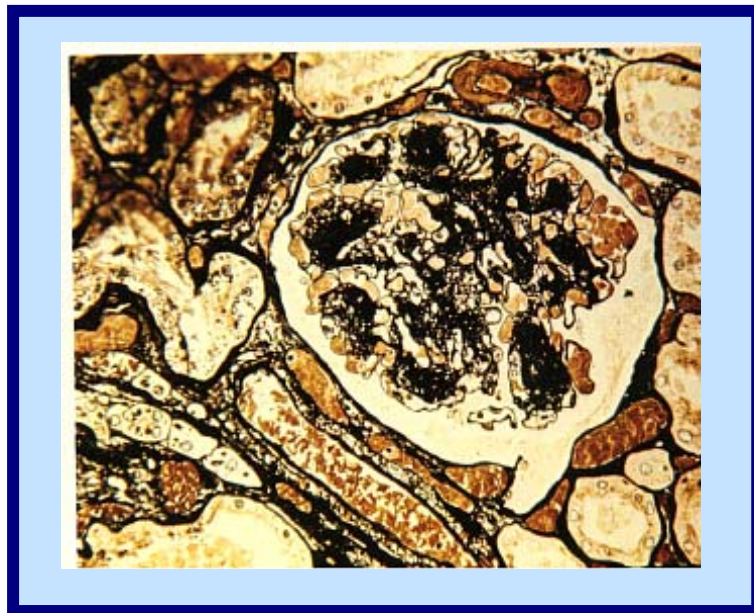


ESSENTIALS OF CLINICAL NEPHROLOGY

Edited by

Mohamed A. Sobh

Professor and Head of Nephrology Department
Urology and Nephrology Center,
University of Mansoura, Mansoura, Egypt.



Dar El Shorouk

**Essentials
Of
Clinical Nephrology**

Essentials of Clinical Nephrology

This is a 422 page book with 47 coloured pathology photographs and 27 coloured illustrations.

This book could be considered practical, applicable and concised guide in nephrology, expressing the international and the local experience. It contains 16 chapters with references for suggested readings up to the year 1999.

This book is written to cover the needs of the nephrology trainees and specialists and those in the field of internal medicine. Also, medical students will find it easy to go through this book and collect informations fitting to their requirements.

© 2000 Dar El Shourouk, All Rights Reserved.

No part of this book may be reproduced in any form or by any means, electroonic or mechanical by an information storage and retrieval system, without written permission from the publishers.

This book is for educational and reference purposes only.

First Edition, 2000.

Revenues of this book are donated to
Mansoura Orphan Institution.

Published by:

Dar El Shorouk

8, Sebawieh Al masry, Nasr City, Cairo, Egypt

P.O. Box: 33 Panorama

Tel.: +202 4023399 - Fax: +202 4037567

email: dar@shrouk.com

Cover & Internal Design:

Hisham Howaidy

Printing & Color Separation:

Shorouk Press

ISBN:

1-1887165-11-8

Essentials Of Clinical Nephrology

Edited by:

Mohamed A. Sobh

Professor and Head of Nephrology Department,
Urology and Nephrology Center,
University of Mansoura, Egypt.

Dar El Shorouk

Dedication

To the soul of my dear father

To my dear mother

To my lovely wife, and

To my children.

ACKNOWLEDGEMENT

Professor Jacob Churg, USA and IGAKU-SHOIN Medical Publishers, Inc Japan are acknowledged for granting a permission to reproduce some of their histopathology figures. Also, Novartis, Egypt, is acknowledged for facilitating the permission to reproduce some of Frank Netter's illustrations (The Netter Collection of Medical Illustrations, Vol. 6, illustrated by M.D. all rights reserved).

The gratitude is for Dr. Fatma El-Husseini, professor of pathology for providing some of her pathology figures. Dr. Tarek El-Diasty, consultant radiologist, is acknowledged for providing the radiology figures. The valuable help provided by Dr. M. Ashraf Foda, Dr. Ahmed Donia and Dr. Mahmoud Mohasseb is highly appreciated.

The clever secretarial work of Mrs. Hend Sharaby and Heba Zaher are greatly acknowledged.

FOREWARD

Although this country is plagued by the highest prevalence of renal disease worldwide, only very few Egyptian nephrologists have attempted to write a book on renal medicine. The dream has always been there, but the major barrier was the pain it takes to produce a work that competes with the plethora of excellent international textbooks and monographs.

No wonder that Mohamed Sobh pioneered the challenge, as he has always done. I have admirably witnessed this young man's progress over the years since he had made one of his earliest contribution in the first Egyptian Society of Nephrology in 1980. His star continued to shine in the horizons of renal medicine until he became one of the best known in Africa and the Arab world, while at home he became the Professor and Chief of Nephrology in renowned Mansoura University. He published a lot on basic renal physiology, schistosomal nephropathy and renal transplantation among many other topics. In addition, he was the author or co-author of a number of excellent monographs published in Egypt and abroad. He made outstanding presentations in a lot of local and international conferences, and received many awards of great honor.

Despite his academic interests, Professor Sobh has a vast clinical experience, which enriches this book. In over 400 pages he intelligently mixes theory with practice, bench with bedside, and international with local experience. He offer the post-graduate student the long-awaited practical an applicable concise guide in nephrology.

I confidently promise the reader a most enjoyable cruise through the very well written and carefully illustrated chapters of the book.



Professor Rashad Barsoum
MD, FRCP, FRCPE
Professor and Head of Department of
internal Medicine, Cairo University.
President of The Egyptian
Society of Nephrology and the
Arab Society of Nephrology
and Renal Transplantation.
Secretary General of the International
Society of nephrology

The Author

Dr. Mohamed A Sobh, MD, FACP
Professor and Head of Nephrology
Department, Urology and Nephrology
Center, University of Mansoura, Egypt.



Professor Sobh was graduated in 1973. He obtained his MSc in 1977 and the MD in 1982. Both are in Internal Medicine from Mansoura Faculty of Medicine.

In 1978, he passed the ECFMG exam and was affiliated to the residency training program in the Nephrology Department in Sherbrooke University, Quebec, Canada. Since his return in 1982, he has hold the responsibility of organizing the Nephrology activity in Mansoura University Hospital.

In 1982 he was promoted as lecturer of Internal Medicine and was then assigned as the head of the Nephrology Department in the Urology and Nephrology Center, Mansoura University. In 1993, he obtained the title of a full Professor in Medicine; and the title of Professor of Nephrology.

So far, Professor Sobh has 20 MDs and PhDs candidates in addition to 38 Masters; both in Nephrology and Internal Medicine. He also published more than 75 papers in the different International journals of Nephrology.

Prof. Sobh was elected as a member in The American College of Physicians in 1996; then as a fellow in the following year. He is also a member of the Egyptian, African, Arab, European and The International Societies of Nephrology.

Prof. Sobh was honoured several times. He was awarded the National Encouragement Prize for medical sciences in 1987; Mohamed Fakhry prize for the most distinguished research in Internal Medicine, (awarded by the Egyptian Academy of Research and Technology) in 1987; the Jordan Prize of Abd El-Hamid Shoman for the Arab Scientists in The Clinical Medical Sciences in 1988; and The Arab Prize for the most distinguished Medical Research, (awarded by the President of the Algerian Republic) in 1993.

CONTENTS

Forward	i
The author	ii
PART I: RENAL FUNCTIONS AND STRUCTURE	
• Kidney functions	1
• Anatomy of the kidney	9
• Anatomic physiology	19
PART II: INVESTIGATIONS FOR KIDNEY DISEASES	
• Biochemical investigations	25
• Microbiological examination of urine	32
• Immunological tests	33
• Radiologic examination	34
PART III: GLOMERULAR DISEASES	
• Pathogenesis of glomerulonephritis.....	53
• Classification of glomerulonephritis.....	57
• Nephrotic syndrome	63
• Acute post-streptococcal glomerulonephritis	69
• Primary glomerulonephritis.....	71
• Lupus nephritis	80
• Renal involvement in vasculitis	84
• Henoch-Schönlein purpura	85
• Essential mixed cryoglobulinaemia	87
• Progressive systemic sclerosis	88
• Diabetic nephropathy	88
• Alport syndrome	92
• Fabry's disease.....	93
• Nail-patella syndrome	95
• Bacterial endocarditis	95
• Shunt nephritis	96
• Malarial nephropathy	96
• Schistosomal nephropathy	98
• Glomerulopathy secondary to virus infections	104
• Treatment of glomerulonephritis.....	108

PART IV: VASCULITIS

- Classification 113
- Polyarteritis nodosa 114
- Wegener's granulomatosis 117
- Churg-Strauss syndrome 118
- Temporal arteritis 120
- Takayasu's arteritis 121
- Relapsing polycondritis 121
- Goodpasture's syndrome 122
- ANCA and vasculitis 125

PART V: THROMBOTIC MICROANGIOPATHY..... 127

PART VI: ACUTE RENAL FAILURE 133

PART VII: CHRONIC RENAL FAILURE:

- Definitions 147
- Etiology 148
- Pathophysiology 150
- Clinical features 158
- Investigations 164
- Management 164
- Dialysis 169
- Transplantation 1

PART VII: RENAL TUBULAR DISORDERS

- Renal glycosuria 185
- Amino acids tubular transport defects 186
- Renal tubular acidosis (RTA) 187
- Nephrogenic diabetes insipidus 193
- Water retention 195
- Cystinosis 195
- Wilson's disease 196
- Oxalosis 196
- Bartter's syndrome 197
- Vitamin D resistant rickets 197
- Pseudohypoparathyroidism 198
- Fanconi syndrome 198

PART IX: TUBULAR AND INTERSTITIAL DISEASES

- Interstitial nephritis..... 201
- Analgesic nephropathy..... 205
- Reflux nephropathy..... 209
- Pyelonephritis..... 212
- Urinary tuberculosis 218

PART X: RENAL CYSTIC DISEASES

- Classification of renal cystic diseases 231
- Autosomal dominant polycystic kidney diseases 231
- Autosomal recessive polycystic kidney diseases..... 234
- Medullary cystic kidney diseases 236
- Medullary sponge kidney 236
- Acquired renal cystic diseases 238
- Tuberous sclerosis 239
- Von Hippel-Lindau syndrome 239
- Simple renal cysts..... 239

PART XI: RENAL STONE DISEASES 241

PART XII: WATER AND ELECTROLYTE DISORDERS

- Disorders of plasma osmolality 247
- Disturbances of plasma sodium concentration 253
- Disturbances of plasma potassium concentration..... 256
- Disturbances of plasma calcium concentration..... 260

PART XIII: DISORDERS OF ACID-BASE BALANCE

- Physiology of acid-base system 265
- Metabolic acidosis 266
- Respiratory acidosis 269
- Metabolic alkalosis 270
- Respiratory alkalosis 271

PART XIV: HYPERTENSION AND THE KIDNEY

- Etiology and classification 273
- Essential hypertension 274
- Renovascular hypertension 286
- Ischaemic nephropathy 291

• Conn's syndrome	291
• Pheochromocytoma	292

PART XV: MISCELLANEOUS

• Proteinuria.....	295
• Haematuria	298
• Value of urine in medical diagnosis	301
• Polyuria and oliguria	302
• Renal manifestations of systemic diseases.....	309
• Renal diseases in hepatic patients	315
• Malignancy and the kidney	321
• Drugs and the kidney	333
• Kidney and the heart	345
• Kidney and the lung	348
• Renal diseases in the elderly	348
• Kidney in pregnancy.....	352

**PART XVI: ENVIRONMENTALLY-INDUCED KIDNEY
DISEASES**

359

RENAL FUNCTIONS AND STRUCTURE

KIDNEY FUNCTIONS:

The function of the kidney is to keep the **internal environment** (internal milieu) of the body stable within the physiologic limits. This is achieved through the following functions:

1. EXCRETORY FUNCTION AND PRODUCTION OF URINE:

The production of urine from the blood perfusing the kidney occurs in two steps: the first is filtration of plasma in the glomerulus; and the second is selective reabsorption or excretion of various substances in the renal tubules. Through urine production there are: **1.** elimination of wastes (metabolic products, ingested toxins such as drugs). **2.** control of water balance (maintenance of total body water and plasma osmolarity), and **3.** control of electrolyte balance (sodium, chloride, calcium, phosphate, potassium, acid-base, magnesium and others). For more detail see anatomic physiology of the nephron, page 20.

2. REGULATION OF THE ACID-BASE BALANCE OF THE BODY:

When excess acids are released into the circulation (e.g. through metabolic process, acid intake, or respiratory failure), the kidney prevents acidosis (accumulation of H^+ and drop in pH) through different mechanisms such as:

- a. Excessive proximal tubular reabsorption of bicarbonate filtered from blood through the glomeruli. This reabsorbed bicarbonate will go through the blood and acts as a buffer to neutralize excess H^+ in the circulation ($H^+ + HCO_3 \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2$).
- b. Excessive consumption and excretion of H^+ by the renal tubules through the increase in the formation of ammonia and titratable acids (phosphates, sulphates and phenols).

In case of alkalosis (low H^+ concentration pH of body fluids), the kidney will compensate by increasing bicarbonate loss in urine. This compensation

occurs by increasing its reabsorption which will then lead to increase of H^+ in the blood through the reaction $H_2CO_3 \rightarrow H^+ + HCO_3^-$. Also formation of ammonia and secretion of titratable acids by renal tubules will decrease. This results in retention of H^+ in blood and tissue fluids with correction of alkalosis. In states of acidosis, in a patient with normal kidney, urine will be maximally acidic (less than 5.5) and in state of alkalosis the urine will be alkalotic.

3. HEMOPOIETIC FUNCTION:

Kidney has an important role in erythropoiesis in the bone marrow through secretion of erythropoietin.

Erythropoietin is a hormone of glycoprotein nature which regulates red blood cell development in the bone marrow. Ninety percent of erythropoietin is produced in renal cortex (by interstitial, tubular or endothelial cells). The main stimulus for erythropoietin secretion is tissue hypoxia, other stimuli are androgens, PGE, thyroid hormone and B-adrenergic agonists. Inability to secrete sufficient amount of erythropoietin as in chronic renal failure results in anaemia. In contrary, in conditions as renal artery stenosis, cystic kidney diseases and renal cell carcinoma, erythropoietin is secreted in excess resulting in polycythaemia (Erythrocytosis). Human recombinant erythropoietin is now commercially available for the treatment of anaemia in uraemic patients.

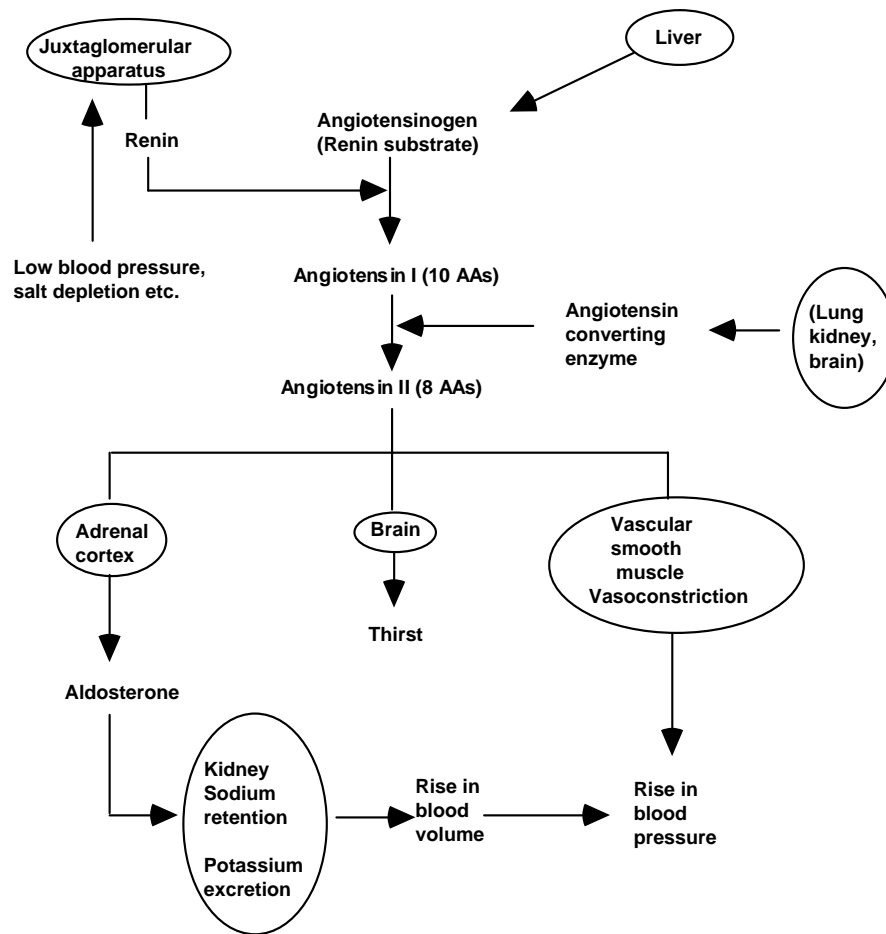
4. ENDOCRINE FUNCTIONS OF THE KIDNEY:

Many hormones and vasoactive substances are either formed, activated, or degraded by the kidney. Examples of these functions are:-

A- Hormones synthesized by the kidney:-

1. Renin (Fig. 1.1):

This is secreted by cells of the iuxta-glomerular apparatus (see page 18). Renin will act on a circulating protein (angiotensinogen) changing it into angiotensin I which is then converted by converting enzyme into angiotensin II which has a vasopressor activity and also stimulates suprarenal gland to secrete aldosterone. This system (Renin- Angiotensin- Aldosterone) is of great importance for the control of blood pressure and body fluid and electrolyte balance.

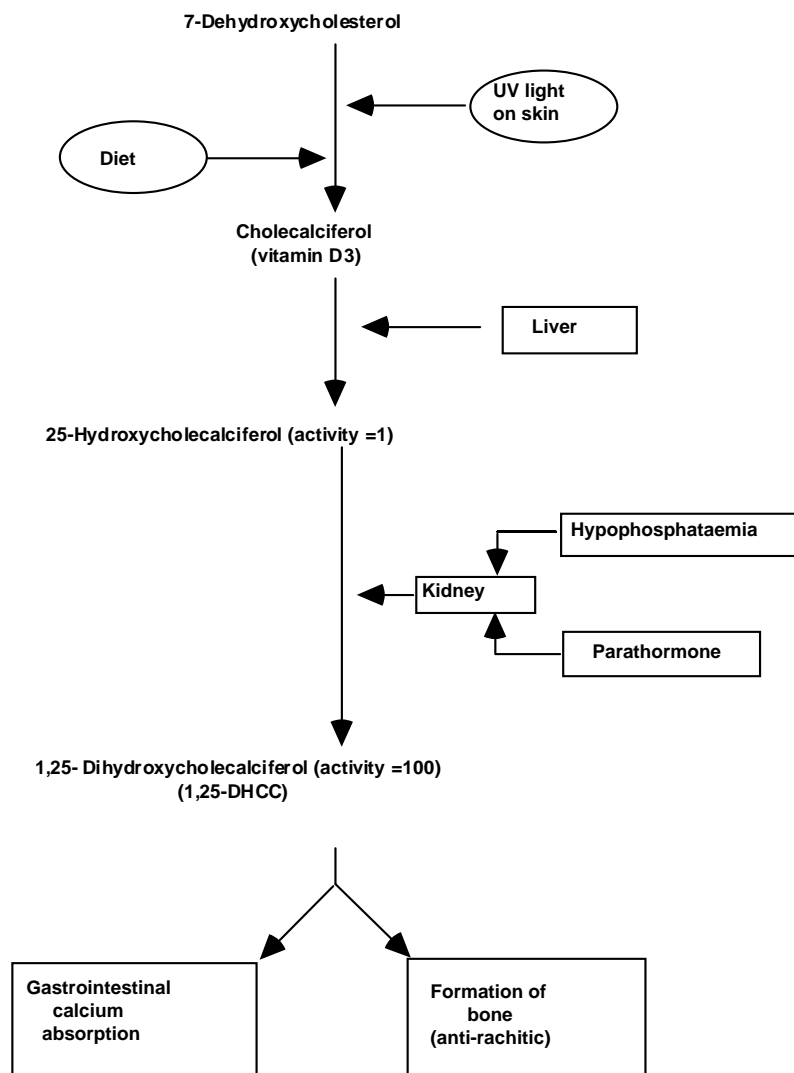


(Fig. 1.1)

The renin-angiotensin system and its interactions

2. Activation of vitamin D (Fig. 1.2):

Vitamin D reaching the body through oral intake or formed subcutaneously (by exposure to sun or ultraviolet rays) is biologically inactive. The activation of this vitamin occurs through hydroxylation (OH). The first step of hydroxylation occurs in the liver (25-OH- Vitamin D), whereas the second step occurs in the kidney (1, 25- (OH)₂ Vitamin D). The 1,25-dihydroxy vitamin D is 100 times as active as 25-hydroxy vitamin D.



(Fig. 1.2)

Activation of Vitamin D

Parathormone and hypophosphataemia are the main stimuli for renal production of 1,25- (OH)₂ vit.D.

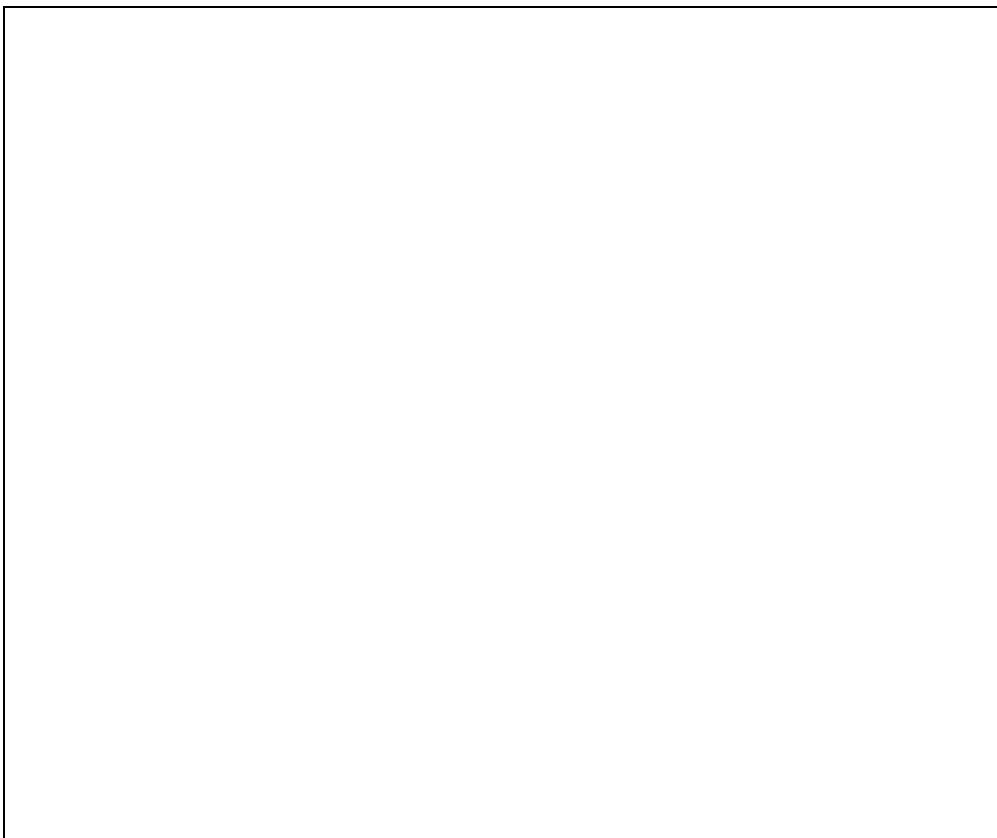
The exact site of synthesis is unknown, although the 1-hydroxylase enzyme is found in proximal tubular cells.

The major effects of vitamin D are to increase gastrointestinal calcium absorption and to promote normal bone calcification. Also vitamin D and its metabolites have important effects on skeletal muscle strength.

3. Prostanoids (Prostaglandins) (Fig. 1.3):

These are derived from oxidation of arachidonic acid and other polyunsaturated fatty acids and have great diversity of structure and biological effects. They are not strictly hormones, since they act in the organ in which they are produced. The term "autacoids" has been introduced to describe such locally acting agents. The kidney has enzymes to produce all known primary prostanoids, and appears to be able to adapt this process according to various circumstances.

Prostanoids may be divided into those with vasodilator, diuretic and antithrombotic effects (prostacyclin, PGE₂, PGD₂), and those with opposing actions (thromboxane).



(Fig. 1.3)

Production and function of different renal prostanoids

Renal actions of prostanoids.

1- Regulation of renal blood flow: The kidney contains both the vasodilator prostaglandins PGE₂, PGI₂, PGD₂ and the vasoconstrictor thromboxane.

When renal perfusion is compromised (e.g. dehydration or hypotension) the vasodilator prostanoids help to maintain renal blood flow. Accordingly, in such circumstances non-steroidal anti-inflammatory drugs (NSAIDs) can precipitate acute renal failure by inhibiting cyclo-oxygenase and thus vasodilator prostanoids production. The production of vasodilator prostanoids is most probably mediated through the high level of angiotensin II.

2- Effect on sodium excretion: Natriuretic prostanoids (e.g. PGE₂) act both directly on tubular cells and by enhancing renal perfusion. NSAIDs as antiprostaglandins have an antinatriuretic action which decreases the effect of thiazide diuretics and can precipitate cardiac failure in patients with heart disease.

3- Effect on water excretion: PGE₂ inhibits tubular effect of ADH (i.e. has diuretic action) while NSAIDs can potentiate the antidiuresis (i.e. water retention).

4- Interaction with the renin-angiotensin system. Prostanoids stimulate the release of renin from the juxta glomerular apparatus. Furthermore, local prostaglandins (particularly prostacyclin and PGE₂) decrease the vasoconstrictor effect of angiotensin II within the vascular pole of the glomerulus.

4. Kallikrein-Bradykinin:

Are vasodilator autacoids found particularly in renal cortex. Effects of kallikrein-kinin include: **1.** decrease the renal vascular resistance, particularly in low sodium states; **2.** augment renal sodium and water excretion; and **3.** activate prostaglandin synthesis and appear to have a role in complex interrelationships with other regulatory substances.

5. Erythropoietin:

(See above).

B- Peptide hormones degraded by the kidney:

The kidney removes many peptide hormones from circulation to be degraded by renal tubules. This removal may come through reabsorption from the glomerular filtrate (from inside) or through binding of the peptide to specific receptors in the basolateral tubular cell membrane.

1. Insulin:

Nearly 25% of insulin, pro-insulin and c-peptide are removed from circulation by the two mechanisms previously described. So, in diabetics insulin requirements often fall in end stage renal failure. On the other hand, uraemia may cause peripheral resistance to insulin with a consequent carbohydrate intolerance.

2- Parathormone (PTH):

About 30% of overall PTH metabolism occurs in the renal tubules. The intact hormone, c-terminal and amino-terminal are removed through glomerular filtration, while intact hormone and amino-terminal are removed from the peritubular circulation by binding to specific receptors. Elevated plasma PTH in uraemia is partially due to failure of its renal metabolism.

3- Prolactin:

Most prolactin metabolism is via renal (glomerular filtration) mechanism. Elevated prolactin levels are observed in 60% of uraemic patients suggesting deranged pituitary feedback as well. Probably this is responsible for gynaecomastia, galactorrhea, infertility and impotence in chronic renal failure.

4- Growth hormone:

The kidney removes 40-70% of growth hormone from circulation (glomerular filtration).

5- Vasopressin:

The kidney removes 30-50% of this hormone through glomerular filtration.

6- Glucagon:

About 30% of this hypoglycaemic hormone is renally excreted.

7- Gastrointestinal hormones:

Gastrin, VIP, and gastric inhibitory polypeptide are all partially renally excreted.

C- Hormones acting on the kidney:

- 1- Antidiuretic hormone (vasopressin):** ADH is produced by the cells of the supraoptic nucleus of the hypothalamus and is released from the posterior pituitary.

The major effects of ADH are: **(1)** it increases collecting tubule permeability to water allowing it to flow back to circulation. This leads to urine concentration and water retention; and **(2)** it causes vasoconstriction, leading to a rise in the arterial blood pressure.

Stimuli to secretion of ADH include: **(1)** decrease in effective blood volume, this triggers pressure sensors in cardiac atria, aortic arch and carotid sinuses. The response curve is exponential. Therefore, the volume stimuli override osmolar stimuli. By this mechanism decreased effective blood volume as in cirrhosis and cardiac failure results in excess secretion of ADH with water retention irrespective of the developing hyponatremia (dilution) and hypo-osmolality; **(2)** increase in plasma osmolality, sensitive osmoreceptors exist in the hypothalamus, and the response is linear. Sodium chloride is a powerful stimulant for secretion of ADH, while urea, glucose and ethanol are very weak stimulants; and **(3)** Many other stimuli, including nausea, hypoglycemia, high ambient temperature, anxiety and stress are also associated with release of ADH.

Synthetic analogues of ADH include the following : **(1)** 8-arginine vasopressin-AVP, which is available for parenteral or intranasal use in ADH deficiency; and **(2)** Desamino-D-arginine vasopressin (DDAVP) is a synthetic analogue which has increased antidiuretic but decreased vasoconstrictor effect compared with AVP.

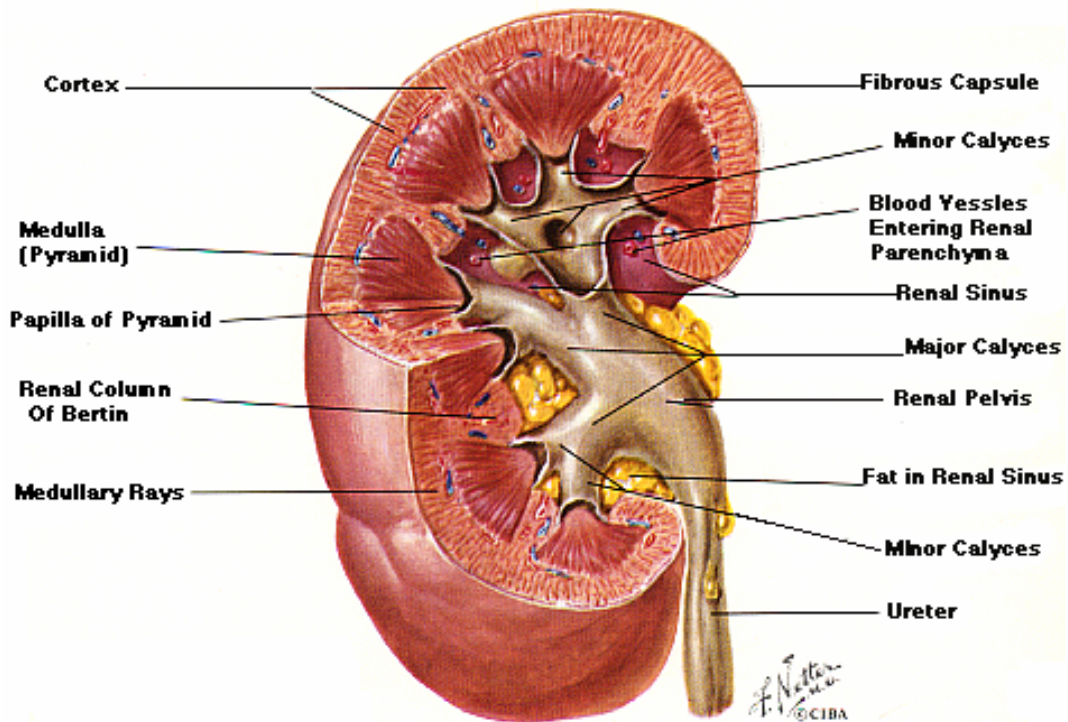
- 2- Atrial natriuretic peptide (ANP),** ANP is a 28 amino acid peptide which is released from granules in the cardiac atria in response to stretch. ANP has renal (diuretic and natriuretic) and hemodynamic (hypotensive) effects. It also has important hormonal actions such as suppression of renin and aldosterone.
- 3- Mineralocorticoids and glucocorticoids:** Aldosterone is a steroid hormone produced by the adrenal cortex in response to adrenocorticotrophic hormone, hyperkalaemia or angiotensin II. Its

main action is on the late distal tubule and the early collecting duct. It reduces excretion of sodium; and consequently increases excretion of potassium. Aldosterone excess can occur as primary phenomenon (Conn's Syndrome) or more commonly secondary to excess renin as in oedema states, renal artery stenosis and with malignant hypertension. Glucocorticoids at high doses have mineralocorticoid effects.

- 4- Dopamine:** Is released by renal nerves probably secondary to stimulation by baroreceptors. It causes renal vasodilatation and natriuresis mainly through stimulation of kallikrein-kinin system. It may be used in some cases of acute renal failure to maintain renal perfusion and urine output.

ANATOMY OF THE KIDNEY:

Each kidney is a bean-shaped structure measuring approximately 11 cm x 6 cm x 3 cm and weighing 120-170 grams in adult. The kidney is contained in a fibrous capsule. The hilum of the kidney which is present medially contains renal artery, vein, lymphatics and pelvis of the ureter. The kidney is contained in peri-renal fat. The kidney lies in the paravertebral gutter on the posterior abdominal wall retroperitoneally and opposite the twelfth thoracic down to the third lumbar vertebra. The right kidney is slightly lower than the left (liver effect), lower pole reaches one finger breadth above the iliac crest. **Figure 1.4** shows a longitudinal section of the kidney. It shows the hilum containing the renal vessels and pelvis of the ureter which branches inside the kidney into 2-4 major calyces, each of which in turn branches into several minor calyces. The kidney parenchyma is divided into outer cortex (1 cm thick) and inner medulla. The medulla is formed of 8-18 pyramids which are conical-shaped, with its base at cortico-medullary junction and its apex projects into minor calyces as papillae. The medullary pyramids are striated in shape. The cortex which is granular-looking may extend between pyramids forming columns of Bertini. Medullary rays are striated elements which radiates from the pyramids through the cortex.



(Fig. 1.4)

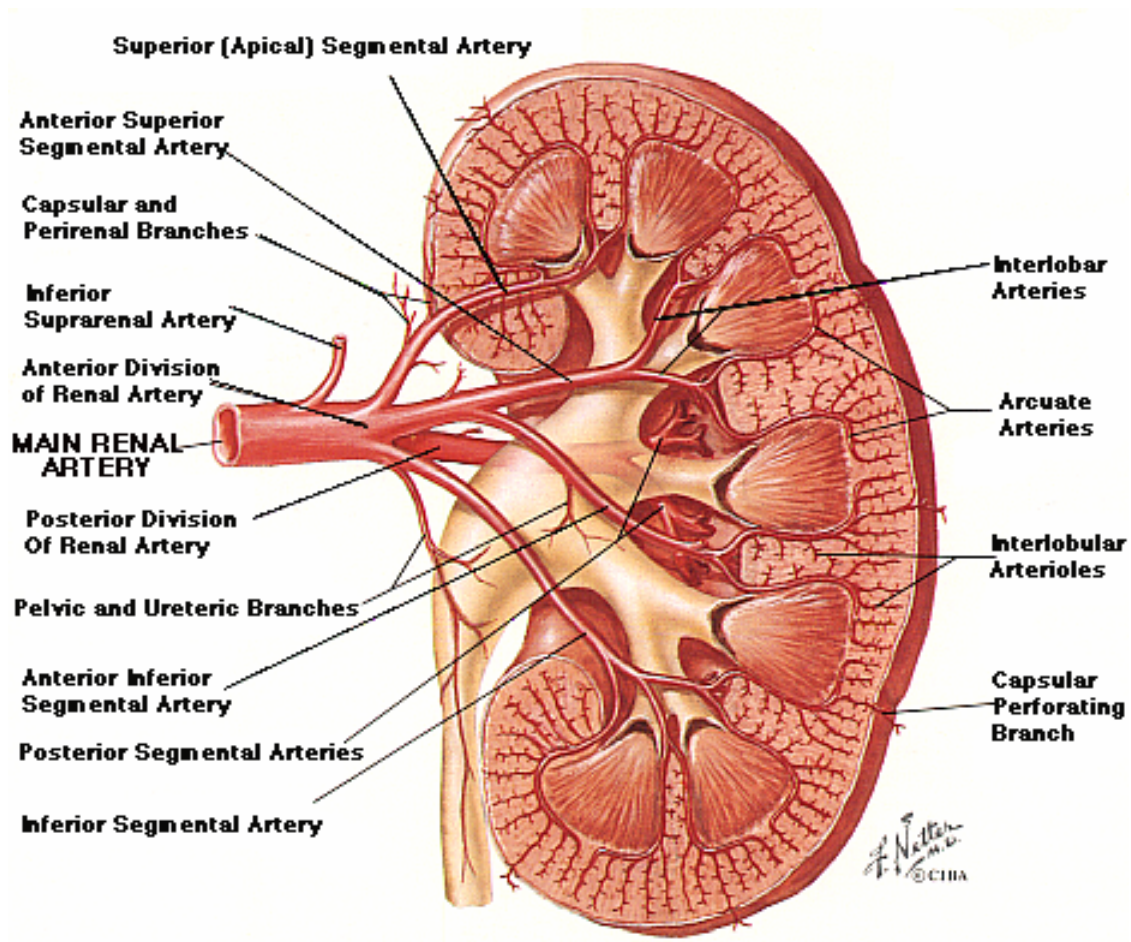
Right kidney sectioned in several planes exposing the parenchyma and renal sinus.

(Reproduced with permission from Novartis, Switzerland).

BLOOD SUPPLY OF THE KIDNEY:

The *renal arteries* arise from the aorta opposite the intervertebral disc L 1-2. In the hilum it gives anterior and posterior branches, which when penetrate the kidney tissue form *the interlobar arteries*, running between renal pyramids. At corticomedullary junction they turn to run along the base of the pyramids, forming the arcuate arteries and at 90° get out the *interlobular arteries (Figure 1.5)* which penetrate into the cortex and from them get the *afferent arterioles*. At the glomerulus, afferent arteriole invaginates the Bowman's capsule forming the glomerular tuft which is a modified capillaries structure from which glomerular filtrate gets out to the urinary space of Bowman's capsule. From the glomerulus the *efferent arteriole* gets out. Efferent arterioles of the outer and middle cortical glomeruli get down between tubules where they divide into capillary networks called peritubular capillaries. The efferent arterioles of the inner cortical glomeruli penetrate deeply into medullary pyramids forming *vasa recta* which share in the medullary counter current exchange system. The vasa recta vessels dip deeply into medullary pyramids, then make a hairpin turn returning to the corticomedullary junction.

- Renal venous system follows the same pattern as the renal arteries.
- Lymphatic vessels run in association with the blood vessels.
- The kidney receives sympathetic and parasympathetic fibers from the caeliac plexus.



(Fig. 1.5)

*Terminal branches of renal artery
(left kidney viewed from in front)*

(Reproduced with permission from Novartis, Switzerland).

REGULATION OF THE RENAL BLOOD FLOW (RBF) AND GLOMERULAR FILTRATION RATE (GFR).

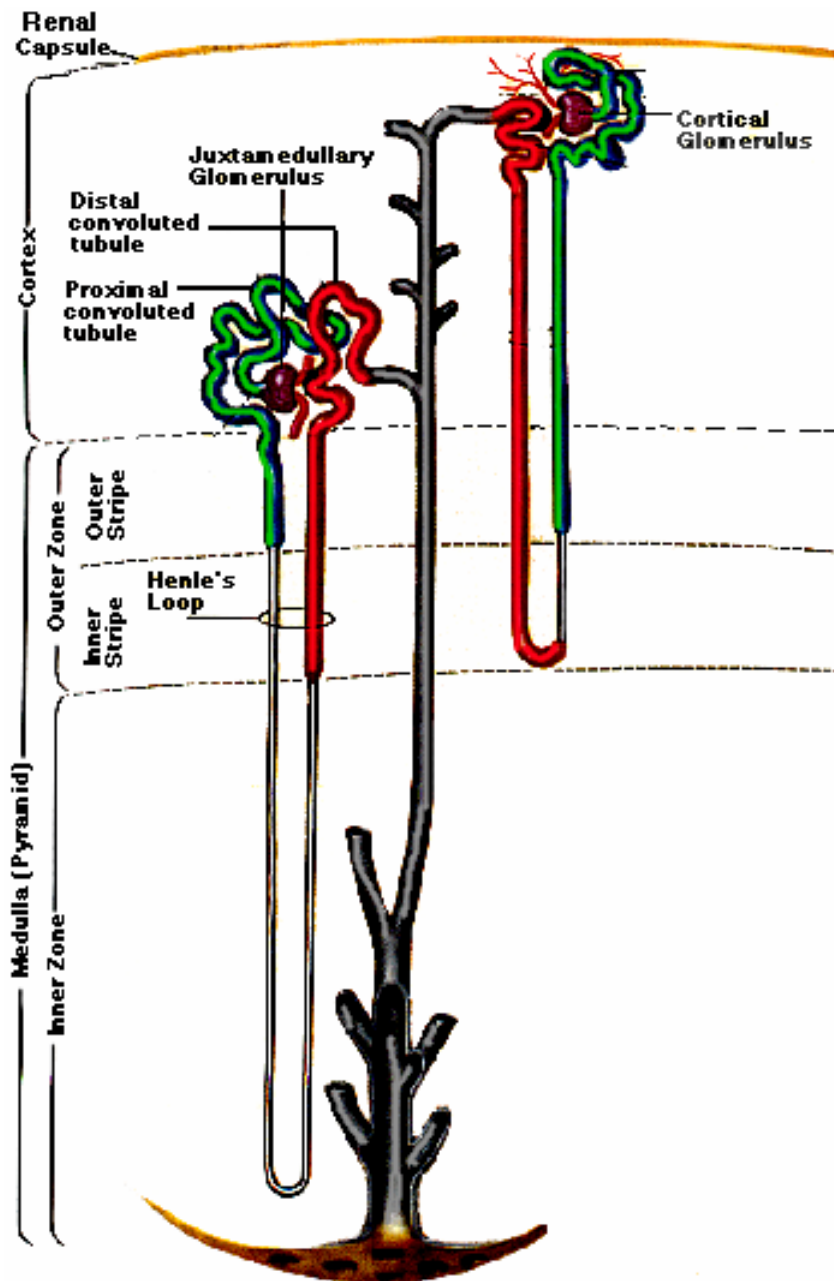
Normally the kidney receives 20-25% of the cardiac output. Extrarenal (prerenal) factors including blood pressure and circulating blood volume will affect RBF and GFR. When blood pressure or circulating blood volume decreases RBF and GFR decrease and vice versa.

Autoregulations of renal haemodynamics:

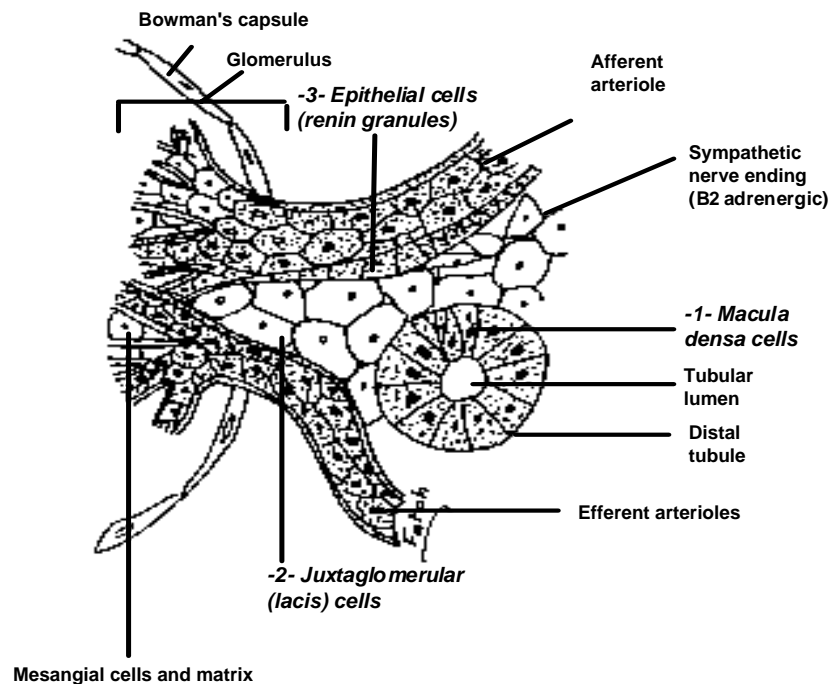
There are intrarenal mechanisms which control RBF and GFR to keep it within normal when there is a decrease in the renal perfusion pressure (e.g. hypotension). Of these are the Juxta-glomerular apparatus and the tone of the afferent and efferent arterioles. With hypotension or hypovolaemia renal blood flow and renal perfusion pressure decrease. This stimulates Juxta glomerular apparatus to secrete Renin which changes a circulating protein called Angiotensinogen into Angiotensin-I. This is changed by a converting enzyme into Angiotensin II, which causes spasm in the efferent arteriole, which will increase the intraglomerular pressure (filtration pressure), this maintains the GFR. Such renal autoregulation mechanisms keep satisfactory renal hemodynamics and GFR down to a mean renal perfusion pressure about 70 mmHg below which renal hemodynamics and GFR fail and renal functions are impaired.

THE NEPHRON:

Is the functional unit of the kidney (**Fig. 1.6**). Each kidney contains approximately one million nephrons. The first part of the nephron is the *glomerulus* (renal corpuscle) which lies mainly in the renal cortex, followed by *proximal convoluted tubule* which also lies mainly in the renal cortex. This is followed by a *loop of Henle* which is partly in the cortex and partly extends deep into the medulla. Loop of Henle is composed of a thin part and a thick part. This is followed by the *distal convoluted tubule* which lies in the renal cortex. Part of the distal convoluted tubule comes into contact with the hilum of the glomerulus and afferent arteriole. Cells in the hilum of the glomerulus and those in distal convoluted tubule and afferent arteriole are modified to form the *Juxta glomerular apparatus* (**Fig. 1.7**). Distal convoluted tubule ends into the *collecting duct* which lies partly in the cortex and partly in the medulla. In the medulla, collecting ducts descend in the pyramids, at the renal papillae collecting ducts unite together to form ducts of Bertini which discharge urine into renal pelvis.



(Fig. 1.6)
 Diagrammatic illustration of the nephrons and collecting tubules.



(Fig. 1.7)

The Juxtaglomerular apparatus. Note: (1) Macula densa of distal tubule. (2) Juxtaglomerular (lacis) cells. (3) Granular renin-secreting epithelial cells of afferent arterioles.

The glomerulus (renal corpuscle):

The renal corpuscle is formed essentially of two modified structures of different embryonic origins:

- A. *The first* is the Bowman's capsule which is present at the beginning of the proximal convoluted tubule and is formed of a space lined by basement membrane and flat epithelial cells.
- B. *The second* is modification of the end of the afferent arteriole, which divides into several primary branches. These in turn give rise to several lobules of capillaries (tuft of capillaries). The other end of this capillary tuft gives rise to the efferent arteriole. Each capillary is lined with basement membrane, lined from inside by endothelial cells and from outside by epithelial cells which lie on the capillary basement membrane by foot process (so it is called podocyte). The capillary tuft will invaginate and occupy the Bowman's capsule to form the renal corpuscle.

Figure 8 shows a cross section of the glomerulus which is composed of:

1. Bowman's capsule with its outer (parietal) layer lined by flat epithelial cells, and inner visceral layer in contact with capillary tuft lined with visceral epithelial cells (podocytes). Between the two layers there is a space called urinary space.
2. Glomerular capillaries are lined by basement membrane which is covered from inside with endothelial cells and from outside by epithelial cells (podocytes). The capillary wall basement membrane is chemically formed of type IV collagen and negatively charged glycosaminoglycans. By electron microscopy, the basement membrane is formed of three layers, inner layer (lamina rara interna), outer layer (lamina rara externa) and in between the lamina densa. The thin cytoplasm of the endothelial cells show multiple open fenestrae, and the outer epithelial cells show elongated foot processes which rest on the outer surface of the glomerular basement membrane. These foot processes interdigitate with those of nearby epithelial cells and in between we can see slit pores. The fenestrae of endothelial cells and slit pores of epithelial cell foot processes are of great value in glomerular filtration.

Fig. (1.8a)

Electron Photomicrograph Of Renal
COPPUSCLE, X1100

Pa=Partial Epithelium Nucleus

U= URINARY SPACE

Ca=PODOCYTE (Visceral Epithelium)
NUCLEUS

En=Endothelium Nucleus

M= Mesangial Cell nucleus

A= Afferent Arteriole

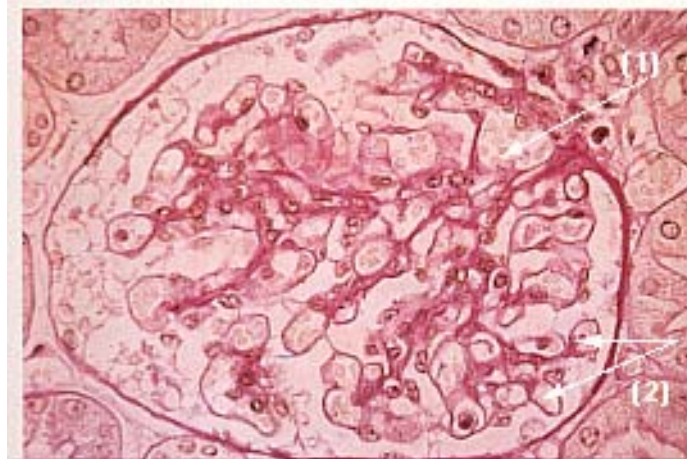
E= Efferent Arteriole

J= Juxtaglomerular Cell

D= Macula Densa Of Distal Tubule
(Tangentially Cut)

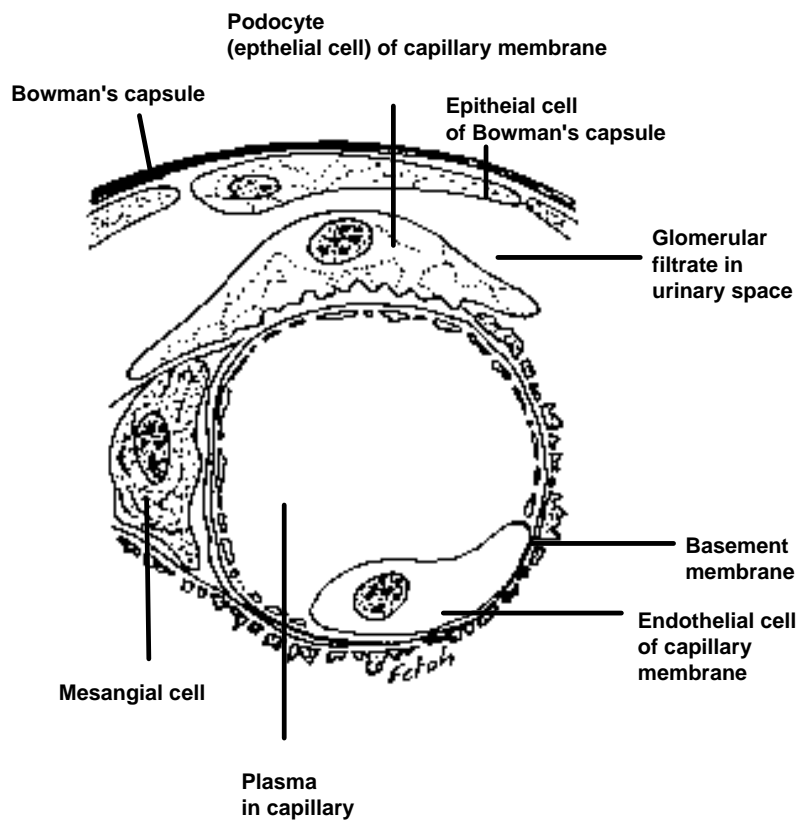
P= Proximal Tubules





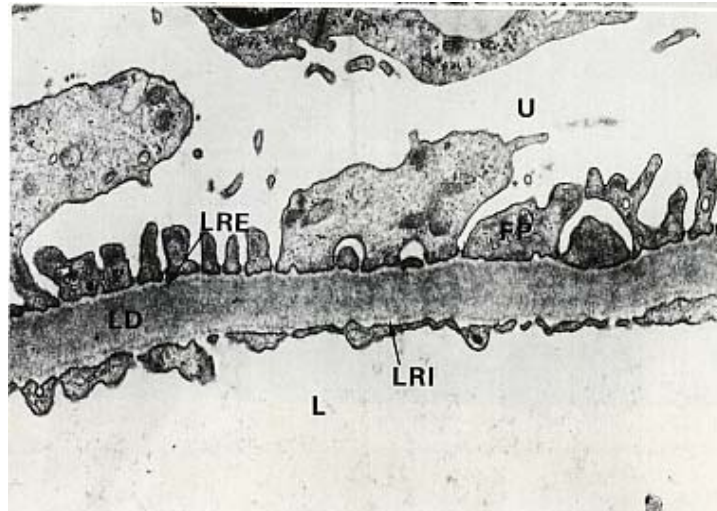
(Fig. 1.8b)

PAS stained kidney section (X 260), which shows a normal glomerulus cut through the hilus. The branching mesangial stalk is clearly seen (arrow-1). The capillaries are attached to the stalk, forming peripheral capillary loops (arrow-2).



(Fig. 1.8c)

Diagrammatic representation of the cell types of the renal glomerulus



(Fig. 1.8d)

Electron micrograph (X 18,000). Part of a glomerular capillary wall under higher magnification. Endothelial pores are visible in places. The basement membrane shows three layers: Lamina rara interna (LRI), lamina densa (LD), and Lamina rara externa (LRE). L= Capillary lumen, U= urinary space.

3. Mesangium is composed of special cells and matrix. It is located mainly at the hilum of the glomerulus, and extends between capillary loops. Its main function is to support the capillary tuft, also, it may have a phagocytic function and contractile function. Phagocytic property of the mesangium helps in clearing the glomerulus from any circulating immune complexes or antigens. The contractile function may help in modulating the renal blood flow and the capillary wall filtration surface.

Juxta-glomerular apparatus:

Juxta-glomerular apparatus is a specialized structure which is present at the hilum (vascular pole) of the glomerulus (Figure 1.7&1.8). It is composed of four groups of cells which contain granules in their cytoplasm (most probably renin). These cells are:

1. The macula densa cells which are modified cells in distal convoluted tubules.

2. The epithelioid cells which are modified cells in the wall of the afferent and to less extent efferent arterioles.
3. The lacis cells which are interstitial cells in continuity with mesangial cells.
4. The peripolar cells which are present at the vascular pole of the glomerulus, separating the podocytes from the flat parietal epithelial cells of Bowman's capsule. More details about JGA will be given on discussing renovascular hypertension (Page 316).

Proximal convoluted tubule:

Is the longest segment of the nephron, lined by a single layer of cells with prominent brush border towards the lumen. The basal part of these cells contains large mitochondria which are important for the high reabsorptive activity of these cells.

Loop of Henle:

Morphologically and according to the type of epithelial cells covering it, loop of Henle can be divided into thick descending limb, thin descending limb, then thin ascending limb and the thick ascending limb. The loops of Henle of superficial and middle cortical nephrons are short while those of deep cortical and corticomedullary junction nephrons are long and go deep in the medulla to reach renal papillae before they ascend up. These later loops are arranged in bundles in association with the collecting ducts and vasa recta (all are participating in the counter current system). Since the morphology of these segments is different, their function is also different.

Distal nephron:

Begins with distal convoluted tubule which starts at juxta-glomerular apparatus and end at the renal papilla. Morphologically and functionally, this can be sub-divided into:

- A. Distal convoluted tubule with its early part somewhat similar to the proximal convoluted tubule and distal part is similar to the cortical collecting tubule.
- B. Cortical part of collecting tubule.
- C. Medullary part of collecting tubule.
- D. Papillary part of the collecting tubule.

ANATOMIC PHYSIOLOGY (FUNCTION OF DIFFERENT SEGMENTS OF THE NEPHRON):

1. The glomerulus (glomerular filtration):

As the blood enters the glomerular capillary tuft through the afferent arteriole, a process of ultrafiltration occurs through the capillary wall to the Bowman's (urinary) space. The total ultrafiltrate in human ranges from 90-120 ml/min. (i.e. 130-180 liters/24h). Through the ultrafiltrate the body gets rid of toxins. The ultrafiltrate is cell free, protein free but contains water and different solutes (e.g. Na^+ , K^+ , Ca^{++} , Urea, and HCO_3^-). The amount and quality (nature) of the filtrate depend on the following factors:

- a. Glomerular capillary wall membrane including its total surface area (which could change such as by contraction and relaxation of the mesangium) and its structure (including the slit pores of the podocytes, fenestrae of the endothelial cytoplasm and the pores), and the negative charges of the basement membrane. These factors together determine what is called the filtration coefficient (Kf) of the glomerular capillary wall.
- b. Filtration pressure which is the net pressure pushing fluid from the capillary lumen to the urinary space. It depends mainly on the glomerular capillary hydrostatic pressure (normally ± 45 mmHg) which is determined by the systemic blood pressure and tone of the afferent and efferent arterioles. Spasm of the efferent arteriole increases the glomerular hydrostatic pressure and increases the glomerular filtration and vice versa. Spasm of the afferent arteriole decreases the hydrostatic pressure and glomerular filtration and the reverse is also true. Forces acting against filtration (opposing the hydrostatic pressure) are the oncotic pressure of the plasma proteins in the glomerular capillaries and the hydrostatic pressure of the fluid in the urinary space. So, the net filtration pressure = Hydrostatic pressure in the capillaries (45 mm Hg) – plasma oncotic pressure in the glomerular capillaries (10 mm Hg) – the hydrostatic pressure of the fluid in the urinary space (25 mmHg) = 10 mm Hg.
- c. Size and charge of the molecule: The smaller the molecular weight of a solute, the easier it passes through the capillary wall. Also, the

molecule of positive or neutral charges passes easier than those with negative charges.

2. Proximal Convolute Tubule (PCT):

- a. The daily glomerular filtration is 130-180 liters. This amount enters the PCT where 65-80% of its H_2O , Na^+ , K^+ and Cl^- are reabsorbed.
- b. In addition, there is a selective reabsorption of important metabolites such as active reabsorption of glucose, amino acid, and HCO_3^- .
- c. At the distal part of PCT, the secretion of weak acids and weak bases occurs. *Glomerulo - tubular balance* is a unique property of PCT in which it adjusts reabsorption rate so as to keep the proportion of reabsorbed to filtered H_2O and salts constant despite the variation in the flow rates.

3. Loop of Henle:

25% of filtered Na^+ is reabsorbed in the ascending thick limb selectively, i.e. not in conjunction with water as this segment is impermeable to H_2O . The fluid leaving this segment is hypotonic to plasma.

4. Distal Nephron:

The function of the distal convolute tubule is to reabsorb some NaCl and calcium. It is impermeable to water and is relatively insensitive to aldosterone or ADH.

The collecting duct- particularly the cortical part- has three functions:

- a. It reabsorbs Na^+ actively under the influence of aldosterone to achieve fine adjustment of its blood level.
- b. It excretes K^+ and H^+ (related to Na^+ reabsorption and also related to aldosterone).
- c. It reabsorbs water under the control of ADH. For example, when there is dehydration (hyperosmolar state), osmoreceptors are stimulated, which stimulate the hypothalamus, which in turn stimulates posterior pituitary, which secretes ADH which increases permeability of distal nephron to water, which becomes reabsorbed and urine becomes concentrated. The reverse occurs in state of excess water intake (hypoosmolar state).

Concentration And Dilution Of Urine:

This function is very important to regulate body water and tissue osmolarity. Normal body tissue and fluid osmolarity is 280-300 mosmol/Liter. This is maintained despite the wide variation in fluid intake (increased intake decreases osmolarity and vice versa) and load of osmotically active substances e.g. salt. Through biologic activity, there is a basal production of 600 mosmol/day. This can increase to over 1200 mosmol/day in states of severe catabolism as in patients with extensive burns.

The kidney is responsible for the control of secretion of water and solutes through process of urine formation so as to keep normal plasma osmolarity. The urine volume is around 1.5 liter/day but can vary from 400 ml to over 20 liter/day according to water and solute intake.

The urine osmolarity may vary from 30 mosmol/liter (when urine is maximally diluted) to 1400 mosmol/liter (when urine is maximally concentrated). The minimum urine output to maintain adequate excretion of waste products (600 mosmol/day) is 400 ml with maximum osmolarity of 1400 mosmol/liter.

Under normal circumstances, over 99% of filtered water is reabsorbed. Water is reabsorbed in an iso-osmotic fashion with sodium chloride i.e. as NaCl is reabsorbed water flows back into the circulation. In addition, further water is reabsorbed in the process of urine concentration which occurs in the distal nephron.

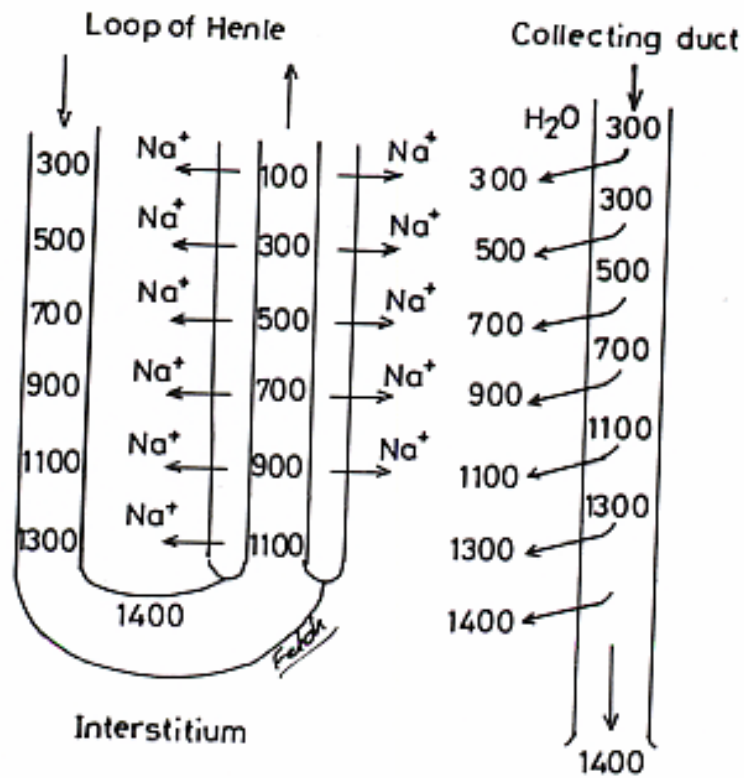
Dilution of urine is achieved through the removal of NaCl from the tubular lumen fluid in the segment which is impermeable to H₂O (thick part of the ascending loop of Henle, DCT), or from the segment which becomes impermeable to H₂O as an effect of ADH (collecting tubule and duct). The most important of them is the loop of Henle which secretes more H₂O and less NaCl in urine making it hypotonic (diluted).

Urine concentration results from the reabsorption of water in excess of nitrogenous wastes and other solutes. Therefore, in urine the concentration of urea is about 60 times that in plasma. In states of maximal urine concentration, urine osmolarity is about 1200 mosmol/liter. Further increase in urine osmolarity to 1400 mosmol/liter can be achieved with persistence of the stimulus for urine concentration. Urine concentration, through excess reabsorption of free water occurs mainly in collecting tubules.

The mechanism of urine concentration depends on passage of collecting tubules through the hypertonic renal medulla. The tonicity of renal medulla is maximum at the tip of renal papillae and decreases gradually towards the direction of the corticomedullary junction. ADH when secreted will increase the collecting tubule permeability to water which gets out to the interstitium leaving tubular contents hypertonic. The interstitial water is picked up by the vasa recta and renal venules and will be drained away.

Hypertonicity of the renal medulla is achieved through the countercurrent multiplier system which is generated by the pump mechanism present mainly in the thick ascending part of loop of Henle. By this pump, sodium and chloride and to less extent urea get out free of water, thus increasing the tonicity of the interstitium. The descending thin limb of loop of Henle is permeable to sodium, chloride and water which pass freely from the interstitium to the lumen (i.e. there is equilibrium between it and interstitial tonicity). There is a sort of recirculation of solutes in the renal medulla (from ascending to interstitium to descending loop to ascending again). The pump system in the loop of Henle is adjusted to achieve maximal tonicity at the tip of the loop and renal papillae of around 1300 mosmol/litre. Also, there is a difference between comparable points in ascending and descending loops of around 200 mosmol/litre. Moreover, the deeper in the renal medulla, the more is the osmolarity (Fig. 1.9).

In states of diuresis the medullary tonicity decreases and in states of anti-diuresis the tonicity gradually builds up to 1400 mosmol/litre. The vasa recta is permeable to water and solutes accumulating in renal medulla. Its loop structure minimizes the loss of sodium chloride and urea from renal medulla maintaining its tonicity which could be lost if the blood flow is in one direction only.



(Fig. 1.9)

Countercurrent mechanisms in the kidney.

In the kidney the loop of Henle acts as a countercurrent multiplier system, capable of generating a deep medullary (tip of the papilla) concentration of about 1400 mmol/litre under conditions of severe dehydration. Sodium chloride is pumped by the thick ascending limb into the interstitium, which it renders hypertonic, and then diffuses into the permeable thin descending limb. In the late distal convoluted tubule and in collecting tubule ADH renders the walls permeable to water but not solutes. Accordingly water diffuses by osmosis into the interstitium, leaving the tubular fluid progressively more concentrated.

Suggested Readings:

- Bruzzi I, et al: Endothelin: a mediator of renal disease progression. *J Nephrol*, 10: 4, 179-83, 1997.
- Nambi P: Endothelin receptor in normal and diseased kidney. *Clin Exp Pharmacol Physiol*, 23: 4, 326-30, 1996.
- Kohan DE: Endothelins in the normal and diseased kidney. *Am J Kidney Dis*, 10: 4, 179-83, 1997.
- Rabelink TJ: Endothelial function and the kidney. An emerging target for cardiovascular therapy. *Drugs*, 53 Suppl 1: 11-9, 1997.
- Klahr T: Angiotensin II and gene expression in the kidney. *Am J Kidney Dis*, 31: 1, 171-6, 1998.

INVESTIGATIONS FOR KIDNEY DISEASES

These include biochemical, microbiologic, immunologic, histopathologic and radiologic investigations.

A. **BIOCHEMICAL INVESTIGATIONS:**

Include the examination of urine, tests for kidney functions, microbiologic and immunologic tests.

I. **URINE EXAMINATION:**

Simple urinalysis and blood pressure measurement could be a valuable method for screening for renal diseases. However, negative urinalysis does not exclude renal disease. Urinalysis is an essential part of physical examination for kidney disease. The urine should be **fresh** and examined for the following:

1. Physical characteristics: these include examination for colour, odour, transparency, froth and foreign materials.

Normal colour of urine is amber yellow due to the pigment urochrome, it could be diluted or concentrated according to the patient hydration status and the diluting and concentrating capacity of the kidney.

A red coloured urine is seen mainly with haematuria, hemoglobinuria which could be differentiated by microscopic examination which can demonstrate RBC's in cases of haematuria but not in cases of haemoglobinuria.

A milky urine is seen in chyluria (lymph in urine). Turbid urine is seen with pyuria or presence of salts (phosphate, urate or oxalates). Cloudy and offensive urine could be seen with infection. Abnormal foreign bodies seen in urine are for example gravels or sloughed renal papillae.

2. Dip-stick test: These are plastic strips, attached to it are pieces of paper impregnated with different enzymes. Each piece contains an enzyme which reacts specifically with certain urine chemicals (e.g. glucose, albumin, acetone, H⁺, nitrite, haemoglobin, etc.). According to the concentration of the chemical tested, a certain change in colour occurs (0, 1+, 2+, 3+, 4+).

By Dip-Stick we can semiquantitatively determine proteinuria (mainly albumin), haemoglobin (haematuria or haemoglobinuria), nitrites (when positive means urinary infection), pH (acidic or alkaline urine), glucose (glucosuria). (**Fig. 2.1**)



(Fig. 2.1)

DIPSTICK TEST

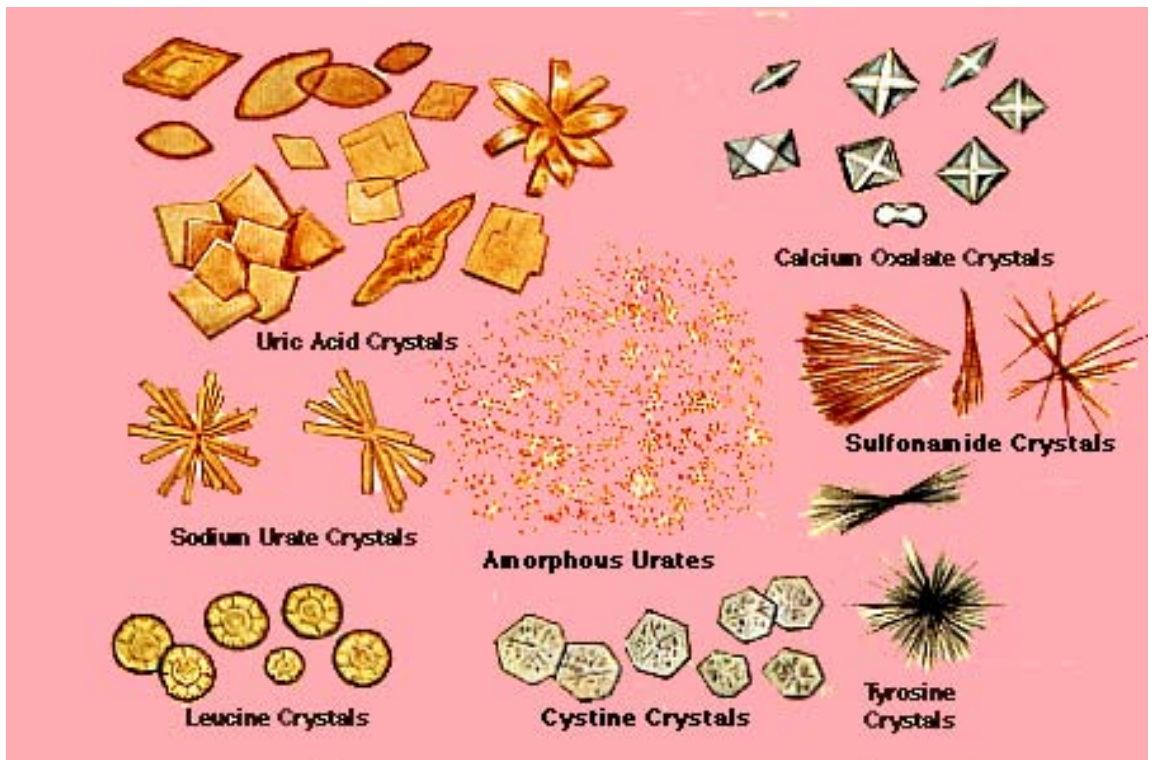
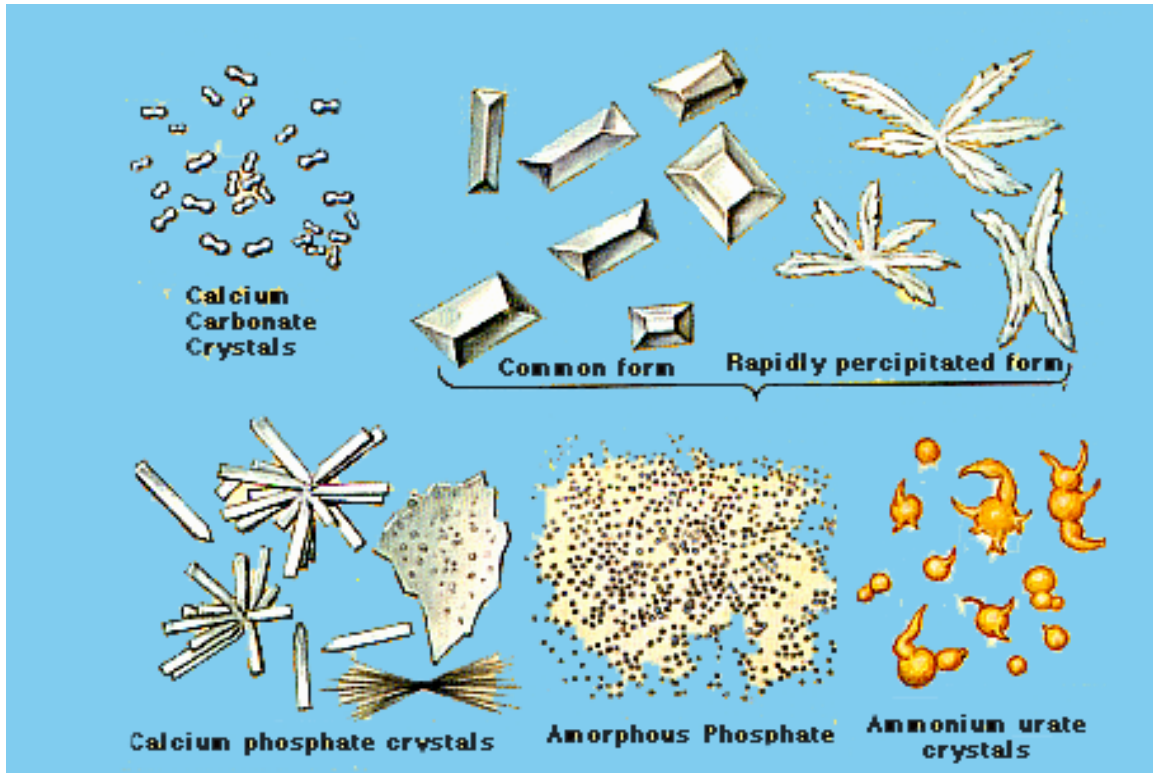
3. Microscopic examination of urine is a method for detection of cells (RBC's, leukocytes, pus, epithelial cells), casts (hyaline casts, red cells casts, leucocyte casts, granular casts or broad casts), or crystals (triple phosphate, uric acid, oxalate or cystine) (Figure 2.2) .
4. Quantitative estimation of proteinuria: This is achieved through quantitation of protein in 24 hours urine collection (normally less than 150 mg/24hours) or through examination of spot urine for albumin and creatinine and estimation of albumin/creatinine ratio (normally < 0.1).
5. Examination of urine for Bence Jones protein: Normally this could not be detected by Dip-Stix and needs immunoelectrophoresis. This protein precipitates on heating at 56°C and redissolves at 100°C or more. It is present in cases of multiple myeloma, amyloidosis and other types of macroglobulinemias.



(Fig. 2.2a)

An Illustration of Urinary Sediment Showing Different Organized Elements

(Reproduced with permission from Novartis, Switzerland)



(Fig. 2.2b)

ILLUSTRATION OF DIFFERENT TYPES OF CRYSTALS WHICH MAY BE FOUND IN URINARY SEDIMENT (Upper are mainly seen in alkaline urine while lower are mainly seen in acidic urine).

For more details on value of urine examination in medical diagnosis see page 301.

II. RENAL FUNCTION TESTS:

These includes tests for glomerular and tubular functions.

A. TESTS FOR GLOMERULAR FUNCTION

These include test for serum creatinine, blood urea nitrogen and glomerular filtration rate (GFR).

1- Serum creatinine: In routine practice serum creatinine level is the best indicator of kidney function (normally is 0.6-1.2 mg/dl or 53-106 $\mu\text{mol/L}$). It is higher in male than in female and in those with bulky muscles than cachectic ones. Creatinine is normally released with stable level from the muscles (unless there is a muscle disease) and is secreted by the kidney.

2- Plasma urea and Blood Urea Nitrogen (BUN) :Unlike creatinine, urea is affected by protein diet, liver disease (because liver changes ammonia to urea), and dehydration (excessively reabsorbed from proximal convoluted tubules giving higher level in blood out of proportion to renal dysfunction). The normal value of blood urea is 15-40 mg/dl (2.5-7.0 mmol/L). Its production is increased by infection, trauma, surgery and corticosteroid intake.

However, blood urea is considered a less reliable measure for kidney function. Still, measuring serum creatinine and urea together may give useful clinical information. For example, if urea concentration is out of proportion to that of creatinine it suggests a state of salt and water depletion, gastrointestinal haemorrhage, increased protein intake, diuretic therapy, infection or, corticosteroid therapy. Serum creatinine is out of proportion to plasma urea in cases of rhabdomyolysis and muscle diseases. Blood urea nitrogen (BUN) is sometimes used as a test for kidney function. Normal value is 8-13 mg/dl (2.9-8.2 mmol/L).

3- Glomerular Filtration Rate (GFR): This is measured by studying the clearance of a substance which is ideally freely filtered through the glomerulus; and not reabsorbed or excreted by the renal tubules (e.g. inulin). In practice, we use endogenous creatinine which is filtered through the glomerulus but some excretion occurs by the renal tubules, so creatinine clearance slightly overestimates GFR.

Clearance (C) of a substance is a measure of volume of plasma cleared by the kidneys of this substance per time unit (e.g. minute or second). Thus

$$C = \frac{UXV}{P}$$

Where C= creatinine clearance
U= urine concentration of creatinine
V= urine flow rate (minute or second)
P= plasma concentration of creatinine

Normal creatinine clearance in adult male is 90 -150 ml/minute. To estimate creatinine clearance, the patient should collect 24 hours urine from which V and U could be estimated then, blood is withdrawn for P estimation.

The major disadvantage of clearance study is the possible faulty collection of 24 hours urine, especially in females.

^{99m}Tc-DTPA or ¹⁵¹Cr-labeled EDTA or iothalamate isotope renal scan is an alternative method which does not require urine collection. The ^{199m}Tc-DTPA is injected I.V. and multiple images of the kidney are obtained over 30 minutes. This study provides the total and split (right and left) kidney GFR.

