria in the rat with mercury-induced acute renal failure. J. Clin. Invest. 44:449, 1965.

From this micropuncture study it was concluded:

1) Interstitial edema played no significant role in producing oliguria.

2) Obstruction of tubules by casts occurred only after tubular flow had markedly decreased, thus was a result of oliguria, not a cause.

3) The primary event in oliguria appeared to be a reduction in GFR. This was not due to hypotension. Possible causes:

a) pre-glomerular construction; b) post glomerular dilatation, or c) pre-glomerular shunting.

70. Arce, M.L., Wilson, D.R. and D.E. Oken. Micropuncture study of myohemoglobinuric acute renal failure in the rat. Clin. Res. 13:300, 1965 (abstract).

Studies similar to those of the previous reference were carried out using myoglobin as the nephrotoxin. Results and conclusions similar to thos reported with mercury were given.

71. Litwin, M.S., Walter, C.W. and N. Jackson. The experimental production of acute renal tubular necrosis in dogs. Surg. Forum 10:370, 1959.

Acid hematin alone in moderate amounts does not produce pathology. However, acid hematin on a background of dehydration, renal vasoconstriction, or renal ischemia all produced varying grades of tubular necrosis or oliguria. After 30 minutes of renal ischemia (a procedure that does not produce damage) the injection of 0.5 gm/Kg body weight acid hematin produced tubular necrosis in all dogs.

Gram negative bacteria produce renal failure only if refractory hypotension is produced in conjunction with hind leg trauma. Thus, blood and/or muscle pigments may play an important role.

72. Mason, A.D., Alexander, J.W. and P.E. Teschan. Studies in acute renal failure: I. Development of a reproducible lesion in experimental animals. J. Surg. Res. 3:430, 1963.

These authors felt that previous methods used in experimental renal failure were unpredictable and, therefore, made meaningful studies of prevention and therapy difficult. Here they describe a method of pigment nephropathy (oxidized hemoglobin) which can be graded with respect to incidence, severity, and mortality.

Physiology (Continued)

73. Teschan, P.E. and A.D. Mason. Studies in acute renal failure. II. Incidence, mortality, urinary and plasma chemical alterations and clinical characteristics of reversible acute renal failure in the rat. J. Surg. Res. 3:442, 1963.

74. Mason, A.D., Teschan, P.E. and E.E. Muirhead. Studies in acute renal failure. III. Renal histologic alterations in acute renal failure in the rat. J. Surg. Res. 3:350, 1963.

These two papers (73,74) describe in detail the results that may be obtained with this method of producing acute renal failure in the rat.

75. Teschan, P.E. Acute renal failure: The cycle of military medical research from combat zone to laboratory and return. Mil. Med. 130:1165, 1965.

This is an excellent summary of Teschan's work on experimental acute renal failure, and describes the problems existing still in the clinical care of patients with acute tubular necrosis. Of most interest are the data presented that show, that on the one hand, mannitol does not increase RFB in the shocked oliguric animal and on the other hand, that mannitol can decrease the incidence of renal failure in the experimental model if given early enough after the nephrotoxic stimulus. Of interest is the observation that mannitol is singularly effective over urea, dextrose and saline.

76. Finckh, E.S. The pathogenesis of uremia in acute renal failure. Abnormality of intrarenal vascular tone as possible mechanism. Lancet 2:330, 1962.

1) Tubular obstruction - too few.

2) Tubular necrosis - seldom widespread - furthermore says he has data that necrotic epithelial cells lead to increased urine flow.

3) Interstitial edema - only scattered. No pressure increase can be measured. Edema does not collapse tubules or blood vessels.

Therefore concludes that change in vascular tone (probably reduction in tone of the post glomerular vessels, i.e., efferent arteriole or veins) is the cause of anuria and oliguria and continues throughout oliguric phase and into the diuretic phase of the disease.

77. Kountz, S.L., Tuttle, K.L., Coh, L.H., Eschelman, L.T. and R. Cohn. Factors responsible for acute tubular necrosis following lower aortic surgery. J. Amer. Med. Assoc. 186: 447, 1963.

In dogs, showed that in order to produce renal damage by means of intrarenal aortic cross-clamping, renal ischemia must occur at the same time. Renal ischemia may be the result of hemorrhage, as in this study, or salt depletion. (See also Ref. 30).

78. LeBrie, S.J. and H.S. Mayerson. Influence of uranium nitrate-induced nephrosis on flow and composition of renal lymph. Physiologist. 3:103, 1960.

Physiology (Continued)

Uranium distal tubular damage was produced in dogs. By direct measurement it was shown that the capsular lymph flow in these dogs was 15 times greater than in normal control dogs.

79. De Wardener, H.E. Intrarenal pressure in experimental tubular necrosis. Lancet 1: 580, 1955.

Necrosis was produced in dog kidneys by clamping the renal artery for 3-4 hours. Several days later the intrarenal pressures were measured. No significant increase or decrease in intrarenal pressure was found. (This was not, of course, true acute tubular necrosis).

80. Parry, W.L., Schaefer, J.A. and B.C. Mueller. Experimental studies of acute renal failure. I. The protective effect of mannitol. J. Urol. 89:1, 1963.

Rats were made oliguric by the method of Mason and Teschan (See Ref. 72). In 214 rats not treated with mannitol mortality was 93.5%. In 87 rats given mannitol (0.3 gm/Kg B.W.) immediately after injecting methemoglobin the mortality was 1.1%.

81. Menefee, M.G., Mueller, C.B., Miller, T.T., Myers, J.K. and A.L. Bell. Experimental studies in acute renal failure. II. Fine structure changes in tubules associated with renal failure induced by globin. J. Exp. Med. 120:1139, 1964.

Human globin was injected into rats. Small amounts are taken up by proximal tubular cells without apparent damage. Larger amounts overwhelm proximal uptake and allow globin to pass to the thick ascending limb and distal tubules where even minor uptake appears to damage cells. Finally, plugs of globin appear in lower nephrons and at that time proximal cells appear damaged, perhaps by back pressure.

A high rate of urine flow, brought about by any means will prevent absorption of globin by the distal nephron and therefore prevent renal damage. (Mannitol may be more effective than water diuresis).

82. Lowe, K.G., Moodie, G. and M.B. Thomson. Glycosuria in acute tubular necrosis. Clin. Sci. 13:187, 1954.

By chromatographic methods these authors found a small amount of glucose in urines from 5 oliguric patients with acute tubular necrosis. It represented a higher concentration of glucose than found in urines of normal subjects or patients with other forms of acute or chronic renal disease. Concluded that, in acute tubular necrosis, bladder urine, in part at least, has passed through damaged tubules.

83. Emslie-Smith, Johnstone, J.H., Thompson, M.B. and K.G. Lowe. Amino-aciduria in acute tubular necrosis. Clin. Sci. 15:171, 1956.

In 2 patients, rather unconvincing evidence of increased amino acid excretion is given. In other studies, amino aciduria has not been found.

84. De Luna, M.B., Metcalfe-Gibson, A. and O. Wrong. Urinary excretion of hydrogen-ion in acute oliguric renal failure. Nephron 1:3, 1964.

Physiology (Continued)

The pattern of acid excretion (measured urine pH and NH_3 excretion) in 6 patients with tubular necrosis was abnormal and fit most closely with findings in chronic renal disease. Suggested that urine in the oliguric phase is derived from a few normal tubules subjected to hyperperfusion.

85. MacLean, P.R. and J.S. Robson. Unselective proteinuria in acute ischaemic renal failure. Clin. Sci. 30:91, 1966.

Studies of urine protein in 6 patients with tubular necrosis disclosed that all plasma proteins were represented. This unselectivity of excreted protein is unlike the proteinuria of chronic renal disease with glomerular lesions. The authors conclude, therefore, that urine protein is present because of failure of tubular reabsorption (tubular lesion) and is not the result of a glomerular lesion.