B. TESTS FOR TUBULAR FUNCTIONS:

- 1. Urine Acidification Test:** This is indicated to test for the ability of the kidney to acidify urine (excrete H⁺). This is done by decreasing plasma pH (i.e. inducing acidosis) by giving gelatin-coated ammonium chloride capsules 0.1 g/kg with water and checking the urine pH hourly for 6 hours. Normally, it should drop < 5.4. Otherwise, it will indicate renal tubular acidosis (RTA). If blood pH is already low (acidosis), there will be no need for giving ammonium chloride and check urine pH directly. As a screening test we can look for urine pH of the first morning voided urine (the highest acidic urine), which should be < 5.4. Presence of urinary infection with urea-splitting organism makes the urine alkaline and interferes with these tests. Therefore, eradication of this infection is mandatory before doing this test.
- 2. Urine Concentration Test:** for screening purpose examine early morning specimen for osmolality. If it is > 700 mosmol/L, concentrating capacity is considered normal and there would be no need for further investigation. Otherwise, we may either do water deprivation test or vasopressin (ADH) test.

In water deprivation test the patient is asked to stop fluid intake completely. This results in a progressive increase in plasma osmolality (normal 290 mosmol/L). In a normal person this should be followed by a

progressive decrease in urine volume and increase in its osmolality (maximum 1200 mosmol/L). In cases of lost ability to concentrate urine (e.g. in diabetes insipidus), this will not occur and urine volume will not decrease so that the patient may pass into severe hypotension, so we have to watch patient body weight (not to decrease by > 5%) and blood pressure (More details, are in page 270).

In vasopressin test we inject 5 IU vasopressin tannate in oil s.c.. This results in urine concentration if the inability to concentrate urine is due to lack of ADH (central diabetes insipidus); but not in cases of renal causes (nephrogenic diabetes insipidus).

3. Urinary B₂-microglobulin: This is a small molecular weight protein (MW 1800) which is normally present in all body fluids. It is formed in the body at a constant rate and is removed through glomerular filtration. Then, it is reabsorbed and catabolised by renal tubules. The urine concentration of this protein is usually <0.1 mg/ml and its upper limit in healthy subject is 0.4 mg/ml.

B₂-microglobulin is degraded in acidic urine. So, the urine sample should be kept with pH >6 to avoid false readings. It is measured by radioimmunoassay.

B₂-microglobulin could be used as a marker for tubular diseases e.g. analgesic and toxic nephropathies, Fanconi's syndrome and Wilson's disease, in these conditions urinary B₂-microglobulin is increased.

4. Urinary Enzymes: Enzymes as lactic dehydrogenase (LDH) and N-acetyl-B-glucosaminodase (NAG) are normally present in high concentrations in renal tubules especially proximal convoluted tubules. They are released in higher concentrations in urine with tubular damage of any etiology (toxic, ischemic or infection).

5. Urinary excretion of sodium (UNa): Many factors- other than renal diseases- affect urinary sodium excretion e.g. body hydration status (extra cellular fluid volume), adrenal function, diuretic therapy and effective circulating blood volume. Fractional excretion of Na (FeNa) means measuring the part of filtered sodium that is excreted to urine. This is helpful in differentiating impaired kidney function which is due to acute tubular necrosis from prerenal failure (see acute renal failure). The FeNa is calculated by dividing Na clearance over creatinine clearance i.e.

$$\text{FeNa} = \frac{\text{UNa} \times \text{v}}{\text{PNa}} \div \frac{\text{Ucr} \times \text{v}}{\text{Pcr}} = \frac{\text{UNa} \times \text{v} \times \text{Pcr}}{\text{PNa} \times \text{V} \times \text{Ucr}} = \frac{\text{UNa} \times \text{Pcr}}{\text{PNa} \times \text{Ucr}}$$

i.e. we need only to measure plasma, urinary Na and creatinine. Urine volume is not required. Normal FeNa is less than 0.1.

B. MICROBIOLOGICAL EXAMINATION OF URINE:

In cases of urinary tract infection, urine specimens are examined for identification of bacteria as well as for its sensitivity to antibiotics by culture techniques. Taking a proper urine sample is mandatory to avoid false results.

A midstream urine sample is required i.e. when the bladder is full, the first 200 c.c. is passed to clean the urethra. Then, 10 c.c. is taken in a sterile container from the urine stream. In the male, glans penis should be cleaned by sterile water, and in the female the vulva is cleaned properly and during micturition labia are held away by fingers. In neonates and young children suprapubic aspiration of urine by fine needle is safe. The presence of more than one type of organisms in culture, usually means contamination rather than infection.

When prostatic infection is suspected, three specimen technique of Stamey is followed. VB1 is the first voided 10 ml of urine (which represents urethral bacterial flora). VB2 is the midstream urine (which represents the bladder flora). After that the patient stops micturition and the prostate is firmly massaged and any discharge comes out is cultured. Then, the patient passes another 10 ml of urine (VB3) which represents prostatic flora.

In urine culture, a bacterial count of 100,000 or more is needed for the diagnosis of urinary tract infection. However, a smaller number may be considered significant in pregnant women, children, and immunosuppressed patients. When there is pyuria; and urine culture is persistently negative (at least three cultures should be done), this is called sterile pyuria. In this condition, urine should be examined by specific types of cultures e.g. Lowenstein-Jensen media for Mycobacterium; anaerobic culture for anaerobes; human blood agar for Gardnerella vaginalis; urea plasma agar for ureaplasmas; irradiated McCoy cells for chlamydia. If the cultures are still negative, we are mostly dealing with either viral infection or non-infectious causes of pyuria e.g. foreign body, malignancy or immunologic disease as SLE or kidney graft rejection.

C. IMMUNOLOGICAL TESTS FOR DIAGNOSIS OF KIDNEY DISEASES

1. Complement:

See pathogenesis of glomerulonephritis (Page 53) to know the value of complement system in renal diseases. Complement System is activated and consumed in immune-complex formation. Hypocomplementemia consequently occur in diseases such as: post infectious glomerulonephritis, shunt nephritis, nephritis associating subacute bacterial endocarditis, lupus nephritis and idiopathic mesangio-capillary (membrano-proliferative) glomerulonephritis. Usually, the complement system is assessed by measuring the total haemolytic complement (CH50) activity, C3 and C4 concentrations. Other complement components are measured if CH50 is low, while C3 and C4 are normal. Low C4 concentration indicates an activated complement system through the classic pathway, while low C3 and C4 indicates the activation of the alternative pathway. C3 nephritic factor (C3 - NeF) is detected in mesangio-capillary glomerulonephritis.

2. Immunoglobulins:

Serum IgA concentrations could be high in IgA nephropathy and Henoch-Schönlein disease. Serum IgE concentration could be high in minimal change nephritis and all allergic nephropathies.

Paraproteins could be detected by immunoelectrophoresis in multiple myeloma, amyloidosis and mixed cryoglobulinemia. Bence Jones protein could be detected in urine also.

3. Circulating Immune Complexes (C.I.C.):

Circulating immune complexes (C.I.C.) are detected in diseases such as cryoglobulinaemias, SLE and collagen diseases. C.I.C. assays have a limited role in clinical practice.

4. Autoantibodies: These include antinuclear antibodies (ANA), anti-DNA, anti-neutrophil cytoplasm auto antibodies (ANCA), and anti-glomerular basement membrane antibodies (anti-GBM). For more details see vasculitis (Page 123).

D. KIDNEY BIOPSY:

Kidney Biopsy is performed to obtain kidney tissue for histological examination to take therapeutic decision and to judge the prognosis of the renal disease.

Indications:

For all adults with nephrotic syndrome, children with steroid resistant nephrotic syndrome and patients with renal impairment of unknown etiology.

Precautions and Technique:

Assure that the patient has two functioning kidneys, a normal coagulation profile (bleeding, clotting, prothrombin time), controlled blood pressure and gave an informed consent.

Patient lies in prone position with a pillow under the rib cage pressing the kidney back to posterior abdominal wall. Skin over the right kidney is sterilized and lower pole of the kidney is localized in deep inspiration by real-time ultrasound. Local anaesthetic is injected subcutaneously and along the biopsy track. Under ultrasound guidance a tru-cut biopsy needle is introduced while the patient is holding his breath in deep inspiration and core of kidney tissue is obtained from the cortex of the lower pole. Two cores are usually taken for light, immunofluorescent and electron microscopy. Firm pressure is applied over biopsy site for 10 minutes. After biopsy the patient should be kept in supine position for at least four hours with observation every 30 minutes for pulse, blood pressure and for haematuria. The patient should be kept in bed for 24 hours with no strenuous activity for two weeks.

Complications:

1. Peri-renal haematoma which is extremely common but of significance only in 1% of cases.
2. Bleeding which could be microscopic or gross with clot retention.
3. Intra-renal A-V fistula which usually closes spontaneously.

E. RADIOLOGIC EXAMINATION OF THE KIDNEY AND THE URINARY TRACT

During the last decade a great progress has been achieved in imaging techniques of the kidney and urinary tract. We have to select the procedure which is the simplest, least invasive, most informative and which saves time for the patient.

1. Ultrasonography (U.S.)

Ultrasound examination of the kidney and urinary tract is either through B-mode scan, Doppler flow examination of renal vessels or duplex ultrasound scanning.

B-mode U.S. imaging is the usual examination requested. Renal ultrasonography should be the first radiologic procedure performed on patient with renal or urologic disorder; and in most instances it will be the only one that is required. Renal ultrasonography carries the advantages of being non-invasive, less costly and does not require special preparation. It can demonstrate clearly the renal size, contour, echotexture (Figure 2.3), stone, back pressure (due to chronic obstruction), renal mass or cyst (Figure 2.4), and perirenal collection. Pelvic ultrasonography may show bladder mass and calculate the residual urine (amount of urine remaining in the bladder after micturation). Ultrasonography can also show the upper and lower parts of the ureter. In addition, ultrasonography can help in examining surrounding organs and help in guiding needle for renal biopsy or aspiration of peri renal or perivesical collection.



(Fig. 2.3)

Normal renal ultrasound: it shows longitudinal scan through the right kidney demonstrating the relationship to the right lobe of the liver anteriorly and the paraspinal muscle posteriorly. The kidney shows echogenicity less than that of the adjacent liver



Fig. (2.4a)

It shows a well-circumscribed right upper polar cyst (c) with a sonolucent "echo-free" pattern, thin wall, well-defined posterior margin and posterior echo-enhancement (due to good transmission of the ultrasound waves through the fluid content).



Fig. (2.4b)

It shows marked left hydronephrosis demonstrating marked dilatation of the calyces and the renal pelvis with thinning of the renal parenchyma.



(Fig. 2.4c)

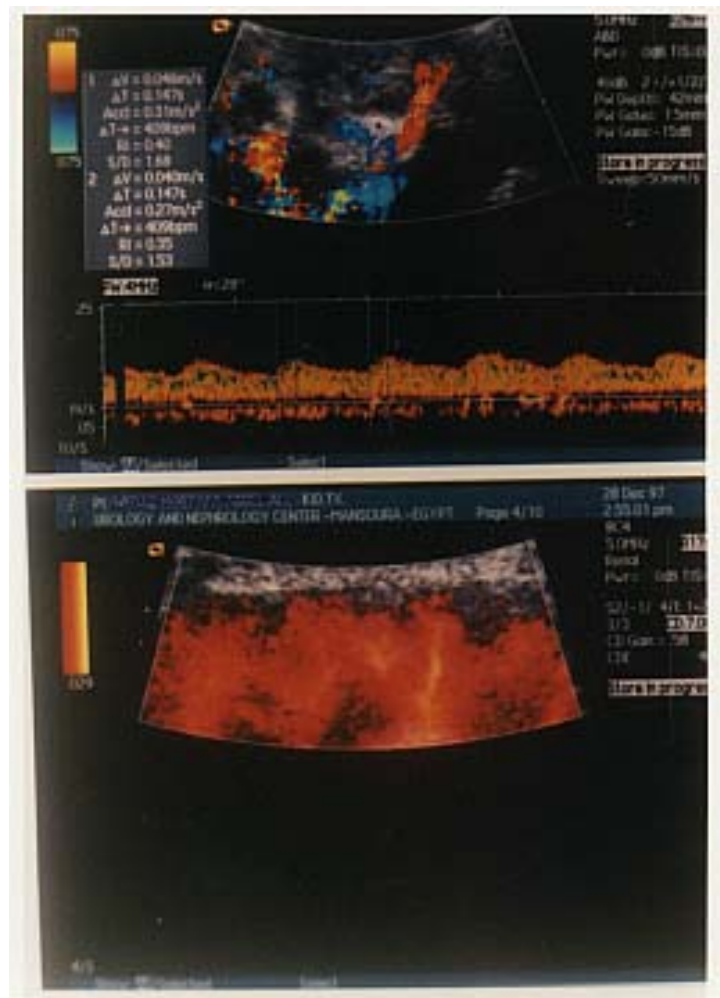
It shows a longitudinal scan of each kidney with bilateral variably sized non-communicating cyst throughout renal parenchyma. Neither back-pressure changes nor communication with the collecting system can be identified.



Fig. (2.4d)

It shows a LS of the left kidney with a stone upper calyx (arrow) as echodense focus casting posterior acoustic shadow.

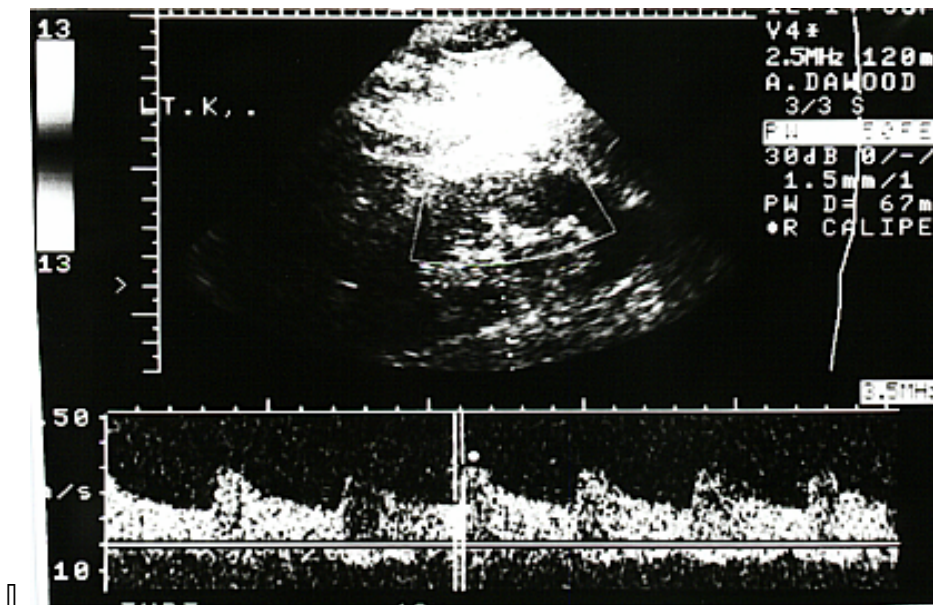
Doppler flow imaging of the renal vessels will assess the integrity of the blood supply of the kidney (Figure 2.5). It may be displayed with standard gray scale or in colour (colour Doppler). It may help in diagnosis of renal artery occlusion or stenosis, renal vein thrombosis and kidney transplant rejection. This examination needs special experience. Colour Doppler ultrasonography increases the sensitivity of this technique. Recently, it has been suggested that colour Doppler U.S. may be useful in diagnosing vesicoureteric reflux.



(Fig. 2.5)

Doppler US of a case with renal artery stenosis, it shows Damped wave form with marked delay in the systolic rise time, a reduction in the pulsatility index with low flow velocities (Parvus tradus pattern). Sampling was from an intrarenal vessel.

Duplex ultrasonography shows the standard B-mode image with superimposed Doppler flow informations (Figure 2.6).



(Fig. 2.6)

Duplex US (Normal)

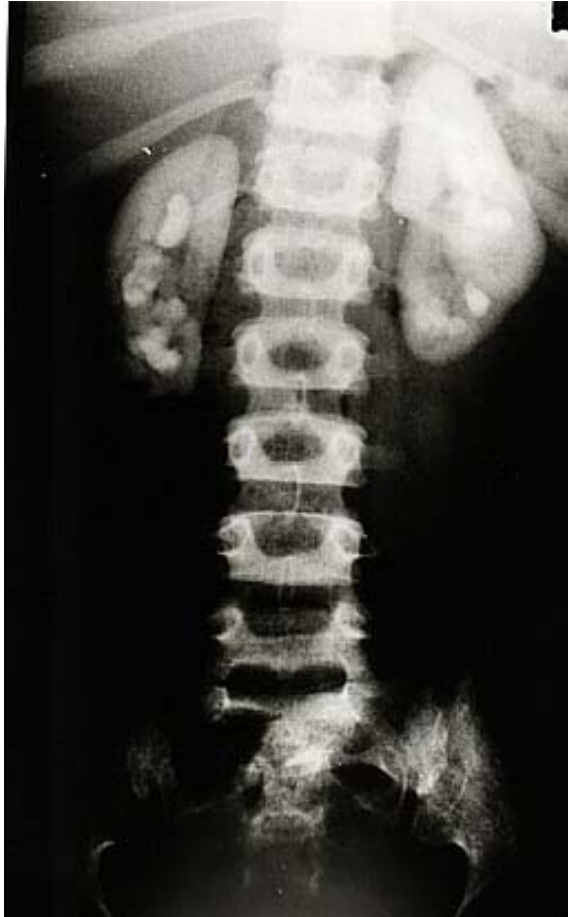
Combined real time US (top) and Doppler US (bottom) showing normal low-resistance waveform with high forward flow throughout systole and diastole.

2. Plain abdominal X-Ray:

For examination of urinary system, this is called plain X-ray abdomen or KUB (kidney, ureter, bladder). KUB may show : 1-stones (80-90% of stones are radio-opaque), 2-Calcification of the kidney, urinary bladder, seminal vesicles or prostate, and 3-In a well prepared patient with no bowel gases, or by nephrotomogram, soft tissue shadow and renal contour could be seen (size and shape of the kidney) (Fig. 2.7).

3. Intravenous urography (IVU):

The patient should come for this investigation after a thorough bowel evacuation (laxative is to be given the night before and enema on the morning of the day of examination) and with the fluid intake restricted (to allow concentration of the dye and consequently proper visualization of the urinary tract). An iodinated contrast media is injected intravenously and x-ray films are taken immediately, 1 minute and 15 minutes after injection. Sometimes late films are taken (e.g. when artery stenosis is suspected).



(Fig. 2.7)

Oxalosis (UTP)

Calcified soft tissue shadow of both kidney (simulating a nephrogram of IVU). Multiple, bilateral radioopaque stones are noted as well.

Nephrogram is the film obtained immediately after injection of contrast medium. It shows the dye concentrated in the nephrons and the kidney appears opacified but no dye yet in the renal pelvis. This film shows the site, the size, the contour of the two kidneys. It also shows whether the kidneys are functioning equally or not. In cases of renal artery stenosis, the nephrogram of the affected kidney appears delayed than the other healthy kidney. After nephrogram, dye will appear in the renal pelvis, ureter then the bladder (Fig. 2.8). So, IVU shows the anatomy of the kidney and urinary system, any mass, stones, back pressure changes and also demonstrates the kidney function.



(Fig. 2.8)

Intravenous urography (IVU) showing:

- Normal excretion and concentration of contrast medium by both kidneys.
- Normal configuration of both kidneys.
- Normal course and calibre of both ureters
- Normal cystogram.

As the contrast media used is ionic and with high viscosity and the technique is done with dehydration, this can result in kidney damage (contrast media nephropathy) with rise in serum creatinine-even acute renal failure may occur. There is a group of patients who are more vulnerable to contrast media nephropathy. These are diabetics, elderly, hyperuricaemics, patients with multiple myeloma, presence of renal dysfunction, patients receiving other nephrotoxic drugs (e.g. gentamycin), and those with congestive heart failure.

To avoid contrast media nephropathy in high risk patients we have to:

1. Do it only when strongly indicated.
2. Avoid dehydration.
3. Avoid concomitant use of nephrotoxic drug.
4. Premedicate the patient with verapamil (80 mg orally, one hour before exposure to contrast media).
5. Use special type of contrast (low viscosity, non-ionic), but this is very expensive and even still risky.
6. Immediately after taking the last film inject 12.5 gm mannitol I.V. to wash the contrast out with the diuresis. If the patient has renal impairment, the dye can be washed immediately by haemodialysis.

Anaphylactoid reaction is another possible risk of the contrast media. Therefore, steroids and antihistaminic drugs should be at hand.

4. Cystography and voiding cystourethrography:

Diluted contrast is injected into the bladder through urethral or suprapubic catheter. When the bladder becomes full, the patient is asked to micturate and films are taken. This is called micturating or voiding cystourethrogram (VCU). Normally the dye does not appear in the ureters because of the normally present antireflux mechanism at ureterovesical junction. If the dye appears in the ureters during VCU. This is called vesicoureteric reflux (VUR); which could be classified according to its severity into five grades (Figure 2.9).

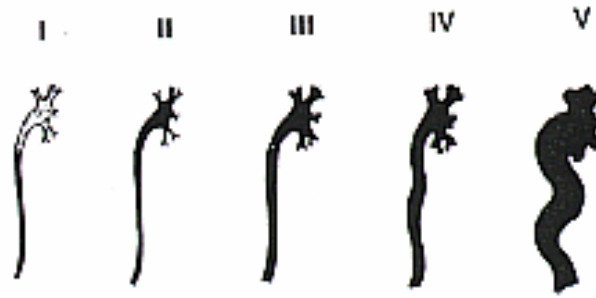
In advanced VUR reflux, the dye may regurge to the nephrons during VCU and the renal parenchyma is visualized. This is called intrarenal reflux.

VUR reflux can damage the kidney through pressure atrophy (in Grade IV), precipitation of chronic infection and through a special type of glomerulopathy (reflux nephropathy).

VUR reflux could also be diagnosed by colour Doppler ultrasonography (which may show the abnormal direction of urine flow at lower end of ureters during micturation) and by radionuclide micturating cystography.

5. Urodynamic studies:

Measuring the intravesical pressure (cystometry) and urine flow will give full anatomic and physiologic assessment of the lower urinary tract.



(Fig. 2.9):

The grading system adopted by the International Reflux Study in Children. Contrast material in the collecting system is represented in black. Grade I is assigned if the contrast material enters the ureter, but does not enter the renal pelvis. Grade II means that contrast material reaches the renal pelvis, but does not distend the collecting system. Grade III occurs when the collecting system is filled and either the ureter or pelvis is distended, but the calyceal demarcations are not distorted. Grade IV is assigned when the dilated ureter is slightly tortuous and the calyces are blunted. Grade V occurs when the entire collecting system is dilated and the calyces have become distorted and indistinct.

6. Angiography: This includes

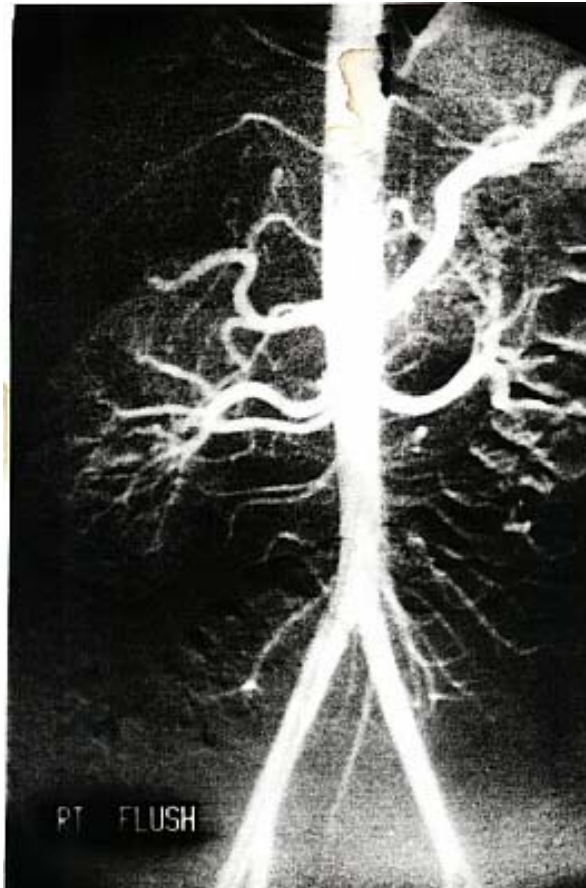
a. Renal Arteriography

A catheter is introduced percutaneously into the femoral artery and proceeded under television (screen) control through the aorta. The dye could be injected into the aorta, above the level of renal arteries (flush aortography) and films are taken which will show renal arteries and nearby vessels or the catheter could be advanced selectively into renal artery and dye is injected (selective renal angiography).

Renal arteriography is mainly indicated for diagnosis of renovascular hypertension or persistent haematuria following trauma.

Digital subtraction angiography (DSA)

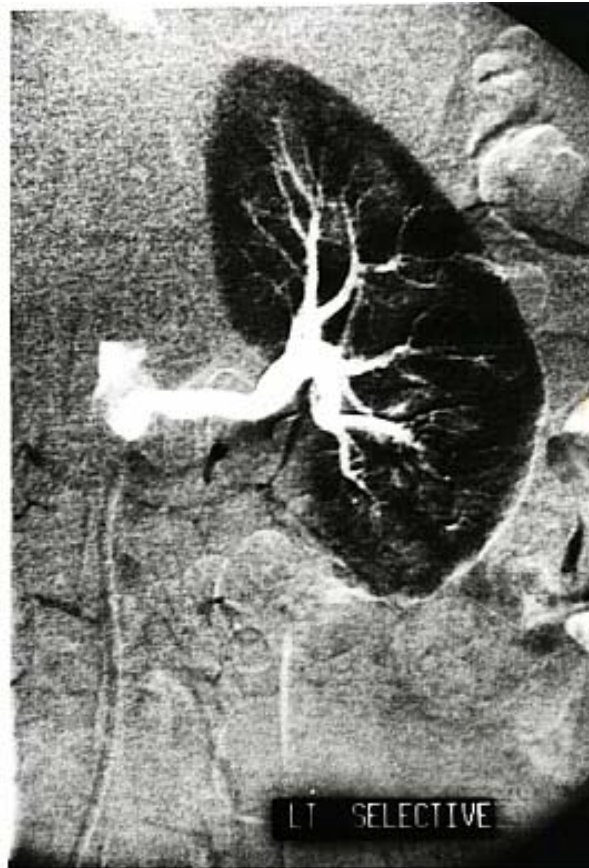
This technique is characterized by: 1. A smaller amount of dye to be injected into the artery. 2. Using a smaller catheter. 3. the images obtained can be processed by a computer program, through which gases and soft tissue images are subtracted from the final image. DSA shows mainly the examined vessels in better quality than the ordinary angiography (Fig. 2.10).



(Fig. 2.10a)

Intra-arterial digital subtraction angiography (IA-DSA) of the abdominal aorta of a potential kidney donor shows single left renal artery and double right renal arteries.

In another approach the dye could be injected into a peripheral vein (less invasive) and through special computer program we can visualize any artery (e.g. renal arteries) and images could be obtained but the quality of these images are far inferior to those obtained by direct intra-arterial injection of contrast media.



(Fig. 2.10b)

IA-DSA of left kidney showing normal main renal artery and intrarenal (segmental, interlobar, interlobular and arcuate) arteries in a delayed arterial phase. Normal parenchymal perfusion is seen as well in the nephrographic phase.

b. Renal Venography

This is indicated mainly for diagnosis of renal vein thrombosis. A catheter is introduced percutaneously into the femoral vein then advanced through inferior vena cava to the renal vein where the contrast medium is injected.

7. Computerized tomography (C.T.)

Generally C.T. carries two advantages over the conventional radiography, 1. It produces axial cross-sectional images. 2. It produces more radiographic contrast which allows different types of soft tissue to be distinguished. The degree of attenuation of the X-ray beam by different tissues and media is expressed as Hounsfield units (H). Water and urine are nearly 0, bone + 1000 H, while air is- 1000 H. Normal kidney and muscle

density is about 30 H and fat is about - 60 H. Injecting contrast media with C.T. scanning will enhance the renal cortical image to 60-80H. C.T. (Figure 2.11) scanning may be superior to other radiologic investigations in the following areas: 1. To characterize lesions in peri-renal, para-renal and retroperitoneal space as lymphadenopathy, tumours or retroperitoneal fibrosis. 2. Solid renal masses, for diagnosis and staging of the tumour. 3. Low density or radiolucent stones. Therefore it is strongly indicated in patients with obstructive uropathy with non-evident cause.



(Fig. 2.11)

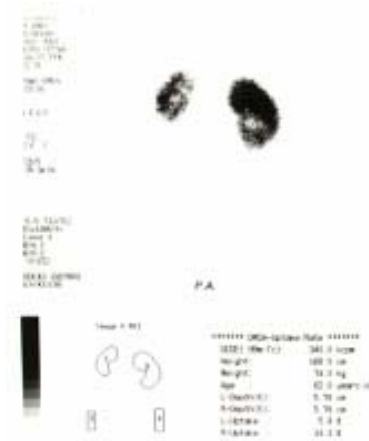
CT scan of the kidney (Normal)

- Axial CT scan of the kidney early after administration of I.V. contrast medium showing normal corticomedullary definition as the medullary pyramids are less enhancing than the cortex. The central hypodense structure represents the renal sinus.

8. Radionuclide Imaging

There are two types of isotope renal scanning: 1. Static imaging, in which the tracer injected is retained by proximal convoluted tubules, giving best chance to visualize the morphology of functioning part of the kidney using gamma camera. So, it is helpful in diagnosing renal scarring (Figure 2.12), renal tumours and anatomic abnormalities. Also, according to the differential isotopic activity, quantification of relative function between kidneys and within a kidney could be achieved. The tracer used for this type of scan is ^{99m} technetium-labelled dimercaptosuccinic acid (DMSA). 2. Dynamic renal imaging in which the tracer is not retained by the kidney, but is immediately

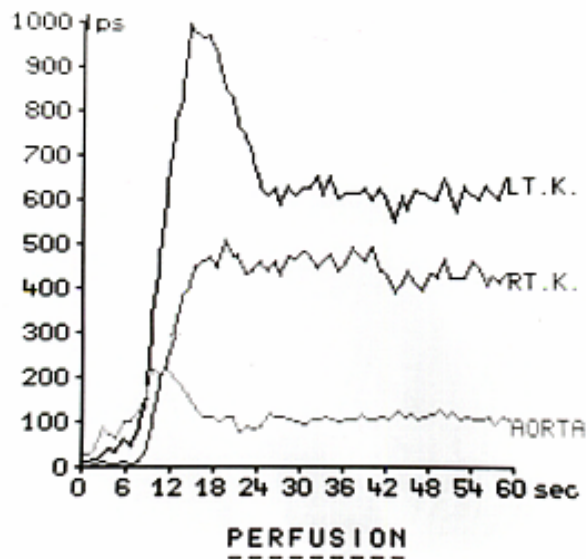
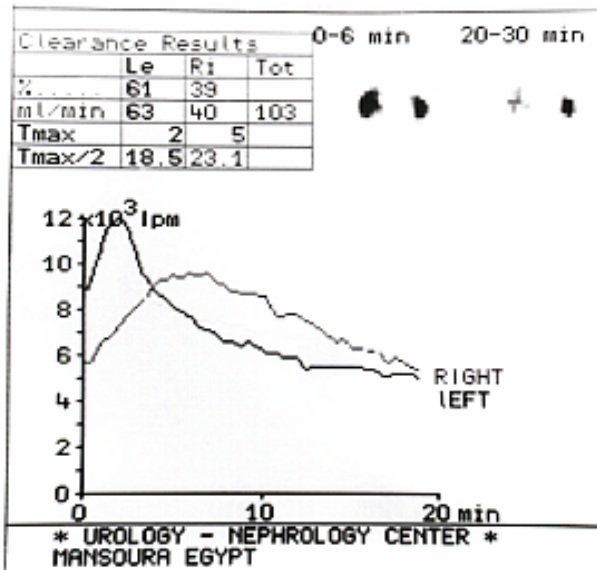
excreted, either by glomerular filtration alone e.g. ^{99m}Tc - diethylenetriamine penta acetic acid (DTPA) or by glomerular filtration and tubular secretion (MAG3), and ^{123}I , sodium iodohippurate (Hippuran). This type of scan is helpful in examining renal perfusion (vascular phase) and dynamic parenchymal images expressing isotope transit and excretion into the bladder.



(Fig. 2.12)

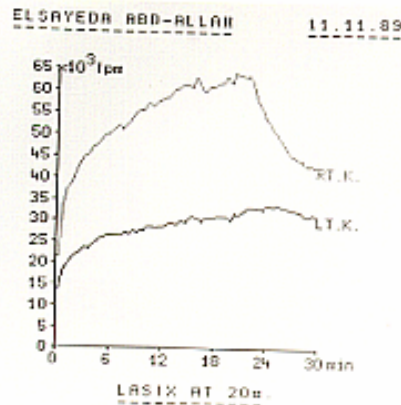
DMSA scan (chronic pyelonephritis) small-sized left kidney with irregular outline and multiple photopenic areas. A photodeficient area is also noted at the lower pole of right kidney.

The vascular dynamic imaging (Figure 2.13) help in diagnosing renal vascular occlusion (embolism or thrombosis) or narrowing (renal artery stenosis). The isotope does not appear in the completely obstructed kidney and show delayed appearance in the case of renal artery stenosis. The dynamic parenchymal imaging (Figure 2.14) helps in diagnosis of ureteric obstruction in which delayed washout of the tracer from the kidney will be observed. Furthermore, the dynamic scan can be helpful in the measurement of the total or individual kidney GFR (DTPA) or effective renal plasma flow (MAG3 or Hippuran).



(Fig. 2.13)

- (a) **Perfusion study:** Reduced perfusion of the right kidney, in comparison to the normal left kidney, with loss of the flow peak.
- (b) **Renogram:** The right kidney shows prolonged time maximum activity (second, accumulation phase), flat peak, and slow rate of excretion.



(Fig. 2.14)

Diuretic Renogram (obstruction)

It shows a non-obstructed right kidney as evidenced by a rapid response to frusemide injection while the renographic curve of the left kidney signifies obstructed pattern as no response is seen after lasix injection.

9. Magnetic Resonance Imaging (MRI)

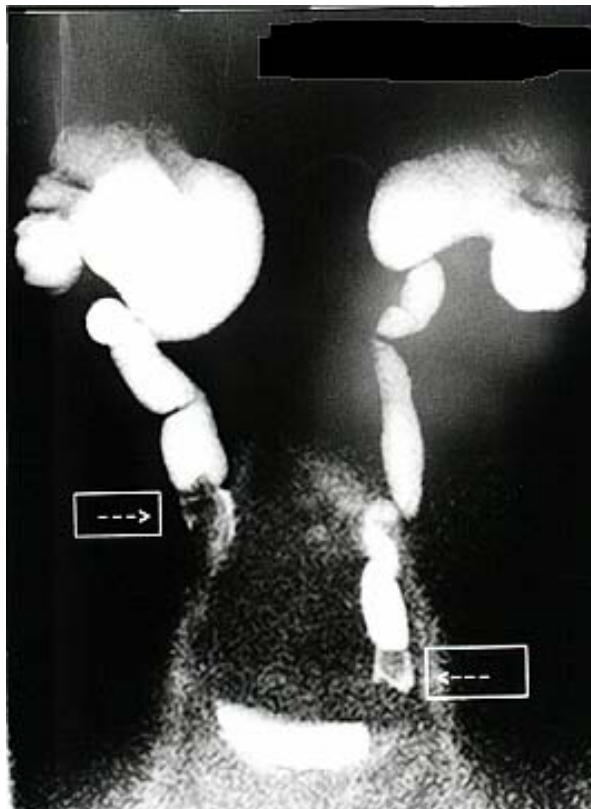
The principle of MRI is the excitation of the nuclei of atoms such as hydrogen in tissues with radiowaves, and detection of echo radiation from these nuclei when the radio source is removed. Thus, the MRI provides information at the cellular level. Currently, this recent technique provides excellent anatomical informations (Figure 2.16) which are very helpful in studying malignancies of the urinary tract. In the future, this technique is expected to provide a very reliable physiologic and metabolic assessment. MRI angiography is being developed which can provide a non-invasive and sensitive technique for assessment of renal vessels.



(Fig. 2.15a)

MRI Kidneys (Normal)

Axial T1-weighted sequence demonstrating hypointensity of the renal parenchyma. The perinephric fat is hyperintense and easily demarcated from the adjacent renal cortex. The renal sinus fat is hyperintense as well.



(Fig. 2.15b)

MR urography (obstruction)

Bilateral hydronephrosis in a patient with 4.8 mg/dl serum creatinine (IVU is not feasible). Note the hypointense ureteric stone bilaterally (arrows).

Suggested Readings:

- Wilcox CS: Ischemic nephropathy, non invasive testing. Semin Nephrol, 16: 1, 43-52, 1996.
- Platt JF: Doppler ultrasound of the kidney. Semin Ultrasound CT MR, 18: 1, 22-32, 1997.
- Rudnick MR et al: Contrast media-associated nephrotoxicity, Semin Nephrol, 17: 1, 15-26, 1997.
- Murphy KJ: Power Doppler: it's a good thing. Semin Ultrasound CT MR, 18: 1, 13-21, 1997.
- Prince MR: Renal MR angiography: a comprehensive approach. J Magn Reson Imaging, 8: 3, 511-6, 1998.
- Kramer LA: Magnetic resonance imaging of renal masses. World J Urol, 16: 1, 22-8, 1998.
- Soltes GD et al: Interventional urology, World J Urol, 16: 1, 52-61, 1998.
- Roy C, et al: MR Urography in the evaluation of urinary tract obstruction. Abdomen Imaging, 23: 1, 27-34, 1998.

GLOMERULONEPHRITIS (GN)

Are group of diseases of inflammatory or non-inflammatory nature involving the renal glomeruli.

PATHOGENESIS OF GLOMERULONEPHRITIS:

Many pathogenic mechanisms are responsible for the development of glomerular injury. These mechanisms are:

- I. Immunologic mechanisms
- II. Metabolic abnormalities
- III. Hyperfiltration injury
- IV. Hereditary abnormalities

I. Immunologic Mechanisms:

Most of the cases of glomerulonephritis encountered in clinical practice are secondary to immunologic attack affecting the renal glomeruli. This attack usually occurs in genetically predisposed person after exposure to toxin or an infection. This will provoke the immune system to attack the glomerular structures. This could be through the formation of antibodies or through a cell mediated glomerular injury.

Antibodies formed by the immune system could be directed to intrinsic (endogenous) antigen (i.e. autoantibodies) or to extrinsic (exogenous) antigens.

A. *The endogenous antigen* could be either in the glomerular basement membrane (GBM) and antibodies are therefore called anti-GBM (causing anti-GBM disease or Goodpasture syndrome) or it could be extraglomerular antigens. Examples of extraglomerular antigens are: 1- nuclear DNA and their antibodies are called anti-DNA (as in systemic lupus erythematosus), 2- circulating immunoglobulin molecules (as in cryoglobulinemia), 3- Neutrophil cytoplasmic antigens and their antibodies are called anti-neutrophil cytoplasmic antibodies (ANCA, as in vasculitis), and 4- tumour antigens.

In experimental animals other intraglomerular antigens have been identified. These are: 1- epithelial cell antigens (in the coated pits of the glomerular epithelial cell surface (subepithelial deposits); 2- mesangial antigens, and 3- endothelial antigens along the filtration slits.

B. Extrinsic antigens include bacterial products (e.g. streptococci), virus (e.g. HBV, HCV), parasite (Malaria, Schistosoma) or drug (e.g. penicillamine, gold).

The formed antibodies attach to the responsible antigen forming immune complex.

Circulating immune complex (CIC) may be trapped in the glomerulus. Alternatively, the antigen may be trapped first (planted) in the glomerulus and immune complex formation occurs in the glomerulus (In-situ immune complex formation).

By immunofluorescent microscopy linear deposition of IgG along the GBM is seen in cases of anti-GBM disease while granular deposition of immunoglobulins in the capillary wall and/or the mesangium is seen in cases of immune-complex mediated diseases.

Persistent antigenemia (e.g. subacute bacterial endocarditis, infected A-V shunt, hepatitis B virus) or recurrent antigenemia (e.g. Malaria) are important for immune complexes formation.

Formation of immune complexes are not always associated with glomerulonephritis. There are many factors necessary for immune complex to be nephritogenic, these include:

1. The charge of the antigen, cationic antigens are easily implanted in the glomerulus and cause disease.
2. The size of the immune complex, those formed at antibody-antigen equivalence are more nephritogenic.
3. The antibody class and affinity.
4. The capacity of the body's mononuclear cell phagocytic system to clear immune complexes.
5. The local glomerular hemodynamic factors.

Immune complex-mediated glomerular injury

The mechanisms through which an immune complex can induce glomerular injury include the following:

1. **Antibody:** The glomerular damage can be induced directly by high amount of immunoglobulin deposited as in cases of anti-GBM disease.

In cases of I.C. mediated glomerulonephritis, glomerular lesions occur through antibody mediated activation of other humoral and cellular components including complement and inflammatory cells (monocytes and neutrophils).

2. Complement: Binding of antibody with antigen activates the complement cascade. There are two pathways for complement activation, the classic pathway which starts with the activation of C1q and the alternative pathway which starts with the activation of C3. Activation of complement results in a series of reactions with liberation of by-products (activated complement components) into target tissue. Some of these complement components have direct damaging effects (vasoactive, chemotactic) or through leucocyte activation. Complete activation of all components of the cascade forms glomerular membrane attack complex (MAC) which causes lysis of the GBM.

The high rate of activation and consumption of the complement components in the inflammatory process results in hypocomplementemia.

Of the diseases which induce hypocomplementemia are:

- (a) Post-streptococcal GN and some cases of bacterial endocarditis (transient hypocomplementemia),
- (b) Primary mesangiocapillary glomerulonephritis (persistent hypocomplementemia), and
- (c) Systemic lupus erythematosus (SLE).

3. Coagulation factors: There is a relationship between the major molecules of intrinsic coagulation cascade which normally activates factor VII and mononuclear cells and macrophages which when activated (through receptor on their wall) by these molecules will produce cytokines which cause tissue damage. Also, fibrin has strong relationship with formation of glomerular crescents in anti-GBM disease and immune complex-induced glomerulonephritis. Anticoagulants and tissue plasminogen activators (as Ancord) have been reported to be of benefit in experimental glomerulonephritis.

4. Eicosanoids: As Prostaglandins (synthesized from arachidonic acid by cyclooxygenase) and leukotrienes (synthesized from arachidonic acid by lipoxygenase) play a role in immune response and glomerular haemodynamics. These compounds could be synthesized by the intrinsic glomerular cells as well as by the invading inflammatory cells.

5. Neutrophils: have an important role especially in proliferative types of glomerulonephritis. These cells are attracted to the glomerulus by the chemoattractant fragment of the complement cascade (activated by antibody). Cytokines (e.g. IL-8) derived from monocytes and endothelial cells also participate in recruitment of neutrophils in the glomerular injury. Neutrophils will induce injury by the release of reactive oxygen species including hydrogen peroxide, hydroxyl and superoxide ions as well as by producing lysosomal proteolytic enzymes as myeloperoxidase.

6. Macrophages: have a potent role especially in proliferative glomerulonephritis. They are recruited and activated within the glomeruli by interaction with cell adherence receptor on the Fc fragment of the glomerular immunoglobulin and by lymphokines secreted by sensitized T cells (migration inhibition factor and procoagulant-inducing factor). Macrophages can control variety of outcomes in glomerulonephritis. For example, they

- a. can produce a vast array of biologically active molecules (e.g. reactive oxygen species, lysosomal enzymes) producing proteinuria.
- b. induce coagulation (procoagulant activity, plasminogen activator and its inhibitor).
- c. have an important role in inducing proteinuria and fibrin deposition.
- d. affect the function of intrinsic glomerular cells by their release of cytokines and growth factors.
- e. may be involved in glomerular repair or sclerosis.

7. Cytokines and growth factors: These are released from infiltrating monocytes and glomerular cells especially mesangial cells. They include:

- a. Tumour necrosis factor (TNF) and interleukin-1 (IL-1): activate inflammatory cells as well as targeting glomerular cells and so, they augment the inflammatory process.
- b. Interleukin-6 (IL-6): stimulates mesangial cell proliferation.
- c. Tumour growth factor-B (TGF-B) facilitates mesangial matrix proliferation in experimental glomerulonephritis.

8. Intrinsic glomerular cells: These include:

- a. Mesangial cells: Inflammatory signals (complement components, I.C., growth factors, cytokines) cause proliferation of mesangial cells which produce IL-6, IL-1, TNF, TGF-B, Prostaglandins and platelet activating factor.

- b. Endothelial cells: Normally these cells have many important functions including: (i) maintenance of the anticoagulation state of the glomerular capillary bed. (ii) maintenance of capillary permeability, and (iii) formation of extracellular matrix.
- c. Epithelial cells: produce plasminogen activator inhibitor molecule. In response to immune injury, they proliferate and-with monocytes in the urinary space- form the glomerular crescent.

Cell Mediated Immune Injury of the Glomeruli:

This has been documented in proliferative, crescentic and minimal change nephritis. In these types of glomerular diseases, glomerular T cells are activated and produce expression of IL-2 receptor and production of cytokines including IL-4 and α -interferon.

In minimal change nephritis these cytokines induce proteinuria.

In crescentic glomerulonephritis, activated T cells activate monocyte-macrophage with production of fibrin and expression of procoagulant activity.

II- Metabolic Abnormalities: See diabetic nephropathy, gouty nephropathy and renal amyloidosis.

III- Hyperfiltration injury: See diabetic nephropathy.

IV- Hereditary Abnormalities: See Alport's Syndrome.

CLASSIFICATION OF GLOMERULONEPHRITIS:

Glomerulonephritis can be classified on the basis of (I) the etiologic cause; (II) the histopathologic findings on examination of kidney biopsy; (III) or according to the clinical presentation.

(I) Etiology of glomerulonephritis:

This could be either:

- a) Primary (idiopathic) when the glomerular disease is not part of systemic disease and the cause is unknown.
- b) Secondary when glomerular disease is part of a systemic disease (e.g. diabetes mellitus) or due to a known cause (e.g. post-streptococcal glomerulonephritis). Secondary glomerulonephritis may be the result of:
 1. *Infection* which may be bacterial (e.g. post-streptococcal), viral (e.g. HBV, HCV, CMV), parasitic (e.g. Schistosoma mansoni, malaria).

2. *Collagen disease* (e.g. SLE, polyarteritis nodosa, rheumatoid arthritis).
3. *Drug* (e.g. Penicillamine, Paraldione, Aspirin, Heroin).
4. *Metabolic disease* (e.g. Diabetes mellitus, amyloidosis).
5. *Malignancy* (e.g. lymphoma).
6. *Hereditary* (e.g. Alport syndrome).

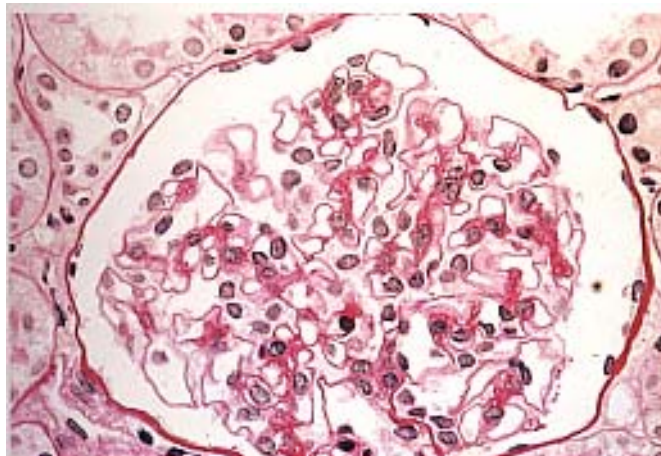
(II) Histopathologic classification of glomerulonephritis:

A paraffin section from a percutaneous needle biopsy of the kidney of a patient with glomerulonephritis (whether primary or secondary), when examined by light microscopy may show any of the following:

1. **Minimal change (Nil-change) disease (lipoid nephrosis) (Figure 3.1):**

Light microscopy may show either no abnormality or minimal increase in mesangial cellularity. Also, immunofluorescent microscopy may show no immune deposits. Electron microscopy may show fusion of foot processes of epithelial cells (podocytes).

Idiopathic type of this lesion usually clinically presents as steroid sensitive nephrotic syndrome with good prognosis.



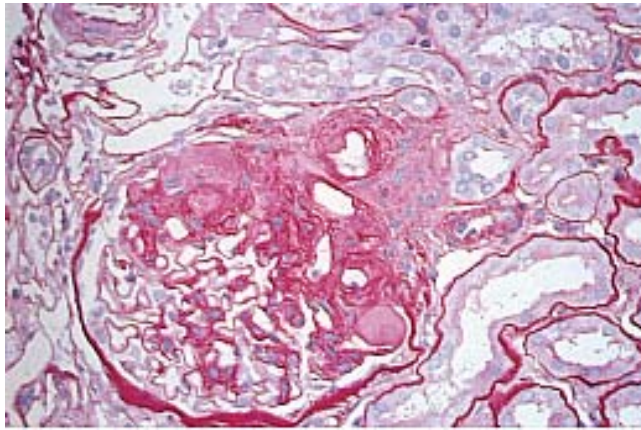
(Fig. 3.1)

PAS stained kidney section(X 410) from a patient with minimal change nephritis. Light microscopic examination shows a normal glomerulus.

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan).

2. **Focal and segmental glomerulosclerosis (Figure 3.2):** The glomerular lesions under light microscopy are sclerotic. These lesions involve only parts of the affected glomeruli (i.e. segmental) and some glomeruli look normal, but in between a glomerulus is affected (i.e. focal).

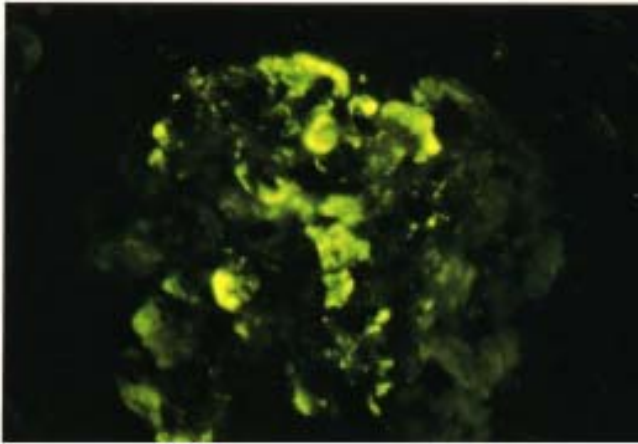
This disease usually presents with nephrotic syndrome with impairment of kidney function and hypertension. Response to steroid treatment is much less than that in minimal change glomerulonephritis.



(Fig. 3.2a)

PAS stained kidney section (X260) from a patient with FSGS. Light microscopic examination of an affected glomerulus shows segmental sclerosis in the hilar region.

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan).



(Fig. 3.2b)

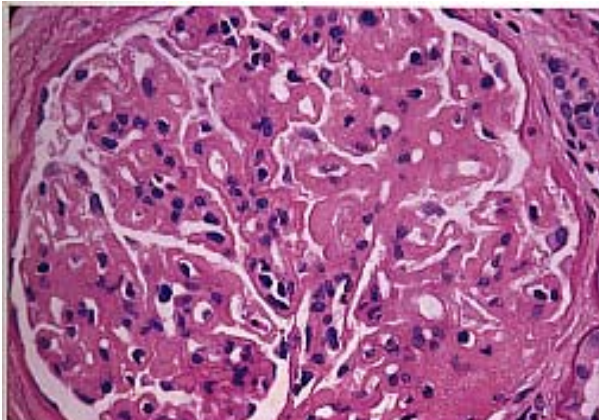
The same case when examined by immunofluorescent microscope shows segmental deposits of complement (C3)

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan).

3. Membranous glomerulonephritis (Figure 3.3):

In this type of glomerulopathy, light microscopic examination shows diffuse thickening of the glomerular capillary basement membrane with no proliferation in the mesangium.

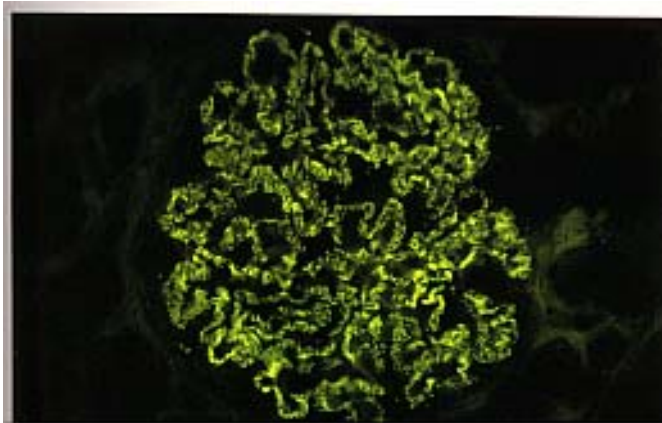
This disease usually presents as nephrotic syndrome with spontaneous remissions and exacerbations. It may be steroid sensitive.



(Fig. 3.3a)

PAS stained kidney section (X320) from a patient with membranous glomerulonephritis. Light microscopic examination shows marked thickening of the capillary walls with no cellular proliferation.

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan).



(Fig. 3.3b)

The same case in Fig. 3a, examined by I.F., it shows diffuse granular deposits of IgG along the capillary walls (X260).

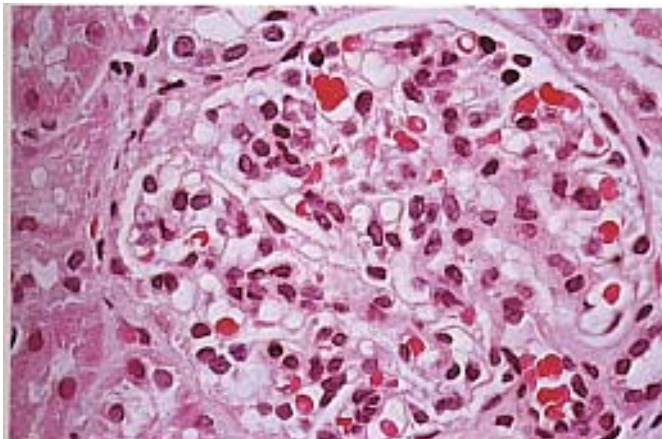
(Reproduced with permission from IGAKU-SHOIN Ltd, Japan).

4. Proliferative glomerulonephritis:

According to the site of proliferation within the renal glomeruli, this type could be sub-divided into:

- a. *Mesangial proliferative glomerulonephritis* (**Figure 3.4**): There is an increase in mesangial matrix and mesangial nuclei by light microscopic examination.

This disease usually presents with haematuria or with nephrotic syndrome.



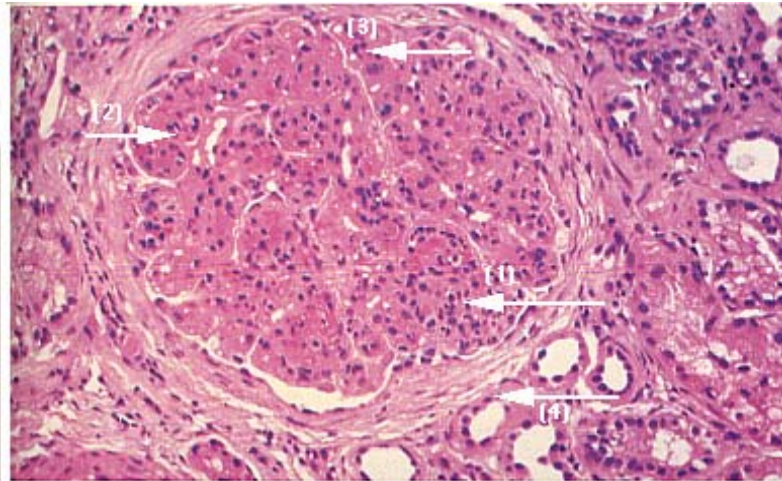
(Fig. 3.4)

PAS stained kidney section (X 410) from a patient with mesangial proliferative glomerulonephritis. Light microscopic examination shows diffuse proliferation in the mesangium with normal capillary walls

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan).

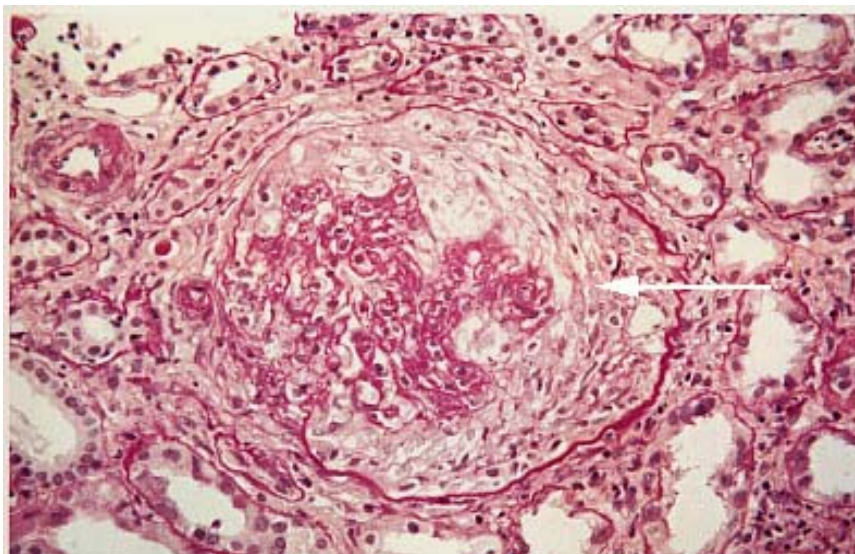
- b. *Mesangiocapillary* (or membranoproliferative) glomerulonephritis (**Figure 3.5**): There are both diffuse thickening of glomerular capillary wall and mesangial proliferation.

This disease may present as nephrotic syndrome. The disease is usually steroid resistant and slowly progresses to chronic renal failure.



(Fig. 3.5)
 Hx & E stain of a case of mesangio-capillary glomerulonephritis, there is mesangial proliferation (arrow-1) with lobulation, (arrow-2), thickening of the GBM (arrow-3). also there is periglomerular fibrosis (arrow-4)
(Reproduced with permission from IGA KU-SHOIN Ltd, Japan).

- c. *Crescentic glomerulonephritis (Figure 3.6)*: There is extensive cellular proliferations in the Bowman's capsule giving the appearance of crescent surrounding the glomerular tufts. This disease is serious and usually presents as rapidly progressive glomerulonephritis.



(Fig. 3.6)
 Periodic acid- schiff stain. High power view of a glomerulus showing Crescentic glomerulo-Nephritis (arrow)
(Reproduced with permission from IGA KU-SHOIN Ltd, Japan).

- d. *IgA nephropathy*: This is a proliferative type of glomerulonephritis characterized with predominant immunoglobulin A deposition in renal glomeruli when kidney sections are examined by immunofluorescence. IgA nephropathy is the commonest glomerular disease presenting with gross or microscopic haematuria.

(III) Clinical manifestations of glomerulonephritis:

Patient with glomerulonephritis may present with any of the following five syndromes:

1. Nephrotic syndrome:

This is characterized clinically with massive oedema of insidious onset. In some cases, it may progress slowly to renal failure. Urine analysis shows massive proteinuria ($> 3.5 \text{ gm}/24 \text{ hr}/1.37 \text{ m}^2$), microscopic haematuria and lipiduria. Serum analysis may show hypoalbuminaemia and hypercholesterolaemia. Serum creatinine is usually normal.

2. Acute nephritic syndrome (acute nephritis):

Characterized clinically with rapid onset of oedema (less in severity than in nephrotic syndrome), oliguria and hypertension. Urine analysis may show red cell casts, proteinuria (less in amount than in nephrotic syndrome), haematuria and leukocyturia. Serum analysis may show increased serum creatinine, normal serum albumin and cholesterol. Prognosis is usually good and recovery occurs.

3. Rapidly progressive glomerulonephritis (RPGN):

Characterized clinically with rapid (within days to weeks) loss of kidney function with development of manifestations of uraemia and the patient needs dialysis treatment. If not treated early and aggressively, the renal damage may be irreversible. Urine analysis may show findings which are similar to acute nephritic syndrome. Serum analysis shows rapidly increasing serum creatinine while serum albumin remains within normal.

4. Chronic nephritic syndrome:

Characterized by slowly (over months to years) progressive uraemia and the patient usually presents with manifestations of chronic renal failure. Urine analysis may show broad casts, loss of ability to concentrate urine (urine specific gravity is equal to plasma), proteinuria (mild) and microscopic haematuria. Serum analysis shows high serum creatinine and phosphate, low calcium, anaemia and metabolic acidosis.

5. Asymptomatic urinary abnormality:

As microscopic haematuria or proteinuria or both. The prognosis is usually excellent and no treatment is required.

NEPHROTIC SYNDROME (NS)

Definition: is a syndrome characterized by heavy proteinuria (more than 3.5gm/24h/1.73m²), hypoalbuminaemia, hyperlipidaemia and edema.

Etiology:

Nephrotic syndrome could be primary or a part of a systemic disease (i.e. secondary).

Secondary nephrotic syndrome may be due to any of the following:

1. Postinfection (e.g. Schistosoma and malaria).
2. Drug (e.g. penicillamine, phenytoin, gold and nonsteroidal anti-inflammatory drugs as aspirin).
3. Metabolic (e.g. D.M., amyloidosis).
4. Collagen and autoimmune disease (e.g. SLE, rheumatoid).
5. Malignancy (e.g. Lymphoma, multiple myeloma).
6. Renal vein thrombosis.
7. Congenital and familial conditions.

Pathology: See pathologic classification of glomerular diseases (Page 59).

Pathogenesis:

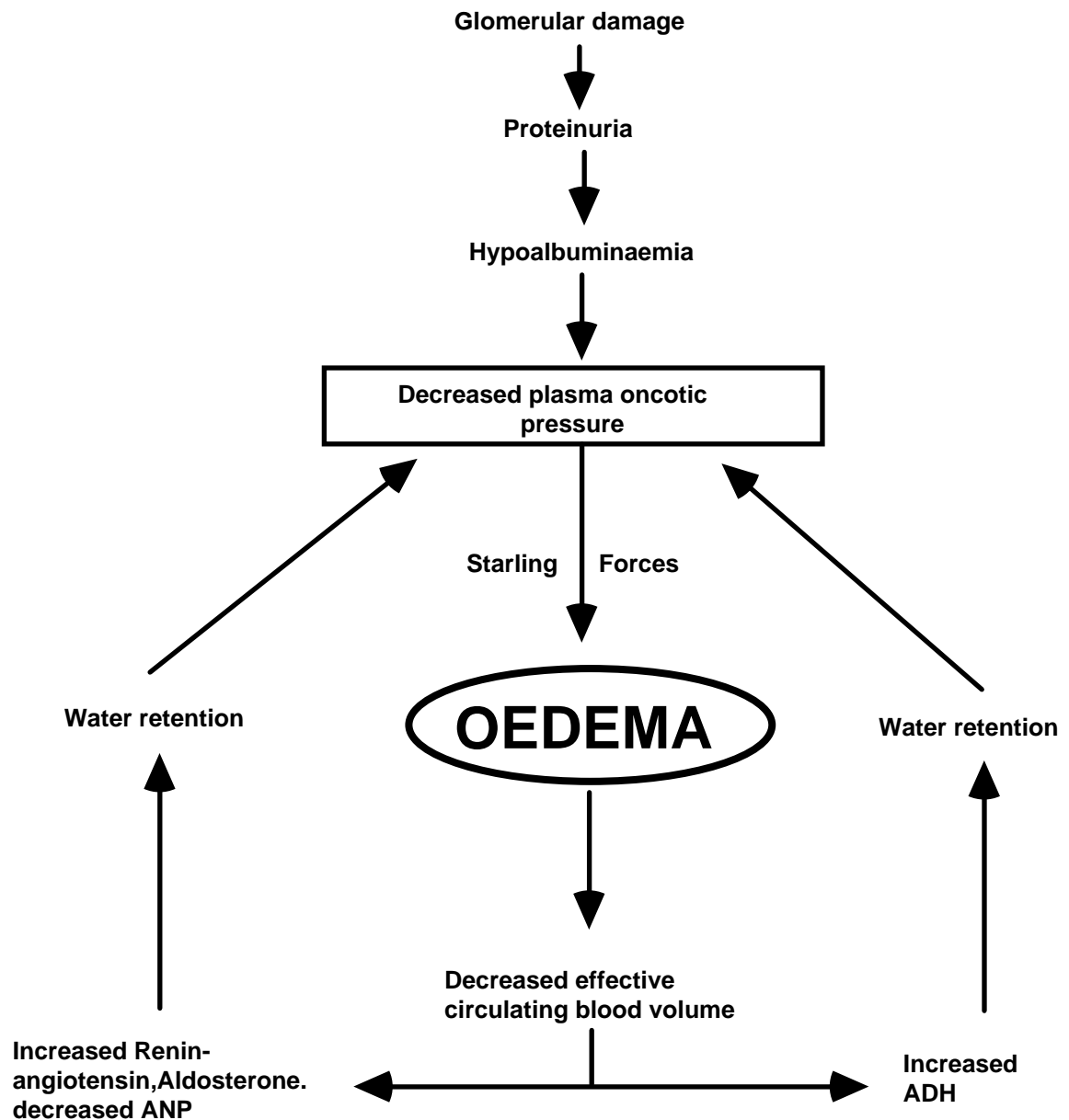
Hypoalbuminemia Is mainly due to loss of albumin through the kidney as a result of the glomerular disease. However, there are other factors which increase the magnitude of this problem such as:

1. The decreased intake (due to anorexia) and decreased absorption (due to oedema of the intestinal wall).
2. The increased concentration of albumin in the glomerular filtrate which is accompanied by increase in its catabolism by the renal tubules.
3. The partitioning of albumin between extra-and intravascular spaces; and
4. Sometimes decreased rate of hepatic biosynthesis of albumin.

Oedema:

The mechanisms incriminated in pathogenesis of oedema in nephrotic patient include the following (**Fig. 3.7**).

1. Hypoalbuminaemia results in a decrease in plasma oncotic (osmotic) pressure which is the power keeping water in the intravascular space. Consequently, water leaks to the interstitial space with formation of edema.



(Fig. 3.7)

Mechanisms of oedema formation in patients with nephrotic syndrome

2. Loss of intravascular fluids results in hypovolaemia (reduction of circulating blood volume) which a. stimulates the kidney (juxtaglomerular apparatus) to secrete Renin, b. stimulates volume receptors which stimulate the hypothalamus that stimulates pituitary secretion of

antidiuretic hormone (ADH), and c. stimulates volume receptors which will result in a decrease in secretion of atrial natriuretic peptide (ANP).

- 3- Renin secreted by juxta glomerular apparatus converts plasma angiotensinogen into angiotensin I which is converted by angiotensin converting enzyme (ACE) to angiotensin II. The latter stimulates secretion of aldosterone from the suprarenal gland. Aldosterone stimulates reabsorption of salt and water from the distal convoluted tubules.
- 4- Antidiuretic hormone stimulates reabsorption of water from the collecting ducts.
- 5- The decrease in the secretion of the atrial natriuretic peptide (ANP) decreases water and salt excretion by the kidney; and
- 6- Salt and water retained through the stimulation of Renin, and antidiuretic hormone secretion, and suppression of atrial natriuretic peptide secretion leak from the vascular space (due to low oncotic pressure) to the interstitial space with more oedema formation.

Hyperlipidemia:

Hyperlipidemia is secondary to hypoalbuminemia. This condition is accompanied with increase in concentration of plasma cholesterol, triglycerides, VLDL and a decrease in HDL. Urine examination may show lipiduria and oval fat bodies.

Clinical Picture of Nephrotic Syndrome:

1. *Edema:* is the main clinical feature of nephrotic syndrome. It starts as morning puffiness of the face. Then, gradually progresses to edema of lower limbs; especially on prolonged standing and at the end of the day. In severe cases edema may progress to be generalized anasarca with ascites- even pleural and pericardial effusion.
2. *Hypertension:* may be detected in nearly 50% of the cases, according to the etiologic and pathologic type of nephrotic syndrome. For example idiopathic minimal change nephrotic syndrome cases are always normotensive while cases with mesangiocapillary glomerulonephritis whether idiopathic or secondary are always hypertensive. Hypertension is either due to salt and water retention or it may be due to the excess secretion of renin.
3. *Other manifestations of nephrotic syndrome* include lassitude, anorexia, loss of appetite and pallor.

4. *Manifestations of the etiologic cause* in secondary cases as manifestations of diabetes in cases with diabetic nephropathy.

Complications:

1. *Subnutritional State:* Due to poor dieting, and urinary losses of protein and other substances.
2. *Infection:* Especially upper respiratory, urinary, skin and peritoneal infections.
Recurrent infection is due to nutritional deficiencies, urinary loss of immunoglobulins and complements.
3. *Clotting episodes:* These manifest as a recurrent deep vein thrombosis (DVT), or renal vein thrombosis. It may be complicated by pulmonary embolism. This clotting tendency in nephrotic patients is due to:
 - a. Increased concentration of coagulation factors resulting from an increased hepatic synthesis e.g. fibrinogen, factor III, and VIII.
 - b. Urinary loss of antithrombin III and protein C which normally act against intravascular clotting.
 - c. Abnormal vascular endothelium.
 - d. Hypovolemic state.
4. *Premature atherosclerosis:* it is due to hyperlipidaemia. This complication occurs mainly in cases with frequent relapses or cases resistant to treatment.
5. *Hypovolaemia:* Which causes postural hypotension.
6. *Drug related complications:* This category includes:
 - a. Diuretics which may cause hypovolaemia, hypokalaemia, or hyponatraemia.
 - b. Corticosteroids that may cause diabetes mellitus, cataract, D.U., infections, and bone disease.
 - c. Other Immunosuppressive drugs as cyclophosphamide which may cause haemorrhagic cystitis, alopecia, infection and malignancy.
7. *Acute renal failure,* this may be due to severe hypovolaemia (due to the severe hypoalbuminaemia and use of big doses of diuretics), or due to acute interstitial nephritis (drug induced as large dose of furosemide).
8. *Bone disease:* Due to hypocalcemia (resulting from deficient intake and urinary loss of vitamin D binding globulin). It causes secondary hyperparathyroidism.
9. *Anemia:* Due to nutritional deficiencies and urinary loss of transferrin.

Investigations of Nephrotic Syndrome:

1. *Urine analysis* for proteinuria, microscopic haematuria, pus cells, casts, also collect 24 hours urine for quantitation of urinary protein excretion.
2. *Blood* for hypoalbuminaemia, hyperlipidaemia, hypocalcaemia and for serum creatinine level.
3. *Investigations for diagnosis of the cause in secondary cases* e.g. fasting and postprandial blood sugar for diabetes and anti-DNA for SLE.
4. *Kidney biopsy*: in children, kidney biopsy is indicated only in steroid resistant or steroid dependent cases as well as in frequent relapsers and those with impaired kidney functions. But in adults, it is wise to obtain kidney biopsy to determine the underlying pathology so that specific treatment can be initiated if indicated.

Treatment of nephrotic syndrome:

The regimen for the treatment of NS is as follows:

1. *Treatment of the cause in secondary cases*- for example- by proper control of blood sugar in D.M. and steroids and immunosuppressive drugs in SLE.
2. *Treatment of complications* as infection by antibiotics and under nutrition by giving proper dieting, minerals and vitamins.
3. *Rest in bed* during exacerbation to promote diuresis and early ambulation with remission to avoid DVT.
4. *Diet*: salt restricted supported with vitamins especially vitamin D and calcium. Protein content should equal the daily physiologic needs (1g/kg) plus the amount of daily urinary protein loss e.g. a 60 kg patient who loses 10 gm daily should be given 70 gm protein containing diet.
5. *Diuretics*: Mainly loop diuretics (e.g. Frusemide) initially can be given orally in variable doses (according to severity and response e.g. 20-60 mg/d.). In severe resistant cases doses up to 120 mg. I.V. may be given. Addition of metolazone (a thiazide diuretic) may have a potentiating effect for frusemide in diuretic resistant cases.
6. *Salt poor albumin* is expensive and when given is lost quickly in urine. So it is indicated only when there is severe oedema resistant to large doses of diuretics and if the nephrotic patient is to be subjected to surgery or invasive procedure (e.g. biopsy). Albumin infusion will improve the plasma oncotic pressure. This improves circulating blood volume and prevents hypotension or shock during the procedure.

7. *Corticosteroids* are given when there is no response to previous lines of treatment. Minimal change glomerulonephritis gives the best response while mesangiocapillary glomerulonephritis is always steroid resistant. Other types of primary glomerulopathy are in between. For patients with secondary glomerulonephritis, steroids are given if indicated for the causative disease as in SLE but not in D.M. The dose and duration of steroid treatment depends on the type of disease and response. In primary (idiopathic) minimal change nephritis 40-60 mg daily prednisone are given orally (for children 1-2 mg/kg/d), for 4-6 weeks followed by gradual withdrawal.
8. *Other immunosuppressive drugs* as cyclophosphamide, azathioprine and ciclosporin in selected cases (See page 118).

ACUTE POST-STREPTOCOCCAL GLOMERULONEPHRITIS

10% of patients infected with nephritogenic strains of group A, β -haemolytic streptococci will develop glomerulonephritis.

Streptococcal infection may be pharyngeal or skin infection. The period between infection and the appearance of glomerulonephritis (latent period) is 1-3 weeks for pharyngeal infection and 2-4 weeks for skin infection.

Children are more affected than adults and males are more than females.

Clinical picture:

Usually the patients present with manifestations of acute nephritic syndrome with oliguria, smoky urine, puffiness of the face and headache (as a result of hypertension). 20% of patients may manifest as nephrotic syndrome, 5% may present as rapidly progressive glomerulonephritis and some patients may be with asymptomatic urinary abnormalities.

Some patients may develop encephalopathy as a result of severe hypertension or hyponatraemia or they develop heart failure because of hypertension and fluid retention.

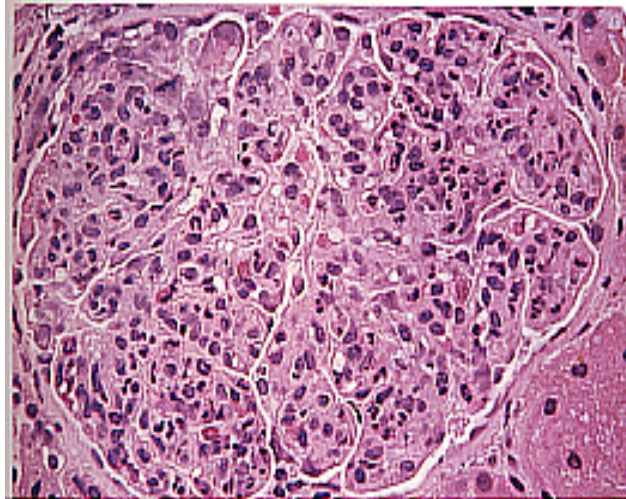
Pathogenesis:

1. Nephritogenic strains of streptococci may secrete substances e.g. neuraminidase and sialic acid which may modify autologous immunoglobulin for which antibodies are formed by the patient (autoantibodies) and immune complexes are formed which will be trapped by the renal glomeruli and cause the disease.
2. Streptococcal antigens stimulate the body to form antibodies to them with the subsequent immune complex formation.

Laboratory investigations:

1. Urine may show red cell casts, proteinuria (less than in nephrotic syndrome), haematuria or leucocyturia.
2. Pharyngeal or skin culture may show streptococci.
3. Markers of streptococcal infection as ASO titre and C-reactive protein are positive.
4. Hypocomplementaemia (C3, C4) which is transient (for few weeks only).

5. Serum creatinine is usually high.
6. Kidney biopsy (**Fig. 3.8**) may show diffuse proliferative glomerulonephritis with neutrophil and monocyte infiltration of the glomeruli. Severe cases may show glomerular crescents (cases presenting clinically with rapidly progressive glomerulonephritis).



(Fig. 3.8)

Hx & E stained kidney section (X 260) from a patient with post infection glomerulonephritis. Light microscopic examination shows diffuse proliferative endocapillary glomerulonephritis. With marked cellularity caused by both mononuclear cells and polymorphonuclear leukocytes.

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan)

Treatment:

Treatment of poststreptococcal glomerulonephritis is mainly symptomatic (rest, salt restriction, diuretics, antihypertensives, treatment of infection and dialysis if renal failure develops). Sometimes steroids and immunosuppressive drugs are given for cases presenting with RPGN.

Prognosis:

Most of the cases (85%) recover completely, 5% die in early phases from complications (hypertensive encephalopathy or heart failure). The rest of the cases pass to chronic glomerulonephritis and develop chronic renal failure.

Prognosis is better in children than in adults. Signs of bad prognosis are persistently rising serum creatinine, heavy proteinuria, persistent hypertension with gross haematuria and presence of glomerular crescents in renal biopsy.

PRIMARY GLOMERULONEPHRITIS
Minimal Change Nephritis
(MCN)

Etiology:

Minimal change nephritis may be primary but as well may be secondary to many conditions such as Hodgkin's and Non-Hodgkin's lymphoma, or the non steroidal anti-inflammatory drugs.

Histopathology (Fig. 3.2):

Light microscopy shows no changes or there may be minimal mesangial proliferative changes, tubulointerstitium will be normal or sometimes lipid droplets may be seen in the proximal convoluted tubules.

Early membranous glomerulonephritis and early focal segmental glomerulosclerosis may look like minimal change nephritis when kidney sections are examined by light microscopy.

Immunofluorescence microscopy shows negative or occasionally mesangial C3 deposits.

IgM nephropathy is a variant of MCN which is characterized by mesangial deposits of IgM.

Electron microscopy shows only fusion of the epithelial foot processes and obliteration of the slit pore diaphragm. These changes are non-specific findings which could be seen in any case of heavy proteinuria.

Laboratory Findings:

Serology shows normal C3, C4, anti-dsDNA, ANA, cryoglobulins and is negative for anti-GBM, CIC and ANCA.

Clinical features of primary MCN:

Frank nephrotic syndrome is the commonest presentation of MCN, patient is normotensive and GFR is normal (unless there is a prerenal factor or drug toxicity).

Urine examination shows heavy proteinuria which is highly selective. Only 20% of cases will show microhematuria.

Nephrotic syndrome in children 2-6 years of age is due to MCN in 90% of cases, this incidence decreases by aging to be only 20% in adults.

MCN is more common in male (male to female ratio is 2 : 1), usually is preceded by upper respiratory tract infection or by immunization. Sometimes, there is history of atopy and there is a correlation with HLA B12.

Pathogenesis:

Minimal change nephritis is most probably due to altered T-cell functions.

Treatment:

See page 108.

Focal and Segmental Glomerulosclerosis (FSGS)

FSGS is responsible for 10-20% of cases of Nephrotic Syndrome in Western countries.

Etiology:

FSGS may be a primary disease or may be secondary to:

- Schistosomiasis or bacterial endocarditis
- SLE or vasculitis
- Heroin abuse
- Hyperfiltration injury or reflux nephropathy
- Sickle cell disease
- Aging

Histopathology (Fig. 3.3):

Light microscopy shows focal glomerular (i.e. each affected glomerulus is surrounded by healthy glomeruli) involvement by segmental sclerosis or hyalinosis. The disease starts in the juxta medullary glomeruli (i.e. superficial biopsy in early phases of the disease will show normal glomeruli). There is deposition of hyaline materials in the subendothelial area with adjacent epithelial cellular proliferation with adherence to Bowman's capsule. These changes are segmental and may proceed to sclerosis. When the lesions are advanced the glomeruli become globally sclerosed.

Minimal change nephritis, FSGS and mild focal mesangial proliferative glomerulonephritis are believed to be either three different diseases or subtypes of them are one disease in different phases of evolution.

Primary FSGS should be differentiated from FSGS involving the remaining nephron after another disease causing glomerular damage. Hyperfiltration of the remaining nephron results-by time-in FSGS in the remaining glomeruli.

Immunofluorescent microscopy: FSGS of haemodynamic etiology shows negative immuno- fluorescence, but primary and other types of secondary FSGS show glomerular C3 and IgM deposits in segmental pattern.

Electron microscopy shows global effacement and fusion of the epithelial foot processes and focal segmental subendothelial deposition of foam cells.

Clinical features of FSGS

The disease usually presents with nephrotic syndrome, haematuria, hypertension and decreased GFR. Decreased capacity to concentrate urine due to early affection of the vasa recta capillaries and the long-looped nephrons is more common with FSGS as the disease starts early in the juxtamedullary area.

Proteinuria is poorly selective and complement components are normal.

Prognosis:

50% of patients with FSGS will develop end stage renal failure within 10 years. Presence of mesangial proliferation is a poor sign.

Treatment:

See page 108.

Membranous Glomerulonephritis (MGN)

Among adults in the western countries MGN represents 17-42% of causes of nephrotic syndrome.

MGN could be primary or secondary to the following:

- . Infection: Malaria, schistosoma, HBV infection
- . Autoimmune disease as SLE and Rheumatoid arthritis
- . Malignancy as GIT malignancy especially in elderly.
- . Drug: Penicillamine, gold, captopril.

Histopathology (Fig. 3.4):

Light microscopy shows that the glomeruli are uniformly affected. In early stages it may look within normal and may be confused with MCN. In full blown picture, there is thickening of the glomerular basement membrane but no cellular infiltration or mesangial proliferation.

Immunofluorescent microscopy shows capillary wall granular deposits mainly of IgG and C3.

Electron microscopy shows subendothelial deposits and fusion of the foot process. Histopathologically, primary MGN passes into four stages.

- In stage 1, the GBM is normal by L.M. but there is discrete electron-dense deposits in the subepithelial sites.
- In stage 2, GBM-like material is found between the deposits giving the appearance of spikes by LM.
- In stage 3, the GBM-like material encircles the deposits.
- In stage 4, the deposits become less electron-dense and the surrounding GBM gives "Swiss cheese" appearance.

Clinical feature:

MGN usually follows an insidious onset. In 80% of patients, it presents with massive proteinuria and nephrotic syndrome, while 20% of patients may have only asymptomatic proteinuria.

Hypertension and uraemia usually occur late in the disease. Proteinuria is either moderately or poorly selective.

In primary MGN complement components are normal (slow consumption and high liver synthesis) and no CIC (in situ complex).

Prognosis:

In children and in 10-30% of adults spontaneous and complete lasting remissions occur. The remaining cases progress to CRF. The 10-year survival in untreated MN is 75%.

Treatment:

See page 108.

Mesangial Proliferative Glomerulonephritis

This disease may be primary or secondary to the following:

- . Infection as schistosoma and malaria.
- . Autoimmune as SLE and Henoch-Shönlein purpura.
- . Metabolic as diabetic nephropathy.

Histopathology (Fig. 3.5):

Light microscopy may show pure mesangial proliferation with abnormality in GBM.

Immunofluorescent microscopy may show fine and granular mesangial deposits of C3, IgG, IgA, IgM. Predominance of IgA is seen in IgA nephropathy and predominance of IgM is seen in the entity called IgM nephropathy.

Electron microscopy shows mesangial electron dense deposits and fusion of epithelial foot processes.

Clinical features:

The disease may present with asymptomatic urine abnormality, gross haematuria or nephrotic syndrome.

In primary types serology is negative for C3, ANA and other immunologic markers.

Prognosis:

Prognosis is excellent in some cases but others follow a course similar to FSGS or MCN.

Treatment:

See page 108.

Membranoproliferative Glomerulonephritis (MPGN)

10% of cases of nephrotic syndrome in the west is due to MPGN.

The disease could be primary or secondary to:

- . Infection as schistosoma, malaria, HCV, HBV, bacterial endocarditis and shunt nephritis.

- . Autoimmune disease as SLE and cryoglobulinaemia.
- . Chronic lymphatic leukaemia.
- . Congenital complement deficiency.
- . Type II MPGN is sometimes associated with partial lipodystrophy.

Histopathology (Fig. 3.6):

Light microscopy shows mesangial proliferation which when severe, will give the lobulation pattern for the glomerular tuft (lobular GN). In secondary types, there may be infiltration of the mesangium with mononuclear cells and neutrophils. The GBM is thick with a double contour appearance.

Immunofluorescent microscopy shows granular mesangial and capillary wall deposits of C3, C4 and IgG.

Electron microscopy shows subendothelial mesangial interposition in type I lesions and intramembraneous dense deposits in type II lesions. Sometimes the deposits are also seen in the subepithelial space (type III MPGN).

Sometimes the mesangial proliferation is lacking but the characteristic GBM changes are evident.

Clinical features:

MPGN is responsible for 50% of N.S. with heavy proteinuria, 30% of asymptomatic proteinuria and 20% of acute nephritis. 50% of cases are preceded with upper respiratory tract infection with high ASO. About 50% of cases have low GFR and 30% are hypertensive at presentation. Sometimes patients become hypertensive only on starting steroid therapy.

There is hypocomplementaemia which is persistent (in post-infection GN it is transient). The pattern of hypocomplementaemia is different between type I and type II. C3 is low in 75% of cases with type I or type II. In only type I, there is low C1 and C4 (early components of the classic pathway of activation).

In 60% of cases with only type II, there is C3 nephritic factor (C3NF) which is an autoantibody to the enzyme C3 convertase of the alternative pathway protecting it from inhibitory proteins. This result in continuous degradation of C3 to its active form with consequent low C3 level. A similar substance is sometimes detected in 10% of cases with type I MPGN.

Type II MPGN is associated with lipodystrophy and HLA-B7. Frequently in MPGN there is Comb's test negative normocytic normochromic

anaemia not matching with the degree of renal dysfunction. RBC's and platelet half life are decreased and there is a high turn over of fibrinogen and microangiopathy.

Prognosis:

10-year survival is 50%, type II carries a worse prognosis than type I. Hypertension, low GFR, severe NS and superimposed crescents in renal biopsies are all bad signs and of poor prognosis.

Treatment:

See page 108.

Crescentic Glomerulonephritis (CGN)

These types of proliferative GN are characterized by cellular proliferation in Bowman's space with crescent formation in more than 50% of the glomeruli.

These could be primary lesions or secondary to systemic diseases (Goodpasture's syndrome, SLE, Henoch-Schönlein purpura, cryoglobulinaemia, vasculitis, or infection related).

According to the immunofluorescent examination of kidney sections, three types of CGN are identified:

Primary (Idiopathic) crescentic GN (Type I)

Represents 30% of cases presenting with RPGN, and is characterized by the presence of anti-GBM (linear deposits of Ig along the GBM).

Patients affected are mostly young or middle age males. The disease is either of insidious onset and progresses to uraemia or presents as acute nephritic syndrome. Beside the renal manifestations the patient may suffer from fever, myalgia, abdominal pains and rheumatoid arthritis-like symptoms. Kidney biopsy when examined by light microscopy may show crescents in more than 50% of the glomeruli. Initially the crescents are cellular (mainly

monocytes), later become fibrous. Glomerular tuft shows no proliferation. There is periglomerular fibrosis and tubulointerstitial changes as dilatation and fibrosis.

Immunofluorescent microscopy may show IgG and C3 linear deposits along the GBM and fibrin deposits in the crescents. When the disease advances and the glomeruli are damaged the deposits may look granular.

Electron microscopy shows gaps in the GBM (the sites of monocyte and fibrinogen leak to the glomeruli and crescents). Endothelial cells may be seen detached from the underlying GBM, usually there are no electron deposits seen.

Serologically, anti-GBM could be detected in 90% of cases with no CIC, normal complement components and ANA. In early phase microangiopathic haemolytic anaemia is detected in some cases.

Poor prognostic signs are extensive crescents, tubular atrophy and interstitial fibrosis.

Treatment should start early and aggressively by plasma exchange, steroids and cyclophosphamide.

Primary (Idiopathic) crescentic GN (Type II)

Responsible for 30% of cases with RPGN.

Clinical features are similar to type I.

Light microscopy shows crescents as in type I. There may be some endocapillary proliferation. But if this is marked, it may denote secondary rather than primary etiology.

Immunofluorescent microscopy shows granular deposits of IgG and C3 along the capillary walls.

Electron microscopy may show subendothelial deposits. Serology will show CIC and hypocomplementaemia.

Treatment is the same as type I.

***Primary (Idiopathic) crescentic GN
(Type III)***

The least common type, Clinical features are similar to the other types. Immunofluorescence microscopy shows no deposits so it is sometimes called pauci-immune crescentic G.N.

Serology shows a presence of ANCA (sometimes the disease is considered as renally localized form of polyarteritis nodosa). There is neither CIC, nor anti-GBM.

Treatment is by steroid and cyclophosphamide.

SECONDARY GLOMERULAR DISEASES

In many diseases renal involvement is a part of a generalized process e.g. diabetes mellitus and systemic lupus erythematosus. Renal involvement may be the dominant lesion or may be just an incidental finding. Generally, when the kidney is involved, the prognosis and type of treatment are changed drastically.

Systemic lupus Erythematosus and lupus nephritis

SLE is an autoimmune disease with systemic manifestations. It affects 1/10,000 population. The incidence is higher in females than in males (9: 1). It affects caucasian more than black and occurs more in adolescents than in elderly. Most probably the disease reflects an exaggerated response to common environmental agents in a genetically susceptible host.

Circulating and in-situ formation of DNA-anti-DNA immune complexes are thought to be the main pathogenic mechanisms for SLE. Complement deficiency may be a promoting factor. Not all SLE patients will show clinically evident renal involvement. But, if kidney biopsies are obtained and examined thoroughly all patients will show glomerular disease.

In clinical practice lupus nephritis is responsible for more than 5% of patients presenting with glomerulonephritis. Sometimes renal manifestations are the main presentation of SLE patient with minor systemic disease.

Pathology of lupus nephritis (Fig. 3.9).

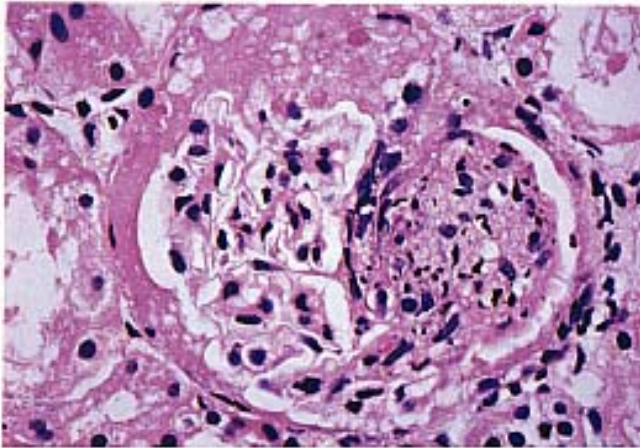
According to the World Health Organization (WHO), lupus nephritis could be one of five classes:

Class I (no change) in which kidney biopsies show no changes by light microscopy, few immune deposits (+) may be seen in the mesangium by I.F. and by E.M.

Class II (mild mesangial proliferative) where mild mesangial hypercellularity may be seen by L.M. and IF and EM may show deposits in the mesangium (++) and sometimes in the subendothelial area (+).

Class III (focal and segmental proliferation), in this type, light microscopy shows evident segmental proliferation, necrosis and occasionally hyaline thrombi, IF and EM show more marked deposits in the mesangium (+++) and to less extent in the subendothelial area (+).

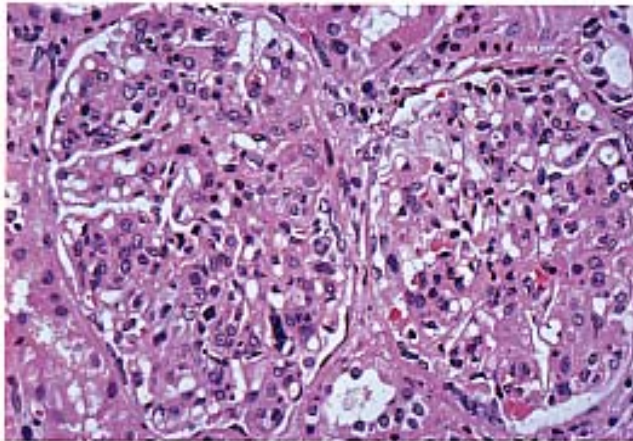
Class IV (diffuse proliferation), light microscopy shows diffuse hypercellularity, membranoproliferative changes, glomerular tuft necrosis, crescents, and wire loops. IF and EM show extensive deposits (+++) in all areas (mesangial, subendothelial and subepithelial).



(Fig. 3.9a)

PAS stained kidney section(X410) from a patient with lupus nephritis (WHO-class III), it shows about one third of the glomerulus Occupied by a necrotic lesion containing Fragmented polymorph-nuclear leukocytes, the rest of the glomerulus shows minimal changes

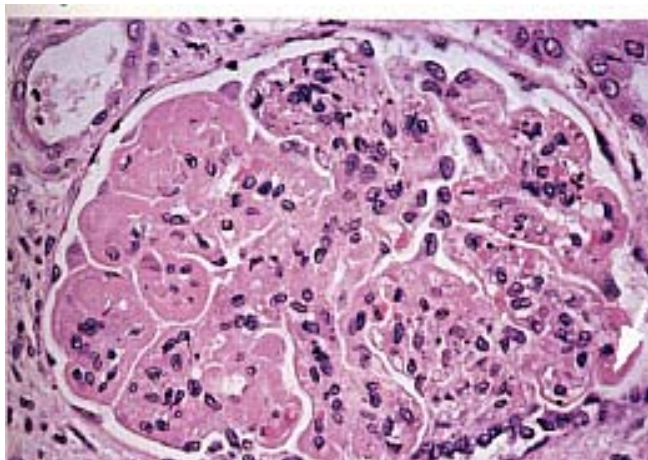
(Reproduced with Permission from GAKU-SHOIN Ltd. Japan)



(Fig. 3.9b)

Hx & E stained kidney section (X260) from a patient with lupus nephritis (WHO-class IV), it shows two glomeruli with diffuse cellular proliferation and exudation of polymorphnuclear leucocytes.

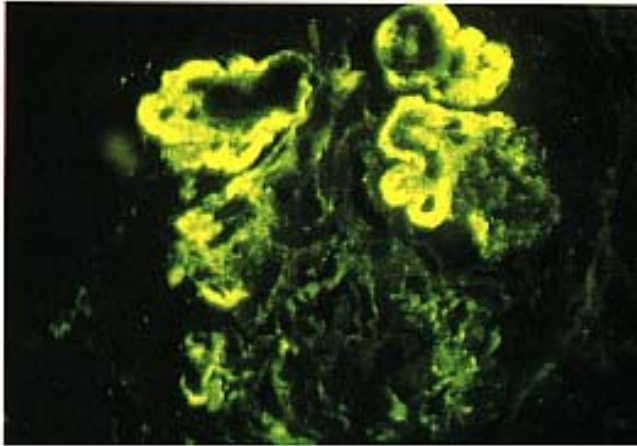
(Reproduced with Permission from IGAKU-SHOIN Ltd., Japan)



(Fig. 3.9c)

Hx & E stained kidney section (X260) from a patient with lupus nephritis (WHO-class IV), it shows cellular proliferation and prominent wire Loops (arrow).

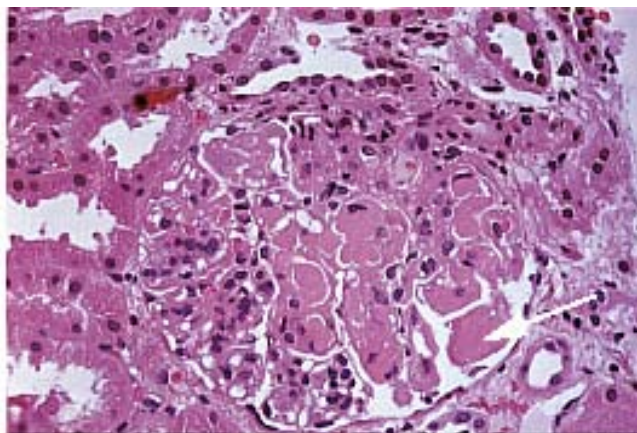
(Reproduced with Permission from IGAKU-SHOIN Ltd., Japan)



(Fig. 3.9d)

Immunofluorescence stained kidney section from a patient with lupus nephritis (WHO-class IV), it shows massive deposits of IgG along the capillary walls (wire loops)

(Reproduced with Permission from IGAKU-SHOIN Ltd., Japan)



(Fig. 3.9e)

Hx & E stained kidney section (X260) from a patient with lupus nephritis (WHO-class IV), it shows cellular proliferation and many hyaline thrombi (arrow)

(Reproduced with Permission from IGAKU-SHOIN Ltd., Japan)

Class V (diffuse membranous), light microscopy shows capillary wall expansion by subepithelial deposits, with some mesangial hypercellularity. IF and EM show deposits mainly in the subepithelial (+++) area, but also deposits may be seen in the mesangium (++) and subendothelial area (+).

Each of these classes can be further assessed according to its degree of activity or chronicity via Activity index (AI) and chronicity index (CI). The pathologist can review the biopsy for activity markers (e.g. glomerular tuft necrosis, wire loops, hyaline thrombi, cellular crescents, mesangial proliferation and cellular infiltrate) to give a score of out of 24 (e.g. AI of 18/24 for markedly active lesion and AI of 2/24 for less active lesion). Chronicity markers in biopsy include fibrous crescents, glomerulosclerosis, tubular atrophy and interstitial fibrosis. Chronicity Index is a score of 12, (e.g. markedly chronic lesions may have a score of 10/12). Assessment of kidney lesion by WHO classification and by chronicity and activity indices is mandatory for proper management of the cases.

Among different pathologic lesions seen in biopsy wire loop lesion, haematoxylin bodies and finger printing like-pattern of electron dense immune deposits are lesions which are highly specific for lupus nephritis.

Clinical Manifestations of Lupus Nephritis:

It is known that 50-90% of lupus patients will show manifestation(s) of renal disease. Many of such patients may not show any clinically oriented renal disease, but when subjected to kidney biopsy glomerular lesions will be detected.

Clinical presentation of lupus nephritis patient may vary from asymptomatic urine abnormality to rapidly progressive glomerulonephritis. Furthermore, some patients show manifestations of tubulointerstitial nephritis (e.g. RTA) or vasculitis.

There is a correlation between the histopathologic findings in renal biopsies and clinical manifestations of lupus nephritis. Patients with class II may show mild haematuria or proteinuria. Patients with class IV show severe forms of renal disease with renal impairment, hypertension, nephrotic syndrome and patients with class V usually present with severe form of nephrotic syndrome.

Diagnosis:

For all patients with glomerular disease, SLE should be considered as a possible etiologic cause particularly in young females. However, renal manifestation could be the only presenting feature. Yet, most of patients show other systemic manifestations of SLE.

For diagnosis of SLE, four or more of the criteria which have been established by The American Rheumatism Association (ARA) should be encountered.

The diagnosis should be confirmed by screening for Anti-nuclear antibodies (ANA) and the more specific anti-double stranded DNA (anti-dsDNA). Measurement of ESR, complement component C3, C4 and Circulating Immune Complexes (CIC) may help in assessing disease activity.

The ARA criteria for diagnosis of SLE include:

- | | |
|---|--|
| 1- Malar rash. | 2- Discoid rash |
| 3- Photosensitivity | 4- Oral ulcers |
| 5- Arthritis | 6- Serositis |
| 7- Renal disease | 8- Neurological disorders
(seizures, psychosis) |
| 9- Hematologic disorders
(haemolytic anaemia, lymphopenia, leukopenia, thrombocytopenia) | |

- 10- Immunologic disorders (positive LE cell test, anti-DNA, anti-sm antibody)
- 11- Positive anti nuclear antibody.

Treatment:

There is no standard regimen for the treatment of lupus nephritis patient. But there are many therapeutic tools which has to be tailored for every case. Patient's age, sex, disease class, activity and chronicity indices and clinical presentation all determine the choice of the treatment. The available treatment protocols include: (1) Prednisolone, oral, 1mg/kg/d, (2) 3-5 days pulses of methyl prednisolone 500-1000 mg each, (3) Cytoxan (cyclophosphamide) 2-3 mg orally/d (4) cytoxan 0.5-1.0 gm/m² surface area monthly for 6 months, (5) Azathioprine 2-3 mg/kg/d, (6) Cyclosporin A 5mg/kg/d, orally; and/or (7) Plasma exchange.

Generally, the target of treatment is to induce remission, then to maintain it by small doses of either one drug (Prednisolone) or combined (e.g. Prednisolone and Azathioprine). The more active the disease, the more aggressive the treatment will be and vice versa.

Beside the specific treatment for SLE, the patient may need other drugs such as hypotensives for hypertension, diuretics for oedema, and supportive dialysis for renal failure.

Renal Involvement In Vasculitis

Among different types of vasculitis, polyarteritis nodosa (PAN) and Wegener's Granulomatosis (W.G.) stand as the more common diseases affecting the kidney. Polyarteritis nodosa is either classic (involving medium sized-vessels as renal arteries with aneurysm formation) or microscopic involving small arteries and arterioles presenting with manifestation of glomerulopathies (mostly PRGN).

The classic type of polyarteritis nodosa may present with ischaemic renal changes, hypertension, immobilization with renal infarctions or haemorrhage related to the kidney (haematuria, peri-renal hematoma resulting from rupture of aneurysm). Concomitant mesenteric, coronary or cerebral vessels affection could be detected.

Wegener's granulomatosis mainly involves small vessels with early, major disease of respiratory tract excluding asthma. Granulomata are characteristic but not essential feature for diagnosis of W.G.

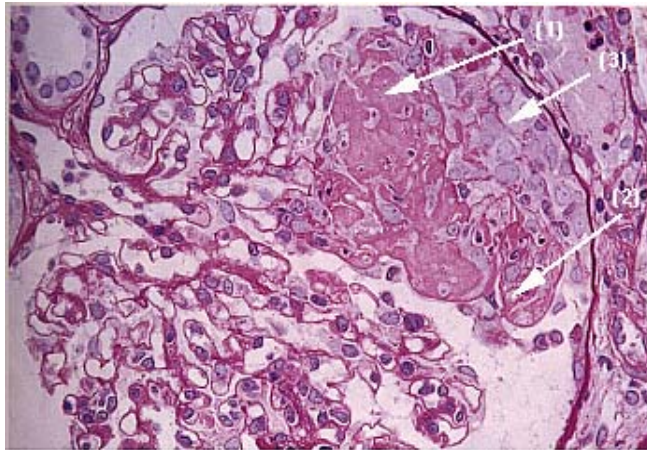
For more details see chapter on vasculitis (Page 126).

Henoch-Schönlein Purpura (HSP)

HSP is a multisystem disease with renal, gastrointestinal and cutaneous manifestations. It usually affects children 5-15 years old with a slight preponderance of males. Full recovery is common in children. But in adults, the course could be problematic. Renal involvement is documented in 10-30% of the cases, but in some series, it reaches up to 90% of the cases. The primary abnormality is most probably defective handling of mucosally presented antigen.

Pathology (Fig. 3.10):

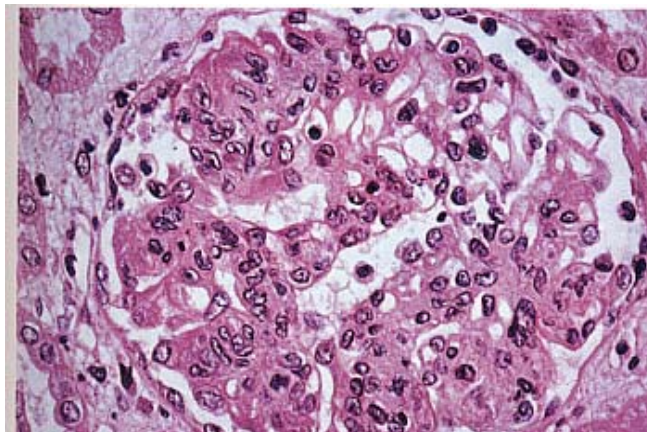
There is a great similarity between HSP and IgA nephropathy. Light microscopy usually shows changes variable from minimal abnormalities, mesangial proliferation, focal mesangial proliferation with crescent formation to membranoproliferative glomerulonephritis. Immunofluorescent microscopy will show predominant IgA deposits which are mainly mesangial, and this is usually accompanied with C3, IgG and to a lesser extent IgM.



(Fig. 3.10a)

PAS stained kidney section(X310) from a patient with Henoch-Schonleinpurpura, it shows segmental involvement of the glomerulus with thrombosis(arrow 1) necrosis (arrow-2), and a small crescent (arrow3). The remaining of the glomerulus looks normal.

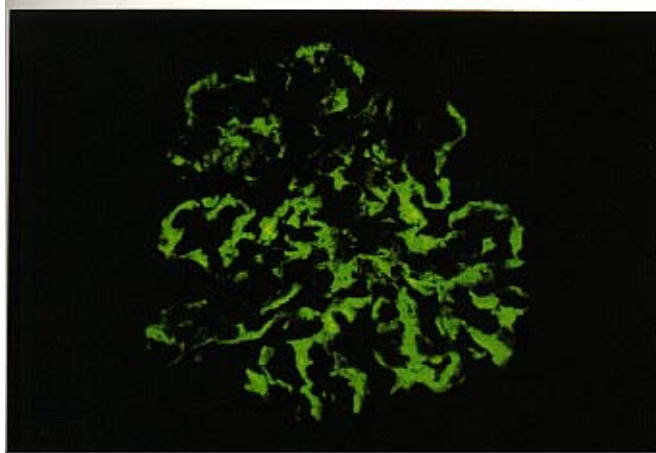
(Reproduced with permission from IGAKU-SHOIN Ltd, Japan).



(Fig. 3.10b)

PAS stained kidney section (X410) from a patient with Henoch-Schonlein purpura It. shows diffuse endocapillary glomerulonephritis.

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan).



(Fig. 3.10c)
Immunofluorescent stained kidney section (X410) from a patient with Henoch-Schonlein purpura. It shows deposits of IgA along the GBM.
(Reproduced with Permission from IGAKU-SHOIN Ltd., Japan)

Clinical features:

- 1- The disease usually occurs in winter, following upper respiratory infection or following exposure to allergen.
- 2- Renal manifestations varies from haematuria (macroscopic or microscopic), N.S., to RPGN. Severe forms of the disease are more encountered in adults.
- 3- Extrarenal manifestations include:
 - a. Purpuric rash which involves mainly the buttocks and lower limbs. It does not blanch on pressure and may extend to other areas.
 - b. Polyarthralgia or arthritis.
 - c. Gastrointestinal manifestations including abdominal pain, bloody diarrhea and or melena.
 - d. Fever, malaise, epistaxis and haemoptysis.
 - e. In more than 50% of cases serum IgA is high.

Treatment and Prognosis:

Generally, the disease is self-limiting. However 5-20% of cases (especially adults) may show persistence or even progression to uraemia.

Signs of bad prognosis include patients with: severe disease at presentation, persistent nephrotic syndrome, severe renal impairment and crescentic G.N.

Cases with mild disease may be treated symptomatically while severe cases should be treated with steroids, cytotoxic drugs and plasma exchange.

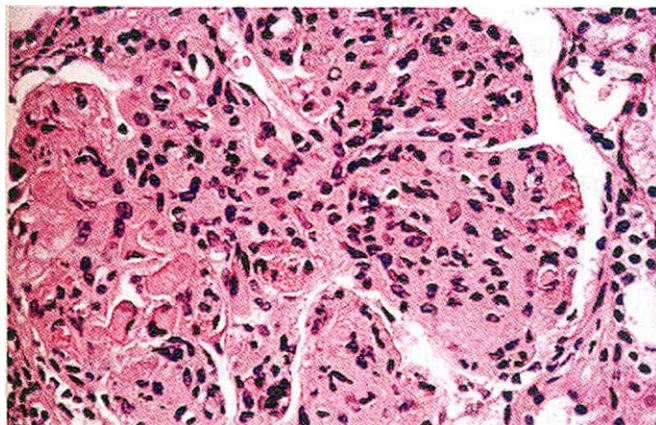
Essential Mixed Cryoglobulinaemia (EMC)

Cryoglobulinaemia is a wide range of diseases associated with formation of cryoglobulins. The cryoglobulin complex is mainly an immunoglobulin (antibody) attached to another immunoglobulin (antigen). The complex has the character of precipitation at cold. According to the nature of the two immunoglobulins, three types of cryoglobulinaemia are recognized: 1- monoclonal cryoglobulinaemia (i.e. both components are monoclonal immunoglobulins), detected in Myeloma, macroglobulinaemia, chronic lymphatic leukaemia and essential cryoglobulinaemia. 2- mixed polyclonal-monoclonal cryoglobulinaemia detected in Sjögren's disease, rheumatoid arthritis and essential mixed cryoglobulinaemia. 3- mixed polyclonal cryoglobulinaemia (i.e. poly-poly) in essential mixed cryoglobulinaemia, autoimmune disease as SLE, PAN, HSP, infection as CMV, malaria and HBV.

While patients with cryoglobulinaemia usually present with the manifestation of the original disease, 20-30% of patients with mixed cryoglobulinaemia present with disease (vasculitis) caused by cryoglobulin itself. This is termed essential mixed cryoglobulinaemia.

Pathology (Fig. 3.11):

Light microscopy usually shows a diffuse proliferative or membranoproliferative glomerulonephritis with or without crescents. Immunofluorescent microscopy shows deposits of C3 and other immunoglobulins similar to those forming the cryoglobulin. Electron microscopy shows the cryoglobulin deposits in the renal glomeruli.



(Fig 3.11)

Hx & E stained kidney section (X260) from a patient with EMC, it shows extensive deposits in the capillary walls and mesangium and appreciable cellular proliferation.

Clinical features:

Clinical manifestations of EMC include the following:

- 1- Renal, including nephrotic syndrome, nephritic syndrome or RPGN.
- 2- Extrarenal, including purpura, arthritis and hepatic dysfunction.

Treatment:

Steroid and cyclophosphamide are usually given in combination to treat EMC. Plasma exchange is indicated with severe disease to lower the level of circulating cryoglobulin.

Progressive Systemic Sclerosis (PSS) (Scleroderma Syndrome)

PSS is a disease characterized by progressive fibrosis of skin and internal organs of undetermined etiology. The condition may follow a long benign or short malignant course.

Renal pathology:

Almost 50-100% of PSS cases show renal involvement. Interlobular arteries show narrowing of lumen and thickening of the wall with onion-skin appearance. Glomeruli usually show intracapillary fibrin deposits, mesangiolysis, rarely mesangial proliferation or crescent formation.

Clinical features:

The basic clinical features of PSS include:

- 1- Renal manifestations which include severe hypertensive, progressive uraemia and proteinuria which is rarely severe enough to cause nephritic syndrome.
- 2- CREST syndrome which includes calcinosis, Raynaud's phenomenon, oesophageal hypomotility, sclerodactyly and telangiectasia.

Treatment:

The only available treatment is symptomatic. In case of hypertension, ACEIs are the treatment of choice.

Diabetic Nephropathy

Microangiopathy with neuropathy, retinopathy and nephropathy are complications known to develop in the majority of long-term diabetics.

Renal failure causes death in up to 40% of diabetics, being 17 times more common than in non-diabetics.

The better the control of diabetes, the longer the survival is and the more the chance to manifest nephropathy and other microangiopathy will be. This explains the prevalence of this disease in countries with better health programs.

The disease affects both juvenile and adult onset diabetics, but juvenile diabetics manifest the disease more; since they survive longer with the disease. Adult onset diabetics usually die earlier with coronary or cerebral strokes.

In Juvenile diabetics, nephropathy passes into 6 stages: 1- very early stage in which GFR is supernormal, 2- stage of microalbuminuria, 3- stage of clinical proteinuria, 4- stage of nephrotic syndrome, and hypertension, 5- stage of renal impairment then, 6- stage of end stage renal failure.

Stage of microalbuminuria and high GFR may continue for several years and clinical proteinuria usually settles 10-15 years later. Once clinical proteinuria is established, the disease becomes progressive to end stage renal failure.

The above described stages are the natural history in insulin dependent (type I) diabetics. In type II diabetics, the renal disease is usually well established when first discovered clinically.

Pathogenesis of diabetic nephropathy:

Two mechanisms are claimed to be responsible for diabetic glomerulosclerosis. These are:

- 1- Hyperfiltration and hypertrophy of the renal glomeruli.
- 2- Glycosylation of glomerular structural proteins.

Hyperfiltration and Hypertrophy: In early stages of diabetic nephropathy when proteinuria is not yet detectable, the GFR is high up to 40% above normal. This elevation is multifactorial, mainly due to hyperglycaemia, high levels of glucagons, growth hormone and prostaglandin concentrations are possible mediators for glomerular hyperfiltration. The increased GFR is associated with glomerulomegaly and increase in renal size. It is believed that long term hyperfiltration may result in glomerulosclerosis.

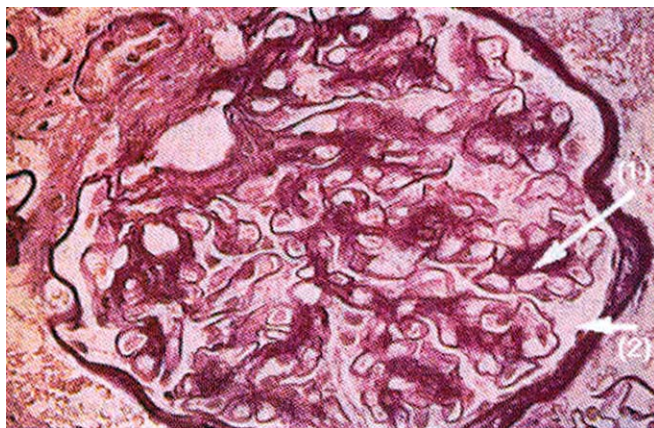
Glycosylation of glomerular structural proteins: Non-enzymatic reactions of glucose with circulating and structural proteins are known to occur with hyperglycaemia e.g. glycosylated haemoglobin (Hemoglobin A1C). Glycosylation of glomerular basement membrane and mesangial protein may

be responsible for the alterations in glomerular basement membrane permeability and the increase in the mesangial matrix.

Pathology:

In the very early phases, there is an increase in kidney size, glomerular diameter and tubular size. As the disease advances the following will be recognized:

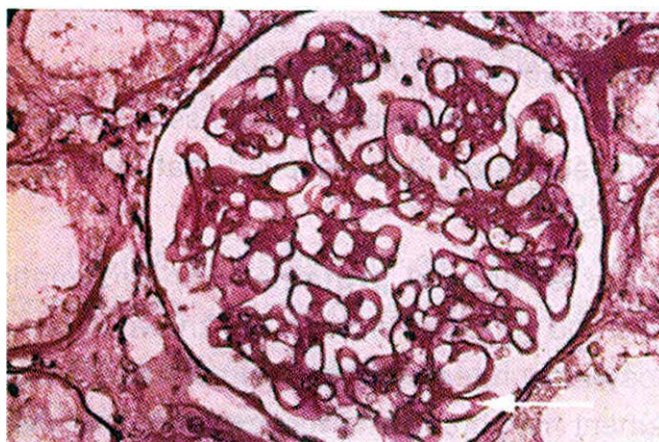
1- progressive thickening of the GBM 2- widening of the mesangium by PAS positive material (Fig. 3.12a,b) 3- focal global sclerotic lesions known as Kimmelstiel-Wilson nodules (Fig.3.12c); and 4- narrowing of glomerular capillaries. Other distinctive lesions which may be seen in kidney biopsies of diabetic patients are fibrin caps, capsular drop lesions and gross hyalinization of arterioles. Also, interstitial scarring infiltration and tubular atrophy are seen.



(Fig 3.12a)

Hx & E stained kidney section (X390) from a patient with diabetic nephropathy. It shows early diffuse sclerosis with mild mesangial thickening (arrow-1) and thickening of the Bowman's capsule (arrow-2).

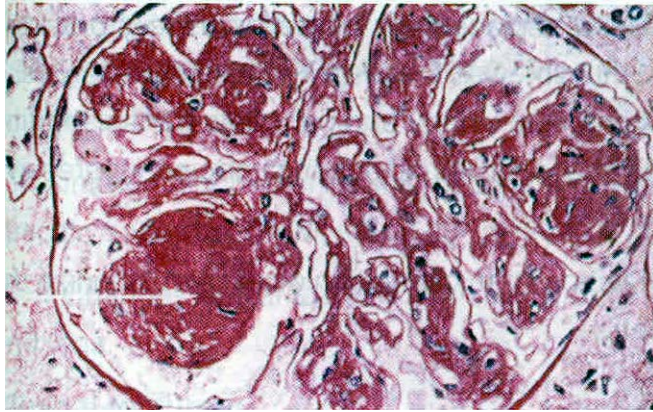
(Reproduced with permission from IGAKU-SHOIN Ltd, Japan)



(Fig 3.12b)

PAS stained kidney section (X390) from a patient with diabetic nephropathy in slightly more advanced stage with thickening the GBM (arrow).

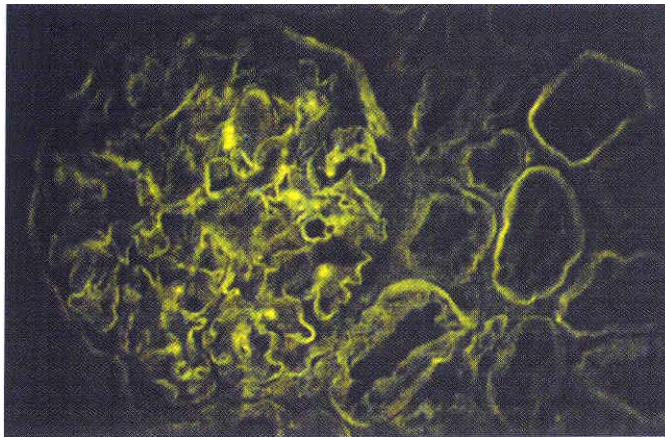
(Reproduced with permission from IGAKU-SHOIN Ltd, Japan)



(Fig 3.12c)

PAS stained kidney section (X260) from a patient with diabetic nephropathy with diffuse nodular glomerulosclerosis. It shows the classic Kimmelstiel Wilson nodules (arrow).

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan)



(Fig 3.12d)

Immunofluorescent stained kidney section (X260) in a patient with early diffuse glomerulosclerosis. It shows linear deposits of IgG along the glomerular and tubular basement membrane.

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan)

By Immunofluorescence microscopy, IgG and albumin are deposited in a linear pattern along GBM (Fig. 3.12d).

Treatment:

Prevention of diabetic nephropathy is ideally achieved by proper control of diabetes and avoidance of smoking and obesity.

If microalbuminuria; which is marker of very early disease; is detected, proper control of diabetes and use of small dose of ACE inhibitors (e.g. captopril 6.25 mg twice daily before meals) will help the normalization of glomerular haemodynamics and prevent progression to diabetic glomerulopathy.

In the stage of clinical proteinuria and nephrotic syndrome, hypertension has to be controlled preferably with ACEI. This in addition to the control of diabetes and hyperlipidemia besides the measures for management of nephrotic syndrome.

When renal failure manifests, supportive treatment and renal replacement therapy (RRT) may be provided. Renal replacement therapy is usually provided earlier for diabetics (i.e. at GFR 10 ml/min). CAPD is superior to haemodialysis. If transplantation is to be provided, combined kidney and pancreas transplantation is the choice for type I diabetics and generally steroid sparing immunosuppressive protocols are preferable.

In the near future, Pancreas islet-cell transplantation would revolutionize the management of diabetic nephropathy.

Hereditary Glomerulopathies

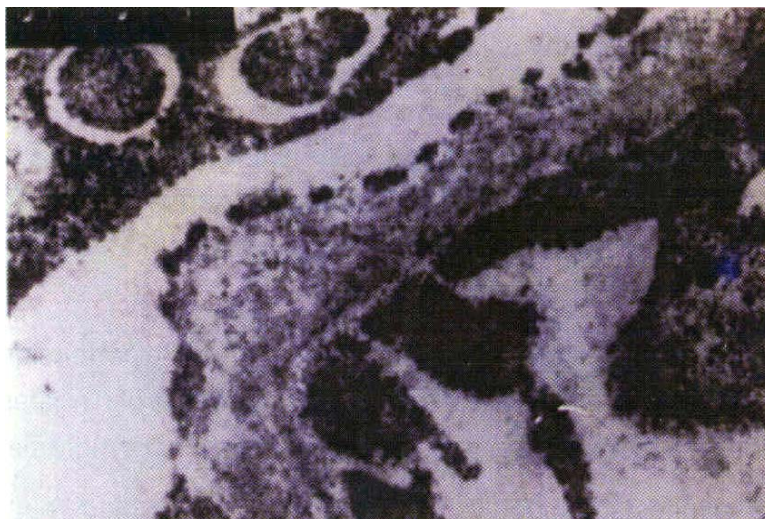
1- Alport Syndrome

Alport Syndrome is an autosomal dominant inherited disease with variable penetrance, sometimes with X-linkage. Clinically, the patients show combination of renal disease, nerve deafness ocular defects (anterior Lenticonus, cataract, macular lesions) and platelet defect (macrothrombocytopathic thrombocytopenia).

The basic defect is in the type IV collagen which is normally present in the GBM, lens and cochlea.

Pathology:

The characteristic feature of Alport's syndrome is seen in kidney sections examined by E.M. which are lamellation, splitting and thinning of the GBM. As the disease progresses the GBM takes the form described as "basket weave" appearance (Fig. 3.13).



(Fig 3.13)

Electron micrographic examination of a kidney biopsy from a patient with Alport syndrome showing the characteristic basket weave appearance of the lamina densa of the glomerular tubular basement membrane.

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan)

In advanced disease stage, non specific L.M. changes could be seen as FSGS, mesangial proliferation, crescents tubular atrophy, interstitial fibrosis and interstitial foam cells.

Immunofluorescence microscopy will be either negative or will show non specific deposits of IgM, C3.

Changes similar to those seen by EM in the GBM could be seen in the cochlea and lens.

Clinical features:

Haematuria is the main feature of this disease. It is microscopic and may be detected even at birth. Later it becomes macroscopic with intercurrent illness. Proteinuria is usually absent or mild but becomes manifest as the disease progresses and even reaches the nephritic range.

Renal impairment starts at the second decade of life and progresses to an end stage renal failure. This progression is more rapid in male than it is in female patients.

Treatment:

The basic purpose of treatment is to slow the progression of kidney disease (control of hypertension and restriction of protein). Dialysis support is provided when ESRD develops.

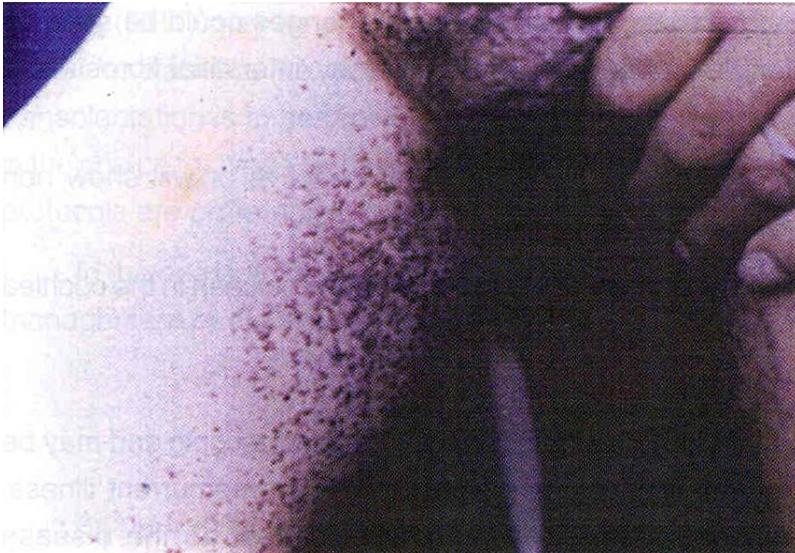
When kidney transplantation is performed we have to be aware of the possible to develop anti-GBM disease. This is due to development of antibodies to type IV collagen in GBM of the transplanted kidney. This is because this antigen is missed from the body of Alport patient and presents in the transplanted kidney. If this occurs, the patient may need plasma exchange sessions.

2- Fabry's Disease (*Angiokeratoma Corporis Diffusum Universale*)

Fabry's disease results from the deficiency of the enzyme α -galactosidase. This, in turn, results in an accumulation in all tissues of glycosphingo-lipids, cerebroside dihexoside and cerebroside trihexoside. The disease is inherited as X-linked, the homozygous males are severely affected while the heterozygous females are asymptomatic.

Clinical Features:

- 1- Skin lesions in the form of angiokeratomas which are red papules in the mouth, lower abdomen, buttocks and pubic region (Fig. 3.14).



(Fig 3.14)

Photograph showing the characteristic skin lesion in the medial aspect of the thigh of a patient with Fabry's disease.



(Fig 3.15)

Masson Trichroma stained kidney section (X400) from the same patient showing foamy vacuolization of the epithelial cells.

- 2- Neurologic manifestations in the form of periodic episodes of severe pain due to involvement of dorsal root ganglia.
- 3- Cardiac manifestations as hypotension and ischaemic heart disease.
- 4- Renal manifestations include, haematuria, proteinuria and progressive uraemia. Kidney sections will show changes in visceral glomerular epithelial cells, endothelial cells and tubular cells in the form of fat accumulations as seen by light microscopy (Fig. 3.15) and myelin as seen by EM. Usually patients die from cardiac or renal disease in fourth or fifth decades of life.
- 5- Screening of family members for α -galactosidase deficiency in serum, leucocytes, hair follicles and biopsy specimens is mandatory.

Treatment:

Is mainly supportive, dialysis is tolerable and transplantation-in spite of being successful-does not provide the missing enzyme.

3- Nail-Patella Syndrome (Hereditary onycho-Osteo-dysplasia)

This is characterized by a generalized disturbance in collagen synthesis leading to dysplasia of nails, skeletal deformities (especially hypoplastic displaced patella, deformed elbow, iliac horns, scoliosis) and renal involvement.

The disease is transmitted as autosomal dominant trait. Renal manifestations include haematuria and proteinuria, but rarely nephrotic syndrome or renal failure occurs.

Histopathologically, there is an irregular thickening of the GBM with numerous lucent areas containing electron dense fibrils.

Bacterial Endocarditis

In bacterial endocarditis occurring in patients with rheumatic valve disease and in intravenous drug abusers the incidence of glomerulonephritis is high.

Pathogenesis and Pathology:

Renal involvement in endocarditis is mainly immunologic. It is a sort of immune complex mediated glomerular damage. The immune complexes are found to contain bacterial antigen, antibodies and complement. The disease is associated with complement activation and consumption.

In cases with subacute bacterial endocarditis, lesions are mainly segmental, focal with necrosis, proliferation and eosinophilic infiltration and deposits are subendothelial. But in acute bacterial endocarditis lesions are diffuse proliferative as in post infectious glomerulonephritis with neutrophil infiltration and subepithelial deposits.

Clinical features and diagnosis:

The clinical features of renal involvement in endocarditis may vary from asymptomatic urine abnormalities especially in the focal and segmental lesions to severe RPGN as in the diffuse proliferative lesions.

In patients with bacterial endocarditis renal impairment could be due to glomerulonephritis, drug induced toxicity or secondary to cardiac failure.

Tests for CIC are positive with transient hypocomplementaemia and sometimes positive ANA and rheumatoid factor.

Treatment:

Treatment is that of endocarditis and symptomatic treatment for renal disease (e.g. dialysis for renal failure).

Use of steroids and immunosuppressives is rarely needed.

Shunt Nephritis

Shunt nephritis is almost due to infection of ventriculo-atrial shunt by coagulase-negative staphylococci. It occurs in a minority of patients, it is an immune complex disease with hypocomplementaemia. Kidney lesions are always mesangioproliferative or mesangiocapillary G.N.

Irradication of infection is followed by a slow recovery of the glomerular disease.

Malarial Nephropathy

The disease is common in malarial endemic areas. It affects children more than adults. It occurs in both quartan and falciparum malaria. Quartan malarial nephropathy tends to be chronic and progressive while falciparum malarial nephropathy tends to resolve completely after antimalarial treatment.

Quartan Malarial Nephropathy:

The disease is caused by plasmodium malariae which is common in Africa.

Histopathologically, the disease is membranous in children while in adults it is membranoproliferative glomerulonephritis, immunofluorescence microscopy will show IgG, IgM and C3 deposits. In 25% of cases P. malariae antigens could be detected.

Falciparum Malarial Nephropathy:

Falciparum malaria is a common cause of acute renal failure in tropics.

Both glomerular and tubulointerstitial nephritis are known to occur.

Glomerulonephritis is usually mild and transient. Histologically, it is mesangial proliferative G.N. with C3, IgM and malarial antigen deposits.

Tubulointerstitial Nephritis:

Usually occurs in patients suffering from high fever, hypovolaemia, hemolytic jaundice, intravascular coagulation, hyperviscosity and heavy parasitaemia. There is acute tubular necrosis (toxic and ischaemic), obstruction of distal nephron with casts and interstitial infiltration with mononuclear cells. Peritubular capillaries are congested with erythrocytes, macrophages laden with malarial pigment and mono-nuclear cells.

Renal failure in falciparum malaria is usually hypercatabolic with rapid rise in blood urea and serum creatinine. Hyperkalaemia and hyperuricaemia occur particularly with intravascular haemolysis.

Haemodialysis is preferable to peritoneal dialysis when dialysis support is indicated. Exchange transfusion is indicated with heavy parasitaemia.

Schistosomal Nephropathy

Introduction:

Schistosomiasis is a parasitic disease which affects man and animals. 500-600 million people are thought to be exposed to infection. Also, over 200 million inhabitants of 74 tropical countries have documented infection. Although this number is almost certainly an underestimate, it still seems to be increasing at least in some parts of Africa.

Among human pathogens, the three most important schistosome species are schistosoma haematobium, schistosoma japonicum and schistosoma mansoni.

Schistosoma haematobium is responsible for schistosomiasis of the bladder in Africa and Asia, while schistosoma japonicum is limited to the Far East and schistosoma mansoni is found in Africa, South West Asia and in South America. The last two species cause intestinal and hepatic lesions.



(Fig. 3.16)
A couple of adult schistosoma worms. The female which is cylindrical lies in the ventral plica (gubernaculum) of the male which is broad shaped (x400).

Adult worm pairs of schistosoma haematobium (Fig. 3.16) are located in perivesical venous plexuses and eggs with their characteristic terminal spine are passed in urine. A granulomatous inflammatory reaction in the bladder will be detected and ureteric wall with subsequent fibrosis which may be complicated by hydronephrosis and hydronephrosis.

Schistosoma mansoni and schistosoma japonicum are found in the mesenteric veins. A large number of eggs produced by female worms find their way to the intestinal lumen and are passed in the faeces. Granulomatous inflammatory reactions occur in the intestinal wall. Many eggs reach the liver via portal vein causing periportal hepatic fibrosis. These schistosome species will give rise to intestinal and hepatic disease.

Schistosomal Antigens:

Schistosomes are antigenically very complex organisms. Many antigens have been identified. The number of which differs according to the technique employed. Schistosoma antigens isolated in-vitro could be defined into three groups:

- **Tegument-associated antigens** are complex set of proteins and glycoprotein on the surface of cercariae, schistosomules and adult worms. They are released with the turnover of the parasite's surface membrane. Tegument-associated antigens are of crucial importance in immunity to infection and reinfection but seem to have a limited role in the pathogenesis of morbidity of the host.
- **Gut-associated antigens** are present in the epithelial cells of the adult worm's gut, primordial oesophagus and caecal bifurcation of cercariae and schistosomula. These antigens are released by regurgitation of the worm's digestive juice and constitute the main part of the circulating schistosomal antigen in-vivo. Of six antigens identified in-vitro, at least two are clearly involved in the pathogenesis of immune-complex mediated lesions. The first of these which is the circulating anodic antigen (CAA) is a proteoglycan produced in large quantities by the adult worm. The second, circulating cathodic antigen (CCA) is a glycoprotein with a polysaccharide moiety that was previously identified as "M-antigen" in the urine and milk of infected animals and humans. Another gut antigen of potential clinical importance is a protein called "antigen 4" which was detected in milk from infected patients. This antigen was shown much earlier to be a genus specific schistosoma mansoni antigen.
- **Soluble egg antigens** are of a large number and have been purified by various techniques. They were found to be protein or glycoprotein in nature. They are released by diffusion through micropores in egg shell into the surrounding tissue fluids. The most well known of the soluble egg antigens are the three major serological antigens (MSA) 1, 2 and 3. Of these MSA 1 is species specific for schistosoma mansoni. Egg antigens are mainly involved

in the pathogenesis of local tissue cell mediated reaction with granuloma formation. Another egg-derived antigen, W1 was more recently described and was shown to be hepatotoxic.

Acquisition of host antigens by the parasite schistosomules grown in-vitro in human blood develop surface antigens which show human blood group specificity of the ABO type. Moreover, schistosomula selectively acquire gene products of the K and I sub-regions of the major histocompatibility complex. The acquired host antigens could serve to protect the parasites from the immune attack by the host.

The main bulk of circulating schistosomal antigens is gut derived, but soluble egg and tegument-associated antigens also contribute.

Patient's response to schistosomal infection:

Human infection is initiated through water exposure (planting, fishing, washing and swimming) where the free-swimming forked-tailed cercariae penetrate the intact host skin. Three major clinical syndromes are recognized after schistosomal infection. These are dermatitis, acute schistosomiasis and chronic schistosomiasis.

Dermatitis is due to skin penetration by cercariae. Then the patients experience itching within one hour (swimmer's itch) skin rash may appear and can persist for days. The symptomatology and histologic picture are consistent with an anamnestic immune reaction. Both humoral and cell-mediated mechanisms participate in the anti-cercarial skin response.

Acute schistosomiasis is a clinical syndrome which is often seen in non-immune individuals (tourists, immigrants, or the indigenous population) who have been exposed in an endemic area to a primary infection by cercariae. The syndrome is sometimes called Katayama fever. Symptoms usually appear 4 to 10 weeks after a heavy exposure to cercariae. This exposure would coincide with the migratory stage of the maturing schistosomula in the lung and liver. The syndrome is manifest by fever, malaise, hepatosplenomegaly, eosinophilia, diarrhea and in some cases, oedema, urticaria, lymphadenopathy and arthralgia. These symptoms are transient and spontaneously disappear. The pathogenesis of this syndrome is most probably an immediate-type and immune complex-mediated hypersensitivity reactions.

Chronic schistosomiasis is due to both cell mediated immune response resulting in granulomatous reaction or due to humoral response with

immune complex formation. Granulomatous reaction occur in the gastrointestinal tract in case of schistosoma mansoni and schistosoma japonicum or in the urinary tract in case of schistosoma hematobium. The humoral response is believed to occur mainly with schistosoma mansoni resulting in diseases such as schistosomal nephropathy.

SCHISTOSOMAL GLOMERULOPATHY:

Two decades ago, clinicians in Brazil introduced the concept of schistosomal glomerulopathy. They reported abnormal concentrations of protein and leucocytes in the urine of patients with the hepatosplenic form of schistosomiasis. This report was subsequently confirmed in man and experimental animals infected with schistosoma mansoni or schistosoma japonicum. More recently, the schistosomal specificity of kidney lesions in patients with hepatosplenic schistosomiasis was confirmed by detection of schistosomal antigens (CAA-CCA) and schistosomal specific antibodies in the renal glomeruli.

Information on glomerular lesions associated with schistosoma haematobium infection are disputed. Some researches reported the absence of glomerulopathy in schistosoma haematobium infection in man, while others reported nephrotic syndrome in patients with concomitant schistosoma haematobium infection and chronic salmonellosis. Recently, a schistosomal specific glomerulopathy was described in experimental animals (hamsters) infected with schistosoma hematobium.

Incidence:

In Egypt, proteinuria was detected in 20 percent of asymptomatic patients with active schistosoma mansoni infection. In the same centre, schistosomal specific kidney lesions were documented in 65 per cent of patients with active schistosoma mansoni who present with overt nephrotic syndrome.

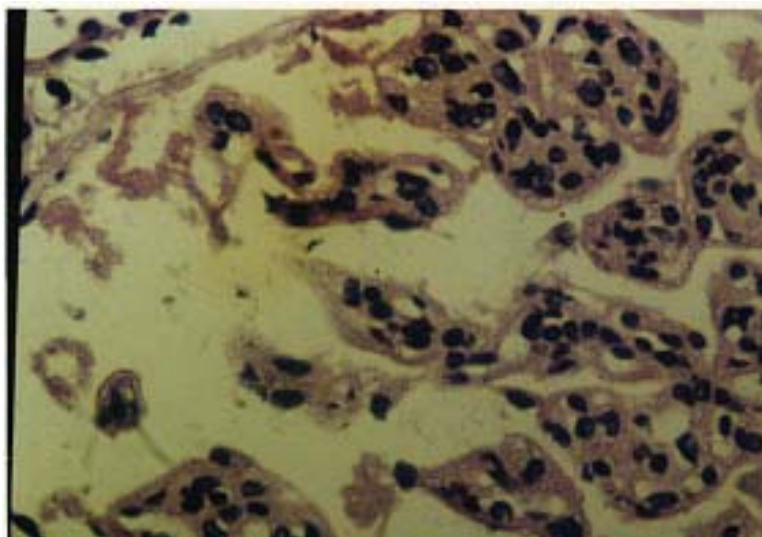
In Brazil, abnormal proteinuria and leucocyturia were reported in 25.7 per cent of patients with hepatosplenic schistosomiasis and 3.8 percent of patients with a milder intestinal form of the disease.

There is a positive correlation between the duration of schistosomal infection and renal involvement. This involvement has been observed clinically (the disease is more common in patients with advanced hepatosplenic disease in comparison with early intestinal disease). It is also

well-documented in an extensive experimental study on hamsters infected with schistosoma mansoni.

Clinical and histopathologic manifestations of schistosomal glomerulopathy:

The disease passes through three distinct phases which are: occult glomerulopathy, overt glomerulopathy and end-stage glomerulopathy. Little is known about factors that promote its evolution from one stage to another. Species and strains of the parasite are important factors in schistosomal nephropathy. Also, HLA types and a degree of hepatic involvement are important factors in schistosomal nephropathy.



(Fig. 3.17)

Renal biopsy of a patient with schistosomal- specific nephropathy Showing mesangiocapillary glomerulonephritis(HX & E X 400).

- **Occult glomerulopathy** is usually silent. Asymptomatic proteinuria is an early expression of the disease which was reported in 20% of Egyptian patients and 26% of Brazilian patients with active schistosoma mansoni infection. Patients in this phase have less hepatic and more intestinal schistosomal disease. Histopathologic examination of kidney biopsy by light microscopy will show either no change or mild mesangioproliferative lesion, with little or no expansion of mesangial matrix but with occasional focal thickening of the basement membrane. Immunofluorescence shows mostly mesangial deposits of IgM- containing immune complexes, schistosomal antigens and complement C3.
- **Overt glomerulopathy** nephrotic syndrome with or without renal impairment is the commonest presentation in this phase. Hypertension is noticed in 30-50 percent of patients. Less commonly, patients may present with non-nephrotic proteinuria. Proteinuria is non-selective and urine sediment may show

leucocytes, red blood cells and casts. Hypoalbuminaemia is severe and hyperlipidaemia is unusual (due to associated liver disease). There is a polyclonal hypergammaglobulinaemia (due to active parasitic infection) with a considerable increase of serum IgG but less frequently IgA. Serum complement is usually normal. There is usually a mild to moderate anaemia not proportionate to the degree of renal dysfunction. This is probably the result of the associated nutritional deficiency and parasitic infection.

Patients in this phase always have hepatosplenic disease. The liver is firm and shrunken. The spleen is enlarged. Ascites may be present and oesophageal varices may be detected. Histopathologic examination of a kidney biopsy shows focal segmental glomerulosclerosis or mesangio-capillary glomerulonephritis (Fig 3.17). Other lesions have been reported such as membranous glomerulonephritis, epithelial crescents and renal amyloidosis. Immunofluorescence classically shows schistosomal gut antigens, IgG and C3 deposits in the renal glomeruli. IgM and fibrin are less frequent whereas IgA is rare.

• **End-stage glomerulopathy:** Recently, through longitudinal studies progression of schistosomal specific glomerulopathy to end-stage renal disease has been reported. Patients usually present with uraemic manifestation in association with hepatosplenic schistosomiasis. Histopathologic examination of kidney biopsy may show glomerulosclerosis, interstitial fibrosis and tubular atrophy.

Treatment:

The results of treatment with both anti-parasitic agents and immunosuppressive drugs have been disappointing. Martinelli *et al* in Brazil observed no benefit in patients treated with a combination of anti-parasitic drugs (oxamniquine or hycanthone) and prednisolone with or without cyclophosphamide. Similarly, in Egypt, Sobh *et al* reported an unsatisfactory response to combined treatment with anti-parasitic drugs (praziquantel and oxamniquine) and prednisolone or cyclosporine. Sooner or later, most patients with schistosomal nephropathy progress to end-stage renal failure. Very early treatment of schistosomiasis may be the only available way of preventing the poor outcome of schistosomal nephropathy.

Glomerulopathy Secondary To Virus Infection

A variety of viral infections may be associated with features of acute glomerulonephritis. However, it is usually milder than it is in post streptococcal glomerulonephritis.

Classification:-

- (1) Herpes virus: - cytomegalovirus
 - Epstein Bar virus.
- (2) Paramyxovirus: - measles
 - mumps
- (3) Parovirus
- (4) Hepatitis viruses: - hepatitis B
 - hepatitis C
- (5) Retroviruses: - human immunodeficiency virus.
- (6) Influenza viruses: - Influenza A & B

Mechanism of Renal affection in viral infection:

- (1) Direct cytopathic effect of the virus on the glomerular cells.
- (2) Immune complex mediated which is due to stimulation of antibody response.
- (3) Direct effect on T-cells.

Hepatitis B Virus and The Kidney

Several major renal syndromes may occur in patients with hepatitis B infection including:

- 1- Serum sickness-like syndrome.
- 2- Membranous nephropathy.
- 3- Mesangiocapillary glomerulonephritis.
- 4- Systemic necrotizing vasculitis.
- 5- Polyarteritis nodosa.
- 6- Crescentic glomerulonephritis.

HBV induced Membranous nephropathy:

Incidence:-

- The majority of cases are children.
- The peak incidence is at a mean age of 6-7 years.
- Usually without clinically apparent preceding history of acute hepatitis but serum transaminases are often mildly elevated.

Clinical manifestations:-

- (1) Proteinuria: nephrotic or non nephrotic range.
- (2) haematuria: usually microscopic but occasionally gross.
- (3) Hypertension: common.
- (4) Normal or mildly elevated serum creatinine.

Evidence of HBV induced membranous nephropathy:

- (1) The 3 hepatitis B antigens (HBsAg-HBeAg- HBcAg) have been identified in the subepithelial immune complexes of patients with membranous nephropathy and hepatitis B infection.
- (2) HBeAg plays important role in the pathogenesis as proteinuria remits in HBeAg positive patients when they produce HBeAb.

Prognosis:

(A) Children:-

Spontaneous recovery is the rule where:

56% of patients remit 1 year after presentation.

85% of patients remit 2 years after presentation.

95% of patients remit 5-7 years after presentation.

(B) Adults:-

Progressive course, usually terminating to chronic renal failure.

Treatment:-

Suppression of the active viral replication could reduce deposition of HBeAg in the glomerular basement membrane. Interferon therapy may be transiently beneficial in adults.

Hepatitis C virus associated nephropathy

Nephropathy could be one of the several extrahepatic syndromes which has been identified with chronic HCV infection. These include:

- 1- Glomerulonephritis.
- 2- Mixed cryoglobulinaemias.
- 3- Arthritis.
- 4- Sjogren's syndrome.
- 5- Chronic corneal ulceration.
- 6- Porphyria cutanea tarda.
- 7- Lichen planus.

8- Autoimmune thyroiditis.

9- Polyarteritis nodosa.

Glomerulonephritis:

The following types of glomerulonephritis can be encountered with HCV infection:-

- (1) Membranoproliferative glomerulonephritis "usually type I"
- (2) Membranous nephropathy.
- (3) Proliferative nephropathy.
- (4) Sclerosing nephritis.

Pathogenesis:-

(1) Immune complex theory:

Deposition of immune complex formed of HCV-anti HCV IgG-Rheumatoid factor in the glomerular basement membrane.

(2) Auto-antibodies theory:

- Many types of autoantibodies are present in patients with chronic HCV infection e.g.:
 - ASMA
 - ANCA
 - Rh factor.
- Antibodies to glomerular antigens were found in sera of HCV-infected patients.

(3) Role of chronic liver disease:-

In patients with chronic liver disease:-

- 9% have microhaematuria.
- 1.6% have nephrotic syndrome.
- High incidence of IgA nephropathy.

Pathogenesis:-

- Impaired clearance of circulating immune complex.
- Defective opsonization due to impaired production of complement components.

Clinical picture:-

- (1) Evidence of chronic liver disease may be absent or mild.
- (2) Renal affection.
- (3) Clinical manifestations of cryoglobulinemia.

Diagnosis:-

- (1) Detection of HCV antibodies by ELISA test.
- (2) Detection of HCV RNA by PCR.
- (3) Positive cryoglobulins.

- (4) Low complement level.
- (5) Positive Rheumatoid factor.
- (6) Detection of viral antigen in the glomerular basement membrane.

Treatment:-

- Optimal treatment strategy for patients with HCV-associated nephropathy has to be established.
- Interferon α is the corner stone for treatment.

Dose: 3 million units given S.C. 3 times weekly.

Duration:- 6 months.

- However higher doses and longer duration are preferable.

Factors associated with good response to interferon therapy:

- 1- Age: less than 50 years.
- 2- Sex: Female sex.
- 3- Sporadic HCV infection.
- 4- Viral titre: $<10^6$ copies/ml.
- 5- Viral Genotype: other than type 1b
- 6- Rapid normalization of ALT levels and clearance of HCV RNA.

Combination Therapy:-

- Result in prolonged sustained response and lower relapse rate.
- Interferon is combined with either:-
 - 1- Ribavirin.
 - 2- Amantadine Hcl.
 - 3- Antioxidant.
 - 4- Cytokines and immunomodulators:
 - Thymosin
 - Levamisole.
 - GM-CSF: Granulocyte macrophage colony stimulating factor
 - 5- NSAID
 - 6- Pentoxifylline.

TREATMENT OF GLOMERULONEPHRITIS

There are two main lines of treatment for patients with glomerulonephritis. The first is general and applicable to all types of GN and the second is specific for different types of GN.

I. General Measures for treatment of GN:

General measures include the following:

1- Treatment of hypertension: This is very important, not only for symptomatic relief and the prevention of systemic complications, but also there is a belief that meticulous control of hypertension may slow or prevent the progression of glomerular lesions. ACE inhibitors are possibly superior to other hypotensive drugs especially in patients with diabetic nephropathy.

2- Fluid control:

Salt and fluid restrictions are indicated with hypertension, oedema causing discomfort or presence of congestive heart failure. Diuretics- preferably loop diuretic- may be used with less salt restriction. Use of diuretics in the absence of oedema especially in hypotensive patient may be dangerous causing prerenal azotaemia.

3- Dietary measures:

Salt and water restriction may be necessary in oedematous and hypertensive patients. Protein should be limited to an amount which is equal to the physiologic need ($0.8=1.0$ g/kg/d) plus the daily urinary protein loss. High protein diet may increase proteinuria and could be injurious for the nephron while severe restriction of protein may lead to nutritional deficiency with high morbidity (e.g. susceptibility to infection).

4- Measures to reduce proteinuria:

These measures are intended to decrease the severity of N.S. and also to slow or prevent the damaging effect of proteinuria on the nephrons. This could be achieved through avoiding high protein diet and the use of ACEI.

ACEIs could be used in small doses in normotensive patient. They achieve their anti-proteinuric effect most probably through combating the vasopressor effect of angiotensin II on the glomerular efferent arteriole i.e. it causes efferent arteriolar V.D. with a reduction in intraglomerular filtration pressure.

5- Control of hyperlipidaemia:

Diet control will not be sufficient and antilipidemic drugs as lovastatin and simvastatin may be required. Diet control may be helpful in the prevention of progression of renal damage.

II. Specific Treatment:

A) Primary glomerulonephritis:

Specific treatment involves response of different types of glomerulonephritis to 1- immunosuppressive, 2- cytotoxic drugs; and 3- the role of some procedures as plasma exchange, induction of antigen excess, immune diffusion (primed columns).

1- Minimal change nephritis (MCN):

Minimal change nephritis is known to be steroid sensitive. In 95% of children a full response is obtained within 8 weeks while in adult only 80% will show slower responses also (i.e. within 16 weeks).

In children, prednisolone will be given in a dose of 1mg/kg/d, while in adults it is given as 60 mg/d. The dose is preferably given in the morning and after breakfast.

Alternatively, to induce remission, methylprednisolone I.V. pulses (daily, for 3 days, 1 gm each) followed by smaller doses of oral prednisolone could be given.

When steroids are contraindicated or when failure to induce remission occurs, other drugs could be used as cyclosporine A, cyclophosphamide, chlorambucil or azathioprine. After remission is induced, 20% of patients will not suffer any more, whereas 50% will show multiple relapses (frequent relapser) or will relapse while they are still on steroid (steroid dependent). The remaining 30% will show an occasional relapse over the next few years.

For frequent relapser and steroid dependent cases, steroids will be given in extended course to avoid nephrotic syndrome. But steroid toxicity will be high. In these situations, we may use alkylating agents (cyclophosphamide or chlorambucil) azathioprine or cyclosporine.

Cyclophosphamide may be given in a dose of 2-3 mg/kg/d for 8 weeks or in resistant cases, it may be given in a dose of 2 mg/kg/d for 12 weeks. But with the later regimen, risks as bone marrow depression and sterility should be considered. Azathioprine, however, may be less effective on the short

term, but an effect may be obtained on long term use. It is much safer than cyclophosphamide.

Cyclosporine may be given in a dose of 5mg/kg/d but the drug is potentially nephrotoxic and needs experience in its handling. While successful remission may be induced in many patients, some cases will be cyclosporine dependent.

Many of the patients showing difficult course when subjected to kidney biopsy will disclose focal segmental glomerulosclerosis rather than the minimal change disease.

2. Membranous Nephropathy (MN):

If untreated, 20-50% of patients with MN will progress to end stage renal failure within 10 years of presentation.

The risk factors for progression are: older age, female sex, impaired initial renal function and marked tubulointerstitial changes in renal biopsy.

Those with non-nephrotic proteinuria with normal kidney function could be treated conservatively.

For those with frank nephrotic syndrome, but with stable kidney function, some nephrologists prefer to keep on conservative treatment waiting for spontaneous remission but other nephrologists prefer to start steroid treatment.

For those with N.S. and abnormal kidney functions, most nephrologists prefer to start immediately with immunosuppressive drugs including steroid alone and/or alkylating agents or cyclosporine. High dose intravenous IgG has been reported to induce remissions.

3. Mesangiocapillary GN:

In 50% of patients with mesangiocapillary lesion, progression to end stage renal failure occurs within 10 years. This lesion is known to be unresponsive to steroids, or alkylating agents in different combinations. Also, anticoagulants, dipyridamol and NSAIDs were shown to be ineffective. In many patients, hypertension appeared after commencing steroids.

Children with this lesion presenting with frank nephrotic syndrome and impairment of kidney function, which are known to progress quickly to uraemia, deserve to receive a trial of a course of alternate day steroids with or without alkylating agent.

4. Mesangial IgA Nephropathy:

In the vast majority of patients, no specific treatment is provided. Phenytoin, fish-oil, cyclosporine, Danazol, steroids, cyclophosphamide all have been tried with no favorable response.

In subgroup of patients with heavy proteinuria, steroids have been claimed to be of help in controlling N.S.

Patients with progressive disease with deteriorating kidney function may be offered a chance of aggressive treatment including steroids, plasma exchange or cytotoxic drugs.

5- Henoch-Schönlein Purpura (HSP):

In cases with mild nephritis (usually children), no specific treatment is required, but long term follow-up is mandatory. For cases with severe disease (usually adults) with heavy proteinuria and deteriorating kidney function, kidney biopsy usually shows crescent formation. These patients are usually treated as those with RPGN with high dose steroids and possibly plasma exchange and cytotoxic drugs. Antiplatelets and anti-coagulants are recommended by some nephrologists.

In these types of RPGN, early institution of steroid treatment with induction by 3 pulses of methyl prednisolone (1gm/daily) is mandatory to save the kidney. Plasma exchange may be needed especially in anti-GBM associated disease and cyclophosphamide especially in ANCA induced variant.

B) Secondary Glomerulonephritis:

Specific treatment is required according to the cause as eradication of septic focus, eradication of a parasite (as malaria, bilharzia), treatment of malignancy and discontinuation of a drug (as Penicillamine).

Suggested Readings:

- Woo KT: Recent concepts in the pathogenesis and therapy of IgA nephritis. *Ann Acad Med Singapore*, 25: 2, 265-9, 1996.
- Merkel F, et al: Therapeutic options for critically ill patients suffering from progressive lupus nephritis or Goodpasture's syndrome. *Kidney Int Suppl*, 64: S31-8, 1998.
- Austin HA, et al: Treatment of lupus nephritis. *Semin Nephrol*, 16: 6, 527-35, 1996.
- Praditpornsilpa K, et al: Hepatitis virus and kidney. *Singapore Med J*, 73: 6, 639-44, 1996.
- Safadi R, et al: Glomerulonephritis associated with acute hepatitis B. *Am J Gastroenterol*, 91: 1, 138-9, 1996.
- Senatorski G, et al: The role of proteolytic enzymes in the pathogenesis of primary glomerulonephritis. *Postepy Hig Med Dosw*, 51: 2, 139-48, 1997.
- Berden JH: Lupus nephritis. *Kidney Int*, 52: 2, 538-58, 1997.
- Ponticelli C: Treatment of lupus nephritis- the advantages of a flexible approach. *Nephrol Dial Transplant*, 12: 10, 2957-9, 1997.
- Pisetsky DS, et al: Systemic lupus erythematosus. Diagnosis and treatment. *Med Clin North Am*, 81: 1, 113-28, 1997.
- Péchère Bertschi A, et al: Renal manifestations of viral disease. *Schweiz Rundsch Med Prax*, 86 : 31, 1204-8, 1997.
- Couser WG: Pathogenesis of glomerular damage in glomerulonephritis. *Nephrol Dial Transplant*, 13 Suppl 1: 10-5, 1998.
- Gibson IW, et al: Glomerular pathology: recent advances. *J Pathol*, 184: 2, 123-9, 1998.
- Julkunen H: Renal lupus in pregnancy. *Scand J Rheumatol Suppl*, 108: 80-3, 1998.
- Merkel F, et al: T cell involvement in glomerular injury. *Kidney Blood Press Res*, 19: 5, 298-304, 1996.

VASCULITIS

Vasculitis is a heterogeneous group of diseases ranging from a self-limited hypersensitivity reaction to an acute or chronic systemic illness that may be fatal.

Classification of Vasculitis:

Vasculitis may be primary vascular disease or a part of other systemic illness.

Primary forms of vasculitis are:

1- Polyarteritis nodosa (PAN) which is subdivided into the following:

- Macroscopic (classic) PAN.
- Microscopic PAN.
- Overlap type of PAN.
- The non immune deposit RPGN.

2- Wegner's granulomatosis

3- Allergic granulomatosis (Churg-Strauss syndrome)

4- Giant cell arteritis, which may be

- Temporal arteritis
- Takayasu's disease

Systemic disease which may be associated with vasculitis are:

1- Connective tissue diseases

- SLE
- Rheumatoid arthritis
- Rheumatic fever
- Dermatomyositis
- Sjogren's disease
- Relapsing polychondritis

2- Schönlein-Henoch purpura

3- Anti-GBM disease

4- Essential mixed cryoglobulinaemia

5- Infections such as hepatitis B virus, endocarditis, poststreptococcal infection, trichinosis and otitis media.

6- Drugs such as allopurinol, sulfa or hyperimmunoglobulins.

7- Tumours as visceral carcinoma, leukaemia, lymphoma and multiple myeloma.

Polyarteritis Nodosa

Incidence:

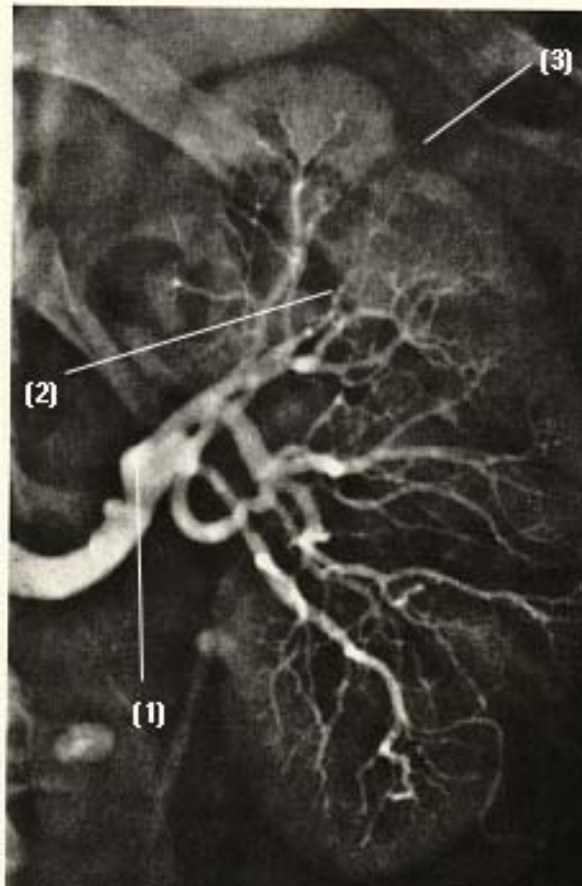
Polyarteritis nodosa is an uncommon but not a rare disease. Male to female ratio of involvement is 2.5 : 1. The peak age of involvement is 45 years, but any age can be affected. Clinical renal involvement occurs in 70% of cases. This is more frequent in the microscopic than in the macroscopic forms.

Pathology:

A- Classic PAN affects mainly medium sized and large vessels. In the kidney the main renal vessels (similar to mesenteric, coronary and cerebral vessels), its main branches, interlobar and arcuate vessels are involved. The vascular involvement is segmental with skipped zones. The involved segments show lesions which are eccentric i.e. not whole the circumference of the segment is involved. Also lesions are of different ages i.e. some show acute inflammation, while others are chronic or healed. By light microscopy, the acute lesion shows necrotizing vasculitis. glomeruli are generally spared or may show changes secondary to the arterial lesions as collapse, sclerosis or hypercellularity of the juxtaglomerular apparatus. Tubulointerstitium may show areas of ischaemic changes and areas of wedge infarction.

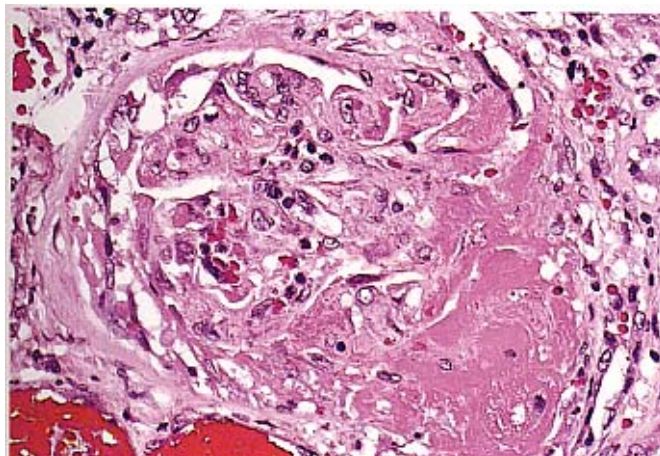
In the classic PAN, the main pathology is in the arteries and arterioles with aneurysm formation (**Fig. 4.1**) which may leak with renal or perirenal haematoma or may be thrombosed with recurrent renal immobilization.

B- Microscopic PAN affects the small vessels including interlobular arterioles and venules, capillaries and the glomeruli. The vascular involvement is circumferential with no aneurysm formation and the lesions are of the same age. The vascular inflammatory process may mimic the classic PAN or may be granulomatous. Glomerular involvement may range from few glomeruli to 100% of the glomerular population with focal, segmental necrotizing lesions with crescent formation (**Fig. 4.2**).



(Fig. 4.1)

Renal arteriogram in a case of polyarteritis nodosa shows multiple aneurysms in the Main artery (Arrow-1) and peripheral Arterioles (arrow-2), also there are areas of Infarction (arrow-3).



(Fig. 4.2)

Hx & E stained kidney section (X260) from a patient with microscopic PAN. It shows fibrinoid necrosis in an arteriole at the glomerular hilus with exudative glomerulonephritis.

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan).

Tubulointerstitium may show infiltration with inflammatory cells. This is mainly perivascular or periglomerular.

Immunofluorescence microscopy is extremely variable. It may vary from negative, weak positive, to strong positive. The deposits are either fibrinogen (40-60%), C3 (25-60%), IgG (8-30%) or others. These deposits are mainly detected in areas of necrosis or sclerosis.

Clinical features of PAN:

- 1- *Constitutional symptoms* which include fever, weight loss and malaise. These symptoms are part of the clinical manifestations in 75% of cases.
- 2- *Renal manifestations* are documented in 60-100% of cases. In microscopic PAN, these include acute nephritic syndrome, rapidly progressive glomerulonephritis, less commonly nephrotic syndrome or chronic nephritic syndrome. In classic PAN, the manifestations are hypertension, renal infarction, renal and perirenal haemorrhage and progressive renal failure.
- 3- *Gastrointestinal manifestations* appear in 50% of cases with nausea, vomiting, bleeding, pain or perforation.
- 4- *Neuropathy* is reported in 50% of cases with peripheral neuropathy or mononeuritis multiplex. These are usually sensory and motor neuropathy.
- 5- *Musculoskeletal manifestations* appear in 50-75% with weakness, myalgia, myositis and arthritis (Large joints).
- 6- *Pulmonary manifestations* are documented in 50% of cases with pleurisy, asthma, haemoptysis and pulmonary infiltrates.
- 7- *Cardiac lesions* are seen in 33% of cases, with ischaemic heart disease, congestive heart failure, pericarditis and conduction defects.
- 8- *Skin manifestations* are mostly in the form of palpable purpura, less commonly petechiae, nodules, papules or ulcerations. Skin biopsy shows leucocytoclastic angiitis.
- 9- *Other manifestations* of PAN include pancreatitis, cholecystitis, eye, adrenal and gonads involvement.

Investigations of PAN:

- 1- Anaemia, high ESR, leucocytosis, thrombocytosis are non-specific findings. Absolute eosinophilia is detected in 10-40% of cases with microscopic PAN, overlap PAN and cases with Churg-Strauss disease. Anti-nuclear antibodies, anti dsDNA are negative while ANCA is positive in some cases. In secondary cases of PAN-like vasculitis, manifestations of the etiologic disease could be documented as HBsAg, cryoglobulinaemia and hypocomplementaemia.
- 2- Angiography shows aneurysms (1-2 mm) in medium sized vessels in 70% of cases with classic PAN. Also, thrombosis, stenosis and irregularities could be seen in some cases.

When PAN is expected, angiography should precede biopsy as an investigative tool to avoid catastrophic bleeding.

3- Biopsy, this is better taken from skin, muscles or testicles, rather than from kidney. It may show necrotizing vasculitis.

^Treatment and Prognosis of PAN:

Without treatment, the 5 years survival is only 15%. Bad prognostic signs are the following: old age, delayed diagnosis and treatment, renal and gastrointestinal involvement.

The main line of treatment is the use of steroid and cyclophosphamide in doses tailored according to the disease activity. This will improve the 5-year survival to more than 50%. Other drugs could be used as azathioprine, busulfan and ATG.

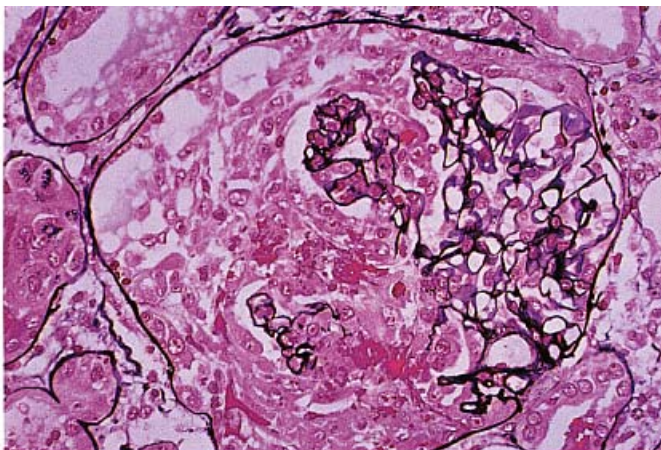
Wegener's Granulomatosis (WG)

Wegener's granulomatosis is an uncommon granulomatous disease associated with necrotizing vasculitis. It usually involves medium sized and small vessels.

Renal pathology in W.G.:

Light microscopy may be similar to the microscopic type of PAN with focal segmental necrotizing GN associated with crescents and intracapillary fibrin thrombi. Crescents could be cellular or granulomatous, mostly seen opposite the glomerular necrosis. Glomeruli in the domain of diseased vessels also show ischaemic changes (Fig. 4.3a).

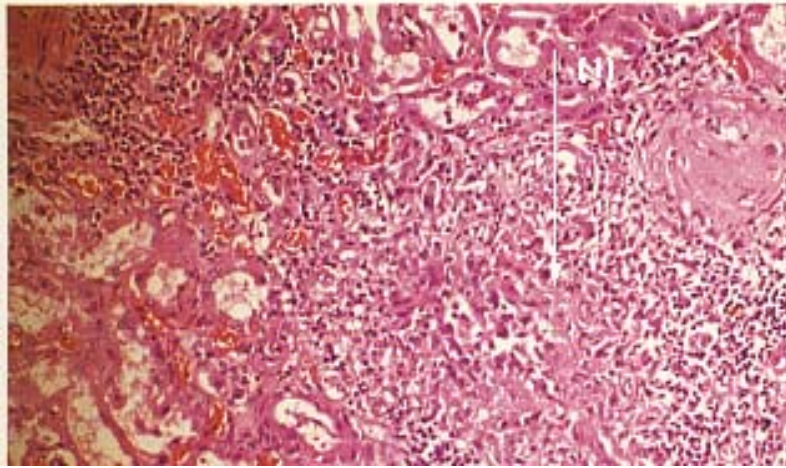
Blood vessels show necrotizing arteritis. Tubulointerstitium shows ischaemic changes, areas of infarcts and inflammatory infiltrates. Sometimes granuloma could be seen, which is necrotizing with vascular nidus (Fig. 4.3b).



(Fig. 4.3a)

PASM stained kidney section (X260) from a patient with W.G., It shows large crescent with collapse of the glomerular tuft.

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan).



(Fig. 4.3b)
Hx & E stained kidney section of a case of Wegener's granulomatosis showing a non-casating Granuloma (arrow).

Immunofluorescence microscopy is almost negative. Sometimes, focal and segmental capillary wall deposits of IgG, IgM, fibrinogen and C3 are seen especially in the areas of glomerular necrosis.

Clinical features of W.G.:

The clinical presentation of W.G. is extremely variable. It could present with insidious onset and prolonged course of constitutional and upper respiratory symptoms or it may present with abrupt onset with severe constitutional and pulmonary symptoms. The systemic manifestations of WG are the following:

- 1- *Constitutional symptoms*, these are observed in 50-100% of the cases, it is usually in the form of fever, weakness and malaise.
- 2- *Upper respiratory symptoms*, these are documented in 70-80% of the cases, mostly as nasal symptoms and/or as sinusitis. Patients with WG may complain of epistaxis, rhinitis, purulent discharge and nasal crusts. In advanced cases, perforation of nasal septum and saddle nose deformity may be seen. X-ray examination may show sinus fluid level, mass, or bony erosion. Maxillary sinus is the most commonly affected sinus followed by the sphenoid and ethmoid sinuses, while frontal sinus is the least commonly involved sinus.
Ear may be involved in 25-50% of cases. Patients may complain of ear pain and tinnitus.
- 3- *Lower respiratory symptoms*, are encountered in 65-75% of cases. Patient may complain of dyspnea, cough, haemoptysis and pleuritic pain.

X-ray examination may show the following:

- Pulmonary infiltrate
- nodular lesions (single or multiple)
- Cavitory lesions
- Pleural effusion.

4- *Renal manifestations* which vary from asymptomatic urinary findings to rapidly progressive GN.

5- *Other manifestations include:*

- Arthralgia and arthritis which are symmetrical and non-deforming.
- Skin palpable nodules, macular erythematous rash and purpura. These are more common on extremities.
- Myopathies due to small blood vessels involvement.
- Mononeuritis multiplex.
- Heart, liver, gall bladder, eye and parotid glands have been reported to be involved with W.G.

Laboratory Assessment of W.G.:

- No specific test for W.G. is available
- Always there are high ESR, leucocytosis or leucopenia, Eosinophilia, thrombocytopenia.
- ANCA is of diagnostic value in W.G. and could be of value in follow-up.

Treatment and Prognosis of W.G.:

- Without treatment, the one year survival is 20%.
- Cyclophosphamide gives striking good results when given in full dose and duration.
- Initially, the patient is usually treated with pulse steroid and cytoxan then maintenance cytoxan with or without Prednisone is provided.
- When remission is induced, cytoxan may be given for 1 year or may be replaced by imuran (azathioprine).

Chrug-Strauss Syndrome (Allergic Granulomatosis)

Allergic granulomatosis is a triad of:

- Necrotizing granulomatous vasculitis with eosinophilic tissue infiltrate and extravascular granulomas.
- Peripheral eosinophilia, and
- Bronchial asthma.

It is a very rare disease which affects males more common than females and occurs more in the third, and fourth decades of life.

Renal involvement is less common (<50% of cases show renal disease) and minority of patients die with end stage renal failure.

Renal pathology:

- Glomeruli show mild focal segmental necrotizing glomerulonephritis, sometimes associated with small crescents.
- Vessels involved are those of small size (periglomerular to arcuate). Light microscopy shows necrotizing granulomatous vasculitis with eosinophils predominating the pulmonary infiltrate. Also, thrombosis and small aneurysms could be detected.
- Tubulointerstitium shows oedema, cellular infiltration and eosinophilic granulomas.

Clinical features:

The disease usually comes in 3 phases with the initial one being asthma or allergic rhinitis which may extend for many years (up to 30 years). This is followed by phase of peripheral blood and tissue eosinophilia (as Loffler's syndrome or eosinophilic gastroenteritis). This phase may extend for months with remission and exacerbation which is then followed by the third phase of systemic vasculitis that is rapidly fatal.

Systemic involvement in allergic granulomatosis includes the following:

- *Constitutional symptoms* with fever, weight loss, fatigue and malaise.
- *Asthma*, allergic rhinitis and other allergic diatheses with peripheral eosinophilia. X-ray chest may show transient patchy pneumonitis, pulmonary nodules, cavitary lesions, interstitial infiltrate and pleural effusion.
- *Ischaemic heart disease and congestive heart failure.*
- *Gastrointestinal manifestations* as diarrhoea, pain, haemorrhage and perforation.
- *Cutaneous manifestations* including skin nodules, petechiae and purpura.
- *Migratory polyarthritis.*
- *Mononeuritis multiplex.*
- *Renal manifestations* usually include microscopic hematuria and mild proteinuria, rarely nephrotic syndrome or renal impairment.

Treatment of Allergic Granulomatosis:

Steroids stand as the main line of treatment. If this failed to control the disease, azathioprine and cyclophosphamide may be used.

Temporal Arteritis

Temporal arteritis which is a sort of giant cell arteritis affects 3/100,000 population. Females are more affected than males, 95% of patients are above age of 50 years.

Pathology:

The disease usually affects the medium-sized and the large vessels with necrosis and infiltration with inflammatory cells including giant cells.

Renal involvement is rare and usually take the form of focal and segmental necrotizing glomerulonephritis.

Clinical features:

These include the following:

- 1- *Constitutional, non-specific symptoms* include fever, malaise and weight loss.
- 2- *Polymyalgia rheumatica* with proximal muscle weakness and stiffness.
- 3- *Temporal artery* may be felt tender with nodules, sometimes temporal pulsation is lost. In this situation, the patient may complain of severe headache, facial neuralgia, vertigo, diplopia or even blindness.
- 3- *Involvement of the aorta* and its branches with ischaemic visceral changes sometimes occur.
- 4- *Renal artery involvement* is extremely rare.

Treatment:

Steroids usually give dramatic response.

Takayasu's Arteritis (Pulseless disease, Aortic Arch Syndrome)

This is a rare disease characterized by transmural inflammation and stenosis of medium-sized and large vessels with predilection of the aortic arch and its major branches.

Females represent 90% of cases with a peak incidence at age of 15-20 years.

Renal involvement may be in the form of:

- 1- Renovascular hypertension.
- 2- Renal ischaemic changes with progressive renal failure.
- 3- Glomerular disease which may precede the other systemic manifestations.

This usually take the form of proteinuria and/or haematuria. The pathologic changes are usually mild mesangial proliferative glomerulonephritis.

Relapsing Polychondritis

Is a disease affecting tissues containing glycosaminoglycans (heart, kidney, blood vessels, sclera, cornea, and ear). It is characterized by recurrent inflammation and destruction of ear, nose, trachea, joints, and

larynx. Vasculitis in this disease is similar to PAN with focal and segmental necrotizing GN.

From the renal point of view the patient may present with hematuria, proteinuria or with rapidly progressive renal failure. Differentiation from W.G. is difficult. Yet, external ear is not involved in W.G. and the lower respiratory tract is not involved in relapsing polychondritis.

Causes of focal segmental necrotizing glomerulonephritis with crescent are:

- SLE
- Wegener's granulomatosis
- Schönlein-Henoch purpura
- Idiopathic RPGN (type II)
- Polyarteritis nodosa
- IgA nephropathy
- Goodpasture's syndrome
- GN associating endocarditis and Rheumatic fever.

Antiglomerular Basement Membrane Antibody (Anti-GBM)-mediated Nephritis (Goodpasture's Syndrome)

This is a disease caused by autoantibodies of IgG type directed against Good pasture's antigen. Goodpasture's antigen is a type IV collagen which is normally present in the basement membrane of renal glomeruli, pulmonary alveoli, cochlea and the choroid plexus.

When the disease is restricted to the kidneys, it is called anti-GBM disease, while the term Good pasture's Syndrome is given when pulmonary haemorrhage and renal disease are manifest.

Etiology:

In UK the disease is known to affect one per 2 million population per year and 1-2% of renal biopsies in America and Europe show anti-GBM disease.

The disease is more common in second and third decades of life. Anti-GBM disease in general affects males more than females with a ratio of 2: 1, while in Good pasture's syndrome the ratio is 9: 1. The disease occurs more in spring and early summer. Localized out breaks occur from time to time.

Genetic predisposition and environmental triggering factors are claimed to be mandatory for the development of this disease.

Genetic factors: strong family history is sometimes given and HLA DR2 is detected in 90% of cases with anti-GBM disease

Environmental factors include upper respiratory tract infection especially influenza, exposure to hydrocarbon fumes (as gasoline), organic fumes or dust, burning oils, and glu. The exposure to these toxins is more among firemen, mining engineers and gas station workers.

The antibodies are specific for GBM and the alveolar basement membrane.

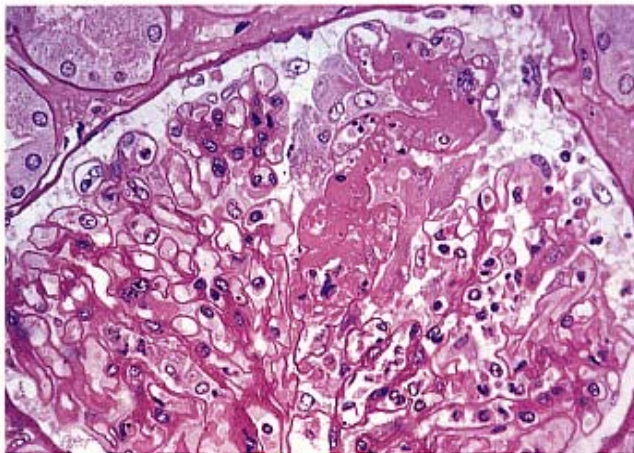
Clinical Aspects of the Anti-GBM Disease:

50% of the patients give history of vague complaints as malaise, weight loss, headache, upper respiratory tract infection, gastrointestinal upsets then they manifest glomerulonephritis. Some patients develop pulmonary haemorrhage as well.

Renal disease:

Most patients have severe glomerulonephritis that progresses rapidly to ESRD. Less than 15% of patients have mild glomerular disease.

Histopathologically, the glomerular disease varies from mild focal proliferative GN to very severe crescentic GN and acute interstitial nephritis (**Fig. 4.4a**).



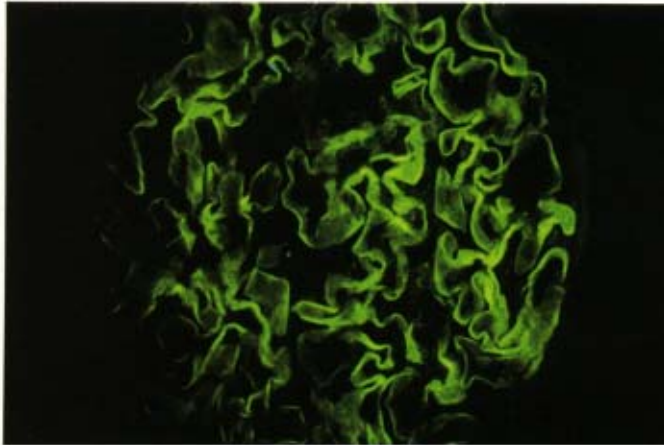
(Fig. 4.4a)

PAS stained kidney section (X310) from a patient with Goodpasture's syndrome. It shows glomerular capillary thrombosis, hyperplasia and tuft necrosis and polymorphonuclear leukocyte infiltration.

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan).

Presence of vasculitis in renal biopsy in cases of anti-GBM disease is controversial. Almost such lesions are absent. Immunofluorescence microscopy shows linear IgG deposits along the GBM (**Fig. 4.4.b**). IgM and IgA deposits are seen in 10-20% of cases and C3 are seen as well in 30% of renal biopsies. IgG linear deposits are also seen on the distal tubular basement membrane.

When anti-GBM disappears from circulation it fades from biopsy. Some patients may develop superimposed subepithelial granular deposits.



(Fig. 4.4b)

Immunofluorescence stained kidney section (X260) from a patient with anti-GBM disease. It shows linear deposits of IgG.

(Reproduced with permission from IGAKU-SHOIN Ltd, Japan).

In untreated patients, the prognosis of this disease is bad.

Pulmonary disease:

Occurs in 60-90% of cases, less in children and elderly women and more among cigarette smokers.

In classic Good pasture's syndrome, patient presents first with pulmonary haemorrhage for 8-12 months then glomerulonephritis appears.

Pulmonary manifestations could be very mild to very severe disease with sudden onset. These manifestations increase by time, infection and by smoking. This is always associated with rising anti-GBM titre.

X-ray chest shows pulmonary haemorrhage (typically apices and supradiaphragmatic areas are free, not bounded by fissures). This could be confirmed by measuring diffusion capacity of carbon monoxide which is increased by 30% due to presence of blood in the alveolar spaces.

Anaemia:

Anaemia may be very severe and out of proportion to renal impairment. It is due to blood loss and bone marrow suppression. It could also be angio-pathic haemolytic anaemia.

Treatment:

Prednisolone, azathioprine, cyclophosphamide and plasma exchange are used in different combinations and doses according to the patient status and the disease activity.

Plasma exchange with use of fresh frozen plasma may be very effective in stopping severe pulmonary haemorrhage and clearing anti-GBM antibodies from circulation.

Anti-Neutrophil Cytoplasm Auto-Antibodies (ANCA) and Vasculitis

These are autoantibodies specific for the constituents of neutrophil azurophilic granules. According to the pattern of distribution of binding of these antibodies (as detected by immunofluorescence microscopy) ANCA is divided into two subtypes, which are:

- Cytoplasmic pattern (C-ANCA) in which the I.F. staining occupies the whole neutrophil cytoplasm. In this type, the auto-antibodies are directed against proteinase 3.
- Perinuclear pattern (P-ANA) in which the I.F. staining is only peri-nuclear. In this type, the autoantibodies are directed against the myeloperoxidase.

Diseases affecting the kidney are almost P-ANCA positive while those with predominant systemic vasculitis, especially with granulomatous pulmonary lesions, are C-ANCA positive.

Detection of ANCA in patients serum is very helpful for diagnosis of vasculitis with 84% sensitivity and 90% specificity. Also, serum analysis for ANCA titre is useful in follow-up for disease activity and response to treatment. Yet, some patients, however, have high ANCA while the disease is quiescent.

ANCA associated diseases include:

- Wegener's granulomatosis.
- Polyarteritis nodosa.
- Leucocytoclastic (hypersensitivity) angiitis.
- Idiopathic, type III crescentic GN.

Suggested Readings:

- Griffith ME, et al: Classification, pathogenesis, and treatment of systemic vasculitis. *Ren Fail*, 18 : 5, 785-802, 1996.
- Rees AJ: Vasculitis and the kidney. *Curr Opin Nephrol Hypertens*, 5 : 3, 273-81, 1996.
- Calabrese LH: Drug-induced vasculitis. *Curr Opin Rheumatol*, 8 : 1, 34-40, 1996.
- Gerber O, et al: Vasculitis owing to infection. *Neurol Clin*, 15 : 4, 903-25, 1997.
- Athreya BH: Vasculitis in children. *Curr Opin Rheumatol*, 8 : 5-84, 1996.
- Jennette JC, et al: Small-vessel vasculitis. *N Engl J Med*, 337 : 21, 1512-23, 1997.
- Gross WL: Systemic necrotizing vasculitis. *Baillieres Clin Rheumatol*, 11 : 2, 259-84, 1997.
- Sneller MC, et al: Pathogenesis of vasculitis syndromes. *Med Clin North Am*, 81 : 1, 221-42, 1997.

THROMBOTIC MICROANGIOPATHY

This includes haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura and the post partum renal failure.

Pathologically, these diseases are characterized by the presence of thrombi which are predominantly in small-sized arteries, arterioles and capillaries.

Etiology of thrombotic microangiopathy:

- 1- Infection, usually by E-Coli but also infection by other organisms have been reported to induce thrombotic microangiopathy as pseudomonas. Shingle and typhoid. The disease may occur in the course of infection or following it.
- 2- Drugs (as cyclosporine A, mitomycin, and vaccines) and toxins (as snake bite, and carbon dioxide poisoning).
- 3- Pregnancy, post partum, eclampsia and contraceptives.
- 4- Immunologic disorders as SLE, Sjögren syndrome disorders, scleroderma, malignancy, bone marrow transplantation and kidney transplantation.
- 5- Genetic predisposition.

Pathologic features:

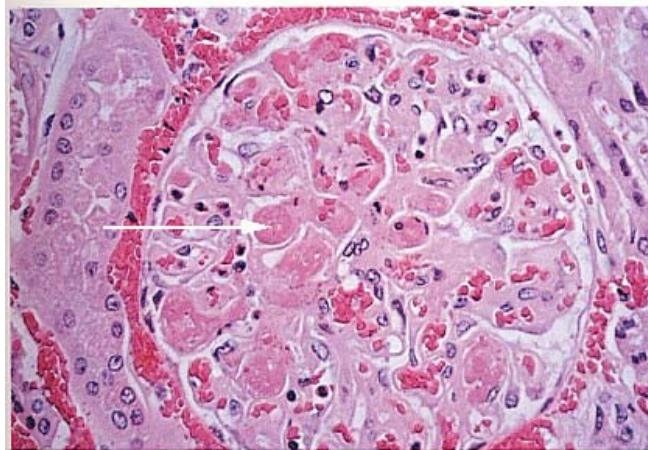
1- Haemolytic uraemic syndrome (HUS):

The characteristic changes are found in the vascular tree including arteries, arterioles and glomerular capillaries; while the tubulointerstitial changes are secondary to ischaemia.

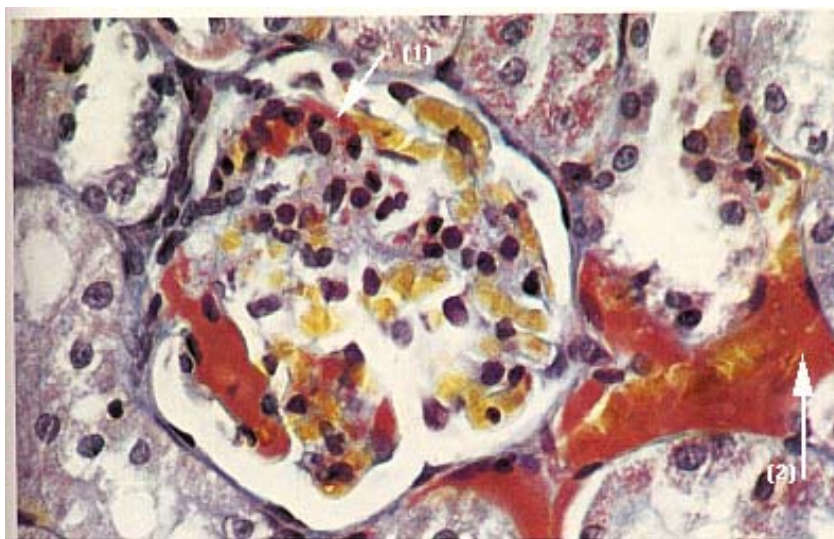
Glomeruli show variable changes, according to the severity and duration of the disease. The characteristic changes are endothelial oedema, degeneration, and separation from glomerular basement membrane which appears thick and of double outline. Also of characteristic features are the intraluminal thrombi and fragmentation of erythrocytes (**Fig. 5.1**). Other glomerular changes could also be seen, but are not characteristic, such as slight mesangial proliferation, mesangiolytic crescents and (in terminal cases) glomerulosclerosis.

Immunofluorescence microscopy shows fibrin deposits along the capillary walls.

Blood vessels show separation of endothelial cells and accumulation of fibrin and other plasma proteins underneath. Later, thrombosis occurs. Fibrinoid necrosis in the arteriolar wall is mostly due to hypertension.



(Fig. 5.1a)
 H & E stained section(X260)
 from a child with HUS, it shows
 numerous thrombi in the glomerular
 capillaries (arrow).
**(Reproduced with permission
 from IGAKU-SHOIN Ltd, Japan).**



(Fig. 5.1b)
 Hx & E stained section
 of a case of haemolytic
 uraemic syndrome
 showing diffuse fibrin
 deposition in
 glomerular (arrow-1)
 and extra glomerular
 capillaries (arrow-2)

Tubules and interstitium shows changes secondary to ischaemia. There is focal degeneration, necrosis and even true infarcts.

In younger children, HUS predominantly affects glomeruli. Whereas in older children and adults, the disease involve mainly arteries and arterioles (poor prognosis).

Lesions of arteries and arterioles outside the kidney (liver, colon and pancreas) are infrequent.

2- Post partum renal failure:

Is similar to HUS regarding changes in the glomeruli and arterioles.

3- Thrombotic thrompocytopenic purpura:

Is similar to HUS. Yet in contraindication to HUS, vascular thrombosis in TTP is widespread affecting arterioles in many organs particularly the brain, heart and the skin.

Clinical features of thrombotic microangiopathy:

1- HUS in children:

Most of patients (78%) are below the age of 3 years. Males and females are equally affected. Always, there is a prodroma of mild gastroenteritis or respiratory tract infection. In 20% of patients the prodroma may take the form of acute abdomen. The disease usually takes a severe course with abrupt appearance of weakness, pallor, oliguria, even anuria. Also, drowsiness, personality changes, seizures and coma are frequent manifestations.

Clinical examination shows pallor, dehydration or overload, hepatomegaly, splenomegaly, purpura and abnormal urinalysis.

Prognosis is poor especially with prolonged oligoanuria, hypertension and in the presence of cortical necrosis. Mortality up to 40% has been reported.

2- Hemolytic uraemic syndrome in adults:

As in children, the disease may present with acute renal failure, microangiopathic hemolytic anaemia and thrombocytopenia. However, the disease in adults is characterized by:

- Higher incidence of hypertensive encephalopathy, neurologic sequelae and cardiac dysfunction.
- Higher incidence of renal involvement (50%), and
- Higher incidence of mortality (50%).

3- Post partum renal failure:

- This occurs within days to several months after an uneventful delivery.
- Clinical features as well as laboratory findings are similar to those with HUS.
- Mortality is high (50-60%) and remission of renal function is rare.

This condition has to be differentiated from other causes of ARF with pregnancy as:

- Prerenal failure owing to volume depletion resulting from hyperemesis gravidarum.
- Acute renal failure with complicated pyelonephritis.
- Acute renal failure with severe eclampsia.
- Acute renal failure with abruptio placenta.
- Acute renal failure with intrauterine foetal death.

4- Thrombotic thrombocytopenic purpura (TTP):

Females are more affected with TTP than males (2 : 1). This disease occurs at any age, but more common in the third and fourth decade of life.

There are 5 outstanding features for TTP which are:

- Fever
- Hemolytic anaemia
- Neurologic manifestations.
- Thrombocytopenic purpura
- Renal disease, and

The disease commonly starts abruptly with headache, disorientation, dysphasia, seizures, cranial nerve palsies or even coma. These manifestations usually fleet and fluctuate.

Laboratory assessment of CSF may show high protein content, blood or xanthochromia.

Less frequently, the disease may present with GIT symptoms, jaundice, lymphadenopathy, pallor, petechiae, retinal hemorrhage, and gastrointestinal haemorrhage.

Renal abnormalities involve 90% of cases with TTP. Renal failure occurs in 50% of cases and is less severe than in HUS.

Hematologic manifestations in TTP include severe anaemia, thrombocytopenia and rarely manifestations of DIC. Blood smear show fragmented erythrocytes (Schistocytes) and reticulocytosis.

Comb's test is negative, LDH level is high, while haptoglobin level is low. Prothrombin time, PTT and fibrinogen are normal.

The course of the disease is variable from acute, chronic, to relapsing.

Treatment of thrombotic microangiopathy:

Is rather empirical. Many therapeutic approaches has been tried, but none of them is satisfactory. These treatment options are used in different combinations. They include the following:

- Plasma exchange
- Plasma infusion
- PGI₂ infusion
- Corticosteroids
- Kidney transplantation.
- Plasma pheresis
- Antiplatelet aggregating drugs
- Anticoagulants and antifibrinolytic drugs.
- Dialysis.

Suggested Readings:

- Moake JL, et al: Thrombotic microangiopathies associated with drugs and bone marrow transplantation. *Hematol Oncol Clin North Am*, 10 : 2, 485-97, 1996.
- Ruggenti P, et al: Pathogenesis and treatment of thrombotic microangiopathy. *Kidney Int Suppl*, 58 : S97-101, 1997.
- Sakakibara K: Renal thrombotic microangiopathy. *Ryoikibetsu Shokogum Shirizu*, 16 Pt 1, 316-9, 1997.
- McCrae KR, et al: Thrombotic microangiopathy during pregnancy. *Semin Hematol*, 34 : 2, 148-58, 1997.
- Mitarai T: Thrombolytic therapy for vasculitis and thrombotic microangiopathy-with special reference to the kidney. *Nippon Naika Gakkai Zasshi*, 86 : 9, 1634-8. 1997.
- Ito K, et al: Advances in the treatment of hemolytic uremic syndrome (HUS). *Nippon Rinsho*, 55 : 3, 715-20, 1997.

ACUTE RENAL FAILURE (ARF)

Definitions:

ARF is a syndrome that can be broadly defined as a rapid deterioration of renal functions resulting in the accumulation of nitrogenous wastes such as urea and creatinine.

Acute renal failure may be pre-renal, renal or post-renal (Fig. 6.1):

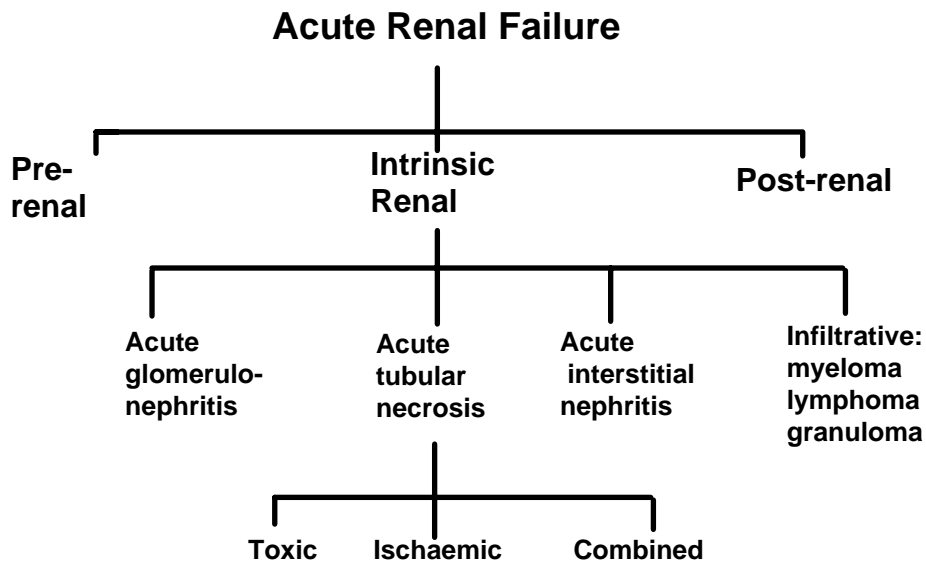


Fig. 6.1

Different types of acute renal failure

In pre-renal failure, the renal tissue is intact and kidney biopsy shows normal renal histology. Oliguria and high serum creatinine are due to functional impairment; since there is no sufficient blood reaching the kidney to be cleared of these toxins.

In post-renal failure, the obstruction of the urinary tract results in increasing the pressure above the level of the obstruction up to the nephron including the urinary space of the renal glomeruli. When this back pressure exceeds that of the filtration pressure in the renal glomeruli, the process of

urine formation will stop with progressive accumulation of wastes and increase of serum creatinine and blood urea.

In renal failure (intrinsic renal failure), there is a damage involving the glomeruli, renal tubules or tubulointerstitium with loss of their functions. Consequently wastes accumulate with increase in serum creatinine and blood urea.

In this chapter we will focus on pre-renal failure and acute intrinsic renal failure, details of post renal failure is found in the chapter on obstructive uropathy.

I. Pre-renal Failure

Combination of hypotension, hypovolaemia resulting in diminished renal perfusion is the most common cause of acute renal failure in hospitalized patients.

Additional causes of prerenal failure- not necessarily associated with a decrease in GFR- are conditions that increase urea production such as large protein intake and increased protein catabolism (fever, surgery, severe illness, steroids and tetracyclines). In patients with gastrointestinal bleeding, the combination of high protein load (blood in the gastrointestinal tract) and contracted circulating volume leads to an increase in blood urea concentration.

When renal hypoperfusion (due to hypotension and/or hypovolaemia) is not severe enough to cause renal tubular damage, it will manifest as pre-renal failure in the form of oliguria and a rise in serum creatinine and blood urea. Since there is no structural renal damage, early diagnosis and correction of renal hypoperfusion result in immediate diuresis and rapid drop in serum creatinine and blood urea levels. If hypoperfusion is severe or neglected, renal compensatory mechanisms will fail and acute tubular necrosis occurs. In this new situation, correction of hypoperfusion will not be followed by diuresis or drop in serum creatinine. Few days or weeks (mean 2-3 weeks) are needed for tubular regeneration and recovery of kidney function to occur.

II. Acute Intrinsic Renal Failure

This includes acute tubular necrosis (ATN), acute interstitial nephritis and acute glomerulonephritis. In this chapter we will focus on ATN. Details of the other two categories are found in chapters 3&9.

Acute Tubular Necrosis

Acute tubular necrosis can be induced by renal hypoperfusion (ischemia) or exposure to nephrotoxins (exogenous or endogenous toxins) and frequently by a combination of both. These two types of insults (ischaemic and toxic) will now be reviewed individually.

Causes of Ischaemic ATN:

A- Intravascular volume depletion:

- Major trauma, burn and crush injury.
- Haemorrhage (post partum, surgical and gastrointestinal).
- Pancreatitis, vomiting, diarrhea, peritonitis, dehydration.
- Hypoalbuminemia.
- Fluid volume depletion secondary to renal losses (diabetic ketoacidosis, diuretic abuse and adrenal insufficiency).

B- Decreased cardiac output

- Severe congestive heart failure or low cardiac output syndrome.
- Pulmonary hypertension and massive pulmonary embolism.

C- Increased (renal/systemic) vascular resistances ratio:

- Renal vasoconstriction: - Alpha adrenergic agonists.
 - Hypercalcemia, amphotericin.
- Systemic vasodilatation: - After load reduction.
 - Antihypertensive medications.
 - Anaphylactic shock.
 - Anesthesia.
 - Sepsis.
- Liver cell failure: results in both systemic VD and renal VC.

D- Renovascular obstruction:

- Renal artery: Atherosclerosis, embolism, thrombosis, vasculitis.
- Renal vein : Thrombosis, compression.

E- Increased blood viscosity:

- Multiple myeloma.
- Macroglobulinaemia.
- Polycythaemia.

F- Aggravation of renal hypoperfusion by interference with renal autoregulations:

- Prostaglandin synthesis inhibitors as NSAIDs
- Angiotensin converting enzyme inhibition in patients with renal artery stenosis.

Causes of Toxic ATN

(A) Exogenous nephrotoxins include:

Antibiotics:	Aminoglycosides	Amphotericin
	Cephalosporin	Polymyxin
	Sulfonamide	Pentamidine
	Quinolone	Acyclovir
	Tetracyclines	Bacitracin

Anaesthetic agents: Methoxy fluorane

Contrast Media: Diatrizoate, Iopanoic acid

Anti-ulcer: Cimetidine, excess milk-alkali

Analgesics: Phenacetin

Diuretics: Mercurials

Metals: as Mercury, lead, arsenic, bismuth, cadmium, antimony,

organic solvents: carbon tetrachloride, tetrachlorethane, tetrachlorethylene.

Glycols: as ethylene glycol, xylitol

Poisons: paraquat, diquat, mushroom (Amanita), snake bite, stings, bacterial toxins.

Chemotherapeutic and Immunosuppressive Agents

Cis-Platinum, Methotrexate, Mitomycin, Nitrosoureas, Cyclosporine A, and D-Penicillamine

(B) Endogenous nephrotoxins include

Pigments:	Crystals:
Myoglobin	Uric acid
Hemoglobin	Calcium
Methemoglobin	Oxalate

Tumour Specific Syndromes:

Tumour lysis syndrome

Plasma cell dyscrasias (e.g. myeloma kidney)

Risk factors associated with contrast media (and other toxins) nephropathy include the following:

- Renal insufficiency
- Diabetes mellitus
- Hepatic insufficiency
- Cardiovascular disease
- Increasing age
- Dehydration
- multiple myeloma
- Hypoalbuminaemia
- Dose of contrast
- Hyperuricaemia

Clinical features of ARF:

- 1- Usually, the patient gives history of the etiologic cause such as trauma, shock, haemolysis, drug intake, infection, or stone disease.
- 2- Patient may notice a change in urine volume and character, oliguria is common, but in 10-50% of cases urine volume will be normal or even higher (as in toxic ATN) this is called polyuric ATN. Absolute anuria is highly suggestive of obstructive ARF (post-renal) or very severe form of ATN (cortical necrosis).
- 3- Manifestation of salt and water retention (oedema, puffiness, hypertension and even heart failure).
- 4- By time, manifestations of uraemia appear as acidotic breathing, dyspnea, nausea, vomiting, headache, muscle twitches and even frank encephalopathy and coma.
- 5- Patient may present as well with any of the following complications:

Complications Of Acute Renal Failure:

Cardiovascular

- pulmonary odema
- hypertension
- myocardial infarction
- arrhythmias
- pericardial effusion
- pulmonary embolism

Metabolic

- hyponatremia
- acidosis
- hyperphosphatemia
- hyperkalemia
- hypocalcemia

Neurologic

- coma
- seizures

Gastrointestinal

- gastritis
- gastroduodenal ulcers

Haematologic

- anaemia
- hemorrhagic diathesis

Infections

- pneumonia
- septicemia
- UTI

Investigations of ARF:

A- Urinary indices:-

May be helpful in the differentiation between pre-renal failure and acute tubular necrosis. Diuretics should not be given at least during the last 48 hours for these parameters to be valid.

Parameter	Prerenal	ATN
Concentration of urine:		
Urine specific gravity	> 1.020	< 1.010
Urine Osmolarity (mosm/lit)	> 500	< 350
GFR and overall tubular reabsorption:		
Creatinine clearance	> 20	< 20
Urine/Plasma urea	> 8	< 3
Urine/Plasma creatinine	> 40	< 20
Tubular handling of solutes		
UNa (mEq/L)	< 20	> 40
FeNa (%)	< 1	> 1

B- Urinary sediment:

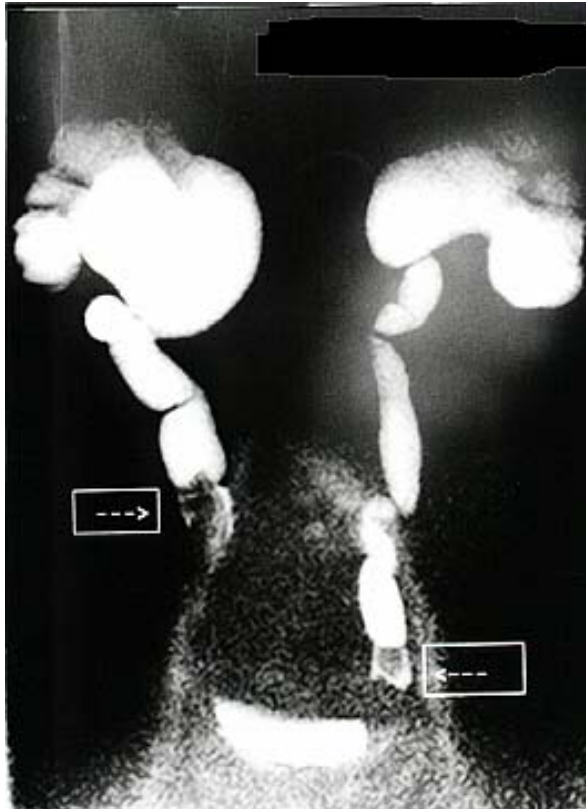
Centrifugation of fresh urine sample and examination of the urinary sediment may be helpful in diagnosing different causes of ARF. See chapter 15 on value of urine examination in medical diagnosis. In pre-renal failure and in ischaemic ATN urinary sediment is usually free.

C- Renal Imaging:

1. Plain film of the abdomen:

This will show kidney parity, size, shape, calcification and stones.

2. **Renal Ultrasonography and echo-doppler of renal vessels:**
Ultrasonography safely assesses kidney size, shape and echogenicity. Cortical thinning or oedema can sometimes be seen clearly. Also, it can exclude obstructive uropathy (back pressure changes). Echo-Doppler of renal vessels can exclude occlusion of the renal arteries and veins.
3. **Retrograde and antegrade pyelography:**
Provide the most reliable information on the patency of the ureter.
4. **Radionuclide studies (Renogram):**
The vascular phase of the isotope renogram can show the pattern of renal perfusion (for diagnosis of reno-vascular diseases). Diuretic renogram can help in diagnosis of urinary tract obstruction. Also, renogram may help in diagnosis of renal parenchymal diseases, but cannot discriminate their different etiologic causes.
5. **Angiography:**
Is useful mainly when an acute reversible renovascular event is suspected such as embolization, thrombosis or involvement in a dissecting aortic aneurysm. It carries the risk of exposure to contrast media which could be nephrotoxic.
6. **C.T. studies:**
Provide reliable information on kidney parity, size, shape and presence of hydronephrosis.
7. **Magnetic Resonance urography:**
Recently MRI urography (MRU) without use of contrast media can provide films similar to IVP. It is thus of great value to exclude U.T. obstruction without the risk of contrast media nephropathy (Fig. 6.2).



(Fig. 6.2)

MR urography shows bilateral hydronephrosis in a patient with 4.8 mg/dl serum creatinine (IVU is not feasible). Note the hypointense ureteric stone bilaterally (arrows).

D. Renal biopsy:

The indications of renal biopsy in ARF are:

1. Equivocal case history.
2. Renal signs suggesting glomerular, vascular or interstitial lesions.
3. Extrarenal manifestation in patients in whom a systemic disease identifiable by biopsy is suggested.
4. Prolonged renal failure (more than 3 weeks).

Diagnostic Approach:

On confirming renal dysfunction (by high serum creatinine) unless the diagnosis is clear, we have to adopt the following approach:

- 1- First exclude pre-renal failure by history of fluid loss, shock, hypotension.....etc and physical examination e.g. hypotension, dehydration, collapsed neck veins. Examination of urine may help to confirm this diagnosis. Urine osmolality is >500 mosmol/L, U Na is <20 mmol/L, and FeNa is <1.0 in cases with pre-renal failure.

If the case proved to be pre-renal, quick approach with I.V. fluid should be followed by diuresis.

2- If the case is not pre-renal failure, we proceed for renal ultrasonography. If it shows a backpressure changes, this could be confirmed by diuretic renogram using $^{99}\text{Tc-DTPA}$. If obstruction is confirmed, we proceed by further investigative and therapeutic approaches such as ureteral catheterization, retrograde pyelography, percutaneous nephrostomy (PCN) and antegrade pyelography. Urologic management will depend on the outcome of these investigations and diagnosis will be post-renal ARF.

3- If the case is neither pre-renal nor post-renal, we will be left with renal causes of ARF.

Again, urine examination will help in the diagnosis. Look for the urine sediment:

a- if there is proteinuria, hematuria, casts and the patient is hypertensive. The case is acute glomerulonephritis which could be confirmed and typed by kidney biopsy.

b- if urine sediment is clear the case is ischaemic ATN.

c- if urine shows minor changes (e.g. trace proteinuria, eosinophiluria), the case is most probably toxic ATN.

If differentiation between **b** and **c** is not clear by history and clinical examination, this sometimes could be achieved by renal biopsy.

Diagnosis of the etiology of ARF is sometimes not easy to achieve, for example:

1- The urine parameters may be misleading or inconclusive as in polyuric ATN, if there is a pre-existing renal, cardiac or hepatic disease or if diuretics have been administered. In these situations, using parameters including plasma values may increase the sensitivity of urine parameters e.g. U/P osmolality (> 1.3 in pre-renal, < 1.1 in ATN) FeNa (< 1 in pre-renal, > 1 in ATN).

Fluid challenge may help in the distinction between pre-renal failure and ATN. Also if furosemide is added it will induce quick response of pre-renal failure to fluid load and even if the case is ATN it may be changed from oliguric to the polyuric type of ATN which is more easy to manage and have better prognosis.

2- Occasionally, obstruction may occur without dilatation of the collecting system e.g. in patient with extensive calculi, with acute obstruction, with retroperitoneal fibrosis and with extensive infiltration of the ureters.

If the doubt persisted about the patency of the urinary tract, cystoscopy and retrograde pyelography remain essential before excluding post-renal AFR.

Acute cortical necrosis:

Is a subset of ATN in which there is a massive necrosis of the tubules and glomeruli of the renal cortex. The condition may be focal or diffuse with irreversible damage of the kidneys. It is suspected when ATN fails to recover after 4-6 weeks.

Acute cortical necrosis usually occurs with complicated pregnancy as postpartum haemorrhage and abruptio placenta.

Diagnosis could be made by biopsy unless the lesion is patchy, then the diagnosis could be achieved by angiography which will show filling of the main renal arteries but failure to visualize interlobular arteries.

When pre-renal and post-renal failure are excluded, if diagnosis of ATN is not sure (i.e. there is possibility of other conditions such as glomerulonephritis), or interstitial nephritis, kidney biopsy should be performed on urgent bases, since these conditions may need early aggressive treatment (such as steroid and cyclophosphamide) for obtaining response.

Sometimes kidney biopsy may reveal an unexpected etiology for ARF as infiltration with myeloma, lymphoma or granuloma.

TREATMENT OF ARF:

A- Treatment of the cause e.g. any condition causing renal hypoperfusion, exposure to toxic drug or chemical or systemic disease.

B- Prevention of acute renal failure:

The timing of intervention to prevent ATN is important. Protective agents must be administered at the time of, or immediately following potential renal insult. This intervention may prevent or at least blunt the severity of ATN.

The intervention could be through the following approaches. In different combinations according to the clinical situation:

- Volume expansion by saline loading.
- Diuretic as mannitol and furosemide.
- Calcium channel blockers as verapamil and nifedipine.
- Vasodilating agents as dopamine in renal dose 1-2 ug/kg/min
- ATP-magnesium chloride.

In case of contrast media, the following additional points should be adopted, these are:-

- Avoid unnecessary contrast procedures.
- Avoid multiple contrast exposure within a few days.
- Avoid contrast exposure in high risk patient.
- Use the smallest dose possible.
- Use of non-ionic contrast is to somewhat safer.
- In high risk patient with renal impairment we can manage to wash the contrast out immediately after the technique (e.g. coronary angiography) by haemodialysis.
- MRU is good alternative for visualization of the urinary tract obstruction.

C- Conservative measures:

1- fluid balance:

Careful monitoring of intake/output and body weight is very important to avoid overload and hypovolaemia. The first may lead to pulmonary oedema while the second may aggravate renal ischaemia.

Patient should receive fluids equal the daily urine output plus the other sensible losses e.g. vomitus or diarrhea fluid; plus an amount equals the insensible loss which is around 600 c.c. for 60kg body weight patient. For example, a 60kg b.w. patient with ARF who produces 200 c.c. urine daily with no vomiting or diarrhea will need a daily fluid intake of about $600 + 200 = 800$ c.c. With every 1°C increase in body temperature, 200 c.c. should be added to the daily fluid intake. Fluid requirement will increase with the increase in the body surface area and the atmospheric temperature and humidity (leading to increase in sweating). Fluids could be given orally or (if not possible), it could be given intravenously.

2- Electrolytes and acid-base balance:

- Prevent and treat hyperkalemia.
- Avoid hyponatremia.
- Keep serum bicarbonate above 16 mmol/L.
- Minimize hyperphosphatemia by giving phosphate binders (e.g. CaCO_3 & AL hydroxide) with meals.
- Treat hypocalcaemia.

3- Nutritional support:

- Restrict protein (to 0.5gm/kg/day) but maintain sufficient caloric intake.

- Carbohydrate intake should be at least 100 gm/day to minimize ketosis and endogenous protein catabolism.

4- Drugs:

- Review all medications.
- Stop magnesium-containing medications.
- Adjust dosage for renal failure.

5- Treatment of hyperkalemia:

- Calcium gluconate I.V.
- Na HCO₃ I.V.
- K-exchange resins (e.g. resonium)
- Avoid diets and drugs causing hyperkalaemia
- Glucose 50% + Insulin
- Salbutamol
- Dialysis

6- Dialysis:

The indications of dialysis in ARF are:

- Clinical:**
 - Poor clinical state, nausea, confusion.
 - Fluid overload, pulmonary oedema.
 - Preoperatively.
- Biochemical:**
 - Plasma K⁺ > 7 mmol/L.
 - Plasma bicarbonate < 12 mmol/L
 - Arterial pH < 7.15.

Prognosis of AFR:

The mortality of AFR remains high, ranging between 50-80% in surgical and post-traumatic cases. It is generally lower in ARF due to drug and toxins. About 75% of deaths occur in the first week of ARF, and 25-50% of these deaths are due to the underlying disease. The overall prognosis is better in non-oliguric than in oliguric renal failure.

The factors influencing patient survival in acute renal failure include the following:

- Aetiology of ARF.
- Severity of ARF.
- Number and severity of coexisting illness.
- Patient's age.
- Presence of complications.

Suggested Readings:

- McCarthy JT: Renal replacement therapy in acute renal failure. *Curr Opin Nephrol Hypertens*, 5 : 6, 480-4, 1996.
- Denton MD, et al: "Renal-dose" dopamine for the treatment of acute renal failure: Scientific rationale, experimental studies and clinical trials. *Kidney Int*, 50 : 1, 4-14, 1996.
- Mandal AK: Management of acute renal failure in the elderly. Treatment options. *Drugs Aging*, 9 : 4, 226-50, 1996.
- Slapak M: Acute renal failure in general surgery. *J R Soc Med*, 89 Suppl 29 : 13-5, 1996.
- Riella MC: Nutrition in acute renal failure. *Ren Fail*, 19 : 2, 237-52, 1997.
- Bock HA: Pathphysiology of acute renal failure in septic shock: from prerenal to renal failure. *Kidney Int Suppl*, 64 : S15-8, 1998.
- Stark J: Acute renal failure. Focus on advances in acute tubular necrosis. *Crit Care Nurs Clin North Am*, 10 : 2, 159-70, 1998.
- Andreucci VE, et al: Role of renal biopsy in the diagnosis and prognosis of acute renal failure. *Kidney Int Suppl*, 66 : S91-5, 1998.
- Mucelli, et al: Imaging techniques in acute renal failure. *Kidney Int Suppl*, 66 : S102-5, 1998.
- Solomon R: Contrast-medium-induced acute renal failure. *Kidney Int*, 53 : 1, 230-42, 1998.

CHRONIC RENAL FAILURE (CRF)

DEFINITIONS:

Chronic renal failure is a progressive loss of kidney functions due to progressive damage of kidney tissue by a disease involving the two kidneys.

In chronic renal failure, there is a persistent and irreversible reduction in the overall renal function. Not only the excretory functions are disturbed but also the endocrine and the haemopoietic functions as well as the regulation of acid-base balance become abnormal. These derangements in the internal environment (internal milieu) of the body will result in the uraemic syndrome.

In this domain there are confusions caused by use of different terms which could be solved by putting them in acceptable definitions. These terms and their definitions are as the following:

Azotaemia: This means that the concentrations of the blood urea and the blood urea nitrogen (BUN) are raised. It is not necessary that the patient has uraemic symptoms. Kidney function could even be normal and accumulation of urea is due to dietary causes, pre renal factors or even from laboratory interference.

Uraemia : is the syndrome resulting from severe renal failure.

Renal impairment: this means that there is a reduction in GFR which is still not severe enough to produce significant uraemic symptoms.

End stage renal failure (ESRF) is considered when chronic renal failure is so severe that the patient cannot live without renal replacement therapy (dialysis or transplantation). This is sometimes called *terminal renal failure* or *terminal uraemia*.

Disease involving one kidney (even if very severe and damaging this kidney) will not result in renal impairment or failure as the other kidney is capable to maintain the internal milieu or environment within normal. In this setting we may say compromised or non-functioning right or left kidney (according to the kidney damaged right or left). Sometimes we say solitary functioning right or left kidney (according to the side of the healthy kidney).

INCIDENCE OF CHRONIC RENAL FAILURE:

This varies from one country to the other. For example, in western Europe and Australia the incidence is about 50 new cases per million population per year. In USA, the incidence is 160 new patients/million per

year, while in Egypt and some developing countries it is believed to be about 200 new patients/million population per year. This variability could be attributed to different socio-economic and environmental factors.

AETIOLOGY OF CHRONIC RENAL FAILURE:

The common causes of CFR are diabetic nephropathy, chronic pyelonephritis, obstructive uropathy, reflux nephropathy, chronic glomerulonephritis and polycystic kidney disease. The complete list of causes include the following:

1. Primary glomerular diseases:

Such as idiopathic crescentic glomerulonephritis, primary focal segmental glomerulosclerosis and primary mesangiocapillary glomerulonephritis.

2. Tubulo-interstitial diseases:

These include the following:

- Chronic heavy metal poisoning such as lead, cadmium and mercury may result in chronic tubulo-interstitial nephritis and renal failure.
- Chronic hypercalcaemia as with vitamin D intoxication and primary hyperparathyroidism.
- Chronic potassium depletion resulting from prolonged use of diuretics without potassium supplementation as in patients with ascites or chronic heart failure.

3. Renal vascular diseases:

These may be in the main renal vessels (artery or vein) or in the intrarenal vessels.

Main renal artery diseases causing renal failure:

Renal failure may occur if there is bilateral advanced renal artery stenosis or a unilateral renal artery stenosis in a solitary kidney.

Renal artery stenosis usually occurs due to advanced atherosclerosis which is more common in elderly males or due to fibromuscular dysplasia which is more common in middle aged females.

Both atherosclerosis and fibromuscular dysplasia manifest first by renovascular hypertension. Later, they may end by renal failure due to progressive renal ischaemia.

Renal vein diseases causing renal failure:

Bilateral renal vein thrombosis; which is more common in patients with nephrotic syndrome. If bilateral or in a solitary kidney it may lead to renal failure.

Small renal vessel diseases causing chronic renal failure:

Example of these diseases are nephrosclerosis secondary to long standing hypertension (very common), polyarteritis nodosa (less common) or malignant hypertension.

4. Chronic urinary tract infection:

Chronic pyelonephritis is considered the most common cause of chronic renal failure in our locality. It may be caused by a specific organism as in tuberculous pyelonephritis or by nonspecific organisms such as E.coli.

5. Chronic urinary tract obstruction:

This may be upper or lower urinary tract obstruction. It results in hydronephrosis which if left untreated may result in CFR.

Causes of upper urinary tract obstruction include bilateral ureteric or renal stones, bilateral neoplasms and bilateral ureteric stricture.

Causes of lower urinary tract obstruction include bladder tumour, senile prostatic enlargement, huge bladder stones and stricture urethra

Association of infection and obstruction is the most common cause of renal failure as obstruction may invite infection and infection may lead to obstruction.

6. Collagen diseases:

Collagen diseases such as S.L.E. and polyarteritis nodosa, rheumatoid arthritis, and systemic sclerosis may cause chronic renal failure. These diseases cause renal failure either through a direct renal involvement by the disease itself or as a complication of the disease (in rheumatoid arthritis renal failure may be caused by secondary amyloidosis or by drug used as NSAIDs and cytotoxic drugs).

7. Metabolic diseases:

Renal amyloidosis; which is usually a complication of Familial Mediterranean Fever (FMF) or chronic suppuration (e.g. osteomyelitis) may end by chronic renal failure.

Gout may cause chronic renal failure either directly (gouty nephropathy) or secondary to abuse of NSAIDs. More commonly it develops by the two mechanisms.

Diabetic nephropathy is one of the common causes of CFR.

Analgesic nephropathy occurs with most of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin. Analgesic nephropathy is a cumulative effect needing a long term drug administration. Nearly an amount of 2-3 kgm of aspirin is needed for chronic renal failure to occur. This condition is frequently seen in patients with chronic pain as those with osteoarthritis and rheumatoid arthritis.

PATHOPHYSIOLOGY OF CHRONIC RENAL FAILURE:

I. Disturbance of water excretion:

Total body water is a major determinant of its solute concentrations. Keeping the total body water within the normal range is mandatory for keeping the body internal milieu. The kidney is the major determinant for adjusting total body water. This is achieved through its capacity to dilute and to concentrate urine. With chronic renal failure, this capacity is deranged as the following:

- a- Loss of the renal ability to concentrate urine: this occurs early in renal failure leading to nocturia and polyuria. This is due to the fact that with kidney damage the number of functioning nephrons is decreasing while the amount of osmotically active molecules produced by the body is stable (about 600 mosmol/day). This will create an osmotic load on the functioning nephrons with subsequent polyuria. If water intake is decreased or if there is fluid loss (e.g. vomiting or diarrhea), the urine volume will not decrease in parallel, but rather a little decrease will occur (due to decreased renal blood flow). As the kidney is unable to concentrate urine to excrete more toxins, retention of wastes will occur. Furthermore, dehydration will result in renal ischaemia which will aggravate the renal damage. When urine osmolarity is as plasma (300 mosmol/L), at least 2000 c.c. of urine is needed for excretion of the daily produced wastes which is the situation in uraemic patients, while in normal kidney only 500 c.c. of maximally concentrated urine (1200 mosmol/L) are sufficient.
- b- Loss of the renal ability to dilute urine: This occurs late in renal failure. If the uraemic patient receives excess fluid he may pass into fluid overload, even pulmonary oedema. In normal persons, urine osmolarity can drop down to 50 mosmol/L (specific gravity 1.001) i.e. urine which is hypotonic to plasma, while with advanced uraemia, dilution will drop down to only 300 mosmol (S.G. 1.010) i.e. equal to plasma. In addition, the diseased kidney will dilute urine very slowly in comparison to the intact one.

2. Disturbance of sodium excretion:

As renal failure progresses, the ability of the nephron to adjust sodium balance decreases. The following disorders may occur:

- a- Hyponatraemia, this is usually dilutional hyponatraemia that is due to retention of excess water taken associated with salt loss such as by sweating, vomiting and diarrhoea.

b- Salt and water retention which may cause hypertension.

c- Salt losing nephropathy which occurs in diseases such as analgesic nephropathy, cystic kidney diseases and tubulointerstitial nephritis. This will manifest with hypovolaemia, dehydration and hypotension which if not treated (by excess salt intake) may lead to acute or chronic renal failure.

3. Disturbed potassium excretion:

The kidney has a high capacity to excrete potassium. Accordingly serious hyperkalaemia rarely occurs unless GFR is less than 10ml/min. Other reasons for hyperkalaemia should be looked for if GFR is more than 10 ml/min, these are:

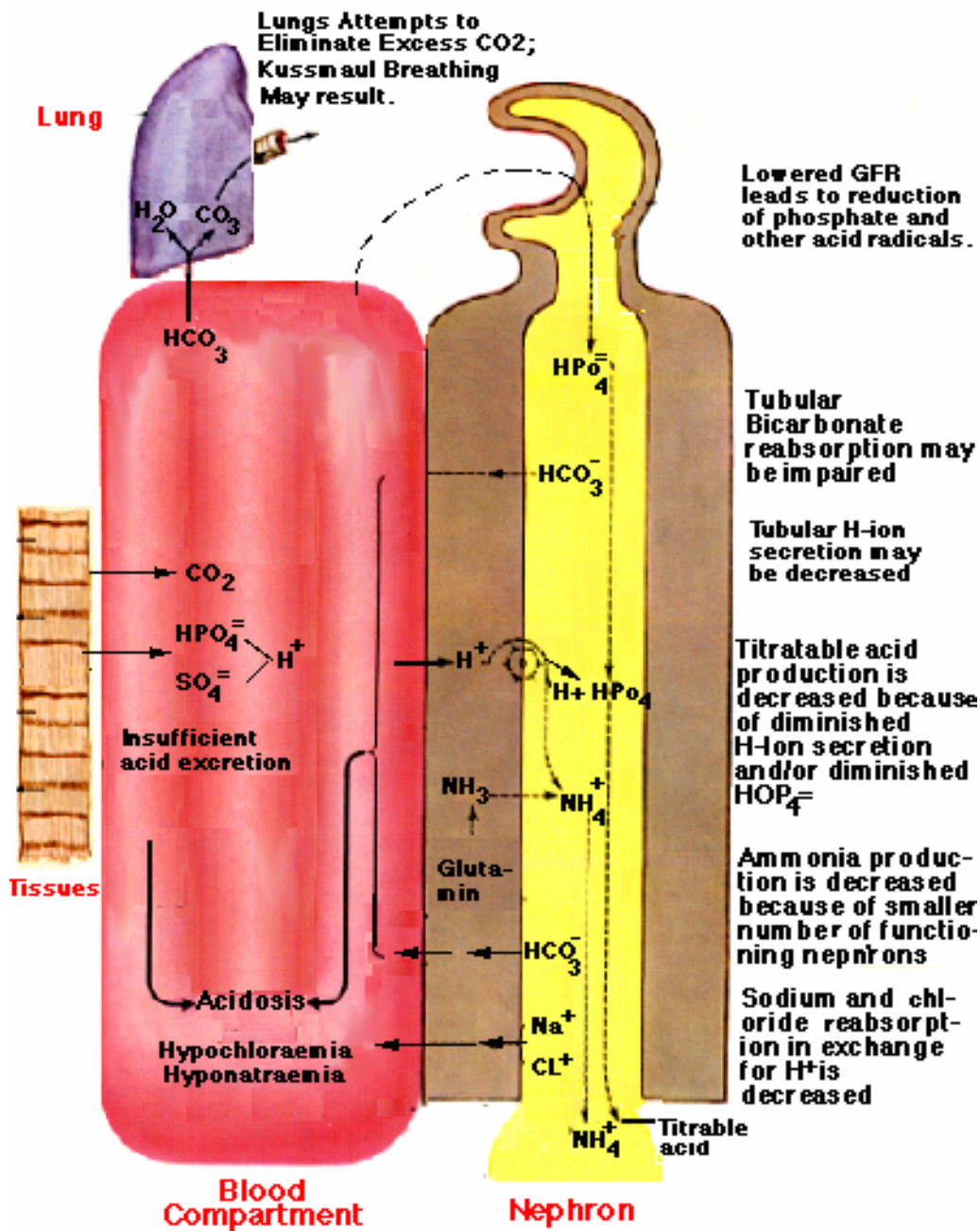
- Excess potassium load
- Hyporeninaemic hypoaldosteronism
- Severe acidosis with volume contraction
- Drugs as ACEI, B-blockers, and aldosterone antagonists.

4. Disturbance of Acid-base balance:

Chronic renal failure may result in metabolic acidosis which will manifest in advanced stages by Kussmaul's breathing (air hunger). In cases with tubulo interstitial diseases, acidosis may manifest earlier (discrepant with serum creatinine). This condition will be aggravated by increased acid load and sodium depletion.

With chronic acidosis, bone will be used as a buffer with consequent skeletal calcium loss and bone disease.

Metabolic acidosis in uraemic patient is due to the following (Fig. 7.1) :
a- decrease in titratable acid (phosphates, sulfates...) excretion due to decreased GFR, b- decrease in ammonia production by the proximal convoluted tubules; and c- bicarbonate wastage.



(Fig. 7.1)

Disturbances of Acid-base regulation in renal failure.

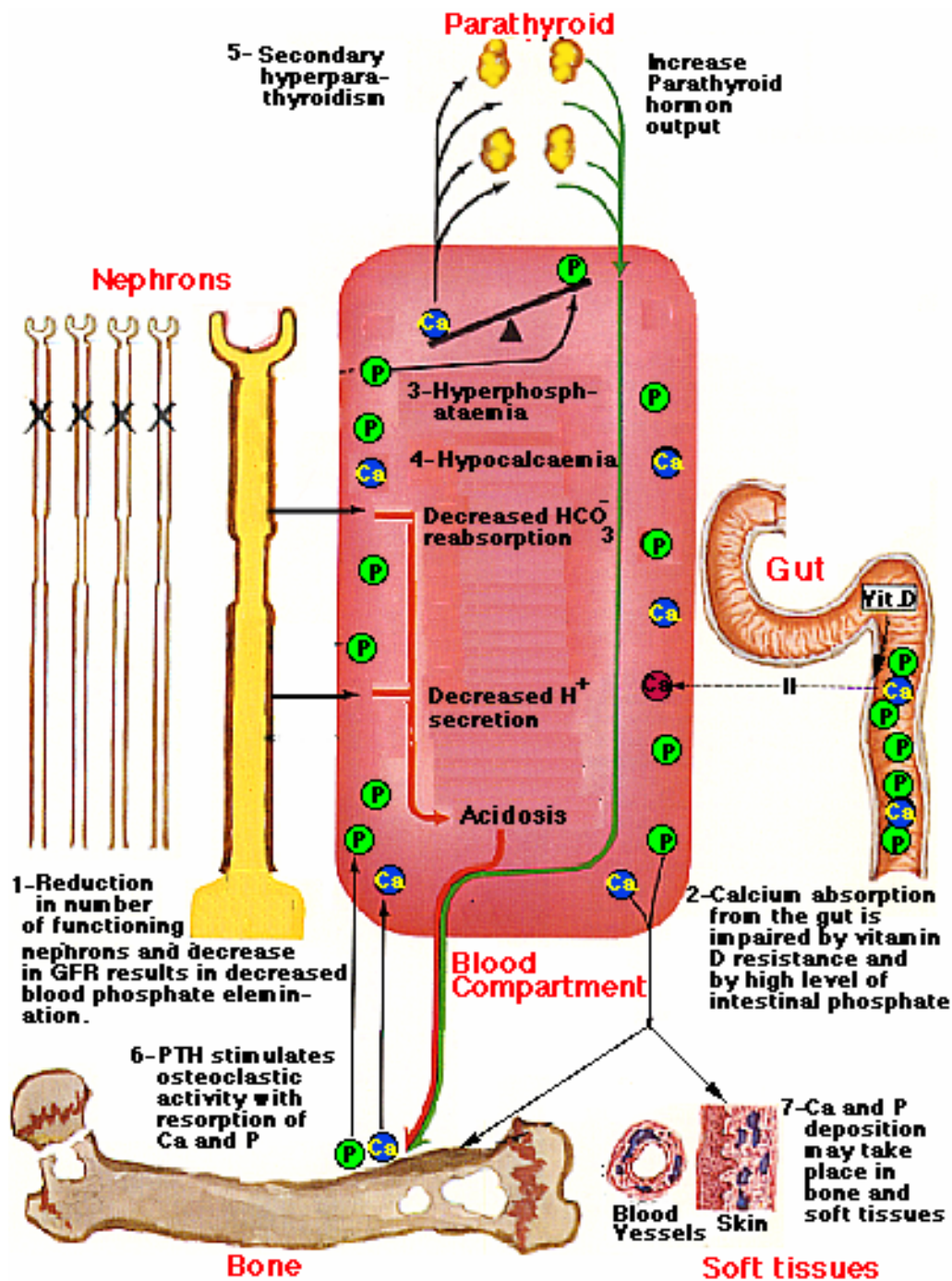
5. **Disturbance of calcium-phosphate metabolism:**

This disorder could be summarized as the following (see Fig. 7.2):-

- a. **Retention hyperphosphataemia:** As the kidney is the main route of phosphate elimination, decrease of GFR below 30 ml/min will be accompanied by hyperphosphataemia. At first, this may occur transiently but later it may be persistent. In earlier phases of uraemia,

hyperphosphataemia may occur post prandially especially with meals heavy in protein and dairy products.

- b- Hypocalcaemia: due to the dynamic equilibrium between serum calcium and phosphate, hypocalcaemia will occur with any increase in serum phosphate. Other causes of hypocalcaemia in uraemic patient are defective activation of vitamin D in PCT and decreased dietetic intake.
- c- Hyperparathyroidism: will occur in response to hypocalcaemia. Secondary hyperparathyroidism will result in bone demineralization through osteoclast activation. This occurs in attempts to correct hypocalcaemia. With correction of hypocalcaemia, parathyroid activity is arrested, yet as phosphate is high, deposition of phosphate and calcium in soft tissues will occur to keep the dynamic equilibrium ($\text{serum Ca} \times \text{serum PO}_4 = 50$). Again, calcium level gets low and parathyroid gland becomes active with consequent bone demineralization. So far uraemia is persistent, this vicious circle will keep active. Long term stimulation of parathyroid gland will result in development of adenoma which is autonomous i.e despite calcium is getting high parathyroid gland will keep secreting parathormone (tertiary hyperparathyroidism). This will lead to more aggressive bone disease and soft tissue calcification. In addition, it will lead to bone fibrosis and aggravation of anaemia.



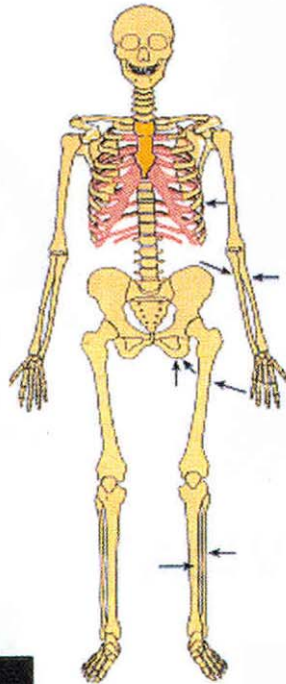
(Fig. 7.2a)

Disturbances of calcium (Ca^{2+}) and of phosphate (P) metabolism in renal failure

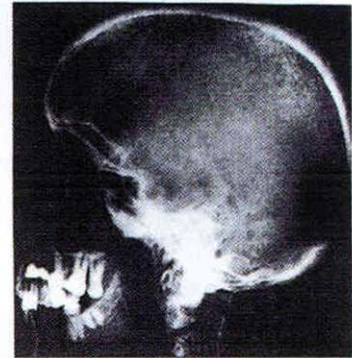
d- Bone disease, sometimes called renal osteodystrophy, it is due to multiple factors including negative calcium and protein balance, lack of active vit. D, hyperparathyroidism as well as aluminium intoxication. Aluminium intoxication is due to long term use of aluminium containing antacids as phosphate binder and the use of aluminium contaminated water in preparation of dialysate for patients under hemodialysis treatment.



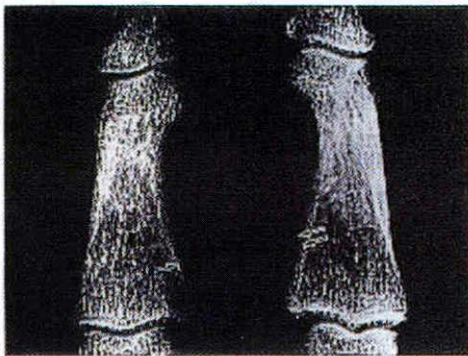
Increased density of ground plates of vertebrae contrasting with radiolucency of the central vertebral slices (rugger jersey spine) in a haemodialysis patient with severe hyperparathyroidism. As well there is severe aortic calcification.



Schematic presentation of the preferential sites for the occurrence of looser zones in aluminium-intoxicated uraemic patients. Less frequent localizations (e.g. at the scapula) are not shown.



Resorptive defects of diploe (pepper-pot aspect) in the skull of a haemodialysis patient with severe hyperparathyroidism.



Radiographic signs in hand skeletons of haemodialysis patients with severe secondary hyperparathyroidism. (A) periosteal new bone formation (periosteal neostosis) (arrow); (B) subperiosteal resorption zones (arrow). Both (A) and (B) show cortical thinning, cortical striation, and fluffy trabecular structure.



Uraemic osteodystrophy in childhood. In this child with chronic renal failure the combination of rickets and secondary hyperparathyroidism affect the skeleton. The femoral metaphysis is irregular and the capital epiphysis shows considerable displacement.

(Fig. 7.2.b)

Bone manifestations of secondary hyperparathyroidism in chronic renal failure

- e- Soft tissue calcification: is due to hyperphosphataemia, secondary hyperparathyroidism, mobilization of bone calcium to blood with the consequent increase of the constant value (serum calcium X serum phosphate). Deposition of calcium occurs in all soft tissues including skin, conjunctiva, vessels wall and even the heart.



Calcified papillae shown in plain film of the renal tract in a patient with uraemia.



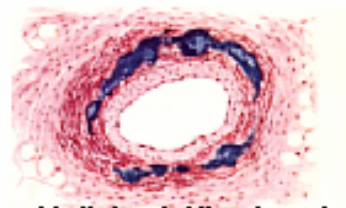
"Uraemic red eye"
due to calcium deposition
in the conjunctive of a
uraemic patient with
hypercalcaemia.



Extensive periarticular calcification in a haemodialysis patient.



**Calcification of
Aorta and/or other
large vessels**



**Medial calcification of
coronary vessels.**

(Fig. 7.2c)

Vascular and soft tissue calcifications in secondary hyperparathyroidism of chronic renal disease.

6. Retention of uraemic toxins:

These retained toxins are responsible for most of the uraemic symptoms, including lethargy, malaise, nausea, vomiting, pericarditis, pleurisy, uremic colitis, platelet dysfunctions...etc.

Removing these toxins by dialysis will be followed by improvement in the manifestations of uraemic syndrome.

The nature of uraemic toxins is yet uncertain. However, they may be:

- 1- Urea, creatinine, uric acid, guanidines, phenols, products of nucleic acid breakdown... etc.
- 2- Middle molecules which are substances of molecular weight 300 to 2000 Dalton.

7. Failure of the renal hormonal functions including:

Erythropoietin, activation of vitamin D and disturbed Renin excretion

CLINICAL FEATURES OF CHRONIC RENAL FAILURE :

Fig-7.3 summarizes the clinical features of the uraemic syndrome. The details of this features include:

I. Gastrointestinal Manifestations:

a. Mouth:

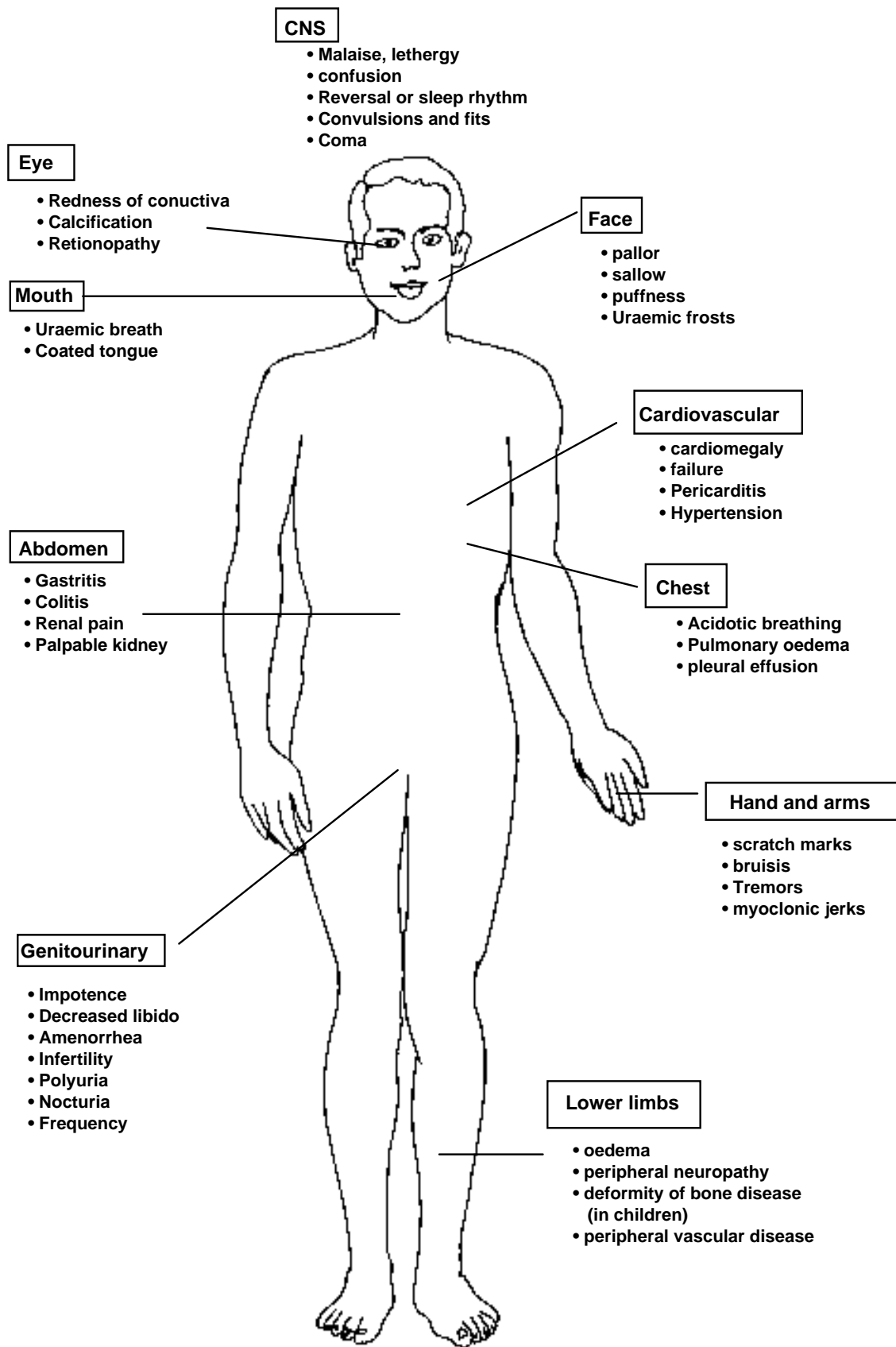
The high concentration of urea in saliva causes unpleasant taste (taste of ammonia) and uraemic odour of the mouth (ammoniacal smell).

The tongue appears dry, dirty, brown or white coated and may be ulcerated. Later, stomatitis, ulceration of the mouth and pharynx may occur. The mouth is always dry due to dehydration and mouth breathing. Dental caries is also common.

b- Stomach:

Gastritis and sometimes gastric erosions may occur. This occurs due to the high concentration of urea in saliva and gastric juice causing chronic irritation of the gastric mucosa. The patient may suffer from anorexia, nausea and vomiting. Upper G.I.T. bleeding (haematemesis) and melena may even occur.

Hiccough occurs in terminal stages of uraemia and is aggravated by food. The cause of hiccough in uraemic patient is most probably due to irritation of the phrenic nerve or may be due to a central effect induced by uraemic toxins.



(Fig. 7.3)
Clinical Features of the Uraemic Syndrome

c- Intestine:

Usually, there is constipation due to dehydration, but diarrhea or even bloody dysentery (uraemic dysentery) may occur in terminal uraemia. This is due to urea deposition in the mucosa of the colon which leads to mucosal ulceration which is liable to superadded infection which may cause diarrhea. In severe cases of mucosal ulceration, there may be bleeding per rectum.

II. Neurological manifestations:

These include the following:

a- Cerebral:

Headache, lassitude, drowsiness, insomnia, sometimes inverted sleep rhythm, and vertigo are common manifestations of uraemia. These manifestations are caused by the retained uraemic toxins. Uraemic coma occurs in advanced cases.

b- Neuromuscular:

The following are the common neuromuscular manifestations of uraemia:

- Flapping tremors (asterixis) and proximal myopathy with paradoxically brisk tendon reflexes.
- Peripheral neuropathy is usually mixed (motor and sensory) and mainly affecting legs. Patients present mainly with paraesthesia.
- Muscle twitches and convulsions are mainly due to hypokalaemia and hypocalcaemia.
- Muscle weakness is due to hyperkalaemia, hyponatraemia and hypovitaminosis D.

III. Hematologic and cardiovascular Manifestations:

a- Anaemia:

Anaemia is a common feature of uraemia and usually normocytic normochromic. It is partly responsible for many of the debilitating symptoms of uraemia such as lethargy, tiredness and exertional dyspnea. The main causes of anaemia in uraemic patient are the followings:

- Bone marrow depression by the uraemic toxins and due to erythropoietin deficiency.
- Short life span of R.B.Cs due to the uraemic toxins.
- Nutritional deficiency due to dietetic restrictions and dyspepsia (protein, Vit. B12, and folic acid)

- Iatrogenic causes as frequent blood sampling in hospitalized patients and the blood loss in the dialyzer at the end of each haemodialysis session.
 - Bleeding tendency as GIT bleeding and metrorrhagia.
 - Aluminium toxicity.
 - Bone marrow fibrosis due to hyperparathyroidism.
 - Hypersplenism especially in multiple transfused patient.
- Sometimes anaemia is microcytic hypochromic due to iron deficiency.

White cell count and platelet count are normal but with decreased functions.

b- Bleeding tendency:

May result from:

- Qualitative platelet defects:

Platelet aggregation is reduced and ADP release is inhibited leading to increased capillary fragility and prolongation of bleeding time.

- Increased fibrinolytic activity of the blood because fibrinolysin is normally eliminated by the kidney.

- Anaemia:

This bleeding tendency is corrected by dialysis, correction of anaemia or administration of DDAVP or oestrogen.

c- Hypertension:

Hypertension in uraemic patients is either due to high renin secretion or salt and water retention. It occurs in about 80% of cases. In uraemics, hypertension is characterised by resistance to drug treatment and by tendency to develop malignant hypertension more than in other forms of hypertension. Hypertension aggravates the renal disease which further increases the blood pressure and a vicious circle is produced.

d- Uraemic pericarditis:

This occurs due to deposition of urea on the smooth inner surface of the pericardial sac changing it into rough surface. Continuous friction between the visceral and parietal pericardium during cardiac systole and diastole results in dry pericarditis which manifests by pericardial pain and pericardial rub on auscultation. Later, haemopericardium develops which progresses to cause cardiac compression (tamponade). This manifests clinically by a triad of:

1. progressive systemic venous congestion with congested neck veins, congested liver, and anasarca.

2. Progressive hypotension due to reduction of stroke volume as venous return is progressively decreasing.

3. Progressive increase in cardiac size on clinical examination and by plain X-ray. Echo cardiography shows that the increase is mainly due to fluid collection in the pericardium. It also shows the defective cardiac filling and reduced stroke volume.

Cardiac tamponade, if not treated urgently, will be fatal. Treatment is by pericardiocentesis. If recurrent, treatment is by making pericardial window (between pericardial sac and pleural sac) or by partial pericardiectomy.

Pericarditis is one of the signs of terminal uraemia which indicates urgent dialysis.

e- Heart failure:

This is usually a left sided heart failure which is due to:

- | | |
|-------------------|----------------------------|
| 1- hypertension | 2- anaemia |
| 3- fluid overload | 4- uraemic cardiomyopathy. |

IV. Cutaneous manifestations:

- Muddy face (sallow skin), due to retention of some toxins (urochromogens).
- Puffy face, due to salt and water retention.
- Pallor, due to anaemia.
- Dry skin with urea frost (white spots due to deposition of urea present in high concentration in the sweat). Also the skin is fragile, thin and bruises easily.
- Pruritis results from skin dryness or from irritation of the cutaneous sensory nerves by calcium deposits or by parathormone.
- Purpura and skin infection.
- Nails may be white with tips discoloured brown.

V. Respiratory manifestations:

These include the following:

- Kausssmaul's (acidotic or hissing) breathing
- Exertional dyspnea, paroxysmal nocturnal dyspnea with heart failure.
- Increased incidence of pulmonary infection.
- Rarely, dry uraemic pleurisy.

VI. Ocular manifestations:

These include the following:

- Retinopathy.

- Uraemic amaurosis (rare): which is sudden transient loss of vision.
- Red eye due to conjunctival congestion and calcium deposition.
- Calcium may be deposited as plaques in the conjunctiva.

VII. Musculo-Skeletal and soft tissue manifestations:

These include the following:

a- Muscular : fatigue, and wasting (myopathy) which is mainly proximal in lower limbs (Waddling gait). It is due to retained uraemic toxins, electrolyte disturbances, vitamin D deficiency, hyperparathyroidism and nutritional deficiency.

b- Skeletal : include bone aches, fractures, and deformity in childhood cases. Table (1) shows the radiologic bone changes in uraemic patients.

Gout (uric acid deposition) and pseudogout (calcium deposition) cause joint pains.

c- Soft tissue calcification which manifests according to the tissue involved e.g. pruritus when skin and sensory nerves are involved, red eye when conjunctiva is affected, arthritis when calcium deposition involves periarticular tissues, and finger tips gangrene when small arterioles are involved (Calcifelaxis).

Table (1) Radiology of renal bone disease.

Secondary hyperparathyroidism

- Generalized decreased bone density.
- Subperiosteal bone resorption (best in phalanges)
- Radiolucent bone cysts (brown tumours) in humerus, neck of femur and pelvis.
- Pepper-pot skull appearance
- Erosion and lucency of the lateral end of clavicle.

Osteomalacia

- Generalized decrease in bone density
- Pseudofractures or looser zones mostly in pubic rami.

Rickets may also be seen

- Widening and fraying of epiphyseal plates.
- Bowing of long bones especially tibia and femur.
- Slipping of epiphyses.

Others

- Tissue calcification, particularly in bursae.
 - Calcification of vessels especially in pelvis and hands
 - Roggers-Jersey spine
-

VIII. Gonadal disturbances:

The following gonadal disorders are commonly seen in uraemic patients:

- In males : decreased libido, impotence, gynecomastia, reduced spermatogenesis.
- In females : decreased libido, infertility and menstrual dysfunctions.

IX. Endocrinal disturbances:

The following are the endocrine disorders which are common in uraemic patients:

- Hyperparathyroidism
- Increased renin activity
- Decreased testosterone level resulting in a decreased libido, potency and spermatogenesis.
- Increased prolactin and L.H. causing menstrual disorders, gynecomastia and infertility.
- Insulin: there are two opposing effects of uraemia on insulin. The first effect is tissue resistance to insulin due to the uraemic milieu. The second is decreased renal tubular degradation of insulin with a consequent increase in the insulin half life. The upper hand is usually for the second effect with consequent fall in insulin requirement (insulin daily dose) in diabetic patients when they become uraemic.
- Lack in activation of vit. D.
- Lack of erythropoietin

X. Features of the underlying disease may be present:

As manifestations of D.M., SLE or renal stone disease.

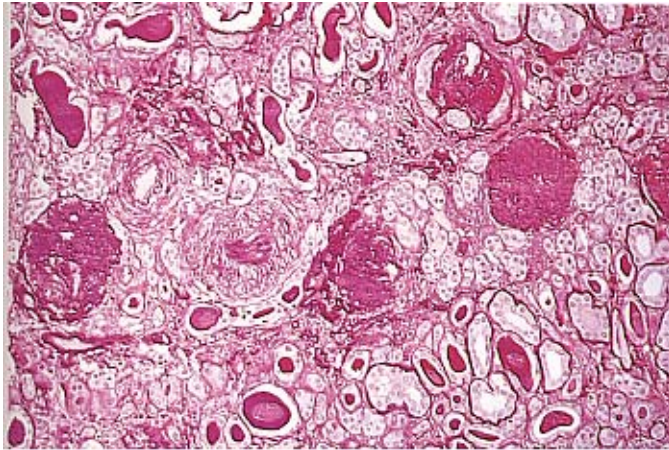
RENAL PATHOLOGY:

1. Gross appearance:

Usually the kidney is small in size with granular surface and adherent capsule. Sometimes the kidney is normal in size as in diabetic nephropathy and in amyloid nephropathy. In cases secondary to PCKD and hydronephrosis, the kidney size may be larger than normal.

2. Microscopically:

Light microscopy shows diffuse interstitial fibrosis, tubular atrophy and hyalinosis of most of the glomeruli (Fig. 7.4). The remaining viable glomeruli and tubules are dilated. Sometimes microscopic examination may show the etiologic cause as renal amyloidosis.



(Fig. 7.4)
PAS stained kidney section (X100) from a patient with end stage renal failure. It shows complete sclerosis of the glomeruli, extensive tubular atrophy and interstitial fibrosis.

INVESTIGATIONS OF A CASE WITH CHRONIC RENAL FAILURE:

1. Urine examination may show the following :

- Polyuria especially nocturia and anuria in terminal cases.
- Urine specific gravity is low and fixed to 1010 (osmolarity 300 mosm/l).
- Urine aspect is pale and watery.
- Albuminuria and granular casts.

2. Blood Changes:

There is an increase in blood urea, creatinine and uric acid levels, metabolic acidosis, normochromic normocytic anaemia, hyperkalaemia, and hyperphosphataemia. Serum calcium may be normal or low in early phases, but it becomes high in stage of tertiary hyperparathyroidism.

3. Kidney Function Tests:

Marked impairment of the renal functions (increase in s. creatinine and decrease in cr. clearance). Plasma creatinine is elevated once GFR is decreased to less than 60 ml/min.

4. Fundus Examination:

May show uraemic retinopathy.

5. Investigations To Know The Cause Of Renal Failure :

Such as Plain X-ray for urinary tract (stone), ultrasonography (obstruction), blood sugar (diabetes), and anti DNA (SLE). Renal biopsy is indicated in cases with average kidney size and unknown etiology of uraemia.

MANAGEMENT OF CHRONIC RENAL FAILURE :

The following steps should be adopted for a proper management of patients with chronic renal failure.

Step 1. CONFIRMATION OF CHRONICITY OF THE KIDNEY DISEASE.

This could be achieved through the following:

a. History: A long history of renal disease suggests chronicity while absent previous history suggests acute renal failure.

b. Kidney size as detected by ultrasonography: A small atrophic kidney favours the diagnosis of chronic renal failure, while a normal sized kidneys is more in favour of acute renal failure.

There are some conditions of chronic renal failure in which kidney size is within normal, these are:

- Diabetic nephropathy.
- Renal amyloidosis
- Infiltration (leukaemia, lymphoma, sarcoidosis)
- PCKD
- Obstructive uropathy
- Bilateral staghorn stone.

c. Magnitude of the increase in serum creatinine in relation to the presenting symptoms: High serum creatinine with minimal symptoms is in favour of chronic renal disease, while relatively low serum creatinine with severe symptoms is in favour of acute renal disease.

d. Hyperphosphataemia and osteodystrophy are present more with chronic cases.

e. Anaemia is more with chronic cases.

f. Renal biopsy: extensive renal interstitial fibrosis and tubular atrophy in renal biopsy are features of chronic cases.

Step 2. SEARCHING FOR REVERSIBLE FACTORS:

These factors are classified as the following:

a. Pre-renal factors such as:

- Bilateral renal artery stenosis.
- Severe cardiac failure.
- Malignant hypertension.
- Hypotension.
- Dehydration and hypovolaemia.

b. Renal causes factors such as:

- Active glomerular disease
- Active tubulo-interstitial disease
- Pyelonephritis

c. Postrenal factors:

Causing obstruction of urine flow from both kidneys such as:

- Stone
- Stricture ureters
- Enlarged prostate
- Bladder neck obstruction

Step 3. CONSERVATIVE TREATMENT OF CHRONIC RENAL FAILURE:

a. Dietary control:

- *Protein* is usually restricted to 0.6-1 gm/kg/day (an amount which satisfies the physiologic requirements). If uraemic symptoms are marked, a further restriction of protein to 0.3 g/k/d may be adopted with addition of supplemental mixture of ketoacids, hydroxy acids and amino acids (10-21 g/d).

Protein restriction will not only decrease the uraemic symptoms but also may help in slowing the progression of kidney scarring.

- *Fluid restriction* equivalent to the patient's daily fluid loss. This equals: the sensible water loss (e.g. urine, vomitus and diarrhea) plus the Insensible water loss (respiratory and sweat) which is about 600 ml/d in an adult of 70 kg. Extra 200 ml fluid should be added in febrile patient for every one degree centigrade increase in the body temperature.
- *Electrolytes:* Sodium restriction with hypertension or oedema, and potassium restriction with severe oliguria and with hyperkalaemia
- *Calories:* Patient should receive about 35 K. calories/kg/day with carbohydrate 60% of non protein calories and fat 40%. The polyunsaturated to saturated fat should be 1 : 1. Total fibers should be 20-25 gm/d.

b. Treatment of Bone disease:

- *Phosphate Binders* such as aluminium hydroxide, magnesium oxide and calcium carbonate or acetate which combine with phosphorus in the gut and are excreted with the stool. Calcium containing compounds are better than aluminium and magnesium salts which could be dangerous on long term use. Calcium carbonate or acetate may be given orally t.d.s. with meals in a dose of 500-1000 mg orally.
- *Active vitamin D* "1-OH vitamin D" which is given orally in a daily dose of 0.25-1.0 ug. Recently I.V. 1-OH vitamin D (one-alpha) is

recommended for better suppression of the hyperparathyroidism.

This is given in a dose of 0.5-2.0 ug twice or thrice weekly.

- *Acidosis is corrected* by oral Na bicarbonate supplementation.
- *Parathyroidectomy* may be done for cases with tertiary hyperparathyroidism. Three glands and part of the fourth are removed and the remaining is implanted subcutaneously.

c. Anaemia:

Is responsible for major part of uraemic symptoms. The first line of treatment is by giving proper nutrition, iron, folic acid, and vitamins especially B12. Failure to respond may indicate repeated blood transfusion or treatment with recombinant human Erythropoietin. Blood transfusion carries the advantage of being cheap but have the disadvantage of transmitting diseases (especially HIV, HBV and HCV) beside other risks of blood transfusion. Erythropoietin (EPO) is given S.C. 4000u three times weekly, it carries the advantage of being safe and effective, but it is very expensive. The dose of EPO has to be readjusted to maintain haemoglobin value of 9-11 gm/dl. If the patient can't afford for EPO, blood transfusion is preferably given only for symptomatic anaemia.

d. Symptomatic treatment of:

- *Hypertension* is controlled by hypotensive drugs. In cases of volume dependent hypertension the main line of treatment is salt and water restriction and diuretics. In cases of renin dependent hypertension, anti-renin such as β -Blockers or ACE inhibitors are used.
- *Itching* is treated by skin soothing creams, anti-histaminics, treatment of hyperphosphataemia, hyper and hypocalcaemia. For severe, intractable cases, parathyroidectomy may be of help. Sometimes pruritus could be controlled by giving xylocain 70 mg in 100 c.c. saline via I.V. infusion over 20 min. at the end of each dialysis session.
- *G.I.T. manifestations* as vomiting could be controlled by antacids and H₂-receptors blockers.

Failure of conservative treatment to provide the patient with a reasonable quality of life is an indication for renal replacement therapy, i.e. dialysis or renal transplantation.

Step 4. RENAL REPLACEMENT THERAPY (RRT):

This includes dialysis (haemodialysis and peritoneal dialysis) and renal transplantation. Early induction of RRT and good nutritional support provide better response to the treatment (less patient morbidity and mortality).

Indications for RRT:

- Failure of conservative treatment with progressive deterioration in patient's general condition and blood chemistry.
- Persistent nausea and vomiting.
- Circulatory overload which is unresponsive to loop diuretics (e.g. frusemide)
- Severe motor neuropathy.
- Uraemic encephalopathy.
- Pericarditis
- Osteodystrophies
- Bleeding diathesis.
- Hypertension unresponsive to treatment.
- Hyperkalaemia (serum K⁺ level > 7 mEq./litre).
- High creatinine levels and decreased creatinine clearance (Cr. clearance < 10ml/min).

Contraindications for dialysis treatment.

1. Absolute:

- Patient's decision (i.e. refusing dialysis).
- Severe extrarenal illness e.g. severe cardiac disease, end stage liver disease, severe cerebrovascular disease and advanced malignancy.

2. Relative:

- Severe disability or handicapping.
- Paraplegia or hemiplegia

DIALYSIS THERAPY

Definition:

Dialysis is a process in which the solute composition of blood is altered by exposing it to a physiological solution (dialysate) across a semipermeable membrane (dialysis membrane). Solutes will move from one compartment to another through the dialysis membrane.

Principles of Dialysis:

Solutes that can pass from blood through the pores of the dialysis membrane are transported by two different mechanisms: diffusion and ultrafiltration.

1. Diffusion:

Is the passage of solutes through the semipermeable membrane independent of water movement.

Factors affecting solute diffusion include:

(A) Concentration gradient:

The net rate of transfer of a given solute from blood to dialysate is the greatest when the concentration gradient for that particular solute is the highest.

(B) Molecular weight and size:

The larger the M.Wt. of a solute, the slower its rate of transport will be across the semipermeable membrane.

(C) Membrane resistance:

Membrane resistance owing to the membrane itself:

The resistance of a membrane to solute transport will be high if the membrane is thick; if the number of pores is small and if the pores are narrow.

Membrane resistance due to "unstirred" fluid layers:

Unstirred layers of fluid inhibit diffusion because they act to decrease the effective concentration gradient at the membrane surface.

2. Ultrafiltration:

The second mechanism of solute transport across semipermeable membrane is ultrafiltration (i.e. convective transport).

Water molecules are extremely small and can pass through all semipermeable membranes. Ultrafiltration occurs when water driven by either a hydrostatic or osmotic force is pushed through the membrane. Those

solutes that can pass easily through the membrane pores are swept along with the water (a process called solvent drag).

Types of ultrafiltration:

Osmotic ultrafiltration:

This depends on the osmotic pressure of the dialysate. The higher the osmotic pressure the more the ultrafiltration.

Hydrostatic ultrafiltration:

This depends on the transmembrane pressure; i.e, the higher the transmembrane pressure the more the ultrafiltration. The semipermeable membrane is not permeable to cells or plasma proteins.

Types of Dialysis

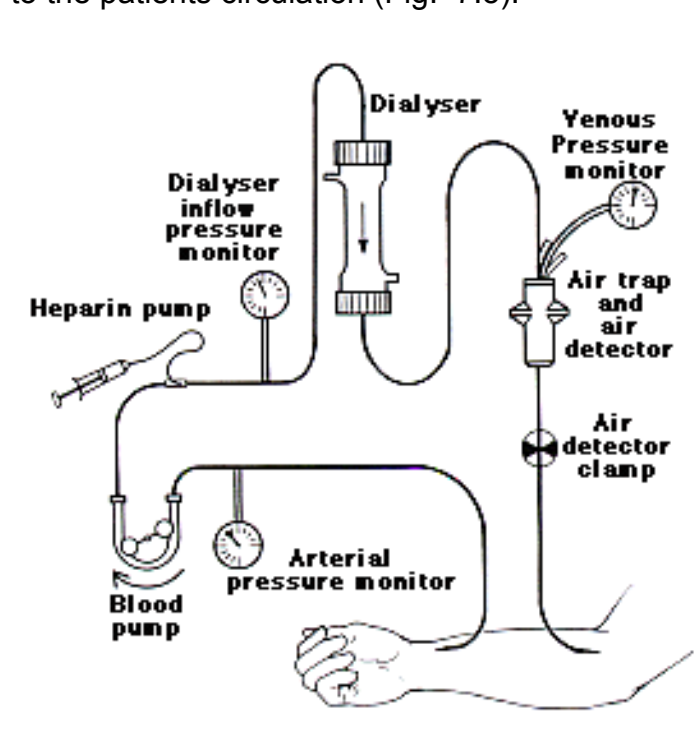
There are two forms of dialysis therapy: (a) Haemodialysis, and
(B) Peritoneal dialysis

(A) Haemodialysis

Definition:

It is the movement of solutes and water from the patient's blood across a semipermeable membrane which is the dialyzer.

This is carried out via vascular access where the blood is pumped by a haemodialysis machine into the dialyzer then the blood returns back filtered to the patients circulation (Fig. 7.5).



(Fig. 7.5)
The extracorporeal blood circuit showing the usual location of the different dialysis monitors

Complications:

(I) Common complications:

(A) Hypotension: This is the commonest complication and may be due to:

1- Causes related to excessive decrease in blood volume:-

- Fluctuation in the ultrafiltration rate
- High ultrafiltration rate
- Target dry body weight set is too low
- Dialysis solution sodium level is too low

2- Causes related to lack of vasoconstriction:

- Acetate-containing dialysis solution
- Dialysis solution is too warm
- Food ingestion (splanchnic vasodilatation)
- Tissue ischaemia
- Autonomic neuropathy (e.g. diabetic patients)
- Antihypertensive medications given at the day of dialysis.

3- Causes related to cardiac factors:

- Diastolic dysfunction may be due to
 - Left ventricular hypertrophy
 - Ischaemic heart disease
 - Other conditions
- Failure to increase cardiac rate which may be due to:
 - intake of beta blockers
 - uraemic autonomic neuropathy
 - Aging
- Inability to increase cardiac output for other reasons such as poor myocardial contractility because of age, hypertension or atherosclerosis.

4- Uncommon causes:

- Pericardial tamponade
- Myocardial infarction
- Occult haemorrhage
- Septicaemia
- Arrhythmia
- Dialyzer reaction
- Haemolysis
- Air embolism

(B) Muscle Cramps:

The pathogenesis during dialysis is unknown, but the three most important predisposing factors are:

- (1) hypotension
- (2) patient below dry body weight
- (3) use of low sodium dialysis solution.

(C) Nausea and Vomiting:

The aetiology is multifactorial, however, most episodes in stable patients are probably related to hypotension. They may be also an early manifestation of the so called disequilibrium syndrome.

(D) Headache:

May be related to the use of acetate containing dialysis solution, disequilibrium syndrome. Also it may occur in heavy coffee drinkers as it may be a manifestation of caffeine withdrawal.

(E) Chest pain and back pain:

May be due to complement activation; thus, there is no management or prevention strategy other than switching to synthetic or substituted cellulose dialysis membrane.

(F) Itching:

It is a common complaint in dialysis patients which may be due to:

- Allergy to
 - Ethylene Oxide (ETO), used for sterilization of the dialysis membrane.
 - heparin
 - plasticizers
- elevated calcium-phosphate product,
- uraemic toxins, and
- Dry skin

It can be managed by topical emollients, antihistaminics, phosphate binders and the switch from ETO to gamma ray sterilized dialyzers.

(G) Fever and chills

May be due to a pyrogenic reaction or true sepsis transmitted to the patient during the dialysis session.

(II) Less Common Complications:

Although they are less common, they are serious complications. They include:

(A) Disequilibrium Syndrome:**Definition:**

Disequilibrium syndrome is a set of systemic and neurologic symptoms which are often associated with characteristic EEG findings that can occur either during or soon after dialysis.

Early manifestations include headache, nausea, vomiting, convulsions and may be coma. In severe cases, death can occur if not treated properly.

Etiology:

The etiology is controversial but many believe that it is due to brain odema due to aggressive and rapid dialysis.

Treatment:

- Prevention is better, this could be achieved by making the few initial dialysis sessions short and smooth (gradually increasing dialysis hours and blood flow rate).
- Treatment of an established case is by stopping dialysis and giving symptomatic treatment, including brain dehydrating drugs as dexamethazon.

(B) Dialyzer reactions:

Type A (anaphylactic type):

The manifestations of this type may be mild in the form of itching, cough, urticaria, sneezing, coryza or watery eyes; or may be severe in the form of dyspnea, chest tightness, cardiac arrest or even death.

Etiology:

- ETO sterilization
- ACE inhibitors used at the same time with AN 69 type of dialyzer due to liberation of bradykinin.
- Contaminated dialysate: this can be managed by more frequent cleaning and sterilization of dialysis machines between sessions, thus reducing the dialysis solution bacterial counts.

Treatment:

- Stop dialysis immediately
- Antihistaminics
- Steroids

Type B (Non specific type):

The patients may complain of back pain or chest pain.

Etiology:

Complement activation

Treatment:

No specific treatment

(C) Arrhythmia:

Arrhythmias during dialysis are especially common in patients receiving digitalis

(D) Cardiac tamponade:

Unexpected or recurrent hypotension during dialysis may be a sign of pericardial effusion or impending tamponade.

(E) Intracranial bleeding:

Underlying vascular disease and hypertension combined with heparin administration can sometimes result in intracranial bleeding.

(F) Seizures: This occur more often in children

(G) Haemolysis:

Acute haemolysis during dialysis may be a medical emergency

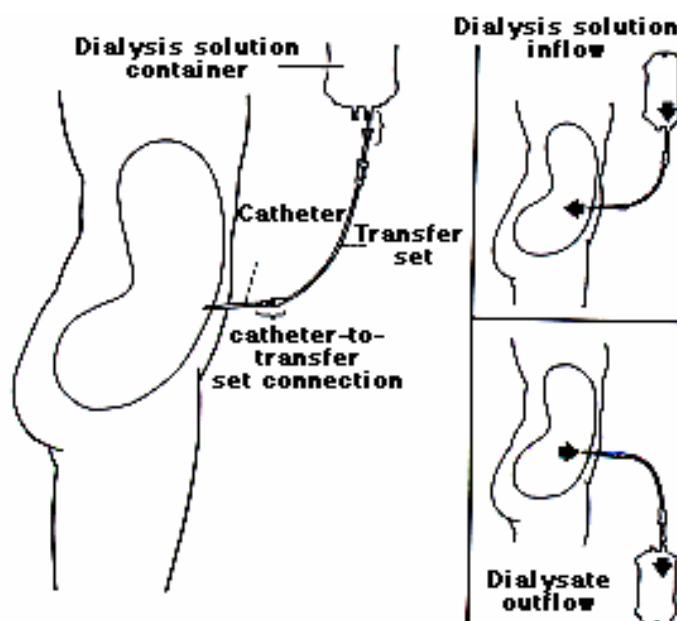
(H) Air embolism:

It is a potential catastrophe that can lead to death if not quickly detected and treated.

(B) Peritoneal Dialysis

Definition: It is the movement of solutes and water from patient's blood across a semipermeable membrane (which is the peritoneal membrane) to the dialysis solution (dialysate).

This is carried out via peritoneal catheter which is inserted into the peritoneal cavity by infusion of the dialysate which is left to dwell then; drain out via the catheter (Fig. 7.6).



(Fig. 7.6)
Basic continuous ambulatory peritoneal dialysis system, with catheter, and dialysis solution container. On the right, inflow and outflow are depicted.

Types:-**(1) CAPD (Continuous Ambulatory Peritoneal Dialysis):**

In which the dialysate is always present in the peritoneal cavity and is exchanged every 4-6 hours/day. This is the commonly used form of P.D worldwide .

(2) CCPD (Continuous Cyclic Peritoneal Dialysis):

In which the dialysate is exchanged at bed time via a cyclor (P.D. machine) 3-4 times and the last exchange fluid is left in the abdomen during the daytime.

(3) NIPD (Nocturnal Intermittent Peritoneal Dialysis):

In which the dialysate is exchanged at bed time via a cyclor 5-8 times/day and the abdomen is left dry the rest of the day.

This is the new trend nowadays, but it is limited because of the high cost of the cyclor.

(4) TPD (Tidal Peritoneal Dialysis):

This is still an experimental form of NIPD which was designed to optimize solute clearance by leaving large volume of dialysate in the peritoneal cavity throughout the dialysis session. Three litres of fluid are introduced first time, then every time two litres are exchanged leaving always 3 litres in the abdomen.

Indications for PD:

Because it provides the best rehabilitation potential as it is safe and easy, it is used for all ages and all sizes of patients with end stage renal failure.

Specific indications for peritoneal dialysis include the following:

- 1- Infant and very young children
- 2- End stage renal failure patients with cardiovascular or haemodynamic instability.
- 3- Haemodialysis patients with vascular access failure (especially diabetics)
- 4- Patients for whom vascular access can not be created (especially diabetics)
- 5- High risk of anticoagulants
- 6- Patients who desire greater freedom to travel

Contraindications:

- Absolute:**
- 1- Extensive peritoneal fibrosis
 - 2- Pleuroperitoneal leak

- Relative:**
- 1- The same as those in haemodialysis
 - 2- Presence of colostomy or nephrostomy

- 3- Recent thoracic or abdominal surgery
- 4- Inguinal or abdominal hernia
- 5- Blindness
- 6 - Mental retardation
- 7- Poor motivation and compliance

Advantages:-

- Ease of performance
- High safety margin
- Portability
- Fewer dialysis-related symptoms
- No routine anticoagulation
- Better control of PTH levels
- More liberal diet
- Fewer medications
- No viral transmission
- Used safely in haemodialysis unstable patients and those with difficult vascular access

Disadvantages:

- Low efficiency
- Body image problem because of the catheter
- Potential protein loss
- Potential infection
- Hypertriglyceridaemia

Complications:

Mechanical:

- Pain during inflow owing to hot dialysate or rapid jetting
- Pain during outflow due to ball-valve effect
- Outflow failure due to constipation, obstruction or malposition of the catheter
- Pericatheter leakage because of very early usage of the catheter
- Scrotal odema
- Intestinal perforation
- Cuff catheter erosion

Cardiovascular

- Fluid overload
- Hypertension
- Hypotension
- Dysrhythmias

Pulmonary:

- Atelectasis
- Hydrothorax
- Restricted chest movement

Neurologic

- Seizures and disequilibrium syndrome which are rare in comparison to hemodialysis

Metabolic:

- Hyperglycaemia
- Hyperlipidaemia
- Hyper or hypokalaemia
- Hyper or hyponatraemia
- Metabolic alkalosis
- Protein depletion
- Obesity

Infectious and inflammatory

- Peritonitis
- Exit site infection
- Tunnel infection

Peritonitis:

The incidence of peritonitis among PD patients is one episode every 12-18 months/patient.

Diagnosis:

- cloudy outflow
- Fever
- Abdominal pain and bowel symptoms (e.g. cramps, diarrhea or constipation)
- Peritoneal fluid WBCs >100 ml with > 50% polymorphonuclear leucocytes.

Etiology:

- Gram +ve organisms account for 65-75%
- Gram -ve organisms account for 25-30%

Treatment:

Aggressive antibiotic therapy from the start which has to be continued according to culture and sensitivity.

Tunnel infection:

- This manifests as swelling, tenderness, redness & hotness
- This is a dangerous form of infection, if persist inspite of proper antibiotics, the catheter should be removed.

KIDNEY TRANSPLANTATION

Definition:

Kidney transplantation means the treatment of chronic renal failure by surgical implantation of a kidney that is obtained from either healthy kidney donor or brain stem dead cadaver.

Principle:

- Kidney transplantation is performed by doing a unilateral nephrectomy for the donor to be implanted into the patient with end stage renal disease "The recipient".
- The new kidney is placed in the patient's abdomen, usually in the right iliac fossa. The artery and vein are anastomosed to patient's vessels (usually internal iliac) and the ureter is implanted into the bladder (Fig. 7.7).

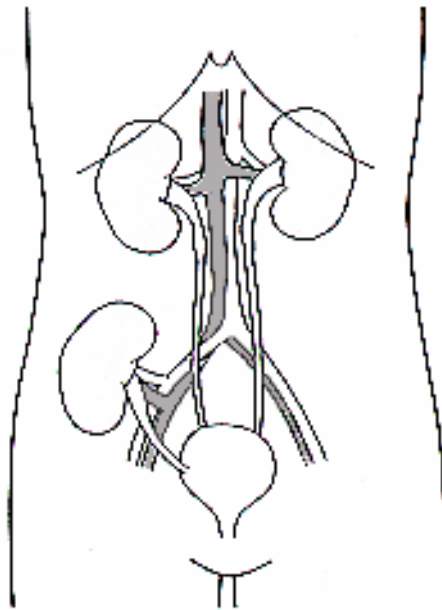


Fig. (7.7)

Kidney transplant in recipient's right iliac fossa with native kidney left in place.

- The native kidneys are left in place, unless there is an indication to be removed e.g. uncontrollable hypertension, infection or if they are hugely enlarged.
- The immune system of the recipient considers the transplanted kidney as a foreign body and tries to destruct it. This is called "rejection" which can be prevented by:
 - Pre operative immunological investigations to be sure that tissue typing of the recipient and the donor is identical or similar and via.
 - Post operative suppression of the recipient's immune system by immunosuppression therapy.

Indications:

Patients with end stage renal failure requiring renal replacement therapy.

Contraindications:

- 1- Patient refusal
- 2- Psychosis
- 3- Age more than 60 years (relative)
- 4- Recurrent disease, if the original kidney disease that caused renal failure can recur in the transplanted kidney and destroy it e.g. oxalosis.
- 5- Systemic disease: Some co-existing systemic diseases may contraindicate transplantation because of their effect on the patient's survival or because of the danger of post transplant immunosuppression therapy. These include the following:
 - Severe respiratory disease e.g. C.O.P.D.
 - Severe cardiovascular disease e.g. severe left ventricular failure
 - Severe hepatic disease e.g. liver cirrhosis
 - Central nervous system e.g. cerebral hemorrhage
 - Active peptic ulceration
 - Malignancy
 - Active infection
- 6- Unrepairable urologic abnormalities.

Types of kidney donors:

1- Living donors:

- a. Blood related donors: one of the relatives of the recipient
- b. Unrelated donors: ethically, the emotionally motivated donors such as patient's partner rather than the commercially motivated donors should be accepted as kidney donor.

2- Cadaveric donors:

These are persons with brain stem death but still with functioning cardiovascular and respiratory system. Cadavers are optimal kidney donors.

Immunological assessment of donor and recipient before transplantation:

In order to prevent or minimize rejections after kidney transplantation, a number of immunological tests are done for both donor and recipient to be sure that they have identical tissue typing or at least with satisfactory similarity. These tests are:

1- ABO blood grouping:

Follows the same rules for blood transfusion

2- Cross matching:

- donor's leucocytes are mixed with recipient's serum.
- The test is considered -ve and donor is suitable if none of donor's leucocytes was destroyed

3- HLA typing:

- The HLA system is a group of antigens present on the surface of all nucleated cells in the body.
- This system is responsible for recognition of immune system to "self cells" and "foreign cells".
- It is the major determining factor for graft rejection
- The more similar the HLA system of recipient and donor, the less the incidence of post transplant rejection.

Contraindications for donation:

a- living donors:

- 1- Donor refusal
- 2- Psychosis
- 3- Age below 21 and above 60 years
- 4- Renal disease
- 5- Family history of hereditary renal disease (e.g. polycystic kidney disease)
- 6- Associated medical diseases:
 - Cardiovascular: (e.g. heart failure, hypertension)
 - Respiratory: (e.g. COPD)
 - Hepatic: (e.g. liver cirrhosis, hepatitis)
 - C.N.S.

- Metabolic (e.g. diabetes mellitus)
- Malignancy
- Infections

b- Cadaveric donors:

- 1- Absence of consent before death
- 2- Age less than 3 or more than 70 years
- 3- Renal disease
- 4- Associated medical diseases: (vide supra)

Immunosuppression after transplantation:

- **Definition:** Immunosuppression therapy is used after kidney transplantation in order to modify the recipients immune system so that rejection is prevented.

- **Duration:** Immunosuppression therapy continues for life.

- **Mode of action:**

- Immunosuppression can be achieved by different drugs.
- Each drug has a different mechanism by which it can depress leukocytes which are responsible for the immune response.

- **Regimens:**

- Many regimens are present
- Steroids are the corner stone drug used
- Triple regimen (steroids-azathioprine-cyclosporine) is the commonest regimen
- Other new drugs: (FK-506, Mycophenolate and Rapamycin).
- Polyclonal antibodies as ATG and ALG
- Monoclonal antibodies as OKT3
- Cymeric and humanized antibodies as simulect (Novartis) and zenapax (Roche).

Complications after kidney transplantation:

1- Rejections:

- **Hyperacute:** usually occurs Immediately postoperative.
- **Acute:** Usually occurs days or weeks to months postoperatively
- **Chronic:** Usually occurs months to years postoperatively.

2- Complications of immunosuppression therapy:

a. General complications:

1. Infection
2. Increased incidence of malignancy

b. Complications due to individual drugs:

1. **Steroids:** hypertension, D.M., atherosclerosis, Bone disease, GIT bleeding and cataract.
2. **Azathioprine:** Bone marrow depression and hepatic dysfunction
- 3- **Cyclosporine:** Nephrotoxicity, hepatotoxicity, hypertension and D.M.

3- Recurrence of the original kidney disease into the graft (e.g. FSGS, MPGN)

Outcome after transplantation:

- The outcome of kidney transplantation is continuously improving with the advances in the immunosuppressive drugs and the immunologic assessment of donors and recipients, technique of surgery and the postoperative care.
- Emergence of cyclosporine as a new immunosuppressive drug in 1980s has much improved the graft survival by preventing rejection which is the commonest cause of graft loss.
- The current 1 year graft survival is about 90-95% and 5 years graft survival is about 60-70%.
- Continuous advancement in immunosuppressive drugs is aims at ideal drug with maximal ability to prevent rejection and minimal side effects.

Transplantation versus dialysis:

Advantages of transplantation over dialysis:

- 1- Better quality of life:
 - a. Independence from machine
 - b. Correction of manifestations of chronic renal failure that are not corrected properly by dialysis such as anemia, bone disease, growth retardation in children, fertility and child bearing in adults.
 - c. More ability to work.
- 2- Avoidance of diseases that may be transmitted through dialysis such as HIV and hepatitis.
- 3- Less cost than dialysis

Disadvantages of transplantation:

- 1- Complications of immunosuppression
- 2- The possibility of graft loss
- 3- The need for kidney donors

Suggested Readings:

- Bohle A, et al: Pathogenesis of chronic renal failure in the primary glomerulopathies, renal vasculopathies, and chronic interstitial nephritides. *Kidney Int Suppl*, 54 : S2-9, 1996.

- Valderrábano F: Erythropoietin in chronic renal failure. *Kidney Int*, 50 : 4, 1373-91, 1996.

- Steinman TI: Kidney protection: how to prevent or delay chronic renal failure. *Geriatrics*, 51 : 28-35, 1996.

- Friedman AL: Etiology, pathophysiology, diagnosis and management of chronic renal failure in children. *Curr Opin Pediatr*, 8 : 2, 148-51, 1996.

- Scarpioni L, et al: Peritoneal dialysis in diabetics. Optimal insulin therapy on CAPD: intraperitoneal versus subcutaneous treatment. *Perit Dial Int*, 16 Suppl 1 : S275-8, 1996.

- Lee HB, et al: Dialysis in patients with diabetic nephropathy: CAPD versus hemodialysis. *Perit Dial Int*, 16 Suppl 1 : S269-74, 1996.

- Brunkhorst R: Kidney transplantation. Indications, results, pre-and postoperative care. *Internist Berl*, 37 : 3, 264-71, 1996.

- Thony F, et al: Detection of renal artery stenoses by MRI with surface reconstruction. Value in patients with chronic renal failure. *J Radiol*, 78 : 9, 643-9, 1997.

- Novikov AI: Methods of correcting hyperphosphatemia in chronic renal failure and in dialysis (review): *Ter Arkh*, 69 : 12, 63-7, 1997.

- Simpson IL, et al: Management of guidelines for progressive chronic renal failure. New Zealand Nephrologists Consensus Group. *N Z Med J*, 110 : 1055, 421-3, 1997.

- Ter Wee PM, et al: Dietary protein restriction for retardation of progression of chronic renal failure: yes or no? (editoria). *Int J Artif Organs*, 20 : 6, 304-8, 1997.

- Grzegorzewska A, et al: Some factors affecting longevity and quality of life in patients treated with continuous ambulatory peritoneal dialysis (CAPD). *Pol Arch Med Wewn*, 97 : 4, 364-70, 1997.

- Betkowska Prokop A: Non-infectious complications during treatment with continuous peritoneal dialysis (CAPD). *Przegl Lek*, 54 : 2, 115-21, 1997.

- Takashi K: Kidney transplantation in long-term hemodialysis patients. *Nippon Hinyokika Gakkai Zasshi*, 88 : 11, 905-8, 1997.

- Salmela K, et al: Kidney transplantation. *Ann Chir Gynaecol*, 86 : 2, 49-100, 1997.

- Leumann E: Kidney transplantation in the child. *Schweiz Med Wochenschr*, 127 : 24, 1039-43, 1997.

- Obrador GT, et al: Early referral to the nephrologist and timely initiation of renal replacement therapy: a paradigm shift in the management of patients with chronic renal failure. *Am J Kidney Dis*, 31 : 3, 398-417, 1998.

- Warady B, et al: Current advances in the therapy of chronic renal failure and end stage renal disease. *Semin Nephrol*, 18 : 341-54, 1998.

Renal Tubular Disorders

These are group of disorders due to primary tubular diseases i.e. the disease starts in the renal tubules then secondarily affects the glomerular and the overall kidney function. This is to be differentiated from other tubular disorders which are secondary to glomerular diseases.

Usually renal tubular disorders are genetically determined or due to certain drugs.

Specific Isolated Defects Of Tubular Transport

A) Carbohydrate tubular transport defect

Glycosuria

Normally glucose does not appear in the urine until plasma concentration reaches up to 180 mg/dl (10 mmol/L). This is called renal threshold. Maximum glucose excretion is reached at plasma concentration of 270 mg/dl (15 mmol/L). This is called (tubular maximum or T_m).

Renal glucosuria means the detection of glucose in urine while plasma glucose is less than 180 mg/dl (i.e. decreased renal threshold). There are two types of renal glycosuria, type A in which both renal threshold and T_m are reduced; and type B in which renal threshold is decreased but T_m is not.

Genetics: It is transmitted as autosomal recessive, few families have been reported with autosomal dominant inheritance.

Clinical features: These are persistent throughout the life with no symptoms unless starvation occurs, the patients will suffer from severe hypoglycemia, hypovolaemia and ketosis.

Diagnosis: By detection of glycosuria while plasma glucose is less than 135 mg/dl (7.3 mmol/L).

Differential diagnosis: Renal glycosuria should be differentiated from: (1) Diabetes mellitus (by glucose tolerance curve); (2) Fanconi's syndrome (multiple tubular defects not isolated glycosuria); (3) Glucose-Galactose malabsorption (combined renal and jejunal defect); (4) Glucoglycinuria; and (5) phosphate diabetes.

Treatment: No treatment is required.

B) Amino acids tubular transport defects

1. Hartnup's Disease

The basic defect is an abnormality in renal tubular and intestinal transport of free neutral (monoamine and monocarboxylic) amino acids. Oligopeptides containing these amino acids especially tryptophan are not handled normally.

The decreased reabsorption in the gut results in the increased breakdown by bacteria which in turn leads to increased amount of indoles and indican in both stool and urine.

Tryptophan is needed for at least half of the normal daily requirement of nicotinamide so that non-absorption causes niacin deficiency. Also indoles may inhibit nicotinamide synthesis; thus creating a vicious cycle.

The abnormality can affect all amino acids in the group or only in individual members.

Clinical features:

1. Aminoaciduria is a constant feature. Normally, total urinary amino nitrogen is less than 50 mg/d. In Hartnup's disease, it is about 500 mg/d.
2. Pellagra-like skin rash which is scaly on the exposed surfaces, sensitive to sunlight and can lead to blister formation.
3. Cerebral ataxia and nystagmus without sensory loss which gets worse when skin rash is worse.
4. "Blue Diaper" syndrome in infant, the abnormality affects only tryptophan handling leading to excess indigo dye excretion (blue colour).

Treatment:

1. Nicotinamide 40-200 mg/d.
2. High protein diet.
3. Sunlight should be avoided and monoamine oxidase inhibitors are contra- indicated.

2. Cystinuria

Is a disease characterized by abnormal transport of amino acids cystine, ornithine, arginine and lysine (COAL) by the intestinal mucosa and renal tubules. This will result in formation of cystine crystals and renal stones .

Clinical features and diagnosis:

1. The disease is more severe in males. It is a stone disease with recurrent urinary tract infection which may be complicated by chronic renal failure, usually manifests in the first to fourth decade of life.

2. In affected homozygote, they excrete more than 250 mg cystine/mg creatinine in urine.

Treatment:

1. To increase the solubility of cystine by increasing urine output to 2-4 L/d by increasing fluid intake and by alkalinizing the urine to pH 7.5-8 by sodium bicarbonate (check with pH indicator paper).
2. To decrease the urinary cystine excretion by d-Penicillamine. Penicillamine could be toxic (anaemia, loss of taste, fever, rash, haematuria, nephrotic syndrome and agranulocytosis).
Tiopronin is an alternative to d-Penicillamine with the same effect but with less frequent toxicity.

C) Renal Tubular Acidosis (RTA)

Is a systemic metabolic acidosis resulting from specific tubular abnormality in handling of H^+ . Usually the patient presents with metabolic acidosis out of proportion to the renal functional impairment. There are four types of RTA; distal (classic, type I), proximal (type II), type III (distal with bicarbonate wastage), and type IV (hyperkalaemic, hyporeninaemic, hypoaldosteronaemic).

Distal (classic) RTA

The normal daily production of hydrogen ions (H^+) is approximately 1mmol/kg/d in adults and 3 mmol/kg/d in children. This H^+ load is excreted by the kidney, through distal nephron. Failure to secrete this hydrogen load will result in metabolic acidosis. Normally, there is a pump mechanism in the distal convoluted tubules pushing H^+ to the lumen (urine). In distal RTA, there is a reduced pump activity or there is back diffusion of H^+ (from lumen to tubular cells and systemic circulation) resulting in systemic acidosis.

Normally, with systemic accumulation of hydrogen ions the kidney will secrete these H^+ to the urine which will be acidified to a urine pH of 5.2 or less. In distal RTA, this is not possible and urine pH is always above 5.7 even with severe metabolic acidosis.

Ammonia and titratable acid excretion in urine depends on urinary pH (needs acidic urine). So, their urinary excretion in RTA is reduced and is retained in the body.

Serum Bicarbonate (HCO_3^-) is used as a buffer for the retained H^+ ($HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$), so its blood level will be low in metabolic acidosis. As the proximal convoluted tubular function is intact in

distal RTA, more HCO_3 and chloride (Cl^-) will be reabsorped from its lumen. Reabsorped HCO_3 will be used for buffering more H^+ .

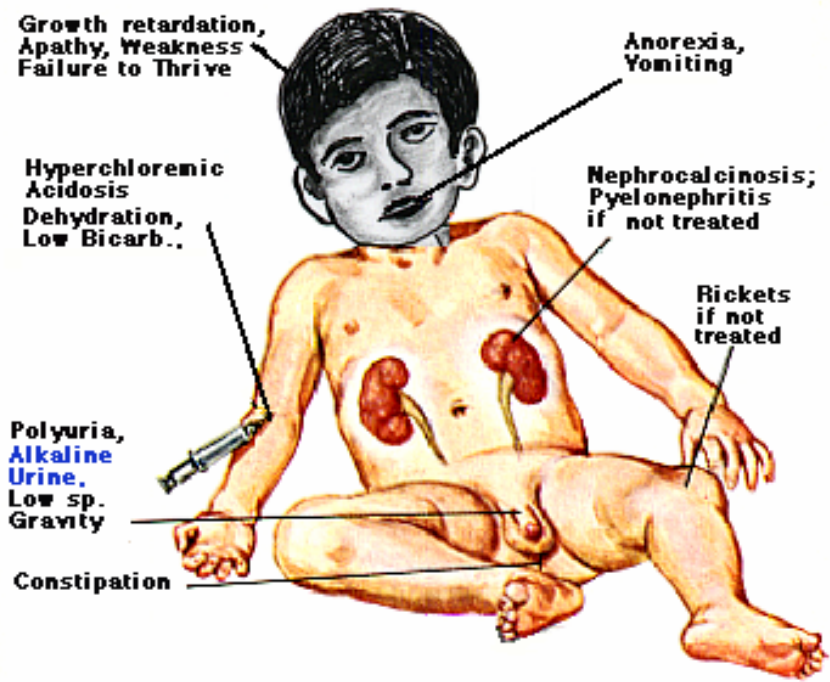
In incomplete RTA urine pH can usually be lowered to 5.7, at which level sufficient titratable acids and ammonium ion excretion can be generated to balance endogenous acid generation and the patient will not be acidotic. But if the acid generation increases (high protein diet or hypercatabolic state or if the incomplete RTA occurred on top of other renal injury) the kidney will not be able to excrete this load and the patient becomes acidotic.

Etiology:

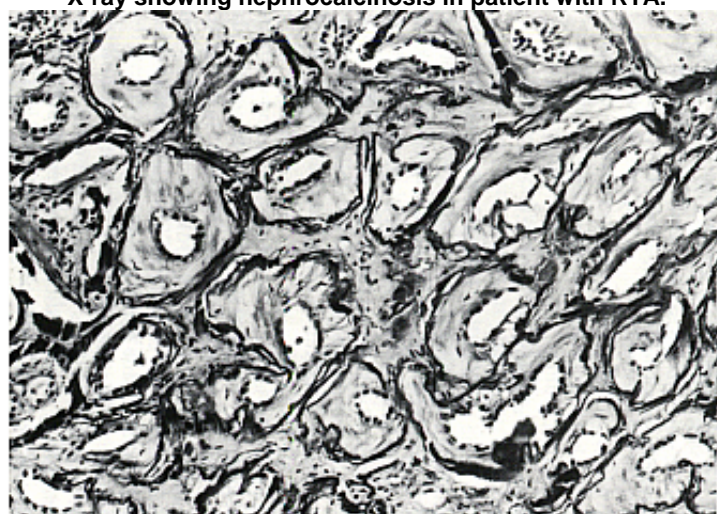
1. **Primary**
 - idiopathic
 - genetic (autosomal dominant)
2. **Complicating a genetically transmitted systemic disease**
 - Ehlers-Danlos syndrome
 - Hereditary elliptocytosis
 - Medullary cystic disease
3. **Autoimmune disease**
 - SLE
 - Sjogren's Syndrome
 - Hypergammaglobulinaemia
 - Chronic active hepatitis
4. **Nephrocalcinosis**
 - Medullary sponge kidney
 - Primary hyperparathyroidism
 - Vitamin D intoxication
 - Idiopathic hypercalcuria
 - Hypophosphatasia
5. **Tubulo-interstitial disease**
 - Chronic pyelonephritis
 - Acute tubular necrosis
 - Obstructive uropathy
 - Renal transplant glomerulopathy
6. **Drugs and toxins**
 - Analgesics
 - Amphotericin B
 - Lithium
 - Toluene
7. **Uretero-sigmoidostomy**

Clinical Features:

1. Male to female ratio is always 1 : 1. Primary RTA usually manifests clinically between the first and the third decade of life (Fig. 8.1).



X-ray showing nephrocalcinosis in patient with RTA.



Kidney section from a patient with RTA showing nephrocalcinosis. There are massive calcium deposits in tubular BM. A wide mucoid layer has developed between tubular BM and epithelium. PAS (X90).

(Fig. 8.1)

Clinical Features of Renal Tubular Acidosis

2. Hypokalemia due to defective handling of K^+ in distal nephron this will manifest as muscle weakness even paralysis and may be complicated by rhabdomyolysis, respiratory arrest or cardiac arrhythmia. Prolonged hypokalaemia may lead to renal concentration defect which will manifest as polyuria and nocturia.
3. Nephrocalcinosis and stone disease that is due to the decreased solubility of calcium salts (oxalate, carbonate or phosphate) due to persistently alkaline urine and reduced urinary citrate, Mg and hypercalcuria (in 50% of congenital and hereditary RTA).
This will result in obstructive uropathy, infection and finally renal failure.
4. Osteomalacia with bone pains and fractures. It is due to acidosis and use of bone as buffer with release of calcium carbonate from bone, also hypophosphataemia causing hyperparathyroidism and suppression of activation of vitamin D and hypocalcaemia.
5. Severe acidaemia will cause tachypnea, dizziness and even coma.
6. Severe acidaemia may decrease extracellular fluid volume and GFR.
7. Incomplete RTA will manifest only as nephrocalcinosis or as a stone disease.

Diagnosis:

1. Suspect distal RTA in patient with metabolic acidosis with hyperchloraemia and hypokalemia.
Urine pH less than 5.2 in the early morning urine or during systemic acidosis or with acid load (by giving ammonium chloride 0.1 g/kg orally) excludes RTA and the reverse is true.
2. In distal RTA urine pH will be > 5.7 in the morning urine sample, also in presence of systemic acidosis. In normal subjects, in these two situations urine pH should be 5.2 or less.
3. If systemic pH is not low, acidosis could be induced by giving ammonium chloride capsules 0.1g/kg orally and we look for urine pH.

Treatment:

Except in drug induced cases of RTA, the disease is always persistent and needs permanent treatment.

1. First treat hypokalaemia and hypocalcaemia.
2. Then give sodium bicarbonate to correct acidosis.

After correction of acidosis no need to give potassium supplementation.

3. In incomplete RTA, give ethacrinic-acid (to reduce urine pH) 50-100 mg three times per week, no need to give sodium bicarbonate.
4. Treatment of infection or obstruction if present.

Proximal RTA

Normally all the filtered bicarbonate is reabsorbed unless the concentration of bicarbonate in the glomerular filtrate is above the HCO_3Tmax which is 25 mmol/L. 80% of reabsorption of HCO_3 occurs in the proximal tubules through H^+ pump. In Proximal RTA, there is a degree of weakness in H^+ pump resulting in a decrease in its HCO_3 reabsorption capacity and a new steady state is settled in which Tmax of HCO_3 is decreased (e.g. to 10 mmol/L or 14 mmol/L). All HCO_3 filtered above this level will be lost in urine (bicarbonaturia) and blood level of HCO_3 will be decreased.

The HCO_3 reaching the distal nephron will turn the urine alkaline. This will interfere with ammonium ion and titratable acids excretion and consequent retention of H^+ in the body.

In this phase, the condition is characterized by metabolic acidosis, hyperchloraemia (excess reabsorption of Cl^- by PCT on expense of HCO_3), alkaline urine, decrease titratable acids and ammonium ion excretion.

When a new steady state is reached (new Tmax) all the filtered HCO_3 will be reabsorbed. The condition is characterized by metabolic acidosis, low plasma HCO_3 , hyperchloraemia, normal acidic urine (less than 5.2), no bicarbonaturia and normal excretion of ammonium ions and titratable acids.

Etiology:

PRTA is more rare than distal RTA. The list of causes of PRTA includes:

1. Primary single tubular defect
 - Genetic (very rare)
 - Transient in infants
 - Idiopathic
2. Multiple tubular defect
 - Genetic
 - idiopathic
3. Genetically transmitted systemic disease.
 - Cystinosis
 - Fructose intolerance
 - Wilson's disease

4. Autoimmune disease
 - Sjogren's Syndrome
5. Tubulo-interstitial disease
 - Medullary cystic disease
 - Renal transplant rejection
6. Drug and Toxins
 - Outdated tetracyclines
 - Streptozotocin
 - Lead, mercury, sulfanilamide
7. Dysproteinaemia
 - Multiple myeloma
8. Other renal diseases
 - Amyloidosis
 - Nephrotic Syndrome

Clinical features and diagnosis:

1. Usually metabolic acidosis with manifestations of other proximal tubular defects e.g. Fanconi Syndrome.
2. Hypokalemia
3. Nephrocalcinosis and renal stone disease
4. Manifestations of acidosis with failure to thrive in children, hypovolaemia, and tachypnea.
5. In contrary to distal RTA, the urine pH is variable. The morning urine pH is less than 5.2. Infusion of NaHCO_3 to increase plasma HCO_3 to normal will be followed by bicarbonaturia and increase in urine pH (alkaline) in proximal RTA and not in distal RTA; since in PRTA all HCO_3 above T_{max} will be lost in urine.

Treatment:

A large amount of alkali is needed (3-10 mmol/kg/d). Potassium supplement (KHCO_3) is needed because the correction of systemic acidosis will lead to bicarbonaturia with more renal loss of potassium.

Type III RTA

This is a distal RAT with HCO_3 wastage (i.e. mixed type I and type II).

Type IV RTA

Characterized by hyperkalaemia, hyperchloraemia, hyporeninaemia and hypoaldosteronism.

This is mainly seen in old diabetics with mild renal impairment. Other causes are chronic pyelonephritis and interstitial nephritis.

Treatment:

9- α -Fluorocortisone (floronif) in a dose of 0.1-0.2 mg/d usually corrects the hyperkalaemia and systemic metabolic acidosis.

B-blockers and ACEI should be avoided in these patients; as they may increase the hyperkalaemia.

ABNORMAL WATER HANDLING

A. Nephrogenic diabetes Insipidus (NDI)

Normally, anti-diuretic hormone (ADH) will make the distal nephron tubular basement membrane permeable to water with its reabsorption from the tubular lumen. In NDI, the tubular basement membrane is not responsive to ADH either due to defect in receptor site for ADH or in the effector site; defect in adenylate cyclase enzyme with reduced formation of cyclic AMP. Other mechanisms could be reduction of the medullary hypertonicity as in chronic renal failure, prolonged low protein intake and with the use of osmotic diuretics (mannitol).

Failure to respond to ADH will result in polyuria.

Etiology of Nephrogenic Diabetes Insipidus

1. Hereditary.
 - Congenital
 - Fabry's disease
2. Non-Hereditary.
 - Idiopathic
 - Cystic disease
 - Obstructive nephropathy
 - Interstitial nephritis
 - Chronic renal failure
3. Electrolyte disorder
 - Hypokalaemia
 - Hypercalcaemia
4. Drugs
 - Diuretics
 - Lithium
 - Demeclocycline (tetracycline)
 - Methoxyflurane
 - Colchicine
 - Amphotericin B
 - Propoxyphene
 - Isophosphamide
 - Sulfonyl ureas (acetohexamide Glibenclamide, Tolazamide)
 - Chlorpromazine

5. Miscellaneous
- Amyloidosis
 - Sjogren's Syndrome
 - Multiple myeloma
 - Low protein intake

Clinical features and diagnosis

1. Mainly polyuria (3-6 litres/day) and polydipsia.
2. Hypernatraemia will develop only in infants or unconscious patients who cannot ask for water or in patients with impaired thirst mechanism (hypokalaemia, hypocalcaemia or hypothalamic lesion). This will be manifested by dehydration, hypotension, restlessness, ataxia, seizures and grand mal fits.
3. NDI should be differentiated from central diabetes insipidus (CDI) and psychogenic polydipsia. Both NDI and CDI could be complete or partial syndrome.

The three conditions could be differentiated by water deprivation test (Figure 1) which aims to increase plasma osmolality to 295 mosmol/kg by water deprivation (alternatively by giving hypertonic saline 5% NaCl in a dose of 0.05 ml/kg/min for 2 hours) then looking for urine volume and urine osmolality.

- Normally, as plasma osmolality increases to 295 mosmol/kg, the urine volume will decrease and urine osmolality will increase to 800-1400 mosmol/kg.
- In psychogenic polydipsia, urine volume will gradually decrease and urine osmolality will increase up to 800 mosmol/kg.
- In complete NDI or CDI the urine volume and osmolality will not change (even the patient may become shocked from hypovolaemia so blood pressure should be watched hourly and body weight should not be allowed to decrease by more than 3-5%).

When plasma osmolality reaches 295 mosmol/kg or hypotension occurs, ADH is given in the form of DDVAP intranasally or 5 units of aqueous vasopressin i.v. Urine volume will decrease and osmolality will increase up to 800 in CDI but no change will occur in NDI.

In partial syndrome (NDI or CDI) water deprivation will increase osmolality to 400-500 mosmol/kg and some decrease in urine volume occurs. On giving vasopressin or DDVAP, urine osmolality will increase to 800 in CDI and not in NDI.

Treatment:

1. Treatment of the cause.
2. Adequate free water intake (without salt) to compensate for water loss and avoid dehydration and hypernatraemia.
3. Thiazide diuretic may help. The mechanism is mostly through induction of hypovolaemia. This will increase proximal tubular water reabsorption and thus reduces the amount of urine reaching to the distal nephron (the site of abnormality).

B. Water Retention:

This is usually caused by drugs increasing sensitivity of distal nephron to ADH leading to excess water reabsorption which will lead to dilutional hyponatraemia. These drugs are: cyclophosphamide, indomethacin, sulfonyleureas (chlorpropamide, tolbutamide), acetaminophen, oxytocin and vasopressin.

Clinical Features and Diagnosis:

The picture is similar to that of the syndrome of inappropriate secretion of ADH (SIADH) but with low plasma ADH level. There is euvolaemic or hypervolaemic state (oedema, high blood pressure, decreased haematocrit ratio), dilutional hyponatraemia and hypoosmolality (irritability, disorientation, lethargy, twitching, nausea, seizures, and even coma), mortality is 10% in chronic hyponatremia and 50% in acute hyponatremia.

Treatment:

Withdrawal of the causative drug. If this is not possible, give demeclocycline 200-600 mg/d.

CYSTINOSIS

Is an autosomal recessive disorder affecting children mainly, and is characterized by deposition of cystine crystals in several organs including the kidney. The pathogenesis is unknown. In children, it causes a rapidly progressive renal failure, Fanconi Syndrome and rickets.

Diagnosis depends on the detection of cystine crystals in the cornea, conjunctiva, bone marrow, lymph nodes, the kidney or leucocytes.

Treatment:

1. See cystinuria.
2. It does not recur in the kidney transplant as the defect is on the cellular level (lysosomal storage defect).

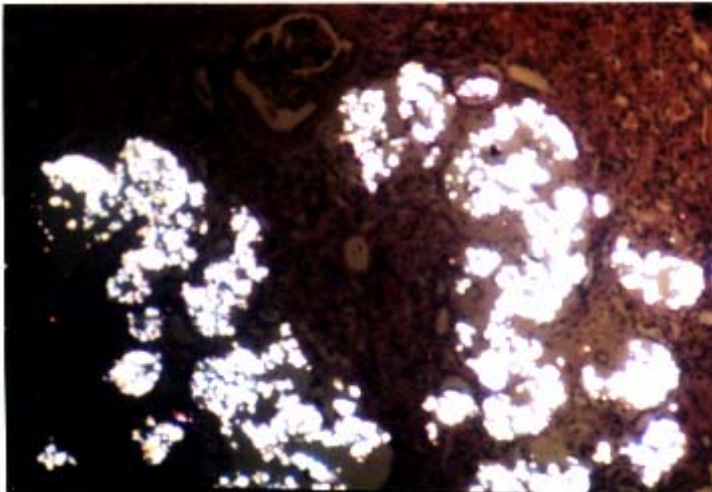
WILSON'S DISEASE

Characterized by accumulation of copper in renal cortex and other organs. Treatment is by chelating agent; namely penicillamine.

OXALOSIS

In the hereditary form, the basic defect is in the transaminase needed to convert glyoxylate to glycine resulting in an increased conversion to oxalate rather than glycine.

Oxalate will be deposited in many tissues including the kidney (Fig. 8.2) with nephrocalcinosis and calcium oxalate stones which lead to renal failure.



(Fig. 8.2)

Hx & E stained kidney section (X400) from a patient with primary oxalosis, examined by polarized light. It shows extensive oxalate Deposits in the renal tubules and interstitium.

Etiology:

1. Hereditary.
2. Acquired
 - Ileal resection and ileostomy
 - Pyridoxine (vitamin B6) deficiency
 - Ethylene glycol (anti-freeze) poisoning
 - RTA
 - Sarcoidosis
 - Excessive vitamin C ingestion
 - Excessive ingestion of oxalate
 - Liver cirrhosis

Clinical features:

1. In the hereditary form, symptoms usually start at the age of 5-10 years with stone disease, infection and progressive renal failure.

2. Urinary oxalate excretion is high (oxalate/creatinine by mmol is normally less than 0.05).
3. Detection of oxalate crystals in bone marrow.
4. Sometimes oxalate in urine or tissues are equivocal especially in adult (acquired types).

Treatment:

1. Mainly by high fluid, diuretic, high magnesium, phosphate and vitamin B₆.
2. The disease may recur in the kidney transplant.

BARTTER'S SYNDROME

A syndrome characterized by:

1. Hyperplasia of juxtaglomerular apparatus.
2. High renin and aldosterone levels.
3. Hypokalaemia.
4. Metabolic alkalosis.
5. Normal blood pressure.

The pathogenesis of the disease is unknown. Possibly, there is a defect in Na⁺ reabsorption in proximal nephron leading to sodium overloading of the distal nephron which impairs K⁺ reabsorption resulting in hypokalaemia. This will lead to hypovolaemia. Hypokalaemia and hypovolaemia will stimulate aldosterone and renin secretion.

Clinical picture is that of hypokalaemia (muscle weakness, constipation, polyuria). Diagnosis is by demonstrating the hypokalaemia with potassium wastage in urine and the presence of normal blood pressure in the presence of high renin and aldosterone. This will differentiate the condition from ACTH-secreting tumour, cathartic abuse and villous papilloma of the colon.

VITAMIN D RESISTANT RICKETS (VDRR)

The basic defect is in proximal tubular and jejunal phosphate reabsorption leading to phosphate loss. Some patients will show as well a defective activation of vitamin D or peripheral tissue resistance to vitamin D. The bone will be unmineralized with increased osteoid.

Clinical Features:

Usually the patient presents with bone pains, fractures or pseudofractures, growth retardation, short stature, genu valgum or varum deformity. X-ray will show rickitic lesions in children and osteomalacia in adults.

Treatment:

1. Vitamin D (either the active form or 500,000 units per day of the inactive form).
2. Phosphate supplementation (1-4 g/d).

PSEUDOHYPOPARATHYROIDISM

The basic defect is renal tubular resistance to the action of PTH due to defect in renal adenylate cyclase system.

Clinical features

1. The disease is sex-linked dominantly inherited. The patient has a round face, depressed nasal bridge, short thick neck and short stature with brachydactyly.
2. Clinical manifestations are those of hypocalcaemia with tetany, muscle cramps, twitching and convulsions.
3. There is hypocalcaemia, hyperphosphataemia and high PTH.

Treatment:

Very high doses of vitamin D.

FANCONI SYNDROME

Is a complex defect of tubular functions including variable combinations of multiple proximal tubular abnormalities (aminoaciduria, glycosuria, uricosuria, phosphaturia, hypophosphataemia and distal or proximal RTA).

Etiology:

1. Hereditary: Primary inherited, cystinosis, Wilson's disease, Fructose inheritance, Tyrosinaemia, vitamin D dependent rickets and Galactosaemia.
2. Acquired: Multiple myeloma, amyloidosis, Sjogren's Syndrome, nephrotic syndrome, kidney transplant rejection and vitamin D deficiency.
3. Drugs: outdated tetracycline, 6-mercaptopurine, gentamycin, lead, mercury and cadmium.

Clinical Features

1. In adults and children, the presentation can be with bone pains and fractures due to osteomalacia or rickets. In children, growth retardation is also seen.
2. Aminoaciduria, glycosuria, phosphaturia and hypophosphataemia.

Treatment:

1. Treat RTA
2. Phosphate and vitamin D supplementation

Suggested Readings:

- Smulders YM, et al: Renal tubular acidosis. Pathophysiology and diagnosis. Arch Intern Med. 156 : 15, 1629-36, 1996.

- Broyer M, et al: Management of oxalosis. Kidney Int Suppl, 53 : S93-8, 1996.

- Bunchman TE, et al: The infant with primary hyperoxaluria and oxalosis: from diagnosis to multiorgan transplantation. Adv Ren Replace Ther, 3 : 3, 315-25, 1996.

- Alon US: Nephrocalcinosis. Curr Opin Pediatr, 9 : 2, 160-5, 1997.

- Lasram, et al: Ocular signs of primary hyperoxaluria type I. J Fr Ophthalmol, 20 : 4, 258-62, 1997.

- Igarashi T: Renal tubular acidosis. Ryoikibetsu Shokogum Shirizu, 19 Pt 2, 578-82, 1998.

- Tomita K: Renal tubular acidosis. Nippon Naika Gakkai Zasshi, 87 :3, 564-8, 1998.

- Gregory MJ, et al: Diagnosis and treatment of renal tubular disorders. Semin Nephrol. 18 : 317-29, 1998.

- Hayashi M: Physiology and pathophysiology of acid-base homeostasis in the kidney. Intern Med, 37 : 2, 221-5, 1998.

- Kemper MJ, et al: Preemptive liver transplantation in primary hyperoxaluria type 1: timing and preliminary results. J Nephrol, 11 Suppl 1 : 46-8, 1998.

- McDowell GA, et al: Clinical and molecular aspects of nephropathic cystinosis. J Mol Med, 76 : 295-302, 1998.

TUBULAR AND INTERSTITIAL DISEASES

Tubulointerstitial Nephritis

Is a pathologic term describing inflammation involving the interstitium and renal tubules. It may be acute or chronic.

ACUTE INTERSTITIAL NEPHRITIS (AIN)

Etiology:

- 1. Drug or Toxin induced:** Antibiotics are the most commonly implicated drugs, in acute interstitial nephritis. Methicillin is the most frequent but penicillin, ampicillin, rifampicin, phenandione, sulfonamides, co-trimexazole, thiazides and phenytoin are frequently implicated and are more important clinically. Drugs that are involved but less frequently are non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, analgesics and H₂-antagonists. Toxins which can induce tubulointerstitial nephritis are organic solvents, ochratoxin (fungal toxin).
- 2. Infection-related acute interstitial nephritis:** May result from direct invasion of the renal interstitium by the organism (mainly the renal medulla which is involved with picture of acute pyelonephritis) or may be associated with a systemic infection without direct renal involvement by bacteria. The lesion will be caused by bacterial toxin or through an immunologic process triggered by bacterial infection. Bacterial infection as streptococcus, diphtheria, brucellosis, legionella, pneumococcus, tuberculosis, mycoplasma, virus infection as measles, cytomegalovirus, Hanta virus, and Epstein-Bar virus, protozoa as toxoplasmosis and spirochetal infection as leptospirosis are known to cause AIN.
- 3. Idiopathic and immune mediated disease:** Such as Sjogren's syndrome, SLE and transplant rejection can be associated with interstitial nephritis.

Pathology:

The mechanism of AIN is mainly immunologic reactions in response to exposure to drug, toxin, or infection. This is mainly a cell mediated immune response and to a lesser extent a humoral reaction with deposition of either anti-tubular basement membrane antibodies or immune complexes.

Macroscopically, the kidney looks normal or increased in size. *Microscopically*, there is interstitial edema and cellular infiltrate. Tubules

may look normal or show necrosis, glomeruli; and blood vessels are intact. The infiltrating inflammatory cells are predominantly lymphocytes and plasma cells. In addition, neutrophils and eosinophils will be seen in drug induced AIN.

The condition may regress completely or progress to chronic interstitial nephritis if the offending cause is persistent.

Clinical Presentation:

The disease varies from severe hypersensitivity syndrome with fever, rash, eosinophilia and acute renal failure to asymptomatic increase in plasma creatinine or abnormal urinary sediment without evidence of renal insufficiency.

In cases of drug induced AIN the interval between exposure to drug and the onset of symptoms varies from hours to months.

Differential diagnosis:

This includes acute tubular necrosis, rapidly progressive glomerulonephritis and athero-embolic renal artery disease.

History of drug intake or exposure to toxic substance or infection is important. Presence of skin rash, fever, eosinophilia, tubular proteinuria (usually < 1g/24 h), leucocyturia, microscopic haematuria and eosinophiluria are findings supporting the diagnosis of AIN. Kidney biopsy will settle the final diagnosis.

N.B. Absence of eosinophilia or eosinophiluria does not exclude AIN.

Treatment:

1. Discontinuation of the causative drug and treatment of infection and supportive treatment may be sufficient to induce recovery.
2. Steroids are sometimes given (unless there are contraindications) to shorten the course of illness and prevent permanent renal damage.

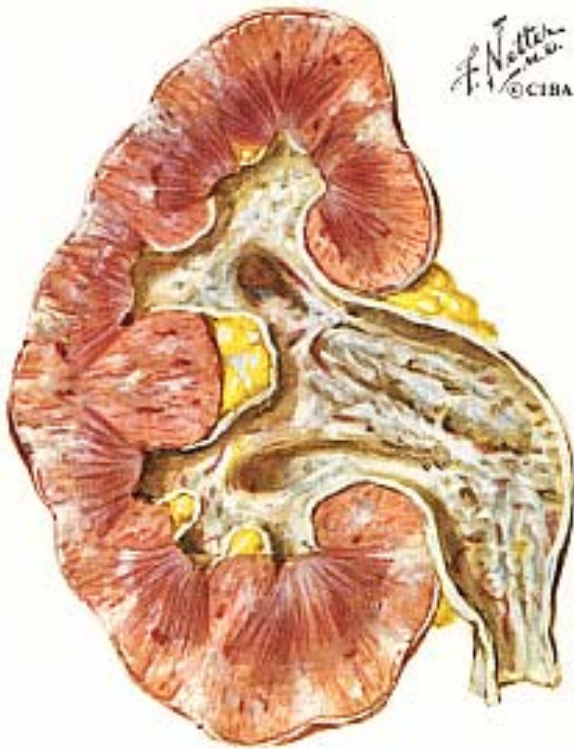
CHRONIC INTERSTITIAL NEPHRITIS (CIN)

There are many conditions that may lead to CIN. The most common are analgesic nephropathy, reflux nephropathy, gouty nephropathy, obstructive nephropathy and chronic pyelonephritis. The complete list of causes of CIN is in table 1.

Pathology:

Macroscopically, the kidney is small, atrophic.

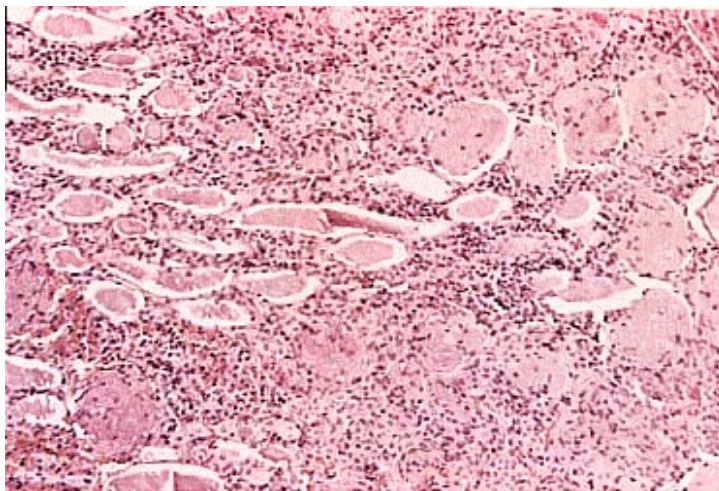
Microscopically, non-specific changes are seen including interstitial fibrosis, chronic inflammatory cellular infiltration and tubular atrophy (Figure 9.1).



(Fig. 9.1a)

Cross section of a kidney with Chronic pyelonephritis, it shows thinning of renal parenchyma with Wedges-shaped subcapsular scars; dilated fibrosed pelvis and calyces.

(Reproduced with permission from Novartis-Switzerland)



(Fig. 9.1b)

Hx&E stained kidney section, it shows thyroid like appearance of renal tubules (atrophic, filled by eosinophilic casts) lymphocytic infiltration and interstitial fibrosis.

Clinical presentation :

1. Manifestations of the etiologic cause.
2. Manifestations of chronic renal impairment (see page 158) which may progress to end stage renal disease.

Treatment:

1. Of the etiologic cause, and
2. Treatment of the chronic renal failure, whether conservative or with renal replacement therapy in advanced stages (dialysis and transplantation).

TABLE 1
Causes Of Chronic Interstitial Nephritis

1.	Chronic phase following acute interstitial nephritis.
2.	Drugs (analgesics, lithium).
3.	Heavy metals (cadmium, mercury, lead).
4.	Reflux nephropathy.
5.	Sickle cell disease.
6.	Medullary cystic disease.
7.	Metabolic (gout, hyperoxaluria, hypercalcaemia).
8.	Obstructive uropathy.
9.	Radiation.
10.	Infection (leprosy, syphilis, tuberculosis)
11.	Sarcoidosis.
12.	Balkan endemic nephropathy.
13.	Renal ischemia.
14.	Sjögren syndrome.
15.	Glomerulonephritis.
16.	Neoplastic disorders (multiple myeloma, leukemia, lymphoma, light chain nephropathy).
17.	Transplant rejection.

RADIATION NEPHRITIS

Occurs as a complication of irradiation when the kidney comes into the field of irradiation. Usually it manifests acutely 6-12 months after irradiation with severe hypertension and progressive uraemia.

BALKAN ENDEMIC NEPHROPATHY

Chronic interstitial nephritis, sometimes associated with transitional cell neoplasms. The disease affects people in Romania, Bulgaria and former Yugoslavia (Danube River) giving a history of living in endemic village. Recently it has been reported in Tunisia.

The etiologic cause is unknown, possibly ochratoxin (fungal toxin) or heavy metal poisoning.

LITHIUM-INDUCED NEPHROPATHY

Beside its effect on tubular functions (see page 212) some believe that lithium can cause interstitial nephritis and chronic renal failure with characteristic histologic lesions. These lesions consist of tubular dilatation, microcyst formation and interstitial fibrosis.

SICKLE CELL NEPHROPATHY

Sickling will cause occlusion of vasa recta and papillary necrosis occurs. Renal failure is a common cause of death in patients with sickle cell anaemia.

ANALGESIC NEPHROPATHY

Analgesic nephropathy is a chronic tubulointerstitial disease, it represents an important cause of end stage renal failure. Of patients under maintenance haemodialysis or those who have received kidney transplantation, 2-2.5% in North America, 9.8-16.7% in Europe and up to 21% in Australia are victims of analgesic nephropathy.

Pathology:

The following pathologic features could be seen in analgesic nephropathy:

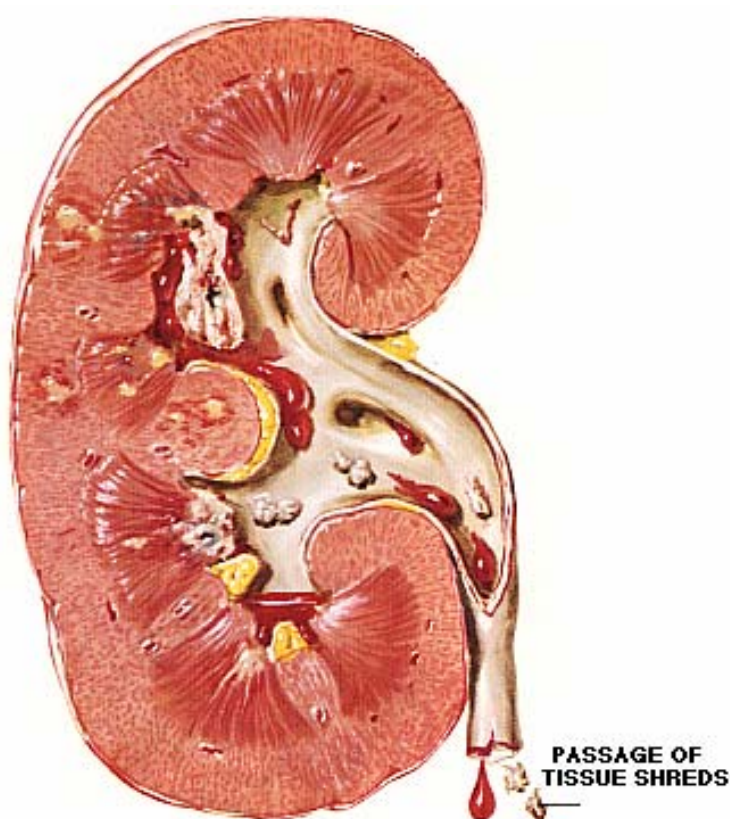
1. Renal Papillary Necrosis (RPN).
2. Chronic Interstitial Nephritis.
3. Vascular (Capillary) Sclerosis.
4. Transitional Cell Carcinoma of the Urothelium.

Macroscopic appearance:

The kidney is small in size. The capsule is thick and adherent, with prominent scars and multiple small cysts seen on the surface. There may be a pale tumour-like nodular tissue between scars which represents hypertrophy of remaining nephrons in columns of Bertini. Cut surface will show the brownish-black necrotic shrunken papillae with atrophy of the overlying cortical tissue and hypertrophy of the intervening columns of Bertini (Figure 9.2). In contrast, in diabetic nephropathy, necrotic papillae are pale and swollen.

Microscopic appearance:

1. **Renal papillary necrosis (RPN):** Is the primary feature of analgesic nephropathy, resulting from medullary cytotoxicity and ischemic infarct. Histologically, RPN may be divided into three stages according to the extent of necrosis, starting by papillary tip necrosis to complete papillary necrosis. A striking feature is absence of inflammatory infiltrate and the presence of calcification of the involved papillae. Separation and loss of a necrotic papilla result in the formation of a cavity which becomes lined by fibrous tissue. Tubules of remaining viable nephron open into pelvicalyceal system through this cavity.



(Fig. 9.2)

Gross appearance of a kidney with Necrotizing papillitis it shows sloughing of the Renal papillae
(Reproduced with permission from Novartis- Switzerland

2. **Chronic interstitial nephritis:** This is attributed to direct drug-related cytotoxicity in the renal cortex and/or secondary to tubular obstruction in tissue overlying the necrotic medulla. Microscopically, there is tubular atrophy, interstitial fibrosis and round cell infiltration. Careful microscopic examination may show a characteristic golden brown lipofuchsin-like pigment in the interstitium and tubules. The glomeruli may be unaffected or show secondary changes in the form of global sclerosis or hyalinosis, hypertrophy or focal and segmental glomerulosclerosis.

3. **Vascular sclerosis:** Affecting small arterioles, venules in the renal medulla and the submucosa of the renal pelvis and the urinary tract. There is a homogeneous thickening and sclerosis of the vessel wall which stain strongly with PAS stain.
4. **Transitional cell carcinoma (TCC) of urothelium:** Although TCC is the commonest analgesic-associated tumour. However, hypernephroma, sarcoma and chorion epithelioma have also been reported. The ratio of bladder to renal pelvis tumours in analgesic nephropathy is 1 : 11 while in normal patients it is 15 : 1. The tumours may be solitary pedunculated or more commonly, broad-based solid infiltrating. They may be multifocal and tend to be poorly differentiated and more malignant.

Pathogenesis of analgesic nephropathy:

Aspirin, paracetamol (the metabolite of phenacetin) and other analgesics are concentrated in renal medulla especially renal papillae. The concentration is in the tubular cells, vasa recta cells and in the interstitium. Dehydration will increase concentration and nephrotoxicity while hydration protects against. Analgesic mixture is more serious than the single drug exposure (synergism). Cumulative dose and duration of drug intake play major roles in nephrotoxicity and the development of renal failure. Other factors which are playing a major role are hydration status, patient's sex (female > Male) climatic factors and genetic factor (more with HLA A₃ and B₁₂).

At cellular level, aspirin and paracetamol will cause a lot of metabolic abnormalities with a release of toxic substances as reactive alkylating agents and glutathione depletion. This will lead to cytotoxicity and cell death. In addition, aspirin will block the synthesis of prostaglandins in the renal medulla with consequent decrease in the blood flow, renal ischaemia and tissue hypoxaemia which will aggravate the direct cytotoxicity.

Clinical manifestations:

Female to male ratio is 7 : 1, in spite of ratio of analgesic consumption is only 2 : 1 denoting female sex preponderance. The patient's age is usually 40-60 years.

Analgesic nephropathy is a part of a much wider clinical syndrome called the analgesic syndrome, in which there are multi-organ manifestations.

A. Renal Manifestations:

Analgesic nephropathy may be asymptomatic and is discovered only on routine medical examination.

The patient may present with manifestations of progressive renal impairment with more marked manifestations of tubular dysfunctions including more severe metabolic acidosis than expected (if we consider serum creatinine), early loss of concentrating ability with polyuria and nocturia, sodium losing state, more osteodystrophy (renal bone disease) and enzymuria.

Episodes of acute-on-chronic renal failure may be precipitated by severe dehydration, acute haemorrhage from bleeding D.U., infection or ureteric obstruction. This is characterized by oliguric acute renal failure with severe systemic acidosis, hyperkalaemia, hypertension and volume overload which may result in pulmonary oedema.

Hypertension occurs in more than 60% of cases either due to renal ischaemia with excess renin-angiotensin or salt and water retention due to nephron loss or due to loss of renal vasodilator prostaglandins.

Gout occurs in 20% of cases. It is more common in males.

Proteinuria occurs in 40% of cases, usually mixed tubular and glomerular (up to 3g/24h).

Haematuria secondary to cystitis, renal calculi, malignant hypertension, malignancy, or less commonly of glomerular origin.

Urinary tract infection may occur in up to 50% of cases, due to epithelial shedding, stones, stasis and instrumentation. Sterile pyuria is very common due to renal calculi or renal tubular epithelial celluria.

Ureteric obstruction by necrotic papillary tissue, stone, tumour or stricture-if associated with infections-may result in a life threatening acute renal failure.

b. Extra-renal manifestations of the analgesic syndrome:

- 1. Gastrointestinal manifestations:** Dyspepsia, gastric ulcers in 30% of cases (tend to be complicated and recur after surgery) abnormal liver function tests and relapsing pancreatitis.
- 2. Haematological manifestations:** Anaemia occurs in 60-90% of cases (due to blood loss, uraemia, paracetamol-related haemolysis), palpable spleen in 10% of cases.
- 3. Cardiovascular manifestations:** These include hypertension, premature atherosclerosis, more common ischemic heart, cerebral strokes, peripheral vascular disease, renal artery stenosis and difficult vascular access for dialysis.
- 4. Neuropsychiatric manifestations:** Including headache, personality inadequacies, usually are smokers, alcoholics, purgative abusers.

5. **Pregnancy and gonadal manifestations:** Subfertility, higher incidence of toxæmia of pregnancy, post maturity (due to suppression of uterine prostaglandins).
6. **Premature aging**
7. **Pigmentation:** Skin, heart, brain and joint cartilage, possibly due to retained phenacetin metabolites (lipofuchsin-like pigment).

Diagnosis:

The diagnosis is based on:

1. History of significant analgesic abuse for long period, at least 2 kg of aspirin or phenacetin or analgesic mixture is required for chronic tubulo-interstitial nephritis to occur.
2. Demonstration of RPN which is best demonstrated by IVU or retrograde pyelography. If there is renal failure RPN could be illustrated by U.S. Pathologic examination of necrotic tissue in urine could help in diagnosis.

N.B. Other causes of RPN are diabetes mellitus, sickle cell disease, obstructive uropathy, chronic alcoholism and renal amyloidosis.

3. Demonstration of chronic interstitial nephritis on clinical grounds and by histological examination of the kidney tissue. The finding of characteristic capillary sclerosis and lipofuchsin-like pigment on examination of pathologic specimens provides a significant clue to an analgesic etiology.

Management:

1. Total avoidance of all NSAIDs is the most important therapeutic approach.
2. Maintenance of a high fluid intake (greater than two liters/d).
3. Treatment of complications e.g. hypertension, acidosis, infection.
4. Careful long-term follow-up for early discovery of complications e.g. malignancy, infection, stones and renal artery stenosis.

REFLUX NEPHROPATHY

Vesicoureteric reflux (VUR) is the back flow of urine from the bladder to the ureter; and reflux nephropathy (RN) is the kidney disease characterized by coarse renal scars as a complication of VUR.

Pathology:

Macroscopically the outer surface of the kidney is irregular with scars which usually affect its upper or lower poles (focal RN). Sometimes scars are extensive and involving the whole kidney (generalized RN). The scar overlies a cortex with tubulo-interstitial nephritis and a scarred pyramid opposite a

clubbed calyx. In between each scar and the other, kidney tissue will show compensatory hypertrophy which exaggerate the irregularity of the outer surface of the kidney. *Microscopic examination* will show extensive tubular atrophy and interstitial fibrosis. The glomeruli may be either intact, or is surrounded by periglomerular fibrosis, show global sclerosis or has a focal and segmental glomerulosclerosis.

Renal tissue in between scar areas will show glomerulomegaly due to hyperfiltration.

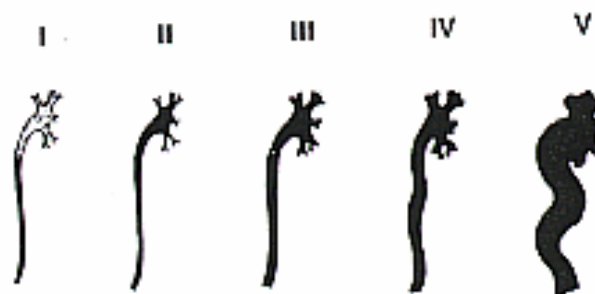
Pathogenesis of Renal scarring in RN:

Renal scars develop during infancy or during early childhood. Three factors are interacting to cause renal scarring. These are:

1. Vesicoureteric reflux.
2. Intra-renal reflux.
3. Urinary infection. As infection reaches renal pyramids in the immature kidney, scars will develop.

1. Vesicoureteric reflux (VUR):

Normally, the ureter at the uretero-vesical junction has a long oblique intramural tunnel. During micturation or when the intravesical pressure is higher than the intraureteral pressure. This will press on the bladder wall closing the ureterovesical junction and urine does not regurgitate up. In about 0.5% of newborn this mechanism is not well developed and the ureter is implanted less obliquely with a wider opening and a shorter junction so the urine may reflux up the ureter especially during voiding. By voiding cystourethrography VUR could be divided into five grades (Fig. 9.3).



(Fig. 9.3):

The grading system adopted by the International Reflux Study in Children. Contrast material in the collecting system is represented in black. Grade I is assigned if the contrast material enters the ureter, but does not enter the renal pelvis. Grade II means that contrast material reaches the renal pelvis, but does not distend the collecting system. Grade III occurs when the collecting system is filled and either the ureter or pelvis is distended, but the calyceal demarcations are not distorted. Grade IV is assigned when the dilated ureter is slightly tortuous and the calyces are blunted. Grade V occurs when the entire collecting system is dilated and the calyces have become distorted and indistinct.

VUR is genetically determined. It has an autosomal dominant mode of inheritance with variable penetrance. The incidence of VUR in siblings of the affected children is as high as 45%.

2. Intra-renal reflux:

This could be demonstrated in high grades of VUR using MCU, in which the dye will be seen in papillary ducts. In the ordinary papillae, the openings of the ducts are usually slit-like and non-refluxing, but in compound papillae (two papillae are mixed in one, about 9% of kidneys have one or more compound papillae which are polar), duct orifices are often gapping and refluxing.

3. Urinary tract infection:

Infection is brought to renal pyramids by reflux, local infection occurs repeatedly and ends by a scar formation. All renal scarring due to VUR is fully developed by adolescence and future progression of kidney disease is either due to development of FSGS in the remaining tissue or due to back pressure by refluxing urine on kidney tissue during micturation.

Prevalence of RN:

About 0.5% of neonates have VUR, but small proportion of them develop R.N., scarring occurs in female more than in male (5 : 1).

1-2% of school girls have bacteruria, and of these 20-30% have VUR. Prevalence of RN in school girls is 0.3-0.5%.

Clinical Features:

- 1. Urinary tract infections:** This is the commonest presentation. In neonates it may present as fever and failure to thrive, in older children it is associated with fever, dysuria, frequency and loin pain. Usually it is recurrent.
- 2. Hypertension:** VUR is responsible for more than 60% of hypertension in children and 60% of adults with VUR are hypertensive.
- 3. Renal failure:** 10% of patients coming for dialysis have RN, usually at age of 30 years. Renal failure occurs due to scarring, infection, and FSGS.
- 4. Other clinical presentations:** As loin pain on voiding, childhood enuresis, renal stone, positive family history, and presence of other congenital anomaly as duplex ureter and posterior urethral valve.

Diagnosis:

1. IVU will show cortical scarring and clubbing of calyx, disparity in kidney size and shape.
2. Renal radionuclear imaging. Using DMSA scan to show scarring or area of inflammation.
3. MCU and cystoscopy.
4. Renal biopsy is indicated only when IVU and DMSA show no scarring.

Early screening for reflux:

Justified only in families with strong history of VUR. Very early diagnosis is important to prevent scarring. U.S. and MCU are the justified tools for diagnosis.

Management of RN:

1. Control of infection by prophylactic antibiotics which should be given daily (e.g. septrin once daily) till puberty or reflux disappears. If infection occurs it should be treated aggressively.
2. Control of hypertension.
3. Anti-reflux surgery: The indication of surgery in treatment of VUR is still controversial. Surgery will not prevent progression of renal disease. It may be indicated with recurrent pyelonephritis or when prophylactic antibiotics could not be given especially with high grade reflux. Either ureter is reimplanted into the bladder with special anti-reflux technique or cystoscopic injection of material (e.g. collagen or polytetrafluoroethylene) around ureteric orifice to narrow it and to prevent refluxing.

PYELONEPHRITIS

Is a microbial infection involving renal pelvis and renal parenchyma. Pyelitis means an infection mainly affecting the renal pelvis. Pyelonephritis is usually associated with constitutional symptoms (fever, rigors,...) due to parenchymatous involvement, while pyelitis like other viscous organ infection (e.g. cystitis and urethritis) is not.

Pyelonephritis may be acute or chronic:***ACUTE PYELONEPHRITIS*****Predisposing factors:**

1. Anatomical abnormalities: as vesico-ureteric reflux, ureteric stricture or congenital kidney disease as horse shoe kidney.
2. Renal stones.

3. Obstruction of the urinary tract causing stasis of urine as in cases of senile prostatic enlargement and bladder neck obstruction.
4. Diabetes mellitus: due to its predisposition to infection this risk will be magnified on presence of diabetic nephropathy.
5. Analgesic nephropathy: due to the interstitial fibrosis and the abnormal urinary epithelium caused by chronic exposure to these drugs.
6. Instrumentation: as cystoscopy which may introduce organisms into the urinary tract.
7. Neurogenic bladder which leads to residual urine in the bladder and stasis creating a good medium for bacterial multiplication.
8. Following primary renal disease e.g. nephrotic syndrome.

Precipitating factors specific for female patients:

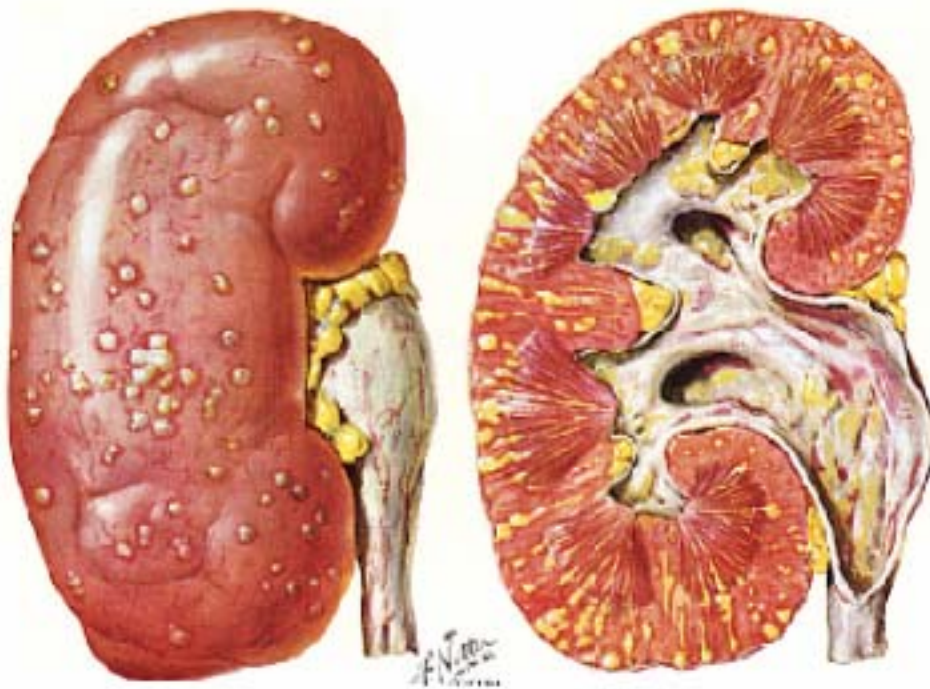
1. Short urethra allowing easy passage of bacteria from the perineal area to the bladder.
2. Trauma such as honey moon cystitis (cystitis occurring in early marriage).
3. Stasis with pregnancy: due to hormones secreted during pregnancy causing relaxation of ureteric muscles and ureteric dilatation.

5% of pregnant women have persistent bacilluria (bacilli in urine) and 30-40% of these may develop acute pyelonephritis.

1-2% of school girls may have bacilluria, 10% of them will have radiologic manifestation of renal scarring later on.

Pathology of Acute Pyelonephritis:

Gross appearance: Kidney appears enlarged, pelvic mucosa appears congested. In severe cases, scattered small abscesses may be seen in kidney tissue (Fig. 9.4a).



Surface Aspects of kidney:
Multiple minute abscesses
(surface may appear relatively
normal in some cases)

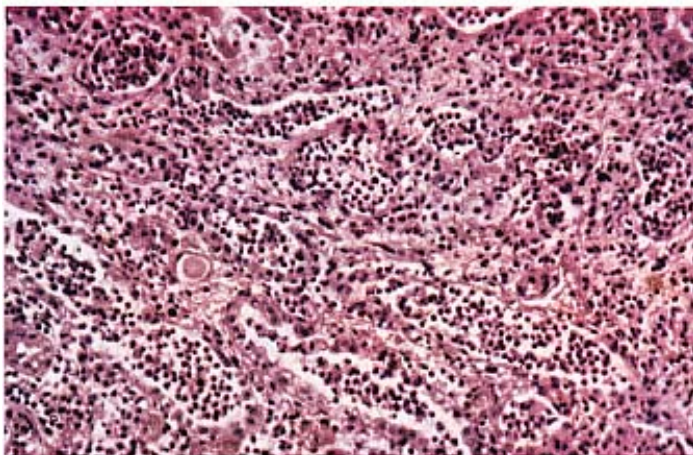
Cut section: Radiating yellowish
gray streaks in pyramids and
abscesses in cortex; moderate
hydronephrosis with infection;
blunting of calyces
(Ascending infection)

(Fig. 9.4a)

Acute pyelonephritis Pathology

(Reproduced with permission from Novartis-Switzerland)

Microscopic appearance: Infiltration of the kidney tissue with polymorphonuclear leukocytes, tubules may show pus cells and leucocyte casts (Fig. 9.4b).



(Fig. 9.4b)

Acute pyelonephritis with exudate
chiefly of polymorphonuclear
Leukocytes in interstitium and
collecting tubules

Symptoms:

Fever, malaise, aches, dysuria, frequency of micturition, hematuria and papillae may pass in urine causing renal colic (especially in diabetic patients). In children, abdominal pain and screaming on micturation.

Signs:

Tender loin and suprapubic area and the urine may look turbid and may smell fishy (in Proteus infection).

Investigations:**1. Urine examination including:**

- (a) Microscopic examination which will show pus cells and sometimes bacteria .
- (b) Urine culture to detect bacterial count (significant count is > 100,000 bacteria/ml urine), for identification of type of organism, and to detect degree of sensitivity to antibiotics which is important for treatment, especially in complicated cases.

For urine culture, the urine should be free of contamination. This could be achieved by using midstream urine sample in adults or suprapubic aspiration of urine in children. This is done by puncturing the full bladder by a fine needle after disinfecting the skin of suprapubic area.

The most common organism causing acute pyelonephritis is E.coli, followed by coliforms bacteria. In cases with anatomic abnormality in urinary tract or with instrumentation the common organisms are pseudomonas, proteus, and k. aurogenosa.

Causes of sterile pyuria (pus cells with negative repeated cultures) are:

1. Urinary T.B. (needs special media to grow).
 2. Renal stones.
 3. Urethritis (caused by virus, fungus or chlamydia.... etc.)
 4. Analgesic nephropathy.
 5. Nonspecific inflammation of the bladder.
- 2. Kidney function tests:** Serum creatinine and creatinine clearance. Renal dysfunction could be a preceding event or a complication of pyelonephritis and its presence will affect the mode of treatment of acute pyelonephritis.
- 3. Renal ultrasonography** to diagnose precipitating factors as stone or back pressure.

4. **IVP:** After single attack in male and repeated attacks in females to diagnose stone disease or anatomic abnormality, e.g. ureteric stricture, back pressure changes.
5. **Kidney biopsy:** Is not indicated for diagnosis as it may disseminate infection (Fig. 9.4b).

Treatment:

1. High fluid intake to induce diuresis to wash pus and bacteria out.
2. Antimicrobial therapy:
For first or uncomplicated infection we may start with Ampicillin, Amoxicillin or Septrin for 7-10 days. For resistant, recurrent or complicated infection antibiotic may be chosen according to urine culture and antibiotic sensitivity test.

Changing urine pH is indicated with anatomic abnormalities especially when the sensitivity test shows garamycin as the best choice. Alkaline urine is needed for garamycin, sulfonamide, streptomycin. Acidic urine is needed for tetracycline and mandelamine.

Relapse of infection (same organism) or reinfection (different organism) is usually due to wrong choice of antibiotic, inadequate dose or duration of treatment, female sex and anatomic abnormality. This could be managed through a proper vulval hygiene, long antibiotic suppressive therapy (after full course of antibiotic give a daily evening dose for 3-6 months) and correcting any anatomic abnormality.

CHRONIC PYELONEPHRITIS

Is believed to be the result of chronic or repeated renal bacterial infection. Often at presentation proof of the bacterial etiology is unavailable.

Pathology:

Gross Appearance: Affected kidney is decreased in size with irregular outline (due to underlying scars) (Fig. 9.1a).

Microscopy: A nonspecific appearance is similar to any type of chronic interstitial nephritis. There is irregular, patchy, cortical infiltration with inflammatory cells, tubular atrophy and interstitial fibrosis (Fig. 9.1b). Vascular changes of hypertension may be evident (thickening of the wall with duplication of internal elastic lamina and narrowing of arterial lumen).

Clinical presentation:

1. History of recurrent episodes of urinary tract infection.

2. Hypertension.
3. Insidious onset of renal failure.
4. Sometimes patient may be asymptomatic with non-nephrotic proteinuria.

Investigations:

1. **Urine culture:** should be repeated 3-4 times. A positive culture is obtained only in 30% of cases.
2. **Ultrasound and IVP:** may show asymmetry in kidney size and distortion of calyx.
3. **GFR:** may be reduced, increase in 24-hour proteinuria and manifestations of distal tubular dysfunction (e.g. renal tubular acidosis, inability to concentrate urine).
4. **Renal biopsy:** is **not** indicated.

Treatment:

1. Antimicrobial therapy: according to culture and sensitivity testing and a long suppressive regimen is indicated.
2. Surgical treatment for anatomic abnormality or stone disease.
3. Treatment of hypertension.
4. If the patient presents with chronic renal failure, treatment will be provided as will be described in section on chronic renal failure.

URINARY TUBERCULOSIS

Definition:

Urinary tuberculosis is a chronic granulomatous infection caused by mycobacterium tuberculosis.

Incidence:

age:

- It occurs in older age in the developed countries, while it occurs in younger age in developing countries.
- The disease is more common in developing countries
e.g.: in USA the incidence is 14/100000 while in Third World the incidence is 400/100000

Genitourinary tuberculosis:

- accounts for 14% of non pulmonary tuberculosis.
- occurs in 15-20% of patients with pulmonary tuberculosis.
- is uncommon in children

Epidemiology:

- The incidence of tuberculosis is decreasing nowadays in developed countries due to improved environmental sanitation and improved individual resistance.
- The basic methods for control of this disease include mass immunization with BCG vaccine, case finding and treatment as well as education.

BCG vaccine:

- Is an attenuated strain of mycobacterium tuberculosis
- Its value is to prevent infection and limit mycobacterial multiplication
- It is given as soon as possible after birth in developing countries but in the developed countries it is given for the older children (11-12 years) with negative tuberculin test.

Drawbacks of BCG vaccine:

- It gives protection for 15 years only.
- It cannot to be given to the infected groups.
- It may be followed by lymphadenitis, lupus vulgaris and BCGitis.

Routes of urinary tuberculous infection:

- a) Blood borne : For kidneys and prostate
- b) Ascending infection : From prostate to urinary bladder
- c) Descending infection : From kidney to ureter to bladder to prostate

d) Direct infection : From epididymis to testis.

1- The tuberculous kidney

- The organism settles in blood vessels close to the glomeruli leading to inflammatory granulomatous reaction with central Langhan's giant cell surrounded by lymphocytes and fibroblasts (tubercle)
- The fate of the tubercle depends on the dose of organisms, its virulence and the host resistance, it may either :
 - a) stop,
 - b) progress, or
 - c) regress.
- With its progression the tubercles coalesce with central area of caseous necrosis which then ulcerate into the pelvicalyceal system and the papillae that leads to the spread of infection to the ureter and bladder.
- With regression or healing, fibrosis of the lesion is followed by calcification leading to stenosis of the calyces and pelviureteric junction leading to abscess formation or hydronephrosis.

N.B.: (i) In duplex kidney; the disease is confined to the infected moiety.

(ii) Renal calcification occurs in 20-60% of cases precipitated by recumbency, hypercalciuria, Recurrent urinary tract infection obstructive uropathy and high calcium intake.

- Renal calcifications never disappear.
- Large calcific areas or non functioning kidneys with intensive calcification should be removed.

(iii) Hypertension and renal tuberculosis:

- hypertension increases by 2 folds due to relative ischemia
- If the tuberculous kidney will be removed, then 2/3 of cases will improve.

2- The Tuberculous Ureter

- The ureter is affected by descending infection from the kidney.
- The commonest site to be affected is the ureterovesical junction with the resultant stricture and hydronephrosis.
- The middle 1/3 of the ureter is rarely affected.
- Fibrosis of the ureterovesical junction will be followed by shortening of the intramural ureter which gives the cystoscopic appearance of golf-hole orifice leading to reflux nephropathy.
- Tuberculous ureter is demarcated from bilharzial ureter by the following:

Bilharzial ureter

Tuberculous ureter

- | | |
|-----------------------|-------------------------|
| - common | - rare |
| - Dilated ureter | - not dilated |
| - mural calcification | - lumenal calcification |

3- Urinary bladder Tuberculosis

- Urinary bladder affection is secondary to renal tuberculosis.
- Infected material leads to vesical irritability (red, inflamed and angry mucosa) and granulomas with tubercle formation around the ureteric orifice.
- The tubercles then coalesce and ulcerate (mucosal surface is irregular, raised and undermined).
- With severe cases, the muscle layer is involved leading to contracted bladder with the resultant v-u reflux and very rarely fistula to the rectum may be found.

4- Prostate and seminal vesicles tuberculosis

- Infection is transmitted via hematogenous or direct spread.
- On PR examination they are hard, nodular and rarely tender or enlarged.
- Extensive involvement will lead to cavitation and perianal fistula or tissue destruction and decreased semen volume.

N.B.: Transmission by sexual contact is rare.

5- Tuberculosis of the Epididymis and testis

- Infection is transmitted via hematogenous spread or may be a descending infection
- Clinically, there is a painful inflamed scrotal swelling with discharging sinus.
- Sometimes, it is difficult to diagnose (no bacilluria)

N.B.: After 2-3 weeks of antibiotics therapy for acute epididymo-orchitis has no response and is followed by antituberculous treatment for another 2-3 weeks has also no response, then exploration is mandatory for possibility of malignancy.

Clinical picture of genitourinary tuberculosis:

Tuberculosis should be considered in the presence of:

- 1- Chronic cystitis non responding to adequate treatment.
- 2- Sterile pyuria
- 3- Gross and microscopic hematuria
- 4- Non tender and enlarged epididymis with beaded thick vas
- 5- Chronic scrotal sinus
- 6- Nodular prostate and thick seminal vesicle in young males.

Symptoms:

- 1- Asymptomatic
- 2- Constitutional symptoms: malaise, night fever and sweating and weight loss
- 3- Symptoms related to kidney and ureter:
 - May be asymptomatic
 - Loin dull aching pain
 - Renal colic (due to blood clot, caseous material or stone)
 - Painless mass (rare).
- 4- Symptoms related to the urinary bladder
 - Cystitis (burning micturition, frequency, nocturia)
 - Hematuria (gross in 10%- microscopic in 50%)
 - Suprapubic pain (due to bladder ulcers)
 - Recurrent E. Coli cystitis.
- 5- Others:
 - Painless scrotal swelling or sinus
 - Haemospermia
 - Incidental discovery after TURP
 - Swollen painful inguinal lymph node in a tuberculous female may direct the attention to husband tuberculosis.

Investigations:***Laboratory:***

- 1- Urine:** - Persistent pyuria with sterile culture (secondary infection occurs in 15-20%)
 - Collection of 3-5 consecutive early morning urine for examination by ZN staining for detection of the acid fast bacilli (positive in 60% of cases).
 - Urine culture for tuberculosis
 - Animal inoculation.
- 2- Blood:**
 - Complete blood picture, ESR, BUN, creatinine, electrolytes and calcium.
 - Repeating ESR after 1 month to detect the response to treatment.
- 3- Tuberculin test:**
 - Is a good negative test.

Radiological investigations:

- 1- Plain X-ray for the abdomen usually shows:
 - Increased soft tissue shadow in one kidney
 - Obliterated renal and psoas shadow (abscess)
 - Punctate calcification (60%)
 - Stones
 - Ureteric calcification casting the ureter
 - Large prostatic calculi
- 2- Intravenous urography (IVU)
 - Moth-eaten appearance of ulcerated calyces.
 - Obliterated calyces
 - Dilated calyces with narrow neck
 - Abscess cavity connected to calyces
 - Ureteric stricture
 - Straightening and shortening of the ureter
 - Non functioning kidney (autonephrectomy)
 - Small contracted bladder
- 3- Retrograde study: rarely indicated.
- 4- Antegrade pyelography:
 - Visualizes the non functioning kidney
 - Determines the condition above obstruction
 - Aspiration of the renal pelvis contents.
 - May inoculate chemotherapy into the cavity.
- 5- Arteriography:
 - Of limited value.
- 6- Radioisotope scanning:
 - May assess the response to the treatment.
- 7- Ultrasound:
 - Of limited value
 - May assess the size of the cavity
 - May show contracted bladder
- 8- CT:
 - can discover the incidental presence of tumour.

Cystoscopy

- May show ulcers or contracted bladder
- Ascending cystography: diagnose reflux
- Help to obtain clean urine sample for culture.
- Mucosal biopsy: Is contraindicated if acute tuberculous cystitis is suspected or tuberculous affection is close to ureteric orifices

Treatment Of Genitourinary Tuberculosis

Aim of the therapy:

- Treating active disease
- Making the patient non infectious as soon as possible
- Preservation of the maximum amount of renal tissue

Classification of antituberculous drugs:

1- Primary: Rifampicin-isoniazid-pyrazinamide, streptomycin (*bactericidal*)

2- Secondary: Ethambutol, ethionamide, cycloserine (*bacteriostatic*)

3- Minor: Kanamycin, thioacetazone (*bacteriostatic*)

Isoniazid (INH):

- Interferes with nucleic acid metabolism
- 70% excreted by kidneys
- Penetrates caseous material and enters macrophages
- Main side effects:
 - Neurotoxicity (lessened by pyridoxine)
 - Hepatotoxicity, lupus like disease or haemolysis with G6PD deficiency

Rifampicin:

- Interferes with bacterial RNA synthesis
- Enters the macrophages
- Its urinary excretion leads to red urine
- Should be given before breakfast
- Main side effects:
 - Hepatotoxicity
 - Gastrointestinal
 - Hypersensitivity
 - May precipitates adrenal crisis (enzyme inducer that increases the metabolism of endogenous steroids).

Pyrazinamide:

- Is a derivative of nicotinamide
- Active against TB bacilli especially in acidic media
- Excreted in urine
- Main side effects:
 - Hepatotoxicity
 - Precipitates gout (decreases urate secretion)
 - Gastrointestinal

Ethambutol:

- 80% excreted unchanged in urine within 24 hours.
- Main side effects:
 - Ocular toxicity
 - Precipitates gout
 - Idiosyncrasy

Different drug Regimens

6- month regimen:

Rifampicin	600mg/day	}	2month
INH	300mg/day		
Pyrazinamide	1gm/day		

Followed by

Rifampicin	900mg/day	}	3 times/week for 4 month
INH	600mg/day		

4 -month Regimen:

Pyrazinamide	25 mg/kg/day (maximum 2gm)	}	2 month
INH	300mg/day		
Rifampicin	450 gm/day		

Followed by

INH	600 mg thrice weekly	}	for further 2 month
Rifampicin	900 gm/day		

Rationale of short antituberculous course in urinary TB

- Fewer organisms in genitourinary TB.
- High concentration of INH, Rifampicin, pyrazinamide and streptomycin in urine
- INH and Rifampicin pass freely into the renal cavities in high concentration.

Some precautions for drug usage:

- All the drugs should be administered in one dose, if they are to be divided, they may achieve subtherapeutic levels.
- It is advised to take all drugs prior to bed times.
- Streptomycin adds nothing to the other three drugs in the initial phase, but it is advantageous in extensive disease with severe bladder symptoms; because it has a high concentration in urine.

Patients in whom short course therapy are unsuitable:

1- Kidney transplantation patients

- Kidney transplant recipients should be given anti-TB drugs for 1 year or longer because immunosuppressive drugs may reactivate TB.
- There is a possibility of reactivation of pulmonary and extrapulmonary foci with immunosuppressive treatment.
- Rarely TB infections are acquired directly from the infected allograft from a donor with occult genitourinary TB.
- Chemoprophylaxis by INH for 1 year to patients with old tuberculosis may be indicated.
- Rifampicin, pyrazinamide, INH and ethambutol enhance the cyclosporine catabolism and decrease its level. They also enhance steroid metabolism

2- Tuberculosis in dialysis patients:

- Incidence: 10 folds higher than the general population.
- There are frequently:
 - Extrapulmonary manifestations or dissemination
 - Negative tuberculin
 - Atypical presentation: Ascites, intermittent fever, hepatomegaly and weight loss.
- Higher mortality
- The diagnosis in extrapulmonary cases is achieved by demonstrating caseous granulomas on pleural or hepatic biopsy.
- Streptomycin and pyrazinamide are dialyzable.

3- Bilateral renal tuberculosis

Follow up of patients after starting antituberculous treatment

- By investigating the patients 3, 6 and 12 months after the course of chemotherapy by examining 3 consecutive morning samples at each visit and by I.V.U.
- If the urine showed the organism, repeat the full dose of antituberculous therapy.

Use of steroids in genitourinary tuberculosis

- May be useful in acute cystitis
- No evidence that steroids influence the sterilizing activity of regimens that include INH, rifampicin and pyrazinamide.
- Prednisolone at least 20 mg tid for 2 weeks with the 4 antituberculous drugs. This helps to alleviate bladder symptoms and allows an earlier appraisal of subsequent treatment.
- The need for this high steroid dose is due to the fact that rifampicin reduces the effectiveness and the bioavailability of prednisolone by 66%.

Topical drugs

- 5% rifampicin + 1% INH + 10ml lidocaine 1% + 100 ml Saline:
 - To relieve bladder symptoms
 - In closed abscess cavity after drainage
- Cream for discharging sinus

Some situations

- Rifampicin and oral contraceptive pills:

Rifampicin decreases oestrogen level so females should be advised to use another method for 3-4 weeks after stopping rifampicin.
- Antituberculous drugs with pregnancy:

Rifampicin may cause foetal limb defects; so, rifampicin should be used thrice weekly rather than daily in the first trimester.
- Antituberculous drugs in lactating mothers:
 - Rifampicin has no harm
 - INH causes neurotoxicity; so pyridoxine is given to both the mother and her baby.
 - Ethambutol reaches the milk very little and baby ocular toxicity is negligible.
- Antituberculous drugs in patients with renal impairment:

The following table shows the different anti-TB drugs, route of elimination and dose adjustment with decreasing GFR and the need of supplemental dose after dialysis.

Drug	Route of elimination	Dose in Normal GFR	GFR 80-50 ml/min	GFR 50-10 ml/min	GFR <10 ml/min	need of post dialysis supplement
1- Streptomycin	Renal	1gm/24h	1gm/48h	1gm/72h	1gm/96h	Yes
2- INH	Hepatic & renal	300mg/24h	The same	300mg/48h	300mg/72h	Yes
3- Rifampicin	Hepatic	450-600mg /24h	The same	The same	450-600mg /48h	No
4- Pyrazinamide	Hepatic	25mg/kg/24h	The same	The same	25mg/kg/48h	Yes
5- Ethambutol	Renal	25mg/kg/24h	The same	25 mg/kg /48h	25mg/kg/72h	Yes

- Surgical treatment:

- Excision of diseased tissues:

Nephrectomy, nephroureterectomy, partial nephrectomy, prostatectomy.

- Reconstructive surgery:

- stricture ureter

- Augmented cystoplasty in cases with

- Increased frequency
- Urgency & hematuria
- Small bladder by IVU
- Creatinine clearance >15 ml/minute

- Augmented cystoplasty is not to be done in case of enuresis or incontinence

- Diversion: incontinence and intolerable symptoms.

Genitourinary Tuberculosis in Children:

- Uncommon below 10 years

- Clinically:

- Some children have other forms of tuberculous lesions.

- Others: - frequency, occasional hematuria

- painful epididymal swelling

- sterile pyuria

- Anti tuberculous therapy should be given according to the weight and age.

Drug resistance:

Definition: Temporary or permanent capacity of tuberculous bacilli or their progeny to remain viable or multiply in the presence of the

Disadvantages:

- Needs experience and equipments
 - Liable to contamination
- 2- Radiometric detection method e.g. Bactec 460 system
 - 3- High performance liquid chromatography
 - 4- Mycobacteriophage typing
 - 5- Genetic probe technology
 - 6- Ligase chain reaction (LCR)
 - 7- Restriction fragment length pleomorphism RFLP
 - 8- New genotyping approach (SSCP-DNS)

(B) Immunochemical:

- 1- ELISA
- 2- Adenosine deaminase activity (ADA)
- 3- Tuberculostearic acid

(C) Drug stimulating lymphocytic transformation rate.

Suggested Readings:

- Friedman AL: Etiology, pathophysiology, diagnosis, and management of chronic renal failure in children. *Curr Opin Pediatr*, 8 : 2, 148-51, 1996.
- Ehara T, et al.: Immune complex mediated tubulo-interstitial nephritis. *Ryoikibetsu Sjukohun Shirizu*, 16 Pt 1, 284-6, 1997.
- Bailey RR, et al: Vesicoureteric reflux and nephropathy: the Christchurch contribution. *N Z Med*, 110 : 1048, 266-9, 1997.
- Shigematsu H: Reflux nephropathy in vesico-ureteral reflux (VUR). *Ryoikibetsu Shokogu Shirizu*, 16 Pt 1, 275-7, 1997.
- Schwarz A, et al: Nephrotoxicity of antiinfective drugs. *Int J Clin Pharmacol Ther*, 36 : 164-7, 1998.
- Siegert CE, et al.: Immunology in medical practice. IV. Mechanisms in the development of primary nephropathies. *Ned Tijdschr Geneesk*, 142: 14, 759-67, 1998.

CYSTIC RENAL DISEASES

Renal cyst is an isolated segment of the nephron which is dilated to a diameter of 200 μm or more. Cystic kidney is a kidney containing 3 or more cysts.

Classification of Renal Cystic Disorders

- I. Polycystic kidney disease.
 - Autosomal dominant polycystic kidney disease.
 - Autosomal recessive polycystic kidney disease.
- II. Renal Medullary cysts.
 - Medullary cystic disease
 - Medullary sponge kidney
 - Juvenile Nephronophthisis
- III. Acquired renal cystic disease
- IV. Renal cyst in hereditary syndrome
 - Tuberous sclerosis
 - Von Hippel-Lindau disease
 - Others
- V. Simple renal cyst
 - Single
 - Multiple

Pathogenesis:

The pathogenesis of cyst formation is unknown. There are four major hypotheses:

1. Increased compliance of the tubular basement membrane which is due to biochemical defect (genetic or acquired) in the basement membrane leading to its cystic dilatation.
2. Intraluminal obstruction by epithelial hyperplasia and micropolyps formation.
3. Abnormal epithelial cell growth and production of excessive basement membrane.
4. Altered secretion: Reversal of direction of net water and solute movement with influx instead of efflux from affected nephrons, creating cysts.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

It is one of the most common genetic disorders and is responsible for approximately 10% of patients with end stage renal failure. It affects 1:400-1:1000 of people all over the world.

Genetics

The disease is transmitted by autosomal dominant inheritance. So, 50% of offsprings inherit the abnormal gene. The gene has been recently discovered to be on the short arm of chromosome 16 (called PKD-1 type). This finding can help in early diagnosis of the disease before any clinical manifestations even in utero. In approximately 5-10% of cases, the gene is not on chromosome 16 (called PKD-2 type). Cases of PKD-2 show milder disease with delayed renal failure.

Clinical Features

A. Renal Manifestations

- Less than 5% of nephrons are involved in cyst formation. Clinically, most patients will have no detectable cyst at birth. Several small cysts will appear in childhood, and during adulthood, the cysts grow and kidney may be as large as 40 cm in length and over 8 kg in weight.
- By the age of 50, nearly 30% of patients, will develop end stage renal failure and by the age of 73 the figure becomes nearly 50%. The bad signs for the development of renal failure are PKD-1 gene, fetal onset of the disease, male gender, hypertension and large kidney. Hypertension will manifest before the development of renal failure in 60% of cases. Also, the inability to concentrate urine (polyuria and nocturia) and metabolic acidosis will appear earlier. Episodic dull aching abdominal pain which is due to cyst enlargement and persistent abdominal fullness by large kidneys are other common complaints.
- Patients with ADPKD tend to be less anaemic with maintained erythropoietin secretion, more hypertensive with high renin secretion.
- Renal complications include:
 - (a) Increased incidence of renal adenoma, and renal cell carcinoma.
 - (b) Haematuria which may be gross or microscopic in 50% of cases secondary to cyst rupture into the pelvis, infection, nephrolithiasis or owing to malignancy.
 - (c) Infection which may be difficult to treat if involving the cysts.
 - (d) Nephrolithiasis.
 - (f) Non-nephrotic range proteinuria in 30% of cases.

B. Extra-Renal Manifestations

1. Cardiovascular involvement.

With ADPKD, there is a higher incidence of mitral valve prolapse (30% while it is only 6% among normal population). In addition to aortic and

tricuspid valve incompetence and left ventricular hypertrophy that are most probably secondary to hypertension.

2. **Gastrointestinal involvement**

Hepatic cysts are the commonest extrarenal manifestations of ADPKD as they occur in 40% of cases. The incidence is higher in female and older patients. They may reach up to few centimeters in size, usually asymptomatic, but sometimes may cause dull aching abdominal pain, may get infected, or (rarely) may cause portal hypertension. Other gastrointestinal manifestations include diverticulosis (may be complicated by diverticulitis, abscess formation or perforation), pancreatic and splenic cysts and inguinal hernias.

3. **Neurological involvement**

Intracranial aneurysm occurs in 10% of cases. It is more common in some families than others. It may rupture leading to subarachnoid haemorrhage.

Pathology.

The two kidneys are massively enlarged (Fig. 10.1), in 80% of cases, the enlargement is symmetrical. Cross section will show hundreds of cysts occupying the cortex and medulla and compressing the normal renal tissue in between.



(Fig. 10.1)

Kidney of a patient with ADPKD, the renal tissue is replaced by large cysts.

Diagnosis:

1. By detecting renal cysts by US or CT scanning. Absence of cysts during the first 3 decades of life does not exclude the existence of the disease; since cysts sometimes appear later.
2. Gene linkage analysis for the detection of responsible gene on chromosome 16. This test entails the presence of at least two family members with clinically evident disease to be used as a reference for the affected gene morphology. This test can diagnose the disease even prenatally. It is only indicated in potential related kidney donor who has no clinically evident disease. Also in any patient with hypertension who is a member of ADPKD family with history of cerebral hemorrhage (i.e. having intracranial aneurysm), this is important for the early diagnosis and management of aneurysm.

Management:

1. Abdominal and flank pain which is due to enlarging cyst is managed by non-narcotic analgesics, rarely percutaneous cyst rupture may be indicated for persistent severe pain.
2. Hypertension should be treated aggressively to prevent progression of the kidney damage and to guard against aneurysm rupture in cases of families with a history of cerebral haemorrhage.
3. Restriction of dietary protein to slow progression of kidney damage.
4. Avoidance of urological instrumentation to prevent urinary tract infection. If infection occurred, give proper antibiotics, especially those which could penetrate into the renal cysts (trimethoprim-sulphamethoxazole, chloramphenicol, and fluoroquinolone drugs as norfloxacin and ciprofloxacin). If cyst infection occurred, drainage may be required.
5. Screening for intracranial aneurysm is indicated in cases with hypertension and positive family history for cerebral haemorrhage. CT scan or MRI should be done. If positive, angiography is indicated and elective surgical repair should be done if aneurysm is accessible and greater than 8-10 mm in size.

**AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY
DISEASE (ARPKD)**

It is a disease characterized with cystic dilatation of renal collecting ducts with variable degrees of hepatic fibrosis. It is an autosomal recessive disease affecting male and female equally. The overall incidence is 1 : 10000 to 1 : 40000 of population.

Pathology:

1. Both kidneys are enlarged with pinpoint cysts corresponding to the ends of dilated cortical collecting tubules are visible on the capsular surface.
2. Liver will show variable degrees of increase in a number of biliary ducts and portal fibrosis. In severe cases, portal hypertension complicated by splenomegaly and oesophageal varices will be seen.
3. Infrequently, small pancreatic cysts are present.

Clinical presentation

The disease appears almost in infancy, but may manifest earlier (in utero or at birth) or later during childhood.

The manifestations are usually renal masses, renal tubular dysfunction, progressive uraemia or portal hypertension.

Diagnosis

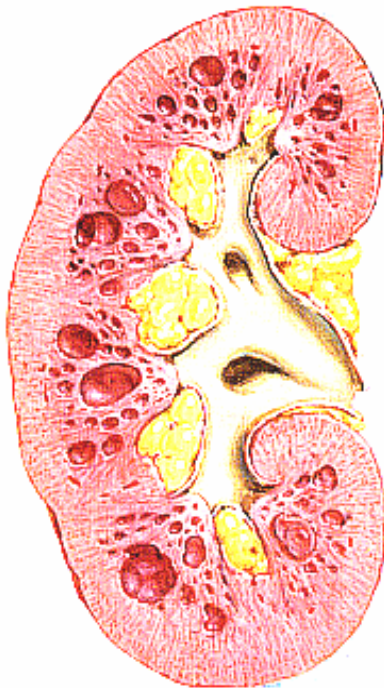
It is mainly diagnosis by renal ultrasonography.

Treatment

1. Treatment of intercurrent renal, hepatic and pulmonary infection.
2. Treatment of RTA by oral NaHCO₃.
3. Treatment of hypertension.
4. When renal failure develops, supportive treatment and renal replacement therapy should be provided.

MEDULLARY CYSTIC KIDNEY DISEASE (MCKD)

Rare autosomal recessive disorder are most often seen in children or adolescents. There is a cystic dilatation of distal and collecting tubules with cysts involving medulla and cortico-medullary junction (Fig. 10.2a), progressive interstitial fibrosis, tubular atrophy and secondary glomerulosclerosis. The kidneys are bilaterally shrunken. The patient presents with manifestations of tubular dysfunction, mainly salt losing and loss of ability to concentrate urine. The condition inevitably progresses to end stage renal failure.



(Fig. 10.2a)

Cross section of a kidney with medullary cystic disease.

(Reproduced with permission from Novartis-Switzerland)

JUVENILE NEPHRONOPHTHISIS

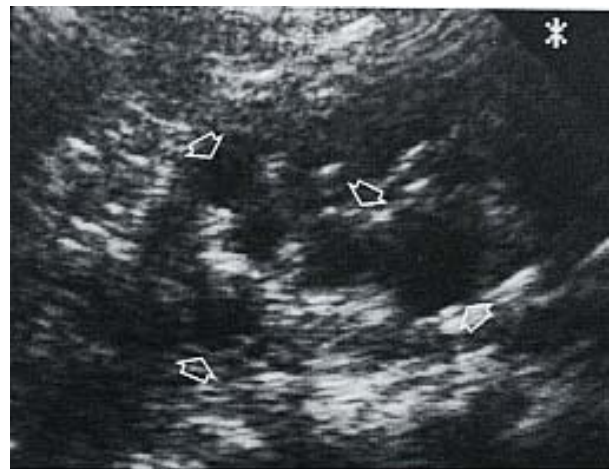
It is a similar condition to MCKD. The only exception is that it is inherited as autosomal dominant and manifests clinically in later age.

MEDULLARY SPONGE KIDNEY (MSK)

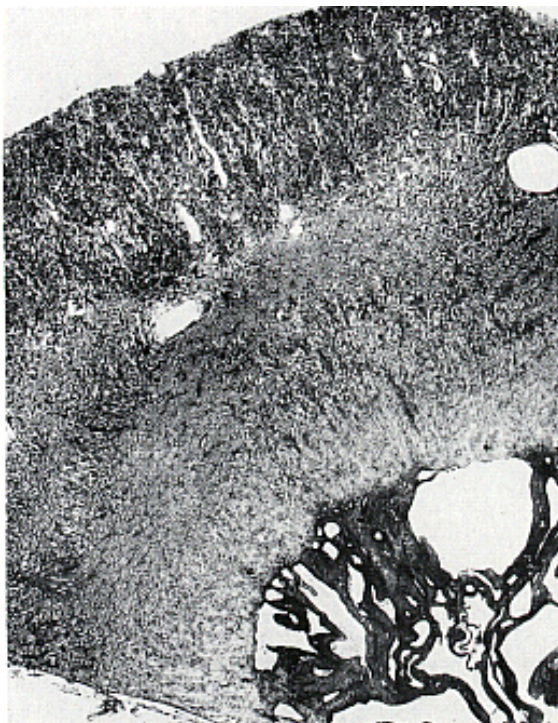
There is a developmental defect leading to dilatation of collecting ducts in the medulla and papillae (Fig. 10.3). There is no familial, racial or sexual preponderance. It affects 1/5000 of general population. The disease is bilateral in 70% of cases.



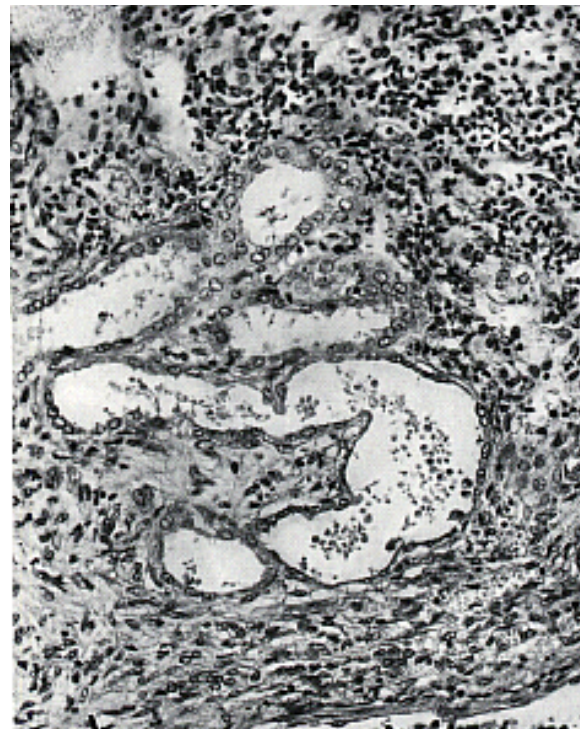
IVU- medullary sponge kidney demonstrating diffuse cyst formation and papillary enlargement.



Medullary cystic disease. Ultrasound demonstrating medullary cysts.



Papillary sponge kidney associated with nephrolithiasis. Renal cortex and outer medulla are normal. Masses of densely packed cysts are present in papilla. HE (X6)



Cystic kidney with acute interstitial nephritis. Tubular epithelium is flattened. A large cyst is seen filled with phagocytes and lymphocytes. Stroma evidences fibroblastic proliferation. HE (X 110)

Fig. (10.3)
Pathologic and Radiologic appearance of medullary sponge kidney

Clinical features

1. Usually asymptomatic, unless complications occur.
2. Manifestations of distal tubular disorders mainly inability to concentrate urine (polyuria) and distal RTA.
3. Stone formation with recurrent colics, infection and haematuria.
4. Ultrasonography and plain X-Ray may show an enlargement of one or both kidneys and variable numbers of radioopaque calculi. I.V.P may show radial or linear structures in papillae or cystic collection of contrast material in ectatic collecting ducts.

Treatment

1. Treatment of complications if existed (infection, stone, RTA).
2. Prognosis is excellent.
3. Urine analysis for diagnosis of infection and stone formation is required.

ACQUIRED RENAL CYSTIC DISEASE (ARCD)

It is a disease characterized with development of renal cysts in patient with other progressive renal disease without history of hereditary cystic disease. This is usually described in patients under maintenance dialysis treatment.

Pathogenesis

It is unknown and is most probably caused by uraemic toxins causing dysplastic changes in tubular epithelium followed by hyperplasia and adenoma formation with lumen obstruction and cyst formation. After longer time some cases will show carcinoma formation. In support of this hypothesis is the cyst involution seen in patients after successful transplantation and recurrence after failure of the renal transplant.

Clinical manifestations

1. 50-90% of patients under dialysis for more than 5 years will be affected. Males are more affected, also, blacks are more liable than whites.
2. The disease may be discovered incidentally by US or CT scan imaging.
3. Gross haematuria, flank or abdominal pain, palpable mass, fever (infection) or even manifestations of malignancy may be found.
4. 5% of patients dialyzed more than 10 years may develop renal cell carcinoma which are bilateral and multifocal.
5. Early, cysts will appear in small sized kidneys, but later the kidney becomes enlarged making it difficult to be distinguished from ADPKD.

Management

1. Patients under dialysis treatment for more than 3 years should be screened annually by CT scanning. If tumour develops, nephrectomy should be done.
2. After transplantation, cysts will regress quickly but not adenoma or carcinoma.

TUBEROUS SCLEROSIS

It is an autosomal dominant disease characterized with:

1. Mental retardation and seizures.
2. Adenoma sebaceum in the butterfly area.
3. Renal angiomyolipomas and multiple cysts. Hypertension, renal impairment and renal cell carcinoma can occur.

VON HIPPEL-LINDAU SYNDROME

This is an autosomal dominant disease characterized with:

1. Intracranial haemangioblastomas.
2. Multiple systemic angiomas (especially retinal).
3. Renal cysts, haemangiomas and renal cell carcinoma.
4. High incidence of pheochromocytoma.

SIMPLE RENAL CYSTS

It is the most common cystic abnormality encountered in the human kidney. About 30% of patients over the age of 40 may show simple renal cyst which may be solitary or multiple, unilateral or bilateral, 0.5-4 cm in diameter.

It is usually discovered by chance during routine ultrasonography. Less commonly it may present with mass, infection, haematuria after trauma or even less frequently malignant transformation.

Suggested Readings:

- Popovic Rolovic M, et al: Cystic kidney disease-genetics, pathogenesis and clinical aspects in children. *Srp Arh Gelok, Lek*, 124 Suppl 1: 222-8, 1996.
- Schneider MC: Advances in polycystic kidney disease. *Mol Med Today*, 2 : 2, 70-5, 1996.
- Choyke PL: Inherited cystic diseases of the kidney. *Radiol Clin North Am.*, 34 : 5, 925-46, 1996.
- Levine E: Acquired cystic kidney disease. *Radiol Clin North Am*, 34 : 5, 947-64, 1996.
- Sessa, et al: Autosomal dominant polycystic kidney disease: clinical and genetic aspects. *J Nephrol*, 10 : 6, 295-310, 1997.
- Griffin MD, et al: Cystic kidney diseases. *Curr Opin Nephrol Hypertens*, 6 : 3, 276-83, 1997.

RENAL STONE DISEASES

Renal stone disease is a frequent illness. In the West, it is estimated that approximately 12% of males and 5% of females will have an episode of renal colic during their lifetime. In countries with hot weather as in Egypt higher incidence is expected especially in the presence of other predisposing factors as bilharziasis.

Type of Stones:

Stones could be classified according to their radiologic and structural features into:

1. Radio opaque stones.
 - Calcium oxalate which represents 60% of renal calculi.
 - Calcium apatite or phosphates which represents 20% of renal calculi.
2. Radiolucent stones:
 - Uric acid stones (7%)
 - Magnesium ammonium phosphate (struvit or infection) stones (7%).
These are caused by infection with urea-splitting organisms, particularly proteus and pseudomonas. These produce ammonium and hydroxyl ions which raise urine pH.
 - Cystine stones (3%)

Pathogenesis of renal stones:

Always there are several factors playing together for stone formation:

1. **Supersaturation of urine by salt** (e.g. calcium oxalate).
Substances as calcium, urate, cystine, xanthine and dihydroxyadenine will be of high concentration in urine because of concentrated urine and/or increased urinary excretion of such substances (owing to increased intake, intestinal absorption or genetic metabolic abnormality).
2. **Increased urinary acidity:**
Persistently low urine pH will result in stone formation particularly calcium oxalate and uric acid stones. The increase in acidity occurs in some conditions as in gout, chronic diarrhoea, ileal resection, gastrectomy and ulcerative colitis.
3. **Loss of inhibitors of crystallization:**
Citrate excretion is reduced in acidosis. Deficiency of glycosaminoglycans (which could be familial), pyrophosphate, magnesium and some polypeptides promotes crystallization.

Specific factors contributing in stone formation:

1. Hypercalciuria

- Defined as 24 hours urinary excretion of calcium by more than 300 mg (7.5 mmol) or more than 0.1 mmol/kg/d.
- This could be due to hypercalcaemia or could be with normal serum calcium (idiopathic hypercalciuria).
- Idiopathic hypercalciuria may be (a) absorptive hypercalciuria because of the inherited abnormality of excess absorption of calcium by the jejunum; (b) renal hypercalcuria as a result of renal tubular defect in calcium reabsorption.

2. Hyperuricosuria

- May be endogenous over production as in (a) marrow overactivity secondary to myeloproliferative disorders, leukaemia or other neoplasms; or (b) Lesch-Nyhan Syndrome in which there is severe deficiency of hypoxanthine-guanine phosphoribosyl-transferase.
- Dietary factors, food as meat, yeast products, and ethanol.
- Hyperexcretion of urate may occur with normal or low serum urate due to tubular disease, uricosuric drugs, or after discontinuation of diuretic treatment.

3. Hypocitraturia

Citrate is an inhibitor of crystallization of calcium oxalate and phosphate. It lowers free calcium ion concentration in urine. Normal value for urinary citrate excretion is > 1.7 mmol/d in male, higher values are secreted in females which may explain lower incidences of renal stones in them. Urinary citrate excretion may be decreased in RTA and with chronic diarrhea.

4. Hyperoxaluria

It may be primary hyperoxaluria which is a rare inherited metabolic disease or secondary to increased colonic absorption which occurs in small bowel diseases, malabsorption or after jejunio-ileal bypass.

5. Cystinuria

There is an abnormal intestinal mucosal and renal tubular transport of the di-basic amino acids resulting in excessive urinary secretion of cystine. Normally, with usual urine pH, approximately 300 mg (1.25 mmol) of cystine are soluble in one litre. Homozygous cystinurics (1 per 10,000 of population) may excrete three times more.

6. Xanthinuria

It is a very rare metabolic disorder characterized with gross deficiency of xanthine oxidase resulting in hypouricaemia and high urinary xanthine and hypoxanthine excretion with xanthine calculi.

7. Inflammatory bowel diseases

These are ulcerative colitis, Crohn's disease and ileal resection which may result in concentrated urine with low pH, hypocitraturia, hyperoxaluria. Acidic urine may promote uric acid and calcium oxalate stones.

Clinical Manifestations of Renal Calculi:

Renal colic is the commonest presentation. Other manifestations include incidental discovery (during routine X-ray), or may present by complications (e.g. urinary tract obstruction, hematuria, or infection).

Investigations:

Not all investigations are indicated for every patient with renal stone. The more recurrent and aggressive the stone disease, the more the investigations needed.

The investigations include:

1. Blood tests:

Serum creatinine (for kidney function), HCO_3^- (for diagnosis of metabolic acidosis and RTA), uric acid (for hyperuricaemia) and serum calcium (for hypercalcaemia). In cases of hypercalcaemia, Vitamin D and parathormone (PTH) levels should be determined.

2. Renal ultrasonography and pyelography:

For detection of renal stones, back pressure changes, infection, kidney size, parenchymal echogenicity, kidney function (secretion of contrast media) and for diagnosis of medullary sponge kidney.

3. Urine microscopy

For diagnosis of infection, haematuria. The presence of calcium oxalate or uric acid crystals is of doubtful value since it could be detected in normal subjects.

4. Urine analysis for pH, 24 hours calcium, uric acid and cystine excretion.

5. Stone analysis to identify its nature. It may help in the treatment of stone formers.

Medical Treatment:

1. High fluid intake to achieve a urine volume of at least 2 liters per 24 hours.
2. Dietary modification: Reduction of sodium, calcium, protein and oxalate:
 - Sodium restriction to 100 mmol/d since excess sodium intake results in excess excretion in urine which inevitably increases calcium urinary excretion.
 - Calcium should be restricted to 1 gm/d to decrease urinary calcium excretion.
 - Protein restriction is adopted because high protein diet increases urine acidity, uric acid and calcium excretion; and decreases citrate excretion.
 - Oxalate should be restricted to decrease urinary oxalate. Oxalate rich food as spinach, strawberry, rhubarb, tea, chocolate and Vitamin C.
3. Potassium citrate increases urinary citrate, decreases urinary calcium and increase urine pH.
4. Treatment of hypercalciuria: Thiazide diuretic will treat renal hypercalciuria (hydrochlorothiazide 50 mg twice daily). If this is proved ineffective cellulose phosphate will treat the absorptive hypercalciuria.
5. Allopurinol: which may be given in a dose of 300 mg/d plus alkalinization of urine and restriction of dietary protein in patients with uric acid stones. Allopurinol has been proven effective in the syndrome of hyperuricosuric calcium nephrolithiasis through prevention of formation of uric acid nidus for calcium oxalate stone.
6. Cystine calculi could be treated by high fluid intake, alkalinization of urine to pH 7-7.5 and diet low in methionine and cystine. Penicillamine 1.5 g/d may decrease urinary cystine but with high side effects (allergic reactions affecting kidney, skin and bone marrow).

Suggested Readings:

- Jaeger O: Genetic versus environmental factors in renal stone disease. *Cur Opin Nephrol Hypertens* 5 : 4, 342-6, 1996.
- Lingeman JE: Lithotripsy and surgery. *Semin Nephrol*, 16 : 5, 487-98, 1996.
- Pak CY: Southwestern Internal Medicine Conference: medical management of nephrolithiasis-a new simplified approach for general practice. *Am J Med Sci*, 313 : 4, 215-9, 1997.
- Stroom SB: Contemporary clinical practice of shock wave lithotripsy: a reevaluation of contraindications. *J Urol*, 157 : 4, 1197-203, 1997.
- Goldfarb DS: Renal stone disease in older adults. *Clin Geriatr Med*, 14 : 2, 367-81, 1998.
- Wasserstein AG: Nephrolithiasis: acute management and prevention. *Dis Mon*, 44 : 5, 196-213, 1998.
- Baggio B, et al: Pathogenesis of idiopathic calcium nephrolithiasis: update 1997. *Crit Rev Clin Lab Sci*, 35 : 2, 153-87, 1998.
- Dussol B, et al: Urinary kidney stone inhibitors. What is the news? *Urol Int*, 60 : 2, 69-73, 1998.

WATER AND ELECTROLYTE DISTURBANCES

The water and solute (electrolyte) content in different body fluid compartments (intra & extracellular) gives its physiologic effect through changes in fluid osmolality. For example, water loss with stable solutes (electrolytes) content will result in hyperosmolality (hypertonicity) and the reverse will lead to hypoosmolality (hypotonicity). Tonicity governs the movement of water across the cell membrane; so discussing osmolality will be a more precise way for direct expression of the changes in body water and electrolytes.

I. DISORDERS OF PLASMA OSMOLALITY

Osmolality is the force created by the presence of solutes in the medium pulling water from low solute to high solute concentration compartment. The higher the difference in solute concentrations, the higher the osmolality and the more the force pulling water.

Osmolality of body fluid is vital for survival and is affected by the amount of body salt and water contents. Kidney and thirst mechanisms through adjustment of solute excretion (by the kidney) or water intake (by thirst center) or water and solute excretion and reabsorption (kidney, ADH) will control body osmolality.

Osmolality is expressed as mosmol/litre plasma but-if expressed as mosmol/kg plasma-it is called osmolarity. So, the term osmolality is more precise to express solute status in body fluids.

The major solute affecting body osmolality is sodium. Higher concentration of sodium (hypernatraemia) will result in hyperosmolality and lower sodium concentration (Hyponatremia) will result in hypoosmolality. Also excess water will dilute the salt content (dilutional hyponatremia) and will result in hypoosmolality. On the other hand, water loss will lead to solute concentration (hypernatraemia) and will result in hyperosmolality.

Actually the clinical manifestations of hyper-and hyponatremia result from the concomitant hyper-and hypoosmolality.

The main solute keeping the extracellular compartment osmolality is sodium; and the main solute keeping the intracellular osmolality is potassium. The balance between water content in the intracellular and extracellular compartments depends mainly on sodium concentration in body fluids. Other

solutes which could affect plasma osmolality are serum glucose, blood urea, plasma proteins and others. Blood urea is ineffective osmol since it passes freely between intra and extra cellular compartments. So, any increase in its concentration will be equal both intra-and extracellularly and will not affect the water content in these compartments. Meanwhile sodium is effective osmol since it will not move intracellularly. So, with hypernatraemia extracellular osmolality will increase and water will move from cells to the extracellular compartment causing cellular dehydration. The reverse will occur in hyponatremia which will result in cellular overhydration (oedema).

Glucose is effective extracellular osmol; therefore, hyperglycemia will result in intracellular dehydration.

The amount of total body water (TBW) equals 60% of body weight in male and 50% of body weight in female. Sixty percent of TBW is intracellular while 40% is extracellular. The extracellular water is distributed between intravascular (20%) and interstitial (80%) compartments. The water is kept intravascularly by the oncotic force of the plasma proteins.

So, in 60 kg b.wt. male the TBW will be : $\frac{60 \text{ kg} \times 60}{100} = 36,00$ litres

The intracellular water will be: $\frac{36,00 \times 60}{100} = 21,60$ litres

The extracellular water will be: $\frac{36,00 \times 40}{100} = 14,40$ litre

and the intravascular water will be: $\frac{14,40 \times 20}{100} = 2,88$ litres

The osmolality of a solute = $\frac{\text{its amount in mg}}{\text{its molecular weight}}$. So, one mg of sodium in a solution is more osmolar than one mg of glucose.

Plasma osmolality is measured by osmometer which depends on the change in freezing point of plasma water caused by its solute contents. Normal osmolality is 270-290 osmol/L. Also, it can be calculated by the following equation:

$$\text{Plasma osmolality} = 2 \times \text{Na}^+ + \frac{\text{Glucose(mg)}}{18} + \frac{\text{BUN(mg)}}{2.8}$$

$$\text{Effective plasma osmolality} = 2 \times \text{Na} + \frac{\text{Glucose}}{18}$$

- Loss of isotonic fluid e.g. diarrhea will not affect plasma osmolality, but if associated with fever (water loss through sweating) and acidosis (causing hyperventilation and water loss), it will lead to hypernatraemia and hyperviscosity. Water should be a part of the treatment of this case to achieve osmotic balance. Then isotonic saline is given to correct the primary (through diarrhea) defect. If the patient is suffering from diarrhea only, he/she should be treated by isotonic saline. Otherwise, the patient will be hypovolaemic but still with normal osmolality. But hypovolaemia will stimulate thirst center. Still, if the patient drinks water to correct his hypovolemia the result will be dilutional hyponatraemia and consequent hypoosmolality.
- With the change in plasma osmolality, water will move between intracellular and extracellular compartments to induce osmotic equilibrium between the two compartments and a steady state is reached. An example of this is loss of water through hyperventilation and sweating in acidotic febrile patient. This will result in hypernatraemia and hyperosmolality of plasma. Water will move from intra to extracellular compartment until equilibrium is reached. Another example is water retention in patient with syndrome of inappropriate secretion of antidiuretic hormone (SIADH). This will result in dilutional hyponatraemia and hypoosmolality. In this condition water will move from extra to intracellular compartment with cellular oedema till osmotic equilibrium is reached.
- In cases of hypo-or hypernatraemia our management is directed to treatment of hypo-or hyperosmolality. For example, in cases of hyperglycaemia, hyperosmolality will occur, water will move from intracellular to interstitial and vascular compartments. This will dilute plasma sodium and dilutional hyponatraemia will occur (for every 100 mg/dl increase in plasma glucose, sodium will decrease by 1.6 mmol/L). Here, the management is not directed to the hyponatraemia, but to the hyperosmolality caused by hyperglycemia.

Regulation of Plasma Osmolality:

1. Osmoreceptors present in the hypothalamus are sensitive to even minor changes (1%) in plasma osmolality. When stimulated, they will trigger the secretion of ADH from the posterior pituitary which will act on the distal nephron, and stimulate thirst center triggering water intake. Both will control body water.

2. Volume receptors are mainly in the right atrium. So they control urinary sodium excretion. With the increase in extracellular fluid volume, kidney will increase urinary sodium excretion while with hypovolaemic states, urinary sodium will decrease and it will be retained in the body. The mechanisms of handling sodium by the kidney were previously explained.
3. Volume receptor mechanisms are more potent than the osmoreceptor mechanisms. So urinary sodium excretion is affected more by the changes in fluid volume status than by the changes in plasma osmolality or plasma sodium concentration.
In SIADH where there is dilutional hyponatraemia and hypoosmolality state, while the fluid volume is increased due to water retention; urinary sodium excretion will be high ($UNa > 20 \text{ mmol/L}$). But when there is hyponatraemia with hypovolaemia (e.g. long use of diuretics), urinary sodium will be low ($UNa < 10 \text{ mmol/L}$).

II. DISTURBANCES IN PLASMA SODIUM CONCENTRATION

Sodium is the major cation (Na^+) contributing to plasma osmolality. Disturbances in plasma sodium concentration in most instances is due to the change in body water. Increase in body water will result in hyponatraemia and the decrease in body water will result in hypernatraemia.

Hyponatraemia

Definition: Hyponatraemia is a state where plasma sodium concentration is less than 135 mmol/L .

Causes: Hyponatraemia is the commonest electrolyte abnormality in hospitalized patients. Usually this is dilutional hyponatraemia due to defective renal water excretion as a result of excess secretion or potentiation of ADH. The complete list of causes of hyponatraemia classified according to changes in total body water include:

1. **Hypovolaemic Hyponatraemic states:**
 - Diuretic therapy.
 - Mineralocorticoid deficit (Addison's disease).
 - Salt-losing nephropathy (analgesic nephropathy, chronic tubulointerstitial nephritis, incomplete urinary tract obstruction, after recovery from acute tubular necrosis and after release of urinary obstruction).

- Gastrointestinal losses (diarrhea or vomiting).
- Fluid loss in third space (peritonitis, ileus, burn or crush injury).
In these conditions volume receptors are stimulated with secretion of ADH which will then stimulate water reabsorption from the distal nephron. This process will continue even with development of hyponatraemia and hypoosmolality owing to the fact that volume receptors are more potent than the osmoreceptors.

2. **Hypervolaemic (oedematous) Hyponatraemic states:**

- Liver cirrhosis
- Congestive heart failure.
- Nephrotic syndrome
- Renal failure with water overload.

In these conditions, although total body water is increased, the effective circulating blood volume is decreased as the excess fluid is extravascular and is interstitial. The decreased effective circulating volume results in excessive stimulation and secretion of ADH with more water retention.

3. **Euvolaemic (Normal volume) Hyponatraemic States:**

- Hormonal (Myxoedema, glucocorticoid deficiency or exogenous ADH vasopressin).
- Massive water load (psychogenic polydipsia, parenteral fluid or excessive water absorption during bladder irrigation at transurethral prostatectomy).
- Syndrome of inappropriate secretion of ADH (SIADH):
 - Drugs stimulating ADH secretion:
Nicotine, Chlorpropamide (also increases renal sensitivity to ADH), Clofibrate, Vincristine, Carbamazepine (Tegretol) or Cyclophosphamide
 - Carcinomas (secretion of ADH-like substances).
Lung (oat-cell), Pancreas, duodenum or bladder
 - Pulmonary disease (secretion of ADH-like substances)
T.B., Pneumonia or abscess
 - Neurological diseases (excess ADH secretion)
Encephalitis, Cerebral trauma, Guillian-Barré Syndrome, Acute psychosis.
 - Postoperative
(post commissurotomy or pain)
 - Idiopathic

- **Essential hyponatraemia:** Occurs mostly with chronic illness, under nutrition or with T.B. There is a resetting of the osmostat (in the hypothalamus) for lower level of osmolality and consequently lower plasma sodium concentration.

Pseudohyponatraemia: Plasma osmolality is measured by osmometer which depends on measuring the freezing point of plasma water (i.e. it is affected by number of solutes dissolved in plasma water and not affected by other compounds non-dissolvable as lipids, plasma proteins and glycine used in bladder irrigation during TURP). So, in hyperlipidaemia and hyperproteinaemia the plasma sample separated by centrifugation of blood will contain a part of its volume as lipid or protein but plasma osmolality will not be affected whatever the changes in concentration of lipid or proteins.

On the opposite side, measurements of plasma sodium is referred to as total plasma volume. So, in cases of hyperlipidaemia or hyperproteinaemia, although plasma water sodium is normal (but since a large amount of plasma volume is not water i.e lipid, protein or glycine) the reading of plasma sodium will appear low (pseudohyponatraemia). In this type of hyponatraemia, plasma osmolality will be normal. Pseudohyponatraemia should be differentiated from other conditions as hyperglycaemia, hypertonic mannitol infusion, methanol or ethanol intoxication in which these substances will dissolve in plasma water and will increase its osmolality with a consequent retention of body water to normalize plasma osmolality resulting in dilutional hyponatraemia. (These conditions are sometimes wrongly included to the list of causes of pseudohyponatraemia).

Osmolal Gap: It is the difference between measured and calculated plasma osmolality which is usually less than 10 mosmol/L.

In cases of pseudohyponatraemia, osmolal gap will be > 10 mosmol/L.

Clinical Features of Hyponatraemia:

- Manifestations of hyponatraemia depend greatly on the rate of its development. A very slowly progressive hyponatraemia can be

asymptomatic while acutely developing hyponatraemia could be very serious.

- With hyponatraemia, plasma will be hypotonic while cells (especially brain cells) will be hypertonic. To achieve osmotic equilibrium, water will move from plasma to cells with a consequent cell oedema (brain oedema).
- Plasma sodium concentrations above 120 mmol/L are usually well tolerated, while the majority of patients will have severe cerebral dysfunction once plasma sodium is below 110 mmol/L (lethargy, anorexia, nausea, vomiting, confusion, disorientation, convulsions, coma and even permanent brain damage).

Diagnosis of the cause of hyponatraemia:

Proper history, assessment of body hydration status (dehydrated, overloaded or normal) as well as the measurement of urinary sodium and blood pH will help in identifying the cause of hyponatraemia.

A. Urinary Sodium (UNa)

- UNa < 10 mmol/L
 - Gastrointestinal loss, third space, oedema state, long use of diuretics.
- UNa > 20 mmol/L
 - With decreased effective circulating volume (dehydration): osmotic diuretics, early diuretic effect, adrenal insufficiency, salt losing nephropathy.
 - With increased effective circulating volume (oedema): SIADH, psychogenic polydipsia, renal failure, hypothyroidism.

B. Blood pH

- Hyponatraemia with normal pH:
SIADH, psychogenic polydipsia, hypothyroidism
- Hyponatraemia with metabolic alkalosis:
vomiting, gastric suction, loop diuretics
- Hyponatraemia with metabolic acidosis:
Diarrhoea, intestinal fistula, renal failure and adrenal insufficiency.

Treatment of Hyponatraemia:

- In severe hyponatraemia, rapid correction with hypertonic saline is contraindicated as it may lead to fatal central pontine myelinolysis. It is wise to increase plasma sodium by only 5-10 mmol/Litre per 24 hours. This is achieved through the administration of loop-diuretic and normal

saline and in severe cases, small amounts (100-200 ml) of hypertonic (double strength i.e. 300 mmol/L) saline may be infused.

- Correction of the underlying cause, in the overloaded patient water restriction can be combined with loop-diuretics as furosemide and sometimes salt supplements.
- In SIADH, lithium or demeclocycline may be given to induce a renal concentration defect.

Hypernatraemia

Hypernatraemia is considered when plasma sodium is more than 145 mmol/litre.

Causes:

Hypernatraemia is usually a consequence of water depletion and to much lesser extent- is due to excess sodium intake. In normal situations water loss (renal or non-renal) or excess sodium intake will induce hyperosmolar state with stimulation of osmoreceptors which will lead to thirst (water intake) and secretion of ADH (water reabsorption from the distal nephron). Water gain will correct the hyperosmolar state and hypernatraemia will not persist. Hypernatraemia persists only when either water intake is not possible (unconscious, very young or very old patient unable to ask for water or absent water supply) or when there is a lesion affecting thirst center in the hypothalamus (tumour) or abnormal osmoreceptors (essential hypernatraemia).

A- Renal causes of water loss:

1. Osmotic diuresis

- Enteral (through a nasogastric tube) or parenteral (intravenous hyperalimentation) feeding, usually hypertonic constituents are used.
- Hyperglycaemia

2. Nephrogenic diabetes insipidus (NDI) which results in renal tubular concentration defect. This could be due to:

- a. Toxin e.g. drug (lithium, amphotericin, demeclocycline) or Bence-Jones protein.
- b. Renal tubular disease as in post obstructive diuresis, recovering ATN, PCKD, chronic tubulointerstitial nephritis, medullary cystic disease and congenital NDI.

3. Pituitary ADH deficiency (CDI) which is due to either trauma, neoplasm, vincristine or idiopathic (50%).

B- Non-renal causes of water loss: gastrointestinal loss.

C- Sodium intake in excess of water.

Clinical features:

- 1- Manifestations of the etiologic cause.
- 2- Polyuria, polydipsia, nocturia and functional dilatation of the bladder and ureters, this is seen in patients with D.I.
- 3- Hypernatraemia occurs only if there is lesion in osmostat (hypothalamic lesion) or patients unable to drink, it manifests as muscle twitches, lethargy, weakness, seizures or even coma and death.

With hypernatraemia, there is a shrinkage of brain cells and a decrease in brain size which if severe it may lead to rupture of blood vessels with focal intracerebral or subarachnoid hemorrhage. If the patient survived, brain cells will adapt and regain size.

Treatment:

- 1- Acute hypernatraemia could be corrected quickly but chronic hypernatraemia must be corrected slowly to prevent cerebral oedema (decrease plasma sodium by about 2 mmol/litre/hour). Usually the hypernatraemic patient is hypovolaemic, we can calculate the water deficit by the equation:

$$\text{Water deficit (litre)} = \frac{\text{Plasma Na}}{140} - 1 \times (0.6 \times \text{body weight})$$

For example, a patient of 60 kg with plasma sodium 160 mmol/L, his water deficit is 5.1 litre.

The water deficit could be given orally as water or intravenous as 5% dextrose in water. If there is Na⁺ loss as well give D 5%/1/2 saline (glucose 5% in half tonic saline) is given.

Rarely the hypernatraemic patient is hypervolaemic, in this situation we have to give furosemide (lasix) and compensate urine loss with either oral water or D 5% I.V.

- 2- Treatment of the etiologic cause as DDAVP intranasally for CDI.

III. DISTURBANCES IN PLASMA POTASSIUM CONCENTRATION

Most of body K^+ is intracellular. The intracellular K^+ is about 150 mmol/litre, while plasma K^+ is only 3.5-5.5 mmol/litre. The capacity of the kidney to excrete K^+ load is large but relatively slow (> 30 min). The shift between intra- and extracellular compartments is quick and fast.

Hyperkalaemia

It is plasma K^+ concentration which is more than 5.5 mmol/litre.

Causes of hyperkalaemia:

These could be summarized as the following:

A- Increased Potassium Intake

- Dietary excess (Banana, citrus fruits...)
- Intravenous load with K^+ containing fluids
- Drugs containing K^+ e.g. potassium penicillin
- Salt substitutes containing KCL rather than NaCL

B- Shift of Intracellular K^+ to extracellular Compartment

- Acidosis
- Cell damage (cancer chemotherapy, crush injury, incompatible blood transfusion).
- Muscle disease
- Convulsions, myositis, periodic paralysis, suxamethonium anaesthesia.

C- Decreased excretion of K^+ by the kidneys

- Renal failure
- mineralocorticoid deficiency
- drug interference as ACEI, cyclosporine, NSAIDS, Tacrolimus and K^+ sparing diuretics.

D- Factitious:

Haemolysis of blood sample, severe leucocytosis or thrombocytosis.

As a result of the strong defence mechanisms against hyperkalaemia, usually more than one factor is present for hyperkalaemia to occur. In practice, usually there is impaired renal excretion combined with other factor as drug intake e.g. ACEI.

Normal K^+ homeostasis involves about 100 mmol/day oral intake and about 10 mmol/d faecal output and about 90 mmol/day being excreted by the kidney. Hyperkalaemia usually occurs only when renal failure is severe (GFR < 10 ml/min) or when a defect in tubular excretion is present, as in salt-depletion, mineralocorticoid deficiency, drug interference or renal tubular disease.

Hyporeninaemic hypoaldosteronism is a common cause of hyperkalaemia in diabetics. This is seen usually in elderly diabetic with mild renal impairment, hyperkalaemia is mild ($K = 5.5-6.5$), the condition is aggravated by hyperglycaemia and/or salt depletion.

Clinical features of hyperkalaemia:

These are due to the effect of hyperkalaemia on cell membrane excitability especially those of the heart and the neuromuscular junctions. The toxic effect of K^+ depends on the rate of development and severity of hyperkalaemia. In patients with chronic renal failure, since the development is usually very slow, there will be a cell membrane adaptation and toxicity to occur needs relatively very high level in comparison with that occurring with acute renal failure.

The manifestations include tingling, numbness, circumoral paraesthesia, muscle weakness with loss of tendon reflexes. The more serious, which can even be the first to appear, is the cardiac toxicity.

ECG tracing in hyperkalaemic patient may show:

- Tall T waves
- Prolongation of the PR interval
- Finally cardiac arrest in diastole
- Widening of the QRS complex

Treatment:

It includes the following:

A- Immediate correction (Emergency) of hyperkalaemia

- 50 ml of I.V. 50% glucose + 20 units soluble insulin every 30 min.
 - B – adrenergic agonists (e.g. salbutamol)
 - Correct acidosis with I.V. $NaHCO_3$ 8.4%(25 – 100ml)
- } Shift K^+ into cells

- Calcium gluconate slow I.V. (5ml of 10% solution)
- } Physiologic antagonist of K^+ on cardiac cell membrane

B- Increase renal excretion of K⁺

Diuresis with saline and furosemide

C- Potassium exchange resin

- Sodium phase e.g. Resonium A, kayexalate
- Calcium phase e.g. sorbosterit
- 25-100 g orally or by enema.
- They will increase faecal K⁺.

D- Dialysis:

Preferably K⁺ low Dialysate haemodialysis for patients with renal failure.

The condition is considered medical emergency if ECG abnormalities are present.

Beside the above therapeutic approaches, we must not forget treating the etiologic cause, restrict K⁺ containing food and drugs.

Hypokalaemia

It is a condition of plasma potassium which is less than 3.5 mmol/litre.

Causes:

Causes of hypokalaemia are numerous. The more common are due to renal or gastrointestinal loss. Less commonly it is due to deficient intake or redistribution between intra and extracellular compartments. The list of causes includes the following:

A- Renal K⁺ loss

1- Causes associated with alkalosis

- Diuretic therapy (the commonest)
- Primary mineralocorticoid excess (Conn's Syndrome)
- Secondary aldosteronism (e.g. renal artery stenosis)
- Glucocorticoid excess (Cushing's syndrome)
- Barter syndrome

2- Causes associated with acidosis

- Diabetic ketoacidosis during recovery phase.
- RTA
- Ureterosigmoidostomy
- Acetazolamide therapy

3- Causes associated with polyuria

- Recovery phase of ATN or post-obstructive ARF

- Tubulotoxicity as cisplatin, amphotericin
- Diabetic hyperglycaemia

B- Gastrointestinal loss

- 1- Prolonged or severe diarrhoea
- 2- Laxative abuse
- 3- Prolonged vomiting
- 4- Ileus with massive intestinal dilatation.

C- Redistribution of K⁺ into cells

- 1- Metabolic alkalosis
- 2- Periodic muscle paralysis
- 3- Beta-adrenergic agonists e.g. salbutamol
- 4- Insulin.

D- Inadequate K⁺ intake

Intravenous fluid without K⁺ in patient without oral intake.

Bartter's Syndrome is a rare disease characterized with hypokalaemic alkalosis, hyperreninaemic hyperaldosteronism, high urinary prostaglandin E and prostacyclin concentration and normal blood pressure. Kidney biopsy will show hypertrophied juxtaglomerular apparatus.

In the non renal causes of hypokalaemia when the kidney is intact, it can decrease urinary K⁺ to < 20 mmol/day:

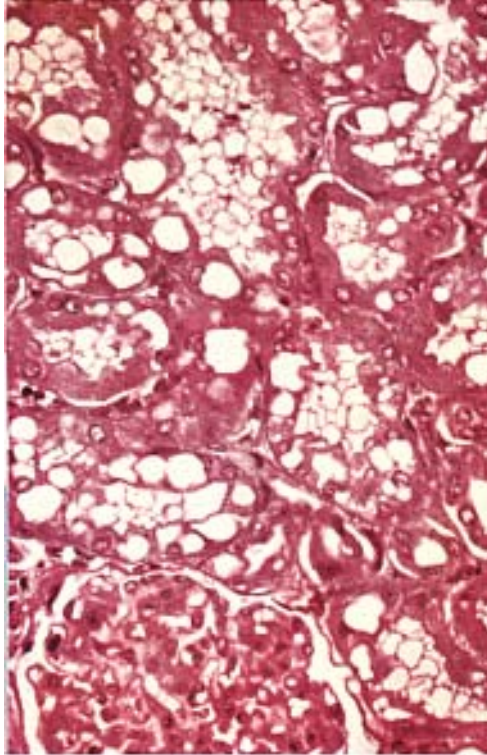
Clinical features:

Usually appear when plasma K⁺ is less than 2.5 mmol/L

- 1- Muscle weakness especially proximal muscles. Tendon reflexes are depressed. In severe cases, muscle necrosis may occur.
- 2- Gastrointestinal hypomotility up to paralytic ileus may occur with further K⁺ loss into dilated intestinal loops.
- 3- In chronic hypokalaemia, renal tubular damage with chronic tubulointerstitial nephritis may occur (Fig. 12.1).
- 4- With severe hypokalaemia fatal cardiac arrhythmia may cause death.

ECG will show the following:

- Depressed T waves and S-T segments
- Appearance of U waves
- Widening of the QRS
- Finally, ventricular ectopics and fibrillation may occur.



(Fig. 12.1)
Extensive vacuolization of renal tubules in hypokalemic nephropathy (H. and E. Stain, X 250).

Treatment:

- 1- Treatment of the etiology
- 2- Potassium supplement either oral or parenteral according to the severity of hypokalaemia. As a rule, we have not to give KCL intravenous more than 10 mmol/hour.

IV. Disorders of Plasma Calcium Concentration

Generally, the kidney, the gastrointestinal tract and the skeleton play a key role in body calcium and phosphate homeostasis.

The contribution of the kidney in calcium and phosphate metabolism includes:

- 1- Synthesis of 1,25 dihydroxycholecalciferol
Inactive vitamin D (cholecalciferol) is activated in the liver by hydroxylation to 25, hydroxycholecalciferol, the second step of its activation is in the kidney to be 1, 25, dihydroxycholecalciferol. The active vitamin D promotes the gut calcium absorption and the normal calcification of bone.
- 2- Renal excretion of calcium

85-90% of the filtered Ca^{2+} is reabsorbed by the PCT while the rest is reabsorbed by the DCT, under the influence of PTH, only <2% of filtered calcium is excreted in the urine (equals about 5.5 mmol/day).

3- Renal excretion of phosphate

Urinary excretion of phosphate varies from 5-40 mmol/day. 80-95% of the filtered load is absorbed in PCT (as Ca^{2+} , glucose, aminoacids and low molecular weight proteins). Phosphate is the major buffer for H^+ excretion.

Hypercalcaemia

Is a total plasma Ca^{2+} concentration more than 2.6 mmol/litre (10.5 mg/dl)

Causes of hypercalcaemia

1- Malignancy

- Multiple myeloma.
- Boney metastasis
- Hormonal factors (PTH-like substance) secreted by tumour cells.

2- Hyperparathyroidism

3- Sarcoidosis

4- Bone disease

- Paget's disease
- Aluminium osteodystrophy

5- Calcium or vitamin D related

- Vitamin D intoxication
- Thiazide diuretics
- Milk-alkali syndrome
- Renal failure

6- Endocrine disease

- Thyrotoxicosis
- Addison's disease

7- Hyperproteinaemia

(only non-ionised calcium is raised)

Clinical features

1- Manifestations of the etiologic cause

2- Renal manifestations

- Polyuria and polydipsia resulting of urinary concentration defect
- Stone disease and nephrocalcinosis
- Acute renal failure may occur with severe hypercalcaemia and the associated dehydration owing to polyuria
- Chronic renal failure due to stone disease, nephrocalcinosis and chronic tubulointerstitial nephritis.

3- Gastrointestinal manifestations

- Nausea and vomiting which are central effects of hypercalcaemia. These may aggravate dehydration induced by polyuria
- Peptic ulcer disease
- Pancreatitis

4- Nervous system

Nausea, vomiting, malaise, fatigue, and even psychosis are all central effects of hypercalcaemia.

5- Tissue deposition of calcium may lead to nephrocalcinosis, vascular calcification, pruritus, conjunctival calcification (red-eye) and band keratopathy.

Treatment:

A- Treatment of the etiologic cause

B- Treatment of hypercalcaemia

- 1- Saline diuresis in patients with reasonable kidney function. If there is no response we can enforce diuresis by furosemide and intravenous saline. Loop diuretics in contrary to thiazide diuretics increase urinary calcium excretion.
- 2- Glucocorticoids are effective in all conditions other than hyperparathyroidism. In sarcoidosis and Vit. D intoxication 10 mg prednisolone may be sufficient while in malignancy doses up to 60 mg/d may be required.
- 3- Others:
 - Methramycin is particularly useful in malignancy related hypercalcaemia, a dose of 20-30 ug/kg may induce fall in serum Ca^{2+} within hours and last for few days.
 - Calcitonin 50-100 units S.C.
 - Phosphate oral or intravenous, but carries the risk of metastatic calcification.
 - Diphosphonate will suppresses hypercalcaemia in hyperparathyroidism
- 4- Dialysis in renal failure especially on using low Ca^{2+} dialysate will be very effective in decreasing serum calcium.

Hypocalcaemia

It is plasma calcium concentration less than 2.20 mmol/litre (8.5 mg/dl).

Causes of hypocalcaemia

- 1- Renal failure
- 2- Hypoparathyroidism

(surgical, idiopathic, pseudohypoparathyroidism)

- 3- Vitamin D deficiency
- 4- Hypoalbuminaemia
- 5- Acute pancreatitis

In renal failure, hypocalcaemia is due to the lack of activation of vitamin D and to the hyperphosphataemia which will cause drop of serum calcium. The presence of acidosis will delay the manifestations of hypocalcaemia by increasing serum ionised calcium.

Vitamin D deficiency may be due to decreased intake, decreased exposure to sun light, defective gut absorption or lack of its activation. Hypovitaminosis D is characterized with hypocalcaemia, hypophosphataemia and hyperparathyroidism.

Clinical features of hypocalcaemia

- 1- Manifestations of the etiologic cause.
- 2- Neuromuscular; in acute hypocalcaemia takes the form of tetany, tingling, numbness, parasthesia, even convulsions. While in chronic hypocalcaemia the main features are depression, irritability, intracranial calcification.
- 3- Bone disease as osteomalacia in vitamin D deficiency and renal failure and hyperparathyroid disease in hyperparathyroidism
- 4- Cataract may be seen with chronic hypocalcemia

Treatment:

- 1- Treatment of the cause
- 2- Calcium and vitamin D supplementation

Suggested Readings:

- Ando K, et al: Emergency therapy of acute kidney failure and water-electrolyte imbalance. *Nippon Naika Gakkai Zasshi*, 84 : 11, 1852-7, 1995.
- Vamvakas S, et al: Alcohol abuse: potential role in electrolyte disturbances and kidney diseases. *Clin Nephrol*, 49 : 4, 205-13, 1998.
- Cserhalmi L: Effect of combined captopril-spirolactone therapy of cardiac insufficiency on kidney function and serum electrolyte values. *Orv Hetil*, 139 : 63-6, 1998.

DISORDERS OF ACID-BASE BALANCE

Physiology Of The Acid-Base System:

The bicarbonate (HCO_3^-) and Carbonic acid (H_2CO_3) pair is the major physiologically active buffer system in the extracellular fluids (ECF).

According to the equation ($\text{pH} = \text{PK} + \log \frac{\text{HCO}_3^-}{\text{H}_2\text{CO}_3 \text{ or } \alpha \times \text{PCo}_2}$), the HCO_3^- and PCo_2 are the major determinants of blood pH.

(where pH is the - log of H^+ concentration, K is 6.1 and α is solubility constant of CO_2 which equals 0.03).

When there is influx of acid or alkali into body fluid the *first line* of defence will be the extra cellular buffer system (HCO_3^-) followed by the intracellular buffer system, (proteins and hemoglobin and phosphates). In the condition of excess acid load, i.e. accumulation of H^+ ions in blood, H^+ will combine with plasma HCO_3^- to form H_2CO_3 which dissociates quickly into H_2O and CO_2 which could be removed by lungs through ventilation. But in case of excess alkali load as HCO_3^- , this will be buffered by plasma H^+ to form H_2CO_3 . These reactions occur according to the equation ($\text{CO}_2 + \text{H}_2\text{O} \times \text{H}_2\text{CO}_3 \times \text{HCO}_3^- + \text{H}^+$). Normally H_2CO_3 is present in blood in very low concentrations as it is very unstable.

The *second line* of defense against acid-base disorders is the lung and kidneys. The lung through hyperventilation will wash CO_2 in states of acid load and through hypoventilation will lead to accumulation of CO_2 in states of alkalosis. Retained CO_2 will react with H_2O resulting in generation of H_2CO_3 which will dissociate into H^+ and HCO_3^- . The respiratory defence mechanism is rapid in the contrary to renal defence mechanisms which are slow.

The renal defence mechanisms involve the adjustment of the reabsorption of the filtered HCO_3^- and the secretion of H^+ . In states of acid load, the kidney increases the proximal tubular HCO_3^- reabsorption ($\text{H}^+ + \text{HCO}_3^- \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}_2\text{O} + \text{CO}_2$, and excrete more H^+ through more titratable acids excretion (e.g. phosphates and sulfates through the glomerular filtration) and through increasing the rate of formation of ammonia ($\text{NH}_2 + \text{H}^+ \rightleftharpoons \text{NH}_4^+$ by the renal tubules). The reverse will occur in states of alkali load, i.e. less HCO_3^- reabsorption with bicarbonaturia, less titratable acid excretion and less ammonia formation.

Daily, as a result of the normal metabolic process, there is **1-** a release of 40-60 mmol (1 mmol/kg/d) of H^+ (mainly from protein metabolism) into the extracellular fluids. These hydrogen ions are removed through the lungs and the kidneys after being dealt with by the first line of defense; and **2-** a release of 13,000-15,000 mmol of CO_2 (mainly of carbohydrate source). This is mainly dealt with through the respiratory system.

Plasma pH is normally 7.35-7.45 which represents a H^+ concentration of 36-44 mmol/litre. The normal plasma HCO_3^- concentration is 20 to 30 mmol/litre. The lowest urinary pH is 4.5 units (with severe metabolic acidosis in presence of normal kidneys) and the highest urinary pH is 10 units (with severe metabolic alkalosis).

Metabolic Acidosis

Metabolic acidosis can result from the generation or the ingestion of acid; or from the loss of bicarbonate ions with consequent accumulation of H^+ in the circulation.

This will be compensated for by the increase in ventilation with a consequent drop in the level of CO_2 and HCO_3^- .

The term acidemia is sometimes used when compensatory mechanisms fail to maintain the pH level within the normal range. But in practice, the term acidosis is usually used whether the pH level is within the normal range or lower.

Features of metabolic acidosis:

- Low plasma HCO_3^- concentration (< 20 mmol/litre).
- Low arterial CO_2 concentration (< 40 mmol/litre).
- Low plasma pH (< 7.35)

Causes of metabolic acidosis:

First we have to know about the concept of *anion gap* which is the difference between plasma concentration of Na^+ and the sum of chloride and bicarbonate [$Na^+ - (Cl^- + HCO_3^-) = 6-16$ mmol]. This gap represents substances which combine with Na^+ other than Cl^- and HCO_3^- which are not measured in routine chemistry such as amino acids.

We may classify metabolic acidosis into those with high anion gap [$Na^+ - (Cl^- + HCO_3^-) > 16$ mmol] and those with normal anion gap:

I- Metabolic acidosis with high anion gap:

The high anion gap is due to the addition into the circulation of anionic toxic substances which combine with Na^+ at the expense of chloride and

HCO_3^- . Since these substances are not measured the anion gap will be high.

Causes of metabolic acidosis with high anion gap are:

- Lactic acidosis; the anion toxic substance here is lactate
- Diabetic ketoacidosis with accumulation of acetoacetic acid; B-hydroxybuteric acid
- Intoxication with methyl alcohol; Ethylene glycol, paraldehyde and salicylates.
- Renal failure with accumulation of sulfates; phosphates and phenols.

II- *Metabolic acidosis with normal anion gap* (hyperchloraemic metabolic acidosis).

This could be due to renal, gastrointestinal or other defects.

A. Renal causes of metabolic acidosis with normal Anion gap:

1- Diamox, a diuretic which causes bicarbonate wastage (bicarbonaturia).

2- Renal tubular acidosis (RTA); resulting from either:

- a. Type I, classic (Distal) RTA: In this condition, there is inability to secrete H^+ load.
- b. Type II, proximal RTA: In this condition, the PCT is unable to reabsorb HCO_3^- as there is a set up of HCO_3^- Tm at low level e.g. HCO_3^- Tm of 16 mmol/l, so any HCO_3^- . Above this concentration will be a loss in urine.
- c. Type III RTA: There is both inability to secrete H^+ load and proximal HCO_3^- wastage.
- d. Type IV RTA: There is hyperkalaemic hyperchloraemic metabolic acidosis with hyporeninaemic hypoaldosteronism. This is usually seen in diabetics with mild renal impairment.

Causes of classic (Distal) RTA:

- Idiopathic
- Hyperthyroidism
- Hyperparathyroidism with nephrocalcinosis
- Hypergammaglobulinaemia (e.g. SLE. Cryoglobulinaemia, T.B., Sjogren's syndrome, Hodgkin lymphoma).
- Medullary sponge kidney
- Liver cirrhosis
- Drugs intoxication as amiloride, vitamin D, amphotericin B
- Chronic kidney graft rejection, chronic pyelonephritis
- Genetic diseases as galactosaemia, Fructose intolerance, Ehlar-Danlos syndrome and Elliptocytosis

Causes of proximal RTA

- Fanconi's syndrome
- Hereditary fructose intolerance
- N.S.
- Graft rejection
- Wilson's disease
- heavy metal poisoning, tetracycline
- multiple myeloma
- Idiopathic

Diagnosis of RTA:

- 1- NaHCO₃ test: Urinary minus blood CO₂ content is less than 10 mmol/l in distal RTA and more than 20 mmol/L proximal RTA.
- 2- Ammonium chloride (NH₃Cl) test: Loading with NH₃Cl till blood HCO₃⁻ is less than 15 mmol/L. In normal persons and in cases with proximal RTA urinary pH is <5.5 while in distal RTA it is > 5.4.
In hepatic patient as NH₃Cl is contraindicated, CaCl₂ could be used instead.
- 3- As a screening test, we can look for the morning urine pH (which is the lowest pH along the 24 hrs) if it is > 6 we may consider Distal RTA.

	Distal (type 1)	Proximal (type 2)
Hypokalemia	Severe	Mild-moderate
Response to K ⁺ therapy	Good	Poor
Bicarbonate Tm	Normal	Decreased
Bicarbonate loss in urine	Small	Large
Serum bicarbonate concentration	May be very low (<16mEq/L)	Usually >16-18 mEq/L
Urine pH when serum HCO ₃ ⁻ :		
> 20 mEq/L	> 5.5	> 5.5
< 15 mEq/L	> 5.5	May be <5.4
Amount of HCO ₃ ⁻ needed to correct acidosis	< 2mEq/kg/day	>5mEq/kg/day
Response to alkali therapy	Good	Poor
Glycosuria	Absent	Often present
Aminoaciduria	Absent	Often present
Hypercalciuria	Often present	Usually absent
Urinary citrate	Low	Normal
Fanconi's syndrome	No	Yes
Nephrocalcinosis	Often present	Rare
Nephrolithiasis	Often present	Absent
Renal insufficiency	Often present	Absent
Bone disease	Often present	Absent

B- Gastrointestinal causes of metabolic acidosis with normal anion gap:

- 1- Diarrhoea; There is loss of K^+ and HCO_3^- , every litre of diarrhoea fluid contains 30-50 mmol of HCO_3^- .
- 2- Fistula or tube drainage: Each litre of the small intestinal fluid contains 60 mmol HCO_3^- while pancreatic fluid contains 120 mmol/litre.
- 3- Ureterosigmoid or ileal loop urine diversion: In these conditions there is loss of mucosal HCO_3^- (normally present in high concentration in intestinal mucous) in exchange with the urinary Cl^- (hyperchloraemia).
- 4- Anion exchange (Cl^- versus HCO_3^-) as with the use of cholestyramine.
- 5- Ingestion of Ca and Mg chlorides.

C- Other causes of metabolic acidosis with normal Anion gap:

- 1- Hyperalimentation using formulas rich in cationic aminoacids and chlorides. This does not occur with formulas containing aminoacids and organic anions.
- 2- Use of Hcl, arginine chloride or lysine chloride
- 3- Dilution with chloride solution.

NB: Causes of Metabolic acidosis with low or even negative anion gap include bromide intoxication and dysproteinaemia.

Treatment of metabolic acidosis:

- 1- Treatment of the cause and compensate for the deficit
- 2- In distal RTA, $NaHCO_3$ should be provided 1-3 mmol/kg/d, sometimes K^+ supplementation is required. In children $NaHCO_3$ will be provided in a dose of 5-15 mmol/kg/d.
- 3- In proximal RTA large amounts of alkali are provided (10-25 mmol/kg/d) and K^+ supplementation.

Respiratory Acidosis

In respiratory acidosis, CO_2 retention occurs and the reaction $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$ results in accumulation of H^+ in circulation and acidosis. The kidney compensates by the secretion of H^+ and reabsorption of HCO_3^- .

In acute respiratory acidosis blood HCO_3^- increases by 1 mmol/L for every 10 mmHg increase in PCO_2 while in chronic respiratory acidosis HCO_3^- increases by 3.5 mmol for every 10 mmHg increase in PCO_2 .

Features of respiratory acidosis:

- high PCO_2

- low pH
- high HCO_3^-
- urine pH is low <5.4

Etiology:

- Severe respiratory disease e.g. obstructive air way disease and severe obesity.
- Central depression of respiratory drive.

Clinical features:

- 1- Manifestations of the cause.
- 2- Confusion, hyperreactivity, headache, tremor, stupor and coma in severe cases.
- 3- Papillaedema and increased CSF pressure due to V.D.
- 4- Pulmonary and splanchnic V.C.

Treatment:

- 1- Treatment of the etiologic cause
- 2- If there is respiratory failure, assisted respiration (ventilator) should be provided.

Metabolic Alkalosis

Because of the high capacity of the kidney to secrete HCO_3^- , metabolic alkalosis can only persist if there is a renal dysfunction with a reduction in HCO_3^- excretion or enhanced renal generation of HCO_3^- .

Features:

- High plasma HCO_3^- (> 30 mmol/litre)
- High plasma pH (pH > 7.45)
- High Pco_2 , for every 1 mmol/litre increase in plasma HCO_3^- there will be a 0.6-0.7 increase in Pco_2 . Hypoxaemia stands as a limiting factor for the respiratory compensation. So, if it exists, we have to give oxygen support.
- Chloride and K^+ are also usually low. K^+ is low as a result of the renal loss and the intracellular shift.

Causes:

A- Renal:

- 1- Adrenocorticoid and adrenocorticoid-like effect (HCO_3^- retention with K^+ and H^+ excretion).
 - Secondary aldosteronism (e.g. cirrhosis)
 - Primary aldosteronism

- Cushing's syndrome
- Bartter's syndrome
- Liquorice ingestion

2- Volume depletion (Cl^- depletion and HCO_3^- reabsorption)

- diuretics • diarrhea
- cirrhosis

B- Gastrointestinal loss of acid:

- Vomiting
- Gastric aspiration

C- Ingestion of alkali:

- NaHCO_3
- Milk-alkali syndrome

Hyperaldosteronism stands as a common mediator in metabolic alkalosis as it lead to enhanced K^+ and H^+ excretion, with sodium and bicarbonate retention (hypokalaemic alkalosis). Diuretic therapy, secondary aldosteronism in cirrhotics and severe vomiting are the common causes of metabolic alkalosis.

Clinical features:

- 1- Manifestations of the cause
- 2- Manifestations of neuromuscular irritability owing to the decreased ionized calcium.

Treatment:

- 1- Of the cause
- 2- Support respiratory and renal compensatory mechanisms.
- 3- If there is renal failure with severe metabolic alkalosis, dialysis may be provided.

Respiratory Alkalosis

Excessive pulmonary wash of CO_2 will result in alkalosis owing to directing the reaction ($\text{H}_2\text{O} + \text{CO}_2 \times \text{H}_2\text{CO}_3 \times \text{H}^+ \text{HCO}_3^-$) to the left with consequent reduction in H^+ .

The renal defence mechanism will include the increase in HCO_3^- secretion and retention of H^+ . This mechanism is relatively slow. It needs 24 hours to be established.

For each 10 mmHg \downarrow in PCO_2 , there is a 2.5 mmol/L \downarrow in plasma HCO_3^- .

Features:

- $\downarrow \text{PCO}_2$
- $\downarrow \text{pH}$
- $\downarrow \text{HCO}_3^-$

Causes of respiratory Alkalosis:

- 1- Iatrogenic in patients under ventilatory support.
- 2- Liver cirrhosis, salicylate intoxication, exercise and hypotension.
- 3- Hyperventilation syndrome in neurotic patients
- 4- Cerebral hypoxia and intracranial disease

Clinical features:

- 1- Manifestations of the cause
- 2- Parasthesia, tinnitus, neuromuscular irritability and/or cerebral vasoconstriction

Treatment:

- 1- Of the cause
- 2- Breathing into a mask (rebreathing of expired air with its high level of CO_2).

Suggested Readings:

- Hanna JD, et al: The kidney in acid-base balance. *Pediatr Clin North Am*, 42 : 6, 1365-95, 1995.
- Hüssinger D: Liver and kidney in acid-base regulation. *Nephrol Dial Transplant*, 10 : 9, 1536, 1995.
- Hayashi M: Disorders of body water regulation and the therapy-acid base equilibrium in the kidney and disorders. *Nippon Naika Gakkai Zasshi*, 86 : 9, 1665-9, 1997.
- Hayashi M: Physiology and pathophysiology of acid-base homeostasis in the kidney. *Inter Med*, 37 : 221-5, 1998.

HYPERTENSION AND THE KIDNEY

The values of systolic and diastolic blood pressures which are accepted as normal are derived from statistical analysis of the values obtained from large population groups.

The level above which blood pressure is considered high (hypertension). Consequently, the patient requires treatment; as this level is associated with risk of morbidity is still debatable.

Most physicians, consider the blood pressure above 140/90 mmHg in patients under the age of 50 years as hypertension thus deserves treatment.

It was believed that diastolic blood pressure was the more important as it represents a more constant stress on the arterial wall. Recently, based on large-scale epidemiological studies it was demonstrated that systolic pressure predicts more accurately the cardiovascular pathologic changes.

Etiology And Classification Of Hypertension:

Hypertension, according to severity and target organ damage (of retina, kidney, heart) could be classified into benign or malignant. Etiologically, hypertension may be classified as essential (primary) or secondary.

Secondary hypertension may be:

1- Renal:

a- Renovascular hypertension:

- Renal artery stenosis
- Polyarteritis nodosa
- Renal artery aneurysm
- Renal artery malformation

b- Renoparenchymal:

- Glomerulonephritis
- Polycystic kidney disease
- Analgesic nephropathy
- Renal tumour as Wilms' tumour
- Other renal parenchymal diseases

2- Endocrinal:

a. Adrenal cortex:

- Cushing's syndrome
- Conn's syndrome

b- Adrenal medulla and splanchnic sympathetic chain:

- Pheochromocytoma

c- Others:

- Acromegaly
- Hyperparathyroidism

3- Iatrogenic:

- Oral contraceptives
- Sympathomimetic amines
(nasal decongestants and bronchodilators)
- Corticosteroids
- Cyclosporine
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Tricyclic antidepressants
- Liquorice
- Pregnancy-associated hypertension
- Acute intermittent porphyria

Essential Hypertension

Pathogenesis Of Essential Hypertension

In normal situation, the blood pressure is controlled via central and renal mechanisms. The central (nervous) mechanism is achieved through the autonomic nervous system which controls the cardiac output and the peripheral vascular resistance.

The renal mechanism depends on handling of sodium and water reabsorption which will control the intravascular volume.

The pathogenesis of essential hypertension is still speculative. There are two major proposed mechanisms. These are the genetically determined; and the behaviorally and dietary determined mechanisms.

The genetically determined mechanisms:

There are many theories which try to explain essential hypertension on genetic basis. Most of these theories come to the conclusions that essential hypertension is due to:

1- Abnormal renal handling of sodium with consequent increased intravascular volume, increased cardiac output and increased tone of peripheral blood vessels (peripheral resistance).

2- Secretion of hormone which causes arteriolar constriction and excretion of retained sodium. This hormone is most probably secreted by the hypothalamus or the adrenal glands. It is Na-K-ATPase inhibitor, probably related to the cardiac glycoside ouabain.

3- Hyperinsulinism with decreased sensitivity of non-oxidative glucose transport. Insulin would raise blood pressure by its action on central nervous system receptors (increasing sympathetic outflow) and on renal tubular receptors (sodium retention). This is consistent with the common finding in hypertensive patients of impaired glucose homeostasis, hypercholesterolaemia and increased coronary artery disease.

4- Abnormalities in atrial natriuretic peptide (ANP), prostaglandins and vascular endothelial factors (Nitric oxide, endothelins).

The Behavioural and Dietary Factors:

These factors will interact strongly with the genetic predisposition to produce hypertension. These factors include obesity, dietary sodium, alcohol and sedentary life.

• Obesity:

There is a strong association between obesity, hypertension and cardiovascular morbidity. This is most probably due to insulin resistance.

• Sedentary life:

Beside contributing to obesity, sedentary low exercise life style appears to be associated with an increased sympathetic outflow; and the increasing exercise has been shown to reduce high blood pressure.

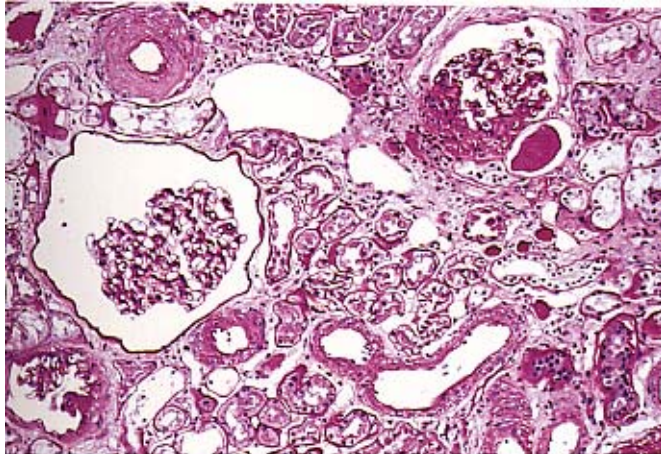
Histopathologic changes with essential hypertension:

1- Changes in blood vessels: These involve all blood vessels with arteriosclerosis, thickening of the wall, duplication of elastic lamina and degeneration of the media. The arterial lumen will be narrow with a consequent ischaemic changes in organs as the brain, the kidney and the heart. Weakness in the media; as a result of the degenerative changes; may result in aneurysm formation; as in cerebral vessels. This may rupture with catastrophic sequelae.

2- Target organ damage:

- The kidney will be affected by the long term hypertension owing to chronic ischaemia. Kidney biopsy will show nephrosclerosis. In early phases there will be wrinkling of the glomerular basement membrane; due to renal ischaemia; and hyaline changes in the afferent arterioles. In the

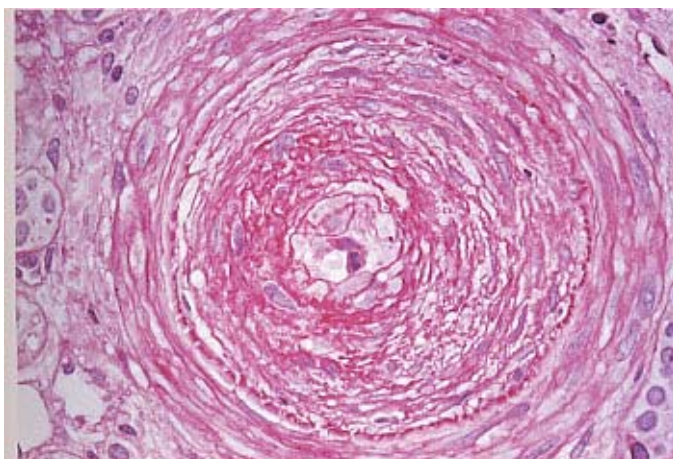
late phases there will be extensive glomerulosclerosis, tubular atrophy and interstitial fibrosis (Fig. 1). In benign hypertension these changes need a longer time (more than 15 years duration) to appear. Black Africans are more liable to these complications.



(Fig. 14.1)
PAS stained kidney section (X 100) of a case of benign nephrosclerosis, it shows sclerosis of glomerular tufts, tubular atrophy and marked thickening of a small artery.

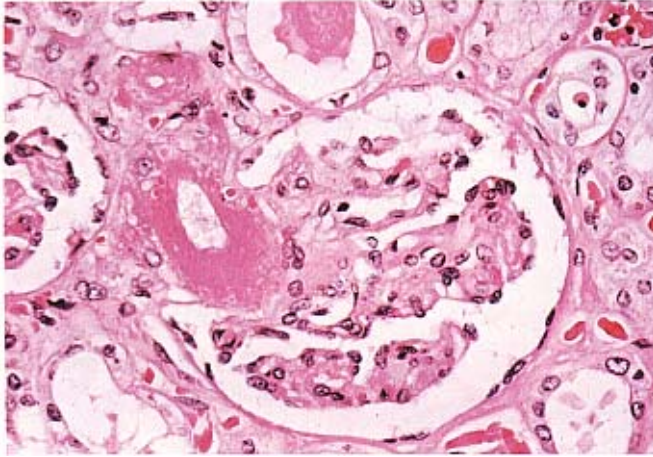
(Reproduced with permission from IGAKU-SHOIN Ltd, Japan)

In malignant hypertension renal changes occur very quickly. There is a marked arteriolar intimal proliferation which is sometimes severe enough to cause occlusion of the arteriolar lumen. Fibrinoid necrosis will affect the arteriolar smooth muscles and adventitia will show fibrosis. The glomeruli will be damaged by the severe ischaemia as a result of the arteriolar occlusion (Fig. 14.2).



(Fig. 14.2a)
PAS stained section (X260) of a case with malignant hypertension, It shows a striking "onion peel" thickening of the intima of a small Artery with marked narrowing of the lumen.

- The brain, myocardium and retina are other organs (Target organs) which are affected by benign and malignant essential hypertension.



(Fig. 14.2b)

Hx&E stained kidney section from a Patient with malignant hypertension (X26), it shows fibrinoid necrosis of an arteriole at the glomerular hilus.

(Reproduced with permission from IGAKU SHOIN Ltd, Japan).

Clinical Manifestations of Essential Hypertension:

- 1- Hypertension may be discovered by chance e.g. during routine medical examination (i.e. asymptomatic).
- 2- Vague constitutional symptoms, especially dizziness, fatigue and morning bilateral occipital headache.
- 3- Manifestations of target organ damage as cerebral stroke, myocardial infarction, left ventricular failure or retinal artery or vein occlusion. Renal wise, hypertension may cause proteinuria or microhematuria; and long standing hypertension may present with chronic renal failure due to nephrosclerosis. Malignant hypertension will present with acute or RPGN.
- 4- Fundus examination will show changes in retinal vessels which resemble those in other organs. These changes are mainly in the form of thickening of the media and narrowing of the arteriolar lumen. Retinal arterioles will show silver wire appearance and at site of arterioles crossing veins will show arteriovenous nipping. In severe forms of hypertension with endothelial damage, permeation of plasma and blood outside the retinal vessels will show exudates and areas of circumscribed hemorrhages, also ischaemic changes in optic nerve appearing as blurring of the disc margins; a picture which could be confused with papilloedema (Fig. 14.3).
- 5- Hyperlipidemia, glucose intolerance, obesity and smoking are more common in hypertensive patients than in general population. These together will significantly magnify the risk of the target organ damage.



(Fig. 14.3)
Appearance of the optic fundus in a patient with malignant hypertension. There are linear of Flame – shaped retinal haemorrhage and **papilloedema**. For clinical diagnosis of malignant hypertension, haemorrhage must be present in both eyes.

Diagnosis of Essential Hypertension:

- 1- As a large proportion of patients are asymptomatic at diagnosis, most of population especially those at risk should be subjected to blood pressure assessment at least once yearly.
- 2- White-coat hypertension (i.e. hypertension occurring only during medical assessment is due to patient's anxiety) should be suspected especially if the patient is asymptomatic with no manifestation of target organs involvement.
- 3- For the diagnosis of labile hypertension or to confirm a mild hypertension or white coat hypertension, we have to frequently measure blood pressure (e.g. 3 times/week), home blood pressure measurement using electronic sphygmomanometer or to do a 24-hour continuous monitoring.
- 4- Diagnosis of Hypertension is considered final with no need for further confirmation in patient with moderate or severe hypertension ($\geq 180/110$), with long standing symptoms, or with the presence of target organs affection e.g. fundus changes or proteinuria.
- 5- Mercury column sphygmomanometer is the standard and electronic devices need to be periodically checked.

The cuff should be comfortably surrounding the arm without being loose or pressing firmly, the tubes should be medial and the air bag should be centered over the brachial vessels with the cubital fossa uncovered for palpation of the brachial pulse. Air is pushed into the bag and the mercury column is raised quickly till brachial artery pulsation is not felt then

pressure is released gradually (2cm/beat). The first sound (phase 1 Korotkoff-sounds) is the systolic blood pressure. This is followed by silence (Phase 2 Korotkoff) which is sometimes called latent period which is responsible for improper measurement if palpation method was not followed. This is followed with reappearance of sound (phase 3 Korotkoff) which can be mistaken as phase 1 Korotkoff if palpation of brachial pulse is not used. This is followed by a sudden decrease in sound intensity (muffling) which is called phase 4 Korotkoff and is considered by some authorities as the diastolic blood pressure in normal persons. In patients with hyperdynamic circulation (Severe anaemia, Aortic regurgite, thyrotoxicosis....) all authorities consider phase 4 Korotkoff as the diastolic blood pressure. Muffling of sound is followed with the disappearance of sound (phase 5 Korotkoff), which is considered as the diastolic blood pressure by some authorities.

On the first time to measure blood pressure for a patient we have to do this for the two arms and the higher one (usually the dominant arm) unless there is anatomic or pathologic abnormalities. It is considered for future assessment of blood pressure for this patient. Blood pressure should be measured in lying and standing positions for the diagnosis of postural hypotension. On standing position, systolic blood pressure fall should not be more than 15 mmHg.

Investigations For Hypertension:

As more than 90% of hypertension is idiopathic, not all hypertensive patients have to be subjected to intensive investigations to identify the etiologic cause. Yet, all the hypertensive patients should be investigated for other risk factors as plasma lipids and glucose tolerance test and serum uric acid.

Indications for the investigations of the etiologic causes of hypertension:

- 1- Absence of family history of hypertension.
- 2- Age below 30 or above 60 years.
- 3- Loss or failure to control blood pressure despite use of combination therapy.
- 4- Presence of symptoms or signs suspecting secondary hypertension as cushingoid features, periodic paralysis, epigastric bruit, symptoms of catecholamine release, episodic hypertension, clinical or laboratory evidence of renal disease as proteinuria.

According to the manifestations associated with hypertension one may plan for investigative priorities. For example paroxysmal hypertension will be an indication for the investigation of pheochromocytoma. In absence of manifestations suggestive of endocrine involvement, one has to start with the investigations for renal etiology being the commonest among the causes of secondary hypertension.

Treatment Of Essential Hypertension:

A- Non-pharmacologic treatment:

It includes weight loss, low salt diet, physical exercise, giving up smoking, reduction of alcohol intake, Yoga and similar biofeedback techniques. This is indicated and may be the only approach required in patients with mild hypertension (BP < 160/105) especially obese and high salt users.

The non-pharmacologic treatment should be kept as a background treatment for those with more severe hypertension.

B- Pharmacologic treatment:

1- Diuretics:

Loop diuretics (Furosemide, bumetanide and ethacrynic acid) which are potent diuretics acting on loop of Henle are not used in the treatment of benign hypertension. They are used only in patients with renal impairment, patients with marked salt and water load and in severe uncontrollable hypertension usually in combination with minoxidil or ACEI.

Thiazides as hydrochlorothiazide are the commonly used diuretics in hypertensive patients. They act on proximal and distal convoluted tubules. They may be used singly (25 mg/d) or in combination with other diuretic (potassium sparing diuretic triamterine or amiloride) or with other hypotensive drug commonly ACEI and B-blockers. The mechanism of the hypotensive action of diuretics is unknown, but mostly through the depletion of body sodium content.

The side effects of thiazide diuretics include:

- Male impotence
- Skin rash
- Thrombocytopenia
- Insulin resistance and hyperglycemia
- Hyperuricaemia
- hypokalaemia
- Hypertriglyceridaemia and decreased high density lipoproteins
- Hypercalcaemia.

2- Vasodilators:

This group includes Hydralazine, minoxidil, diazoxide and sodium nitroprusside.

Hydralazine is mainly used in hypertension with pregnancy. It carries the risk of the development of lupus erythematosus like syndrome especially when large dose is used or in slow acetylators which metabolize the drug very slowly.

Minoxidil is the most potent hypotensive drug. It is administered as last resort when all drugs fail to control blood pressure. The main side effects of minoxidil are oedema, palpitation, hirsutism and pericarditis; so it should be given in combination with B-blocker and diuretic.

Diazoxide is given as intravenous bolus mainly in hypertensive emergencies.

3- Centrally Acting Hypotensives:

These mainly include clonidine (catapress) and α -methyl DOPA (Aldomet). Beside the central action, Aldomet acts also through formation of a false neurotransmitter in peripheral nerves.

The main side effects of this group are drowsiness and male impotence. Moreover, Clonidine, causes depression and increased thirst. Aldomet may trigger autoimmune disease causing haemolytic anaemia and hepatic fibrosis.

Since the introduction of B-blockers in practice, the use of centrally acting hypotensive drugs has been much reduced. Aldomet is still the drug of choice in hypertension with pregnancy.

4- α -Adrenergic blockers:

Prazosin (Minipress) is the main currently available drug among this group.

Centrally acting drugs have a peripheral α -adrenergic inhibitory effect through stimulation of CNS α -adrenergic receptors and consequent reduction of outgoing sympathetic nerve traffic.

Longer-acting α -adrenergic blocking agents are becoming available as doxazosin, terazosin and trimazon.

α -adrenergic blockers inhibit the sympathetic vasoconstrictor response to upright posture so postural hypotension is a predictable adverse effect. This problem occurs mainly with first dose, in elderly and when big dose is used. To avoid this adverse effect we have to start with smaller doses. The first dose should be given immediately before the patient goes to bed.

α -adrenergic blockers are mildly hypocholesterolaemic and may have an inhibitory effect on cell growth (similar to ACEI); so, this group of drugs may be of special privilege in the presence of hypercholesterolaemia and left ventricular hypertrophy.

5- B-Adrenergic Blockers:

The non-selective B-adrenergic blockers (propranolol) is rarely used now as hypotensive drugs due to their many side effects.

The cardioselective B-adrenergic blockers (e.g. Atenolol and Metoprolol) are widely used as hypotensives although are not purely selective.

Several effective compounds have been synthesized. They have B-adrenergic blocking activity and another property such as labetalol (Trandat) which has both α and B-adrenergic blocking activity; carvedilol (Dilatrend) which has both α and B-adrenergic blocking effects as well as an anti oxidant properties, and celiprolol which has both B-blocking and smooth muscle relaxing action.

B-adrenergic blockers are of choice in hypertensive patients with anxiety, arrhythmia, left ventricular diastolic dysfunction or with ischaemic heart disease.

B-blockers (even cardio-selective) are better avoided in hypertensive patients with bronchospasm, diabetes mellitus, peripheral vascular disease, conduction defect; or with systolic dysfunction. Fatigue and bronchospasm are the major causes of conversion from B-blocker to other drug groups.

6- Calcium channel blockers:

This group of drugs block cellular calcium traffic essential for the calcium dependent phase of action potential causing a direct smooth muscle relaxation and consequent arteriolar vasodilatation. Beside peripheral vessels, these drugs may affect cardiac contractility (negative inotropic) and conducting system of the heart (negative chronotropic) as with verapamil and diltiazem, or may cause coronary vasodilatation as with Nifedipine or mainly peripheral vasodilator with non-significant cardiac effect as Amlodipine.

These drugs may cause unwanted effects such as:

- Flushing, headache or oedema lower limbs (mainly nifedipine)
- Systolic dysfunction and bradycardia (mainly verapamil)

7- Angiotensin-converting enzyme inhibitors (ACEI):

ACEI are group of drugs introduced to the medical practice so as to control blood pressure through the interference with the vasopressor action of

the angiotensin II. There are three generations of these drugs, the first is the short acting captopril and most of the second generation are long acting drugs as fosinopril, Ramipril and quinapril. These two generations achieve their action through the inhibition of the angiotensin I converting enzyme. The third generation of these drugs e.g. valsartan (targ) are not ACEI, rather they are blockers of the angiotensin II receptor sites. As angiotensin converting enzyme is originally classified as kininase II degrading many small physiologically active peptides including bradykinin. The first two generations of ACEI extend their hypotensive action through this mechanism while the third generation drugs are specific in their action as blockers of angiotensin II receptor site.

Initially, ACEIs exert their hypotensive action through an action on circulating angiotensin II, but later, this is extended to pulmonary tissue and arterial wall renin-angiotensin system.

ACEI are the drug of choice in the presence of proteinuria (especially in diabetics), congestive heart failure, and in the presence of peripheral vascular disease (unless there is concomitant renal artery stenosis).

ACEI, are better not to be given with B-blockers or Aldosterone antagonist for the risk of hyperkalaemia.

ACEIs cause systemic arteriolar vasodilatation, inhibit the synthesis of aldosterone and reduce α -adrenergic supply to arterioles, the proximal tubule sodium absorption and suppression of thirst.

ACEI may block the vasoconstrictor action of angiotensin II on the glomerular efferent arterioles decreasing the intraglomerular pressure. This action could be one of the mechanisms of the anti-proteinuric action of ACEIs.

Adverse effects of ACEI include:

- 1- Renal impairment resulting from loss of the compensatory efferent arteriolar vasoconstriction which is an important mechanism maintaining the GFR in situations as in renal artery stenosis and in congestive heart failure especially when diuretics are used.
Renal failure may be severe with renal artery stenosis but gradual and partial with CHF. With RAS, renal failure will be manifest only if it is bilateral. Otherwise the unilaterally involved kidney will be lost unnoticed.
- 2- Cough is a major disadvantage of an unknown mechanism encountered in up to 15% of cases. It is claimed that this adverse effect is not observed with the third generation ACEI drugs.
- 3- Neutropenia is a class effect observed mainly in patients with renal impairment.

- 4- ACEI with sulfhydryl groups may cause proteinuria and membranous nephropathy.
- 5- Loss of taste, abnormal taste sensation or scalded mouth are observed in minority of cases due to abnormal metabolism of some peptides as substance P.
- 6- Hyperkalaemia as a result of the effect of ACEIs on aldosterone.

Treatment Strategies of Essential Hypertension:

- The treating physician has to develop a skill in the use of one or two members of each drug group.
- There is no fixed treatment protocol for hypertension; and the treatment should be tailored to individual patients.
- Patient economic status, compliance potentials and the presence of co-morbid condition are of value in drug selection. The same hypotensive effect obtained by expensive drug could be obtained by a cheaper one. Long acting hypotensive drugs with single daily dose are preferable in poor compliant patients. ACEIs are preferable when avoiding impotence is in mind. For hypertensive patients with concomitant heart failure diuretic and ACEIs are preferable. The patient with arrhythmia or ischaemic heart disease B-blockers may be of choice. ACEIs are preferably avoided with hyperkalaemia and B-blocker avoided with bronchospasm and with diabetics liable to hypoglycaemic attacks.
- Patients presenting with severe hypertension with true hypertensive emergency as acute left ventricular failure and pulmonary oedema, intracranial haemorrhage or encephalopathy, central retinal artery occlusion or intraocular haemorrhage or in patients with eclampsia. In such patients blood pressure should be dropped rapidly. This could be achieved either by oral or intravenous drugs. Oral drugs include Nifedipine sublingual (or the capsule could be crushed orally then swallowed), sublingual ACEI or large doses of labetalol (400 mg), prazosin or amlodipine. Intravenous drugs include diazoxide in 15 mg boluses at 1-5 min. intervals, or sodium nitroprusside intravenous infusion.
- In patients presenting with severe hypertension of 180/120 or above with only severe headache, dizziness, blurring of vision or nausea, abrupt reduction of blood pressure may cause cerebral stroke and blood pressure should be decreased steadily, i.e. over 6-8 hours.

Secondary Hypertension

A- Renal Hypertension:

Renal hypertension is the commonest type of secondary hypertension. This may be due to diseases of the renal artery as renal artery stenosis (renovascular hypertension) or disease of the renal parenchyma as glomerulonephritis (Renoparenchymal hypertension).

Pathogenesis:

Hypertension may develop owing to either:

- Excess secretion of renin with a consequent more angiotensin II activity. Angiotensin II has a vasopressor activity and stimulates Aldosterone which causes salt and water retention.

Excess renin release may occur mainly with renal artery stenosis. However, this will occur in some types of renoparenchymal hypertension due to kink or distortion of intrarenal vessels as in case of renal cyst in PCKD or by scar in reflux nephropathy and analgesic nephropathy.

- Vasopressor substances as Endothelin will be released by the diseased kidney. Endothelins are cyclic peptides released by arteriolar endothelium. They may have a vasoconstrictor action and strong platelet activation.
- Failure to secrete salt and water load because of the decreased nephron mass. This will lead to the expansion of the extracellular volume and hypertension.
- Failure to secrete vasodilator substances such as prostaglandins, platelet activating factor and kinins due to decreased nephron mass.

Treatment:

- 1- Treatment of renal disease as renal artery stenosis by balloon dilatation or bypass surgery and SLE by steroids and immunosuppressive drugs.
- 2- Control of hypertension in renal patients may be a part of the treatment of the renal disease as it is known that uncontrolled hypertension is one of the major factors causing progression of renal damage and scarring.
- 3- Any drug which controls hypertension will be valuable but it seems that, in the presence of significant proteinuria, ACEIs may be superior in the prevention of glomerular scarring. On the contrary, in the presence of renal artery stenosis this group of drugs are contraindicated.

Renovascular Hypertension (RVH)

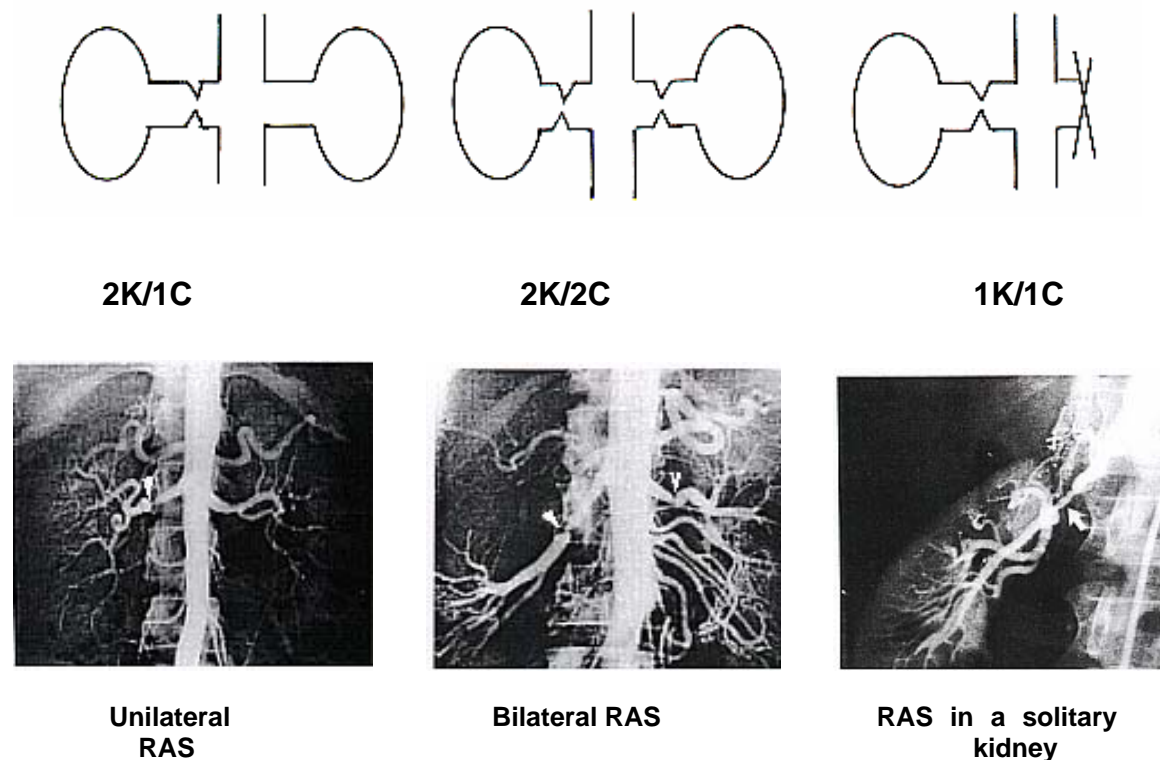
Renal artery stenosis (RAS) is the most common cause of potentially curable secondary hypertension. It has been reported to occur in 0.5% of hypertensive population. The prevalence may be much higher among selected a group of patients, e.g. elderly with severe hypertension and high serum creatinine. In such a group of patients a prevalence up to 70% of RAS has been reported.

Pathogenesis of Renovascular Hypertension:

For better understanding of the pathogenesis of renovascular hypertension, we have to go through the experimental models of RVH.

Goldblatt experimental model of Renovascular hypertension (Fig. 14.4):

Goldblatt and his colleagues induced hypertension in dogs by putting a clip around the renal artery causing renal artery stenosis with 75% reduction of the arterial lumen. Two experimental models have been described. They have comparable clinical situations, the first is called two kidney on clip (2k/1C) and the second is either two kidney, two clip (2K/2C) or one kidney, one clip (1K/1C).



(Fig. 14.4)

Different experimental models of renovascular hypertension and their corresponding clinical examples.

A-Two-kidney-one-clip (2K/1C) model for renovascular hypertension :

In this model, renal artery stenosis is induced in one kidney and the contralateral kidney is left intact. In the early phase of this model, it is observed that:

1- In the ischaemic side :

- The kidney secretes more renin; and more angiotensin II is formed causing systemic hypertension.
- As this kidney is hypoperfused, excess sodium and water are reabsorbed by the renal tubules. Consequently, the urinary Na^+ is low, urine volume is low and urine osmolarity is high.

2- In the contralateral side.

- There is a suppression of renin activity by the excess circulating angiotensin II.
- There is a decreased tubular reabsorption of water and sodium in addition to increased urine volume; as a reaction to the extracellular fluid volume expansion induced by the ischaemic kidney.
- The changes in this side are attempts by the healthy kidney to compensate for the changes in the ischaemic side.

3- Systemic hypertension in this phase is renin dependent and shows a good response to ACE inhibitors or releasing the arterial clip while no response will occur to diuretic therapy.

In a late phase (long time after induction) of this model, it is observed that:

- 1- In the contralateral kidney, the long standing hypertension will cause structural changes in its vascular bed and it will become ischaemic as well with failure of its capacity to compensate for the changes occurring in the side of RAS. Consequently, there will be no compensatory natriuresis or suppression of its renin activity.
- 2- There will be extracellular fluid volume expansion which will suppress renin secretion; and angiotensin II level will go down.
- 3- Hypertension in this phase is mainly volume dependent with no response to ACEIs or to releasing the arterial clip. Diuretics may decrease the blood pressure, but the dog will always be hypertensive because of the irreversible changes in the systemic vascular bed induced by the long standing hypertension.

B-One-kidney-one clip (1K/1C) and two-kidney-two clip models of RVH :

In the very early phase of these models, the hypertension is renin-dependent but by time-as the salt and water retention induced by the renal hypoperfusion is progressive-the animal will be volume expanded and hypertension will be volume dependent.

In the late phase of 2K/1C, 1K/1C and 2K/2C models, if there is no systemic vascular bed damage, diuretics if given will render these models renin dependent.

Etiology of Renovascular Hypertension :

The two most common causes of RAS are atherosclerotic RAS and fibromuscular dysplasia of renal artery.

Atheromatous RAS is more common in males than it is in females (2 : 1) with a peak age of incidence of 60 years. The disease usually starts unilateral but may extend to be bilateral. It usually involves the proximal part of the vessels and is a part of systemic disease with a concomitant coronary, mesenteric and peripheral vascular involvement. In 20% of cases RAS may occur without other major vessels affection. Usually the obstruction involves the proximal part of the renal artery. Not uncommonly the lesion may be osteal (i.e. in the aorta or at the origin of the renal artery).

Fibromuscular dysplasia (hyperplasia) is more common in middle-aged females, the disease starts in the middle of the renal artery and extends distally to its main branches. The disease is multifocal, giving the renal artery the beaded appearance (Fig. 14.5). It starts unilateral and may progress to be bilateral, but the total arterial occlusion is much less common than it is in the atheromatous renal artery disease.

Screening for renal artery stenosis :

The criteria of patients in whom RAS should be suspected, and consequently have to be subjected to aggressive investigations are the following:-

- 1- Those with hypertension starting at age below 30 years.
- 2- Those with abrupt onset of hypertension.
- 3- Those with a definite worsening of previously well-controlled hypertension.
- 4- Presence of epigastric bruit (Systolic and diastolic).
- 5- Hypertension resistant to triple therapy which includes a diuretic, especially in atherosclerotic patient.



(Fig. 14.5)

An angiogram showing a renal Artery stenosis due to fibromuscular dysplasia. There are alternating areas of constriction and dilatation -the so-called "beaded" appearance.

6- Deterioration of the kidney function, especially with the use of ACE inhibitors.

7- Patient with peripheral vascular disease as gangrene, claudications or vasculitic-like rash.

Diagnosis of Renal Artery Stenosis:

Renal artery stenosis can exist incidentally in patient with essential hypertension. In this situation, intervention (surgical or with PTCA) is of no clinical value.

The tests used for the diagnosis of RAS include:

- | | |
|-----------------------------------|---|
| 1- Ultrasonography | 2- Echo-Doppler renal vessels |
| 3- Rapid sequence urography (IVP) | 4- Isotope Renogram |
| 5- Angiography | 6- C-T (spiral, Digital, 3 dimensional) |
| 7- MR angiography | |

For more details see chapter-1 (Radiologic Investigations)

The ideal test for diagnosis of RAS is the one which will not only diagnose the anatomic abnormality, but also predicts the functional significance of the RAS; and the also least invasive.

Renal angiography is currently the best test for the diagnosis of RAS but it carries the disadvantage of being invasive and of less predictive value as regards the response to treatment.

Use of captopril will increase the sensitivity and the predictive value of isotope renogram and Doppler ultrasonography. These two tests have the advantage of being non-invasive, but require experienced hand.

Assessment of renal vein renin (RVR) will help in predicting the outcome after interference (PTCA or surgical). This is achieved by obtaining venous samples from the renal vein of the stenosis side, renal vein of the contralateral side and from the vena cava inferior to the renal veins. The best response to PTCA or surgery will be obtained when the RVR of the ischaemic kidney is higher than that of the vena cava renin and both are higher than that from the contralateral kidney (local suppression). Also, the higher the ratio of RVR of the ischaemic to the contralateral side ($> 1.5 : 1$) the better is the response to the interventional treatment.

Ultrasonographic finding of a unilateral smaller sized kidney may be suggestive of RAS and may indicate further investigations.

Treatment of Renal Artery Stenosis:

The target of treatment of RAS is to achieve both the proper control of hypertension and the prevention of ischaemic kidney damage (ischaemic nephropathy).

The small sized kidney will not recover after revascularization. So we have to treat RAS early so as to conserve the kidney tissue and function. Collateral circulation may maintain the renal blood supply till a reduction of renal artery lumen by RAS up to 50-60%. More reduction will be followed by significant renal ischaemia with a consequent hypertension and ischaemic nephropathy.

The treatment options are either medical, percutaneous i.e. transluminal angioplasty (PTCA- balloon dilatation with or without stenting), or surgical treatment (bypass, endarterectomy....).

The decision regarding the type of treatment depends on :-

- 1- Local experience and facilities available.
- 2- Patient's age.
- 3- Degree of control of blood pressure.
- 4- State of kidney function.
- 5- Site of arterial stenosis.

PTCA will be tried as example in young patient with accessible renal artery stenosis caused by fibromuscular dysplasia. Successful correction in these cases could reach up to 90%; and the cure from hypertension could be achieved in 60% (i.e. in 30% of cases hypertension may persist despite successful dilatation). After dilatation of the renal artery a stainless-steel stent will be left in place to prevent re-stenosis.

Balloon dilatation carries the risk of recurrence, vessel trauma haemorrhage, cholesterol emboli and even the kidney loss.

Atherosclerotic patient with uncontrollable hypertension or with a failing kidney function should be treated either by angioplasty or by surgical correction.

Medical treatment is the best choice in patients who are responsive to hypotensive drugs, with stable kidney function; or when PTCA or surgical interference are risky or unavailable. Medical treatment includes giving up smoking, the treatment of hyperlipidaemia and hypotensive drugs (other than ACEI). In future, laser will be routinely applicable for vessel dilatation, especially in atherosclerotic RAS.

Ischaemic Nephropathy

Ischaemic nephropathy is a progressive kidney damage resulting from a progressive decrease of the renal artery lumen. At least 75% loss of arterial lumen is required for the ischaemic renal damage to occur. Development of collaterals may help in slowing or minimizing the kidney damage induced by RAS. If the renal artery stenosis is unilateral, it will manifest as hypertension. But if it is bilateral, it will manifest by both hypertension and progressive loss of kidney function.

Angioplasty is indicated in patients with ischaemic nephropathy even when hypertension is not severe and responding to medical treatment. Good response is obtained when serum creatinine is less than 4 mg/dl.

Ischaemic nephropathy is usually suspected in patient with advanced atherosclerosis presenting with hypertension and serum creatinine is > 1.5 mg/dl. In such cases, urine sediment is normal and renal U.S. shows no urinary tract obstruction but may show that one of the two kidneys smaller than the other. Further investigations as Echo-Doppler will show the bilateral renal artery stenosis.

B- Conn's Syndrome-Primary hyperaldosteronism:

This is characterized with excess aldosterone which is due to excess secretion by adenoma or hyperplasia of the zona glomerulosa of the adrenal cortex. This will result in hypokalaemia and metabolic alkalosis. Plasma sodium will be high and bicarbonate will be above 30 mmol/L, also plasma renin will be low. Patients with Conn's syndrome usually present with muscle weakness and mild hypertension. In few cases with Conn's syndrome, the course of this disease will be marked with malignant hypertension and stroke.

Treatment depends mainly on surgical excision and in bilateral cases steroid replacement may be needed.

C- Pheochromocytoma:

This is a tumour of chromaffin cells occurring in all age stages. In children, the tumour is always highly malignant (neuroblastoma and medulloblastoma), while in adults the tumour is always benign. Yet, hypertension will have a sinister prognosis if untreated properly.

In 90% of cases the tumours is in adrenal medulla while in 10% the tumour is extra-adrenal affecting the sympathetic chain. It could be multiple and malignant. The extra-adrenal tumour could be abdominal or even thoracic.

Beside the clinical criteria of this tumour, serum and urinary catecholamine assay will confirm the diagnosis.

Localization of tumour site is mandatory for surgical excision. This is usually carried out by isotope scanning using the tracer meta-iodo benzaguanin (MIBG). The tumour is extremely sensitive to X-ray contrast media, on exposure it will secrete a huge amount of catecholamine with fatal outcome. So, in hypertensive patient if pheochromocytoma is expected, this should be excluded first; by catecholamine assay before the patient is subjected to the contrast media.

Treatment is by hypotensive drugs having α and B-adrenergic blocking properties as labetalol and carvedilol. They are the drug of choice. The definitive treatment is surgical excision.

Suggested Readings:

- Stanley JC: David M. Hume memorial lecture. Surgical treatment of renovascular hypertension. *Am J Surg*, 174 : 2, 102-10, 1997.
- Ram CV: Renovascular hypertension. *Curr Opin Nephrol Hypertens*, 6 : 6, 575-9, 1997.
- Tikkanen T, et al: Diagnosis and therapy of renovascular hypertension. *Duodecim*, 111 : 15, 1453-60, 1995.
- Koomans HA, et al: Tony Raine Memorial Lecture. Hypertension and the kidney: culprit and victim. *Nephrol Dial Transplant*, 11 : 10, 1961-6, 1996.
- Rodicio JL: Does antihypertensive therapy protect the kidney in essential hypertension? *J Hypertens Suppl*, S69-75; Discussion S75-6, 1996.
- Cowley AW, Jr, et al: The role of the kidney in hypertension. *JAMA*, 275 : 20, 1581-9, 1996.
- Perazella MA: Lead and the kidney: nephropathy, hypertension, and gout. *Conn Med*, 60 : 9, 521-6, 1996.
- Chapman AB, et al: Hypertension in autosomal dominant polycystic kidney disease. *Kidney Int Suppl*, 61 : S71-3, 1997.
- Zucchelli P, et al: The kidney as a victim of essential hypertension. *J Nephrol*, 10 : 4, 203-6, 1997.
- Navar LG: The kidney in blood pressure regulation and development of hypertension. *Med Clin North AM*, 81 : 5, 1165-98, 1997.
- Whelton PK, et al: Kidney damage in 'benign' essential hypertension. *Curr Opin Nephrol Hypertens*, 6 : 2, 177-83, 1997.
- Ram CV, et al: Renovascular hypertension. *Semin Nephrol*, 15 : 2, 152-74, 1995.

- Stanley JC: Renovascular hypertension in women. *Semin Vasc Surg*, 4, 306-16, 1995.

- Aurell M, et al: Treatment of renovascular hypertension (editorial). *Nephron*, 75 : 3, 373-83, 1997.

- Romero JC, et al: New insights into the pathophysiology of renovascular hypertension. *Mayo Clin Proc*, 72 : 3, 251-60, 1997.

- Tesar V: Hypertension in kidney failure and its treatment. *Cas Lek Cesk*, 137 : 14, 438-41, 1998.

- Tesar V: Hypertension in diseases of the kidney. Pathogenesis and therapy. *Cas Lek Cesk*, 29 : 137-13, 410-4, 1998.

MISCELLANEOUS

PROTEINURIA

Proteinuria is a rare presenting complaint of patients. Yet, when severe enough, it may cause hypoalbuminaemia and oedema. As protein in urine decreases the surface tension, it causes frothy urine which may be observed by some patients (bile salts and detergents used in toilets do the same).

Abnormal protein excretion is usually albumin, small molecular weight proteins, immunoglobulins and Bence Jones protein.

The urine is tested for proteinuria by dip stick test. Dipstick is a plastic strip, attached to it is a paper impregnated with chemical substance (tetrabromophenol) which is normally yellow in colour and changes according to amount of protein in urine (0, +, ++, +++). It can detect a protein down to a concentration of 300 mg/l. Proteinuria detected by dip stick test should be confirmed by collecting the 24 hours urine and testing for quantity of proteinuria using chemical methods.

Definitions:

- *Proteinuria* is a secretion of an abnormal amount of protein in urine. Normal protein excretion per 24 hours in adults is less than 200 mg. Most of this protein is albumin and Tamm Horsfall protein with smaller amounts of immunoglobulins.
- *False positive proteinuria* by dip stick occurs mainly when urine is alkaline and very concentrated; or if the stick test is left in urine for long time.
False negative proteinuria is observed when protein excretion is mainly Bence Jones proteinuria and when urine is very diluted.
- *Bence Jones protein* which is the light chain fraction of immunoglobulin appears in abnormal amounts in urine in cases of multiple myeloma, clots at temperature 45-55°C, above and below that range it dissolves in urine. Presence of Bence Jones proteinuria should be confirmed by immunoelectrophoresis.
- The causes of Bence Jones's proteinuria include: multiple myeloma, amyloidosis, adult Fanconi syndrome, benign monoclonal gammopathy and hyperparathyroidism.
- *Microalbuminuria* is defined as an abnormal amount of urine (> 200 mg/24hr) but below the sensitivity of dipstick (< 300 mg/l). It could be detected by sensitive methods e.g. Radioimmunoassay or ELISA. In diabetic patients the presence of microalbuminuria means that the patient may develop frank diabetic nephropathy within few years.

- *Orthostatic proteinuria* means proteinuria related to posture. The first voided urine in the morning is free of protein, but at the end of the day the urine will contain abnormal amount of protein, it is very common in the young, being present in about 30% of children, but only 5% of young adults. The mechanism is unknown. Possibly, the lordotic position of vertebral column encroaches upon the venous return from the kidney causing proteinuria.
- *Tubular proteinuria* means proteinuria of tubular origin (i.e. due to tubular disease), usually it is of low molecular weight e.g. B₂-microglobulin and less than 2 grams/day.
- *Glomerular proteinuria* means proteinuria of glomerular origin (i.e. due to glomerular disease). Usually it is albumin and globulins and more than 2 grams/day.
- *Selectivity of proteinuria* If the abnormal protein excreted is mainly albumin (> 85%). It is called selective proteinuria. If both albumin (low molecular weight protein) and globulins (large molecular weight protein) are nearly equal it is called non-selective proteinuria. Proteinuria in minimal change nephritis is highly selective while that in bad prognostic lesions as mesangiocapillary glomerulonephritis is poorly (or non-) selective.

Mechanism of proteinuria:

There are four known mechanisms for proteinuria. These are:

1. Abnormality in permeability of the glomerular basement membrane because of glomerular disease or abnormal glomerular hemodynamics.
2. Increased concentration of small molecular weight protein in blood (MW 60000- 70000) e.g. hemoglobin, myoglobin and immunoglobulin light chains. These will pass easily through the normal GBM
3. Tubular disease with inadequate reabsorption of normally filtered proteins of MW <60000 e.g. B₂-microglobulin.
4. Secretion by renal tubular cells of Tamm-Horsfall protein (urinary glycoprotein).

Differential Diagnosis of Proteinuria:

I. Functional proteinuria:

There is no organic change in the kidney tissue: it is usually less than 1 gm/d and is reversible. Possibly, it is due to hemodynamic changes or to minor glomerular disease which are reversible.

- a. Strenuous exercise
- b. Fever
- c. Orthostatic proteinuria
- d. Miscellaneous
(Thyrotoxicosis, severe anaemia, CNS lesions)

II. Patients with proteinuria of 0.5-3.5 gm/d:

- a. Acute interstitial nephritis.
- b. Chronic interstitial nephritis such as bacterial (pyelonephritis), gouty nephropathy, analgesic nephropathy or nephrolithiasis.
- c. Tubular proteinuria such as Fanconi syndrome, heavy metal intoxication (lead, cadmium), multiple myeloma, hypokalaemic nephropathy, polycystic kidney disease and medullary cystic kidney disease.

III. Patients with proteinuria of more than 3.5 gm/d:

Usually caused by glomerular disease.

- a. **Primary glomerular disease:** refers to all types previously discussed under glomerulonephritis.
- b. **Secondary glomerular disease** is Previously discussed under glomerulonephritis.

Investigations of a case of proteinuria:

1. **Characterization of proteinuria:** After diagnosis of proteinuria by dip stick test, it should be confirmed by quantitative estimation of 24 hours proteinuria. Further assessment may include electrophoresis or immunoelectrophoresis to determine the type of abnormal protein excreted.
2. **Urine analysis:** For pus cells (to diagnose U.T. infection), RBCs and casts (to diagnose glomerular disease), also urine volume (oliguria or polyuria), pH of urine, specific gravity and test for glycosuria; and aminoaciduria and B₂ microglobulin (may help in the diagnosis of tubular disease).
3. **Blood and serologic examination:**
 - a. Kidney function tests: serum creatinine, creatinine clearance, electrolytes (Na, K, Ca, Po₄).
 - b. Total protein, albumin, cholesterol to diagnose nephrotic syndrome.
 - c. Serologic examination e.g. for anti-DNA and complement component C₃ and C₄ for diagnosis of lupus erythematosus.

4. **Radiologic assessment including:**
 - a. Examination of the kidney for its size, state of parenchyma, the presence of stone, back pressure change or pyelonephritic changes. It is achieved through ultrasound examination, plain X-ray, and IVP (if the kidney function is normal).
 - b. Investigations to discover malignancy which could be the etiologic cause of proteinuria e.g. skeletal survey for multiple myeloma, X-ray chest and bronchogram or CT scan for bronchogenic carcinoma.
5. **Renal biopsy** will give the final answer for the diagnosis of the kidney lesion causing proteinuria.

HAEMATURIA

Definitions

- Normally the number of RBC's in urine should not be more than 5 RBCs/high power field on microscopic examination of fresh centrifuged urine sample. So, haematuria is defined as a secretion of more than 5 RBCs/HPF in urine.
- Haematuria may be the only symptom or associated with other symptoms, according to the etiologic cause e.g. loin pain and fever with infection and renal colic with renal stones.
- Haematuria could be gross (causing red-coloured urine) or microscopic (urine appears normal. But RBCs are seen on microscopic examination).

In gross hematuria, urine looks red if alkaline, but brown or coca-cola like if urine is acidic due to denaturation of the hemoglobin.
- Also, hematuria could be glomerular (because of glomerular disease, sometimes called medical); or non glomerular (sometimes called surgical). Glomerular could be differentiated from non glomerular haematuria by:
 1. The shape of RBCs in urine is dysmorphic in cases with glomerular haematuria while it will be normal in case of non glomerular haematuria.
 2. The size of RBCs whose mean corpuscular volume in urine of patient with glomerular haematuria which is smaller than it is in peripheral blood. But in non glomerular cases it is equal.
 3. Proteinuria is present in most cases of glomerular hematuria but not in cases of non glomerular hematuria.

4. Casts such as proteinuria.
5. Blood clots indicate non-glomerular bleeding and can be associated with pain & colic.

Differential Diagnosis of Hematuria:

A. First, hematuria should be differentiated from other causes of red or brownish urine:

- Microscopy will show RBC's only with hematuria.
- Dipsticks (Hemastix) will be positive with hemoglobinuria (hemolysis) and myoglobinuria (muscle damage) but negative with other causes e.g. porphyrins (in porphyria), bile (in jaundice), melanin (in melanoma), alkaptonuria, food dyes and drugs as PAS or phenylphthalein.

B. Hematuria may be of renal, ureteral, bladder or urethral origin.

I. Haematuria of renal origin:

- a. **Glomerular haematuria:** Either primary glomerular disease (e.g. IgA nephropathy, mesangial proliferative glomerulonephritis or crescentic glomerulonephritis); or secondary glomerulonephritis i.e. renal involvement is a part of systemic disease (e.g. post-streptococcal glomerulonephritis, Henoch-Schönlein purpura, SLE, polyarteritis nodosa).
- b. **Renal infection:** Pyelonephritis (especially with papillary necrosis) or renal tuberculosis.
- c. **Renal neoplastic disease:** Renal cell carcinoma, transitional cell carcinoma of the renal pelvis and others.
- d. **Hereditary renal disease:** Medullary sponge kidney or polycystic kidney disease.
- e. **Coagulation defect:** Use of anticoagulant, liver disease and thrombocytopenia.
- f. **Renal vascular disease:** Renal infarction, renal vein thrombosis or malignant hypertension.
- g. **Exertional haematuria.**

II. Hematuria of ureteral origin:

- a. Malignancy.
- b. Nephrolithiasis

- c. Ureteral inflammatory condition secondary to nearby inflammation e.g. diverticulitis, appendicitis or salpingitis.
- d. Ureteral trauma e.g. during ureteroscopy.

III. Hematuria of bladder origin:

- a. Infection: schistosoma, viral or bacterial cystitis.
- b. Neoplasms.
- c. Foreign body in the bladder e.g. stones.
- d. Trauma: During instrumentation or accidental.
- e. Drug: e.g. cyclophosphamide induced haemorrhagic cystitis.

IV. Hematuria of urethral or associated structures:

- a. Prostate: acute prostatitis, benign prostatic hypertrophy.
- b. Urethritis, foreign body or local trauma to the urethra.

Investigations of a case of hematuria:

1. First exclude haemoglobinuria and myoglobinuria since both of them can also cause positive dipstick test for haematuria. This is done by microscopic examination of fresh urine sample. In case of haematuria, RBCs could be seen while in the other two conditions no RBC's could be seen.

In case of myoglobinuria, clinical examination may show manifestations of muscle disease and the examination of urine by immunoelectrophoresis may show myoglobin. In case of haemoglobinuria, manifestations of haemolysis may be evident.

2. Examination of urine for proteinuria and casts (to diagnose glomerular disease), pus cells and urine culture (for diagnosis of infection), Zeil-Nelson stain and specific media (for diagnosis of T.B.).
3. Plain X-ray, I.V.P. (if serum creatinine is normal), ultrasound and possibly angiography, for the diagnosis of surgical diseases e.g. stone, malignancy or infection.
4. RBCs in urine could be examined for its shape to differentiate glomerular from non glomerular causes (by phase contrast microscopy).
5. Kidney function tests.
6. Specific investigations for diagnosis of systemic diseases causing haematuria e.g. SLE.
7. Kidney biopsy for glomerular haematuria.

VALUE OF URINE EXAMINATION IN MEDICAL DIAGNOSIS

Normal Urine Characters:

1. Volume is 600-2500 ml/24 h (average is 1200 ml/24 h).
2. Colour is umber yellow.
3. Specific gravity is 1003-1030 (represents amount of solids in urine).
4. pH is 4.6-8.8 (average 6.0)
5. Protein: The amount as detected by semiquantitative methods is 0.0-0.1 gm/24 hr urine.
6. Cells and casts:
 - R.B.C.s and W.B.C.s. < 5 by H.P.F.
 - Hyaline casts occasionally present (protein collected in the renal tubules taking a cylindrical shape producing occasional hyaline casts).
7. Glucose: should be negative.
8. Some other substances may be present e.g.:
 - Calcium < 150 mg/24 hr.
 - Phosphate : 1mg/24 h.
 - Amylase: 260-950 mg/24h.
 - Creatinine: 1.6 gm/24 h (15-25 mg/kg/24h).
 - Porphyrin: 50-300 mg/24h.
 - Ketones: qualitative amounts.

How to examine urine:

We have to comment on the following items:

- Volume/24 h
- Specific gravity (osmolality)
- Colour of urine
- Dip stick examination of urine
- Microscopic examination.

1. **Volume of urine:**

Changes in urine volume may be oliguria or polyuria:

Polyuria:

(Urine volume > 2500 ml/day) may occur with:

- Diuretics
- Excessive water intake (within the normal range).
- Compulsive water drinking in psychological cases (psychogenic polydipsia).
- Uncontrolled D.M.

- Diabetes insipidus which may be central or nephrogenic.
 - In central D.I. there is a decreased A.D.H. secretion.
 - In nephrogenic D.I. the renal response to A.D.H. is defective as in analgesic nephropathy and medullary cystic kidney disease.
- Early stage of chronic renal failure.
- Diuretic phase of acute renal failure.
(for more details see chapter on hypernatraemia)

Oliguria:

(Urine volume < 600 ml/day), may occur with:

i. Obstructive causes:

Mainly produce anuria i.e. no urine at all, should be differentiated from urine retention by detecting urine in the bladder (suprapubic dullness, by U.S., or by urethral catheter).

- Removal of solitary functioning kidney.
- Bilateral ureteric obstruction (or unilateral ureteric obstruction of a solitary functioning kidney).
- Retro-peritoneal fibrosis blocking ureteric flow.

ii. Nonobstructive causes:

Mainly produce oliguria:

- Inadequate renal perfusion e.g. with vomiting, or diarrhea will cause depletion of body salts and fluids.
- Intravascular volume depletion e.g. with internal haemorrhage or rapidly developing ascites.

iii. Oliguria with intrinsic renal disease:

- Oliguric phase of acute tubular necrosis.
- Rapidly progressive glomerulonephritis.
- Bilateral cortical necrosis.
- End stage renal failure.
- Acute nephritic syndrome.
- Nephrotic syndrome.

2. Specific gravity:

Specific gravity represents the amount of solids in urine:

- Specific gravity is measured by urinometer or by another special complicated apparatus which is more perfect (osmometer).
- Specific gravity is one of the kidney function tests. In D.I. repeated measurement of urine specific gravity in face of water deprivation and after vasopressin administration is mandatory for proper diagnosis.

3. **Colour:**

- Normal: umber yellow
- Examples of colour changes of urine:
 - Red urine: with hematuria, myoglobinuria and haemoglobinuria (with haemoglobinuria the colour is red brown).
 - Pink: with rifampicin.
 - Orange: concentrated normal urine, urobilin, bilirubin,
 - Deep yellow: Mepacrine.
 - Milky: Chyluria.
 - Smoky: acute glomerulonephritis.

4. **Dip stick examination of urine:**

- Dip stick is a plastic strip with squares of paper impregnated with enzymes which change in colour on exposure to target chemicals.
- Dip stick is used for detection of protein, ketones, glucose, pH, haemoglobin, bile, bacteria, pus cells and leucocytes....

i. **Proteinuria:**

- Normal protein in urine (by quantitative assessment) is <0.1 gm/d by dip stick. It is mainly albumin and Tamm Horsfall protein which is synthesized by renal tubules.
- Abnormal proteinuria may contain albumin, globulin, Bence Jones protein and low molecular weight protein (e.g. B-microglobulin).
- Proteinuria may be of:
 - Glomerular origin e.g post infectious G.N., drug induced G.N., collagen disease and idiopathic G.N.
 - Tubular origin (usually low molecular weight proteins) e.g. heavy metals intoxication, analgesic nephropathy.
- For more details see chapter on proteinuria (page 339)

ii. **pH:**

- Normal urine is acidic, average 6.
- Highly acidic in uric acid stones.
- Alkaline in stones caused by infection and in renal tubular acidosis.
- pH is important in:
 - The treatment of stones, it is advised to give alkalies e.g. Na HCO₃ in acidic stones, or acids e.g. vitamin C in alkaline stones.

- Drug intoxication, it is advised give alkalies in acidic drug intoxication as salicylates and acids in alkaline drug intoxication as pethidine.
- Increase potency of some antibiotics in urinary tract infection, alkalies with aminoglycosides and acids with tetracyclines are given.

iii. **Haemoglobinuria:**

- Haemoglobin may be present in urine in haemoglobinuria or haematuria (differentiated by presence of R.B.C.s in case of haematuria).
- RBCs may rupture in cases of hypotonic urine but RBCs ghosts could still be seen.
- Ascorbic acid may produce false test for haemoglobinuria.

Causes of Haemoglobinuria

- Intravascular haemolysis e.g. in severe exercises or severe burns.
- Chemicals e.g. naphthalene and hydroquinone derivatives.
- Mismatched blood transfusion.
- Black water fever.
- Paroxysmal cold Haemoglobinuria.
- Paroxysmal nocturnal Haemoglobinuria.
- Snake bites.
- Vegetable toxins e.g. mushroom poisoning.
- False Haemoglobinuria.
- Trans-urethral prostatectomy with post operative washing with water, which when absorbed cause hypotonicity of blood with consequent haemolysis.

iv. **Bacteruria:**

- To collect a urine sample one of the following methods should be used:
 - Cleaning of the area around the urethra and a midstream urine is collected.
 - Urine specimen may be obtained by a urethral catheter (especially in females).
 - Supra-pubic puncture in children.
- Detection of bacteruria is by colony count what is significant if >100,000/ml (indicate infection). False low count may occur with high urine flow, antibiotic treatment or contaminated container.

- Direct microscopic examination of urine (stained or unstained) has the reliability of about 85-90% of colony count.
- Microscopic detection of pus cells in urine is less sensitive and produces more negative results.
- **Bacteruria may occur in:**
 - 10% of pregnant ladies.
 - 15% of diabetic patients.
 - 20% of patients with prostatic enlargement.
 - 95% of patients with catheter for more than 2 days without prophylactic antibiotics.

v. Glycosuria:

May occur in:

- Hyperglycaemia which may be endocrinal (e.g. in D.M.) or non endocrinal (as liver disease) or due to administration of hormones (e.g. corticosteroids, A.C.T.H., thyroid and adrenaline drugs).
- In renal tubular defects e.g. renal diabetes, heavy metal poisoning or Fanconi syndrome.

N.B.

In renal glycosuria, hypoglycaemic attacks may occur. At the same time someone may wrongly give hypoglycaemic drugs which are dangerous in such cases so caution should be taken on diet and treatment of glycosuria.

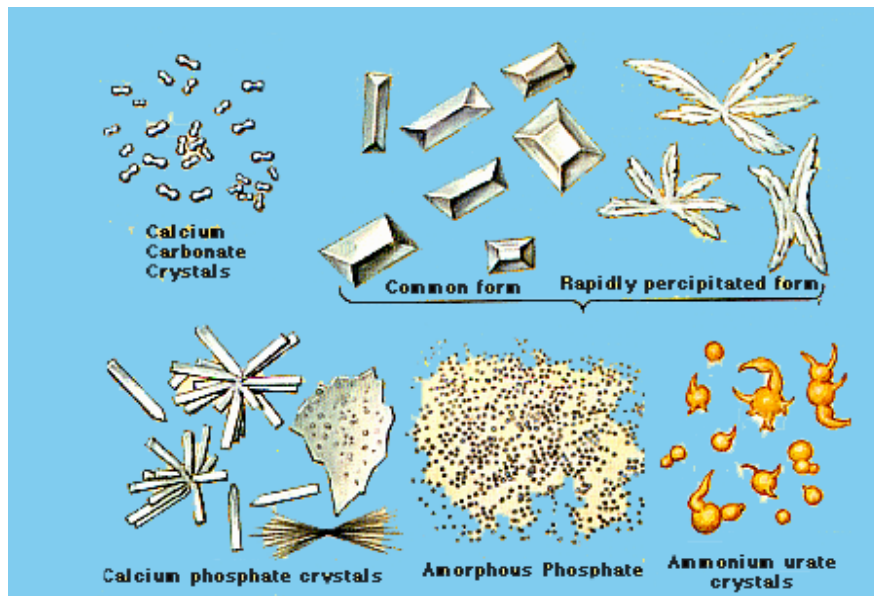
Concomitant hyperglycaemia should be detected before giving hypoglycaemic drugs.

5. Microscopic examination of urine:

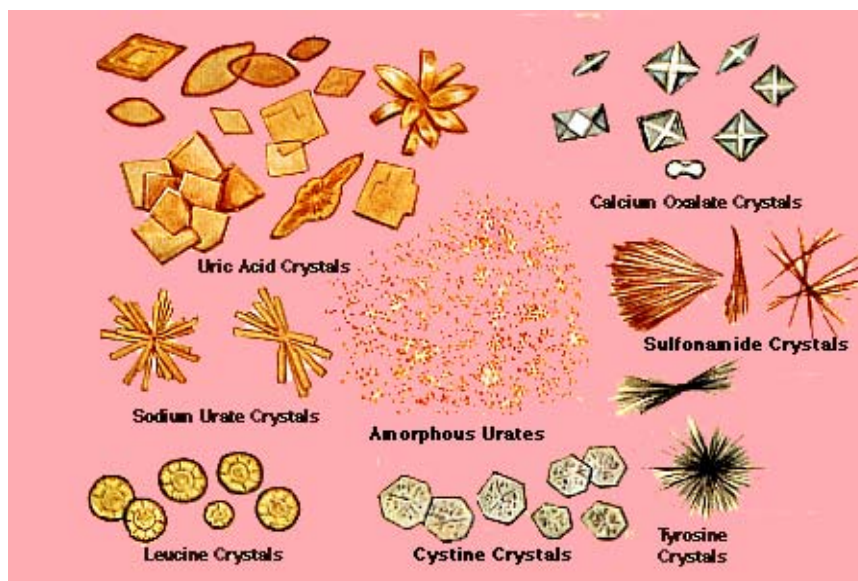
- For cells (type and count).
- For casts (type and count). Casts may be:
 - Fine granular casts (in chronic renal disease).
 - Hyaline casts (in chronic renal disease).
 - RBCs casts (acute nephritic syndrome).
 - WBCs casts (in U.T.I.).
 - Fat casts (in nephrotic syndrome).

6. **Crystals (Fig.1):**

- Crystals mainly appear in alkaline urine e.g. urate, phosphate (Treatment depends on the acidification of urine by vitamin C then follow up of pH by dip sticks).
- Crystals in acidic urine e.g. oxalate or uric acid.



(Fig. 15.1a)
Shows different crystals which could be seen by microscopy of urine with alkaline pH.



(Fig. 15.1b)
Shows different crystals which could be seen by microscopy of urine with acidic pH.

7. **Chemicals:**

Determination of 24 hours urine of some chemical substances e.g.

- Calcium: Increases in hyper-parathyroidism, Vitamin D intoxication.
decreases in hypo-parathyroidism, rickets.
- Porphyrin: Increases in lead poisoning, liver cirrhosis or infective hepatitis.
- Urinary L.D.H. (lactic dehydrogenase): increases in carcinoma of the kidney, prostate and bladder, glomerular disease or myocardial infarction.
- Urine catecholamine : Increase in pheochromocytoma (also increases level of V.M.A.) and neuroblastoma.

Suggested Readings:

- Ishida M: Approach to proteinuria. Nippon Naika Gakkai Zasshi, 85 : 9, 1534-9, 1996.
- Roy S: Proteinuria. Pediatr Ann, 25 : 5, 277-8, 281-2, 1996.
- Harris KP, et al: Proteinuria: a mediator of interstitial fibrosis?. Contrib Nephrol, 118 : 173-9, 1996.
- Jerums G, et al: Why is proteinuria such an important factor for progression in clinical trials? Kidney Int Suppl, 63 : S87-92, 1997.
- Mahan JD: Evaluation of hematuria, proteinuria, and hypertension in adolescents. Pediatr Clin North Am, 44 : 6, 1573-89, 1997.
- Chen L, et al: Proteinuria and tubulointerstitial injury. Kidney Int Suppl, 61 : S60-2, 1997.
- Ahmed Z, et al: Asymptomatic urinary abnormalities. hematuria and proteinuria. Med Clin North Am, 81 : 3, 641-52, 1997.

RENAL MANIFESTATIONS OF SYSTEMIC DISEASES

Systemic diseases which may involve the kidney include the following groups:

- 1- Systemic lupus erythematosus.
- 2- Systemic vasculitis
 - Polyarteritis nodosa.
 - Wegener's granulomatosis
 - Henoch-Schönlein purpura
 - Churg-Strauss disease.
 - Giant cell arteritis
- 3- Anti-GBM disease.
- 4- Thrombotic Microangiopathy
 - Haemolytic uraemic syndrome.
 - Thrombotic thrombocytopenic purpura.
 - Postpartum renal failure.
- 5- Connective tissue diseases.
 - Rheumatoid arthritis.
 - Sjogren's syndrome.
 - Behcet's diseases
 - Rieter's syndrome
 - Systemic sclerosis (scleroderma).
 - Mixed connective tissue disease
- 6- Metabolic diseases.
 - Diabetes mellitus.
 - Amyloidosis.
 - Gout.
 - Abuse of NSAID's.
 - Nail-patella disease
 - Fabry's disease.
- 7- Haematologic diseases.
 - Cryoglobulinaemia.
 - Sickle cell anaemia.
 - Leukemia and lymphoma.
 - Multiple myeloma.
 - Paraproteinaemias.

8- Malignancy.

9- Systemic infections as

- Tuberculosis.
- Schistosomiasis.
- Malaria.
- Hepatitis virus infections.
- HIV infection (AIDS).

Most of these diseases are described in details in this book. In this chapter we will give some details on the remaining disease of clinical importance.

Rheumatoid Arthritis And The Kidney

Renal involvement in patients with rheumatoid arthritis are almost due to toxicity of drugs used in its treatment.

The list of causes of renal disease in rheumatoid arthritis are :

- 1- Drug-related (NSAIDs, Gold, Penicillamine).
- 2- Secondary to amyloidosis occurring as a result of long standing rheumatoid arthritis.
- 3- Vasculitis.
- 4- Renal disease secondary to the disease itself.

Histopathologically, the disease may show any of the following forms :

- 1- Interstitial nephritis (acute and chronic, induced by NSAIDs).
- 2- Minimal change nephritis (NSAIDs-induced).
- 3- Renal amyloidosis.
- 4- Membranous glomerulonephritis (gold or penicillamine induced).
- 5- Mesangial proliferative or focal proliferative glomerulonephritis which is due to rheumatoid arthritis or as a part of systemic vasculitis.

Amyloidosis

Amyloidosis may be primary or secondary to the following :

- 1- Familial mediterranean fever (FMF).
- 2- Rheumatoid arthritis.
- 3- Tuberculosis.
- 4- Multiple myeloma.
- 5- Chronic sepsis as empyema and osteomyelitis.

Amyloid material may be deposited in the renal glomeruli, tubules, blood vessels and interstitium. Renal manifestations of amyloidosis may include :-

- 1- Nephrotic syndrome.

2- Nephrogenic diabetes insipidus.

3- Renal tubular acidosis, and

4- Retroperitoneal fibrosis.

Nephrotic syndrome is the commonest clinical presentation. Hypertension is uncommon finding.

When the disease progresses it may lead to chronic renal failure.

By U.S., the kidney size may look normal or even enlarged unless the disease is far advanced when the kidney may look decreased in size.

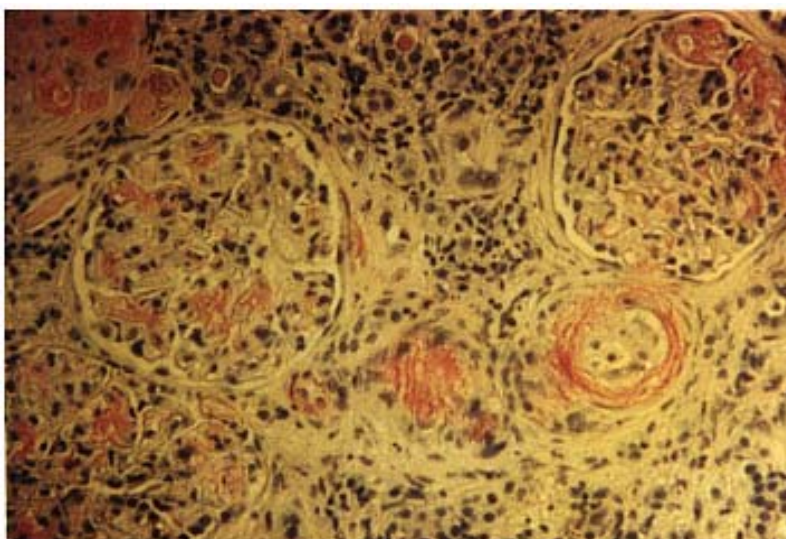
Amyloid protein in primary amyloidosis and in cases with multiple myeloma is formed of immunoglobulin (condensation of light chain fragments of immunoglobulin and is called AL protein) while in that of the secondary amyloidosis; it is formed of a protein which is similar to the one present in plasma (serum amyloid A protein and is called AA protein).

Amyloidosis may involve different organs with different systemic manifestations as :

- 1- Gastrointestinal tract with malabsorption, chronic diarrhoea and motility disorders.
- 2- Cardio-vascular system with hypertension and cardiomyopathy.
- 3- Neurologic with neuropathy (sensory, motor, and autonomic).
- 4- Cutaneous with skin rash.

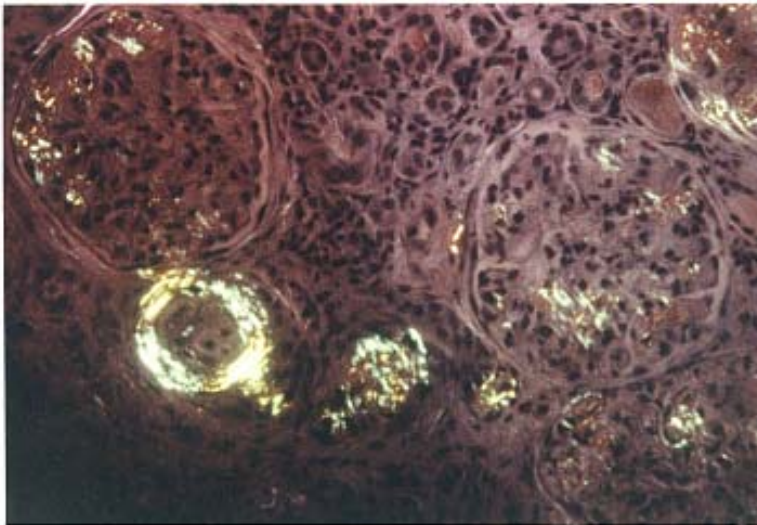
Diagnosis

Diagnosis is settled by the demonstration of amyloid material in tissue biopsy (kidney, liver, gum, rectal mucosa or subcutaneous fat). Biopsy is stained by Congo-red and amyloid. When seen by light microscopy, it should be confirmed by polarized light microscopy (Fig 15.2).

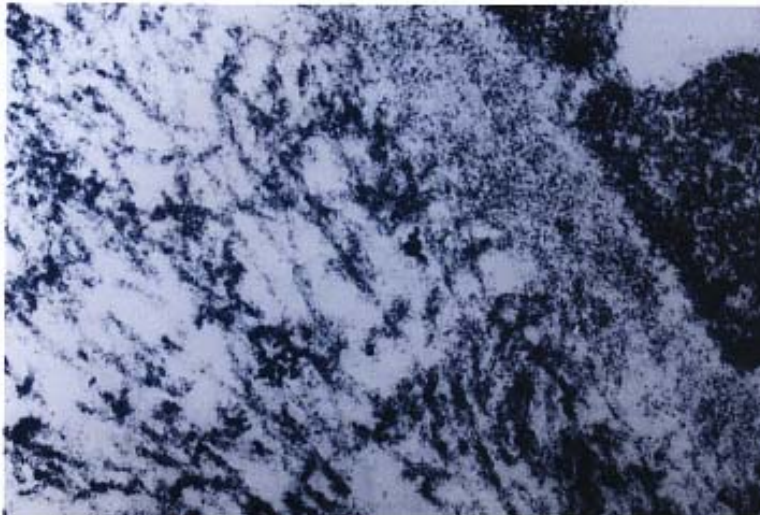


(Fig. 15.2a)

Cong-red stained kidney section (X250), it shows amyloid deposits in the glomeruli, and the arterioles.



(Fig. 15.2b)
The same section examined by polarized light, it shows apple-green birefringence which is specific for amyloid.



(Fig. 15.2c)
Electron micrograph of a kidney section from the same case, it shows subendothelial amyloid fibrils.

Treatment

- 1- Mainly prophylactic by early eradication of the cause. In patients with FMF, colchicine will abort the attacks and will prevent amyloidosis.
- 2- Symptomatic and supportive treatment when the disease is settled (as diuretic in NS and sodium bicarbonate in RTA).
- 3- In primary amyloidosis with renal involvement, melphalan, steroid and colchicine have been used with limited response. So, they could be used in some selected cases.

Gout and Kidney

Patient with gout may suffer from renal disease through the following mechanisms :

- 1- Chronic interstitial nephritis which is due to deposition of urate crystals in the interstitium.
- 2- Uric acid stones which may lead to obstructive uropathy.
- 3- Chronic pyelonephritis triggered by renal stones.
- 4- Nephrotoxicity by NSAIDs drugs.

Proper control of hyperuricaemia by diet control and the use of Allopurinol, giving colchicine rather than NSAIDs for control of joint pain, and the alkalinization of urine to prevent crystallization and stone formation are all mandatory to prevent renal disease in gouty patients.

Sickle Cell Anemia and the Kidney

Sickle cell disease (SS haemoglobin) and sickle cell trait (SA haemoglobin) may cause kidney disease. It is commonly a tubular disorder (Nephrogenic diabetes insipidus or RTA) which is due to sickling of the red cells in the hypertonic renal medulla leading to papillary necrosis and sclerosis. Less commonly sickle cell anemia may be complicated by glomerular disease with proteinuria and nephrotic syndrome. It is caused either directly or through a concomitantly acquired HCV or HBV infection (through blood transfusion). Histologically, the glomerular lesions are either membranous or membrano- proliferative.

The renal disease (tubular or glomerular) may progress to chronic renal failure.

Mixed Connective Tissue Disease

Mixed connective tissue disease is a mixture of features of scleroderma, polymyositis and SLE associated with a pronounced autoantibody response to a saline-extractable nuclear RNP antigen. The serum complement component concentrations are typically normal.

Renal disease usually involves 25% of the cases with mixed C.T. diseases. It usually takes the form of proteinuria or nephrotic syndrome. Histologically, there is membranous or MPGN, it seldom progresses to renal failure and is steroid responsive.

Sjogren's Syndrome

This syndrome is characterized with a triad of xerostomia (dry mouth), keratoconjunctivitis sicca (dry eye) and a connective tissue disorders.

The systemic manifestations are:

- 1- Oral:** dry mouth, difficult mastication, dental caries and episodes of bilateral painful enlarged parotid glands.
- 2- Ophthalmic:** burning eyes and photosensitivity.
- 3- Joints:** manifestations similar to rheumatoid arthritis, even subcutaneous nodules.
- 4- Renal manifestations:** mainly of tubulointerstitial disease including inability to concentrate urine (polyuria) and metabolic acidosis (RTA).
- 5- Other manifestations:** nasal dryness, crusting, otitis media, upper respiratory infection hoarseness, pleurisy, atelectasis, and pericarditis.

Investigations for Sjogren's Syndrome include:

- 1-** Schimer's test, in which a filter paper when put in the conjunctival sac, it shows no tear production.
- 2-** Biopsy from mucous membrane of the lip which when examined by light microscopy it shows infiltration of the minor salivary glands by lymphocytes.
- 3-** Hypergammaglobulinaemia (especially IgG).
- 4-** Parotid sialogram shows a dilatation of parotid duct.

Treatment of Sjogren's Syndrome:

Is by methyl cellulose eye drops (artificial tears), glycerin for dry mouth.

Steroids and possibly cyclophosphamide may be used, according to the severity of the disease.

RENAL DISEASES IN HEPATIC PATIENTS

There are many renal disorders which are known to occur in cirrhotic patients. These are :

- 1- Hepatorenal syndrome
- 2- Cirrhotic glomerulopathy
- 3- Glomerulopathy induced by infection common in cirrhotic patients such as:
 - Malaria
 - Bilharziasis
 - HBV
 - HCV
- 4- Tubulointerstitial disorders that are due to:
 - Infection (brucellosis, mononucleosis, tuberculosis)
 - Systemic disease (sarcoidosis, Sjogren's syndrome, lymphoma)
 - Drugs (methicillin, ampicillin, penicillin, sulfonamides, rifampicin, acetaminophen, Allopurinol).
- 5- Drugs and toxins producing combined Hepatic and Renal damage.

A- Drugs causing hepatic injury and acute tubular necrosis:

- Halogenated hydrocarbons as carbon tetrachloride, chloroform and chlorethylene
- Halogenated anaesthetics as Halothane and Methoxyflurane
- Tetracycline
- Rifampicin
- Methotrexate
- Copper sulphate
- Sulfonamides
- Acetaminophen
- Arsenic

B- Hepatic injury and acute interstitial nephritis

- Sulfonamides
- Rifampicin
- Phenindione
- Allopurinol

Hepatorenal Syndrome (HRS)

Definitions :-

HRS is an unexplained, functional renal failure occurring in patients with advanced liver disease. The diagnosis of HRS is considered when there is no laboratory or anatomic evidence of other known cause of renal failure.

HRS occurs in patients with cirrhosis, acute hepatitis, fulminant hepatic failure and with hepatic malignancy.

Cirrhotic patient may have a reduced GFR before coming to medical attention. That is, the kidney of cirrhotic patient is always vulnerable to renal failure whether functional or ischaemic acute tubular necrosis.

Etiology :-

HRS usually develops in hospitalized patient, indicating that iatrogenic factors are playing important role in the pathogenesis of this disorder.

Abdominal paracentesis, vigorous diuretic therapy and bleeding- especially gastrointestinal-are known precipitating factors. Sometimes HRS is idiopathic.

Pathogenesis of HRS:

1- HRS is a functional renal failure, the arguments supporting this concept are:

- Pathological abnormalities in renal specimens obtained from patients with HRS are minimal and inconsistent.
- Tubular functional integrity is maintained. Sodium reabsorptive capacity and concentration ability are relatively unimpaired.
- Kidneys from patient with HRS will show immediate diuresis when transplanted in uraemic patient.
- When a cirrhotic patient with HRS receives a liver transplant, his kidney recovers immediately.
- Postmortem renal angiography in patients died with HRS discloses a striking reversal of all the intrarenal vascular abnormalities.

2- There is renal hypoperfusion with preferential cortical ischaemia.

- The effective circulating volume is decreased as a result of ascites and oedema formation.
- There is peripheral arterial vasodilatation

3- HRS constitutes an extreme extension of underfilling of the arterial circulation with the most extreme elevation of vasoactive hormones, including plasma renin activity, vasopressin, with a maximum degree of renal vasoconstriction.

4- Hormonal changes contributing in the pathogenesis of HRS are :

- Activation of the renin-angiotensin system: an increase in plasma renin activity due to renal hypoperfusion, decrease hepatic synthesis of α_2 -globulin, the renin substrate. This will contribute to renal vasoconstriction.
- Alterations in renal eicosanoids, there is decrease in the vasodilator prostaglandins and increase in the vasoconstrictor thromboxanes.

- Elevated plasma endothelin (E) levels (E-1, E-3) which are renal vasoconstrictors.
- Enhanced Nitric Oxide (NO) synthesis in peripheral vessels (by endotoxins) which results in an intense peripheral V.D. and renal hypoperfusion.
- Relative impairment of renal kallikrein production
- There is glomerulopressin deficiency

5- The role of systemic endotoxaemia and HRS

- Endotoxins are lipopolysaccharide constituents of the cell wall of certain bacteria. They are potent renal V.C. and may produce V.D. of other vascular beds.
- Enteric endotoxins are liberated into the systemic circulation through the porto-systemic shunts, thus bypassing the hepatic kupffer cells.

6- Neural and haemodynamic factors in HRS

- There is increase in sympathetic nervous system activity in cirrhosis with renal V.C. and sodium retention. Also there is an alteration in the intrarenal blood flow distribution.

Clinical features of HRS

The patient usually presents with manifestations of advanced liver disease and on development of HRS. There will be further progression of the bad general condition, disturbance of consciousness, mental concentration, increase in oedema, ascites and progressive oliguria and even anuria. Laboratory assessment will show a progressive increase in serum creatinine and blood urea.

Differential Diagnosis:

HRS should be differentiated from other causes of azotaemia in patient with advanced liver disease especially prerenal azotaemia and acute tubular necrosis. The following table presents the important differentiating points.

Pre renal	Hepatorenal	Acute tubular azotemia	syndrome	necrosis
Urinary sodium(mmol/L)	<10	<10	<10	>20
Urine/plasma creatinine ratio	>30/1	>20/1	>20/1	<20/1
Urine osmolarity (mosmol/l)	≥200 higher than plasma	≥200 higher than plasma	≥200 higher than plasma	relatively similar to plasma (isothernic)
Urine sediment	Normal	Normal	Unremarkable	Casts, cellular debris

Treatment of Hepatorenal Syndrome

- Treatment of HRS is largely supportive.
- Prevention is more important. Toxic agents as NSAIDs, demeclocycline, aggressive diuresis or aggressive paracentesis have to be avoided.
- If azotaemia is discovered in hepatic patient, the precipitating factor as volume contraction, cardiac decompensation and urinary tract obstruction have to be discovered and promptly treated.
- If prerenal azotemia is possible we have to give a volume expander (colloid as albumin or crystalloid as saline).
- Abdominal paracentesis with plasma volume expansion (e.g. by salt free albumin) may decrease the intra-abdominal pressure, decrease inferior vena cava obstruction and may increase the cardiac output and the renal perfusion.
- Dialysis may be indicated in selected patients with HRS. Mainly those with potentially reversible acute liver disease and those awaiting orthotopic liver transplantation.

The purpose of dialysis is to: 1- keep the biochemical profile in best possible shape, 2- remove excess fluid; and 3- allow giving required fluid or hyperalimentation.

The technique of dialysis suitable for patient with HRS is either the conventional haemodialysis or continuous arteriovenous haemofiltration (CAVH). The former is employed in patients with stable cardiovascular system while the later is used in hypotensive patient or in those with significant cardiac disease.

- Peritoneovenous shunt (e.g. Le Veen Shunt) which is a synthetic tube shunting fluid from the peritoneal cavity to the venous system (subclavian vein) has been used in patients with HRS.
Initial reports on this line of treatment demonstrate stabilization of renal function but with no prolongation of patient's survival.
- Transjugular intrahepatic portosystemic shunt. The rationale for this procedure is similar to that for the establishment of a side-to-side portocaval shunt (to decompress the portocaval system). Preliminary reports on the use of this technique in patients with HRS are successful, but they are few and anecdotal.

- Orthotopic liver transplantation is the definitive line of treatment in patients with end stage liver disease and HRS. The renal function is resumed immediately after transplantation.
- New experimental trials for the treatment of HRS include:
 - 1- The use of renal dose dopamine (i.v. 1-2 ug/kg/min)
 - 2- Misoprostol (PGE1 analogue) 0.4 mg orally four times daily plus albumin infusion.
 - 3- Thromboxane-receptor antagonist (ONO-3708)

Suggested Readings:

- Pol S: Hepatitis C virus infection in hemodialyzed patients and kidney allograft recipients. *Adv Nephrol Necker Hosp*, 24 : 315-30, 1995.
- Martin P: Chronic viral hepatitis and the management of chronic renal failure. *Kidney Int*, 47 : 5, 1231-41, 1995.
- Rüz HR, et al: Acute kidney insufficiency in an alcoholic patient with liver cirrhosis (clinical conference). *Schweiz Med Wochenschr*, 126 : 1306-13, 1996.
- Praditpornsilpa K, et al: Hepatitis virus and kidney. *Singapore*, 37 : 6, 639-44, 1996.
- Zeniya M, et al: Kidney in chronic active hepatitis. *Roikibetsu Shokogun Shirizum* 17 Pt 2, 471-4, 1997.

MALIGNANCY AND THE KIDNEY

The spectrum of renal involvement in malignancy includes the following:

- 1- Renal and urothelial tumours.
- 2- Renal and urinary tract metastatic involvement.
- 3- Renal involvement in multiple myelomatosis.
- 4- Renal infiltration by haematologic malignancy (lymphomas and leukemias).
- 5- Renal complications as a result of alterations induced by cancer as:
 - Glomerulonephritis.
 - Vasculitis.
 - Amyloidosis
 - Hemolytic uraemic syndrome.
 - Fluid and electrolyte disorders as hypercalcaemia, hypocalcaemia, hyponatraemia, hypernatraemia, hypophosphataemia hypokalaemia.
 - Tumour lysis syndrome.
- 6- Renal complications induced by cytotoxic drugs.
- 7- Malignancy in patients under renal replacement therapy.

(1) Renal and urothelial tumours

Renal and urothelial tumours include the following types:

- a- Renal cell carcinoma (Hypernephroma)
- b- Nephroblastoma (Wilms' tumour)
- c- Urothelial tumours such as squamous cell carcinoma of the bladder and transitional cell carcinoma of the urinary tract.
- d- Sarcoma

(2) Renal and urinary tract involvement by metastasis

It is usually due to carcinoma metastasizing into retroperitoneal lymph nodes with a consequent ureteric obstruction and hydronephrosis.

(3) Renal involvement in multiple myelomatosis

Multiple myelomatosis may affect the kidney through one or more of the following mechanisms:

- 1- Deposition of amyloid (AL amyloid), light chain, uric acid, or calcium into the kidney tissue .
- 2- Hyperviscosity and dehydration.
- 3- Renal infiltration by plasma cells.
- 4- Nephrotoxicity by drugs used for diagnosis or treatment of multiple myelomatosis.
- 5- Depression of immunity leading to pyelonephritis.

This may manifest clinically by one or more of the following syndromes (Fig. 15.3):

- 1- Glomerulopathy (Amyloid, fibrillary....)
- 2- Tubulointerstitial diseases as Fanconi's Syndrome, mostly due to the toxic effect of light chain on proximal convoluted tubules.
- 3- Acute tubular necrosis which is either:
 - Ischaemic (dehydration, hyperviscosity), or
 - Toxic (uric acid, drugs as NSAIDs, cytotoxic and contrast media).
- 4- Myeloma cast nephropathy.
- 5- Polyuria (hypercalcaemia)
- 6- Pyelonephritis.

Myeloma cast Nephropathy:

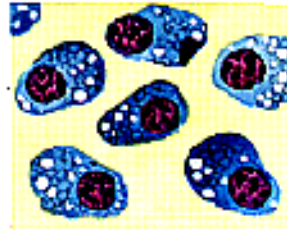
It is characterized with casts mainly of light chain protein and Tamm-Horsfall protein occupying the distal convoluted tubules and collecting ducts. These sometimes may be seen in the proximal convoluted tubules and even in the urinary space of the glomeruli.

Myeloma cast nephropathy is the most frequent lesion seen in myeloma patients (45%) and is the major cause of the renal failure among them.

Pathologically, the casts may be seen in the DCT with tubular atrophy. The casts look hard and sometimes look fractured, associated with crystal deposition and surrounded by inflammatory mononuclear cells and giant cells. Interstitium will show the fibrosis and infiltration by mononuclear cells.



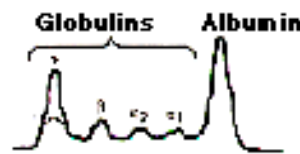
Typical localized lesions of myeloma are demonstrated in the upper femur of an adult female patient. The sharply defined rounded defects with endosteal erosion of the cortex are characteristic.



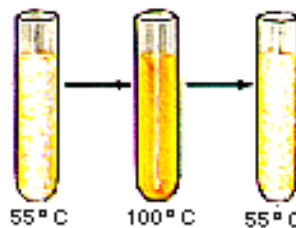
Bone marrow biopsy may show characteristic malignant myeloma cells



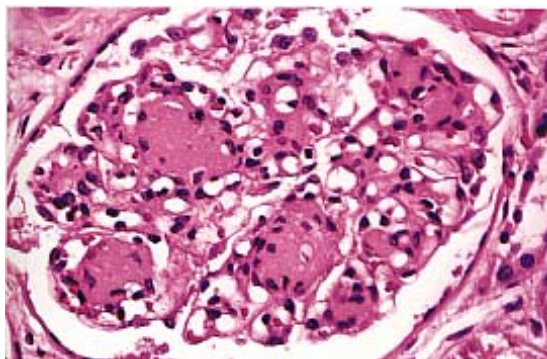
Peripheral blood may show Anemia; rouleau formation; increased blood viscosity



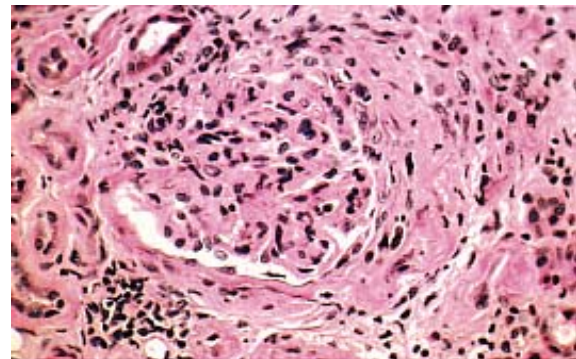
Presence of abnormal proteins in serum (Gamma spike); Also hypercalcemia



Bence Jones protein in urine in 60% of cases (precipitates at 45 to 60° C, redissolves at boiling, and reprecipitates on cooling to 60 or 55° C)



Multiple myeloma. Case of light chain disease. Glomerulus showing homogenous mesangial nodules with a few cell nuclei along the periphery. These nodules strongly resemble nodular diabetic glomerulosclerosis. PAS stain. X 260.



Multiple myeloma. Light chain disease. Proliferative glomerulonephritis with a fibroepithelial crescent. H & E stain. X 260.

(Fig. 15.3)

MULTIPLE MYELOMATOSIS WITH RENAL INVOLVEMENT

The glomeruli may be normal, show secondary sclerotic changes or may show glomerulopathy.

Fanconi's syndrome:

Usually, the diagnosis of Fanconi's syndrome precedes that of plasma cell dyscrasia (smoldering myeloma).

Pathologically, proximal convoluted tubules may show crystal deposition and degenerative changes.

Monoclonal immunoglobulin deposition disease (light chain deposition disease):

This constitutes a systemic disease due to deposition of light chain proteins in different organs including the kidney, liver, heart, nerve fibers, choroid plexus, lymph nodes, bone marrow and spleen.

In the kidney, the light chain proteins are deposited in the renal glomeruli and tubules. Light microscopy shows:

- *Tubules and interstitium:* There is deposition of refractile, eosinophilic PAS positive, ribbon-like materials along the outer part of the tubular basement membrane with variable degrees of tubular atrophy and interstitial fibrosis.

- *Glomeruli:* The most characteristic lesion is nodular glomerulosclerosis and resembling nodular diabetic glomerulosclerosis, but the distribution of the nodules here is fairly regular in a given glomerulus. In mild forms, the mesangium looks thickened.

Immunofluorescent microscopy is the key step for the diagnosis of light chain deposition disease. It may show light chain deposits in the tubular and the glomerular capillary basement membrane. Electron microscopy may show the electron dense deposits on the outer surface of the tubular and glomerular capillary basement membrane.

Amyloidosis:

Beside renal involvement, other clinical features which strongly suggest AL amyloid may appear as:

- Cutaneous purpura (non-thrombocytopaenic)
- Macroglossia
- Carpal tunnel syndrome
- Peripheral and autonomic neuropathy

POEMS Syndrome

(P= polyneuropathy, O= organomegaly, E= Endocrinopathy, M= M protein, S= Skin changes)

This is a rare multi-systemic disorder of an unknown origin occurring in association with plasma cell dyscrasias including the non-malignant monoclonal gammopathy and multiple myelomatosis.

POEMS syndrome may involve the kidney (but uncommonly) with proteinuria, microscopic hematuria or with renal failure.

Histopathologically, there will be interstitial nephritis, mesangio-capillary glomerulonephritis or any form of myeloma kidney.

Treatment is by steroids especially if the renal failure occurs.

Treatment of Myeloma kidney:

1- To prevent deposition of light chain and renal failure.

- Proper hydration
- Alkalinization of urine
- Treatment of hypercalcaemia
- Avoid nephrotoxic drugs as NSAIDs and contrast media
- Treatment of infection

2- Treatment of multiple myelomatosis:

- Alkylating agents (as Melphalan) and corticosteroids (prednisolone)
- Vincristine and Doxorubicin (especially with hypercalcaemia or ARF)

3- Plasma exchange

Especially with hyperviscosity, hypercalcaemia and ARF. Usually in conjunction with the other measures.

(4) Renal infiltration in Hematologic Malignancy

Generally, the renal involvement in haematologic malignancy takes one of the following forms:

- 1- Obstructive uropathy (mass effect)
- 2- Infiltration of the renal parenchyma, urinary tract or blood vessels
- 3- Urate nephropathy
- 4- Glomerulopathy
- 5- Therapy-related kidney damage
- 6- Amyloidosis
- 7- DIC

Renal involvement with lymphoma:

- Renal failure develops in up to 20% of lymphoma patients. It usually occurs through bilateral ureteric obstruction, renal vein thrombosis or the compression of the renal arteries.

- Renal parenchymal infiltration occurs in 50% of lymphoma patients. This manifests as a renal mass which is palpable clinically or is detected only by ultrasound. Histopathologically, diffuse lymphoid cells may be seen infiltrating the kidney tissue.

- Minimal change nephritis may occur especially with Hodgkin's lymphoma. This is most probably due to an increase in release of proteases or lymphokines by T-cells which increases the glomerular permeability to protein. Renal failure may occur with lymphoma or leukaemia due to infiltration.

Renal involvement in leukaemia

- Renal invasion was found at autopsy in 50-60% of patients who died from leukaemia. The infiltration is always bilateral and may be nodular or diffuse.

- Acute renal failure is common in acute leukaemia, while chronic renal impairment occurs in 1% of patients.

(5) Renal complications by alterations induced by cancer

A- Malignancy-related glomerulopathy

The occurrence of massive proteinuria in association with malignant neoplasia is uncommon, but highly instructive event. The renal lesions may antedate the discovery of tumour in two thirds of cases. This is usually encountered in patients above the age of 50 years.

Type of malignancy:

Glomerular diseases, principally manifested as heavy proteinuria or progressive renal failure, have been observed to occur in association with carcinoma such as carcinoma of the lung, breast, stomach and colon in addition to pheochromocytoma, Wilms' tumor, Hodgkin's disease, Burkitt's lymphoma and chronic lymphatic leukemia.

Histopathology:

Glomerular diseases complicating cancer usually present with the following histologic features:

- 1- Membranous glomerulonephritis (mainly with solid tumours)

- 2- Minimal change glomerulonephritis (Hodgkin's disease, pancreatic carcinoma, malignant mesothelioma, renal cell carcinoma and prostatic cancer).
- 3- Other lesions may occur as mesangiocapillary and crescentic glomerulonephritis.

Pathogenesis of malignancy-related glomerulopathy:

Glomerulopathy in cancer patient may be induced by cytokines released from abnormal T-cells or by released tumour antigens which may trigger immune complex mechanism for glomerular disease.

Evidence of causal relationship:

- Close temporal relationship between the clinical appearance of the renal lesion and of the tumour.
- Remission or complete removal of tumour should be associated with remission of nephropathy.
- Recurrence of tumour would be accompanied with the recurrence of nephropathy.

N.B.: patients over the age of fifty presenting with nephrotic syndrome should be thoroughly investigated for malignancy.

B- Malignancy-related vasculitis:

Systemic vasculitis and Henoch-Schönlein purpura have been reported in patients with haematologic malignancies and carcinoma. In these conditions, malignant neoplasia might act as an immunologic stimulus with the formation of immune complexes.

C- Malignancy-related amyloidosis

Renal amyloidosis has been reported in patients with multiple myelomatosis, lymphoma and carcinoma.

D- Malignancy-related hemolytic uraemic syndrome:

This has been observed with disseminated cancer and may be complicated with renal failure.

E- Malignancy-related fluid and electrolyte disorders.

1- Hypercalcaemia:

Malignant tumours are the single most common cause of hypercalcaemia. This may be mediated through release of PTH-like substance, PGE, transforming growth factors, interleukin, or 1.25 (OH)₂ Vit D.

2- hypocalcaemia:

It is very rare, but may occur in diffuse bone forming metastasis as in cancer prostate and cancer breast. Also, it may occur after extensive neck surgery for cancer thyroid with a damage of the parathyroid glands.

3- Hypophosphataemia:

It may result in what is called *oncogeneous osteomalacia* which is characterized by bone pains, muscle weakness, and pathological fractures. Biochemically, it is characterized by hyperphosphaturia, hypophosphataemia, high alkaline phosphatase, low 1, 25 (OH)₂ Vit. D and normal PTH levels. Starvation, malnutrition, vomiting, diarrhoea, use of AL (OH)₃ and parenteral hyperalimentation without phosphate supplementation may lead to hypophosphataemia.

4- Hyponatraemia:

It is common with malignancy. It may be due to gastrointestinal losses, heart failure, liver cell failure or due to SIADH.

5- Hypernatraemia

It may be due to craniopharyngioma or metastasis leading to the loss of secretion of ADH with CDI or due to hypothalamic tumours damaging the thirst center.

6- Hypokalaemia

This is mostly due to GIT losses as in villous adenoma or adenocarcinoma of the pancreas; or due to tumour secreting ACTH, renin or Aldosterone.

F- Acute tumour lysis syndrome:-

It occurs in patients with rapidly growing haematopoietic or lymphopoietic tumour (high turnover tumours) that are responsive to therapy. The massive cytolysis caused by anti-neoplastic agents or radiation therapy generates high levels of uric acid, potassium, phosphates and xanthine that cause acute renal dysfunction.

Acute hyperuricemic nephropathy is due to precipitation of urate crystals in the tubules.

Severe hyperkalaemia that may result from cell lysis with acute renal failure may result in lethal cardiac arrhythmias.

Hyperphosphatemia may precipitate calcium and phosphate in the kidney tissue leading to ARF

Prevention of tumour lysis syndrome is achieved by good hydration, use of allopurinol before chemotherapy and intensive monitoring of uric acid level and kidney function. When severe hyperuricaemia and ARF occur, dialysis prevents further kidney damage and promotes recovery of renal function.

(6) Renal complications of anti-neoplastic treatment

Anti-neoplastic drugs may be nephrotoxic. This is favored by dehydration, use of NSAIDs, aminoglycosides and amphotericin B.

• Cisplatin:-

- Produces dose-related nephrotoxicity.
- Pathologically, there are PCT dilatation, vacuolization, and hydropic degeneration.
- Adequate hydration, alkalinization of urine and forced diuresis with furosemide will decrease the risk of ARF

• Methotrexate:-

- High dose (1gm/m²) causes increase in serum creatinine
- The cause of toxicity is precipitation of the drug in the renal tubules

• Mitomycin:-

- It may induce HUS

• Methramycin:-

- This agent produces cumulative and persistent renal toxicity.
- Acute rise in serum creatinine can occur after a single dose therapy.

• Interferon:-

- May rarely induce proteinuria, increase in serum creatinine and ARF.
- This may be due to development of autoantibodies that trigger interstitial nephritis or glomerular abnormalities.

• Radiation nephritis:-

- It may occur when the kidneys are included in the field of therapeutic irradiation.
- It is now uncommon due to the development of advanced techniques for localized irradiation.

(7) Neoplasia as a complication of chronic renal disease

Uraemic patients are known to be at more risk to develop malignancy. This is even more pronounced in the following circumstances:

A- Analgesic-induced renal disease:-

Transitional cell carcinoma has high incidence in the patients with analgesic nephropathy.

B- Auto-immune renal diseases:-

- There is an increase in the incidence of cancer in SLE and in patients with primary GN.
- Auto immune diseases lead to functional defect in T cells (that normally limits the extent of B cell reaction). This may favour B cell hyperplasia in response to self antigens or viral infections in patients who are genetically predisposed. This uncontrolled B cell reaction progresses from hyperplasia to neoplasia.
- Immunosuppressive therapy can also predispose to neoplasia.
- Acute leukemia is the most frequent cancer induced by alkylating agents
 - Cyclophosphamide increases the risk of urinary bladder cancer.
 - Cyclophosphamide predisposes to malignancy after a cumulative dose of 80gm with a mean duration of 50 months.

C- Dialysis patients:-

- Dialysis patients have a greater incidence of cancer than general population.
- Pathogenesis
 - 1- original kidney disease.
 - Autoimmune disease.
 - Analgesic nephropathy.
 - Previous immunosuppressive therapy.
 - 2- Altered immune system by uraemia
 - 3- Dialysis itself has a carcinogenic potential due to the exposure to substances such as ethylene oxide, nitrosamine in haemodialysis and glutamic acid products in peritoneal dialysis.
 - 4- Acquired renal cyst may be complicated by renal carcinoma.
- Dialysis patients should be carefully monitored for the early diagnosis and the treatment of cancers.

D- Renal transplant recipients

- Renal transplant patients have an increased risk of cancer.
- The incidence of tumours in transplant patients ranges from 1-18%
- Cancer accounts for 26% of deaths in patients who have received transplantation for 10 years or more.
- Tumour may develop at any age with a mean age of 40 years.
- The pattern of tumours is radically different from that of the general population where the more frequent types are lip cancer, carcinoma of uterine cervix, hepatoma, carcinoma of the vulva and anus and skin cancer (squamous cell carcinoma)

- Non Hodgkin's lymphoma, and Kaposi's sarcoma have the greatest incidence in the transplanted patients.
- There is a strong association between EPV infection and post transplant malignancy, it has a poor prognosis with mortality rate up to 80%.
- Kaposi's sarcoma accounts for more than 6% of cancers in transplant recipients (frequently in mediterranean area).
- The mean interval of development of cancer is 22 months for Kaposi's sarcoma and 65 months for other tumours.

(8) Renal replacement therapy in patients with cancer

Dialysis:

- Generally dialysis therapy is provided only to patients with operable, chemo, or radiosensitive cancer.
- The 5-year actuarial survival of patients submitted to bilateral nephrectomy and dialysis because of bilateral renal cell cancer is 44% and the quality of life for them is similar to that of the overall dialysis population.
- In multiple myeloma complicated with irreversible renal failure, the bad prognostic criteria include large tumour mass, extensive osteolysis, severe hypercalcaemia and bone marrow hypoplasia.

Renal transplantation

The risk of tumour recurrence after transplantation is as follows:

- 1- Nil: In incidentally discovered renal neoplasms
- 2- Low (3-18%): In testicular carcinoma and insitu uterine carcinoma,
- 3- Intermediate (11-25%): In cancer body of uterus, Wilms' tumour, cancer colon, prostate and breast.
- 4- High (>25%): In cancer urinary bladder, sarcoma, melanoma, multiple myeloma symptomatic renal carcinoma and in non melanoma skin cancer.

2 years wait is recommended for most cancers but a longer period (5-year or more) is needed for colorectal, breast, prostatic cancer and in melanoma.

Suggested Readings:

- Dagher F, et al: Renal transplantation in multiple myeloma. Case report and review of the literature. *Transplantation*, 62 : 11, 1577-80, 1996.
- Kamaeva OI: Multiple myeloma and the kidneys. *Ter Arkh*, 69 : 6, 73-5, 1997.
- Gordeev AV, et al: Kidneys involvement in multiple myeloma. Therapeutic issues. *Klin Med (Mosk)*, 75 : 8, 60-2, 1997.
- Ozu H, et al: Multiple myeloma. *Ryoikibetsu Shokogun Shirizu*, 17 Pt 2, 340-2, 1997.

DRUGS AND THE KIDNEY

In this chapter we will discuss the following items:

- 1- Drug-induced kidney diseases
- 2- Drug handling in renal diseases, and
- 3- The clinical use of diuretics

I. Drug induced kidney diseases

The following kidney lesions may be drugs induced:

(A) Glomerular lesions:

- 1- Minimal change nephrotic syndrome may occur with NSAIDS
- 2- Membranous nephropathy may occur with gold, penicillamine, capoten, phenytoin and propenicid.
- 3- Acute nephritis may occur with penicillin, sulfa and amphetamines.

(B) Interstitial lesions:

- Chronic interstitial nephritis may occur with the long term use of NSAIDS
- Acute interstitial nephritis may occur with lasix, methicillin, thiazides and Rifampicin.

(C) Tubular lesion

- A.T.N. may occur with aminoglycosides, cephalosporins, outdated tetracycline, polymyxin and contrast media.

Renal Tubular Acidosis (RTA): Proximal RTA may occur with Tetracycline and heavy metals, while, Distal RTA may occur with vit. D toxicity and amphotericin B.

- Nephrogenic D.I.: May occur with Vincristine, lithium and colchicine.

(D) Obstructive uropathy:

- Nephrocalcinosis e.g calciferol toxicity
- Extrarenal by retroperitoneal fibrosis e.g methergide, methyl dopa and hydralazine.
- Intrarenal deposits as with urate and Dextran.

II. Drug handling in kidney diseases

Although renal impairment has its most important effect on drug excretion, other aspects of pharmacokinetics and pharmacodynamics may be affected. Here, we consider the basic pharmacokinetic changes that occur in the presence of renal impairment and how they affect drug usage.

(A) Drug Absorption:

1- Gastrointestinal Absorption:

- **Ammonia** produced in chronic renal failure buffers HCl of stomach Cl^- gastric HCl \rightarrow absorption of drugs that need low PH such as: Ferrous sulfate, chlorpropamide, folic acid, and cloxacillin.
- Aluminium OH used as phosphate binder for several drugs as iron, aspirin and ciprofloxacin.
- Diuretic resistance is reported in some nephrotics and is most probably due to binding of the drug in the tubular lumen and not due to poor absorption from edematous intestine because the addition of oral thiazide overcomes this resistance.

2- peritoneal absorption:

- Peritoneum is an absorptive surface during peritoneal dialysis.
- Absorption of gentamycin is unidirectional to the plasma.
- With peritonitis, insulin requirement may decrease as absorption increases with the mesothelial damage.

3- Subcutaneous and intramuscular routes of absorption:

The absorption of drugs from these sites is impaired in critically ill patients.

(B) Drug Distribution:

- Renal impairment increases acidic components that compete for binding sites on albumin decreasing drug protein binding
- Hypoalbuminaemia in nephrotics, elderly, cachectics lead to:
 - 1- The decrease of binding sites for drugs; and
 - 2- Free drug/bound drug ratio increases, this leads to great fluctuations in the free drug concentration following each dose.
- Binding of phenytoin to plasma protein is decreased in direct proportion to the decrease in GFR, and the free fraction can be removed by dialysis.
- Tissue binding of digoxin decreases in renal failure and smaller loading dose is needed. Also, the maintenance dose is smaller.

(C) Drug Metabolism:

- uremia affects drug metabolism and reduces non-renal clearance of drugs as:

acyclovir	(zovirax)	captopril	(capoten)
aztreonam	(azactam)	cimetidine	(tagamet)
cefotaxime	(claforan)	metoclopramide	(primperan)

- Uremia may reduce drug metabolism e.g. the activation of sulindac to active sulfide metabolite is reduced in uremia. Also, vit. D activation is impaired in uremia.
- First pass metabolism by the liver of some drugs such as inderal or cimetidine may be reduced in renal impairment.

(D) Renal drug excretion:

It depends on {
 Filtration
 Active tubular secretion/reabsorption
 Passive diffusion.

- Drugs of MW < 60,000 Dalton are filtered through the glomerulus.
- Lipid soluble drugs that diffuse readily across tubular cells whereas water soluble compounds do not.
- Organic acids e.g (penicillins, cephalosporins, aspirin, frusemide and thiazide) and organic bases as (amiloride, procainamide) have active tubular secretion. Some drugs decrease such secretion as probenecid.
- Drugs present in tubular fluid may affect excretion of other compounds such as:
 - Aspirin decreases excretion of methotrexate.
 - Low protein diet increases urine pH which leads to reabsorption of oxipurinol (metabolite of allopurinol) with more adverse reactions.
- Factors affecting clearance of drugs by haemodialysis or haemofiltration:

• Properties of the drug {
 MW
 protein binding
 volume of distribution

• Delivery of the drug to the filters {
 Blood flow to filter
 Blood flow within filter

• Properties of the filter {
 pore size
 surface area
 Duration of use

Drug prescription in renal impairment

The dose can be adjusted in two main ways:

- (1) The size of dose can be reduced. Or
- (2) The frequency of administration is reduced.

1- Antibacterials:

Most of antimicrobials have a wide therapeutic index and require no dose adjustment [except aminoglycosides and vancomycin] until GFR is < 20 ml / min.

- Penicillins:

- Both piperacillin and augmentin require the addition of half dose post hemodialysis
- Piperacillin should be given in half dose when GFR 20 -50 and 1/3 - 1/2 dose if GFR <20
- Benzyl penicillin daily dose should not exceed 20 million unit with renal failure.

- Cephalosporins:

- Oral first generation (cephalexin) is used in the usual dose till GFR is 10 ml below which the dose must be halved.
- Third generation cephalosporin dose is adjusted by increasing the dose interval.

cefotaxime 1-2 g / 12 hrs ceftazidime 0.5-0.75 gm /24hrs

- Aminoglycosides:

- Factors that increase the risk of their nephrotoxicity are:-
 - 1- previous or prolonged treatment
 - 2- hypovolemia or dehydration
 - 3- combined use with diuretics, hypokalemia or hypomagnesaemia
 - 4- obstructive jaundice
- Loading dose 1-1.5 mg / kg for gentamycin with trough level not more than (6-10 ng/l)

- Vancomycin:

- It is used extensively in resistant staph. infections; especially in peritonitis in C.A.P.D.
- The loading dose is 1.5 mg/ kgm, then 500 mg/5th day. i.v. or intraperitoneally.
- It is not dialyzable except when using high flux dialyzers.

- Aztreonam:

- It is monocyclic β -lactam
- It acts against Gram-ve organisms

- It's usual dose is 1gm / 8hrs.
- The loading dose is 250 mg / 8hrs when GFR < 10 ml / min.
- It is dialyzable, half dose is given after each dialysis session.

- Imipenem / cilastatin:

- It is a broad spectrum antibiotic except against pseudomonas.
- Cilastatin is dipeptidase inhibitor.
- The dose is 0.5 - 1gm /6hrs, reduced to 0.5 gm / 12hrs with renal impairment.

- Erythromycin:

- It is used in upper respiratory tract infection especially legionnaire's disease.
- It is not dialyzable
- It inhibits metabolism of cyclosporin

N.B. clindamycin is used with usual dosage while clarithromycin is usually used in half dose (0.5 gm / 12h).

- Tetracyclins:

- All are excreted renally except doxycycline and minocyclin
- They are contraindicated in renal disease except doxycycline
- They are not dialyzable
- Demeclocycline is vasopressin antagonist used in treatment of SIADH.

- Sulfonamides

- Eliminated by acetylation, excreted by kidneys, cause crystalluria and tubular damage
- Alkaline urine promotes sulfamethoxazole excretion, acidic urine promotes trimethoprim excretion.
- Half the dose is used if GFR = 20 ml /min, supplemented after dialysis.
- Are used in p.carinii infection Ø side effects, being balanced against seriousness of the condition.

2- Antiviral drugs:

- Acyclovir: 5gm / kg /8hrs In uremia Ø 2.5 mg / kg / day.
- Amantadine: 200 mg /day In uremiaØ200 mg every other day.
- Foscarnit: 90 mg/kg/day I.V. In uremiaØ unknown.
- Gancuclovir: 5 mg / kg /12 hrs In uremiaØ 1.25 mg/kg /24 hrs.

3- Antifungal drugs:

• Amphotericin B:

- Nephrotoxic; newer preparation encapsulated in liposomes avoids much of toxicity (liposomal amphotericin B).

- Protein bound & dialyzable, dialysis patients should receive the drug after dialysis.
- **Imidazoles (ketoconazole, miconazole):**
 - Extensively metabolized by liver (used in the usual dose)
 - When given with CsA, it increases its blood level
- **Fluconazole:**
 - Used in candida, and cryptococcal infection
 - Give half the dose if GFR < 50 ml / min., first, give loading dose of 400mg then, 200 mg / day
- **Griseofulvin:**
 - usual dosage does not interfere with CsA

4- C.N.S. drugs:

- Antidepressants:

- Tricyclics can be used in usual dosage.

- Tranquilizers:

- Major tranquilizers require no adjustment.
- Minor tranquilizers:
 - Benzodiazepines used in usual dose
 - Midazolam, cases with renal impairment are more sensitive, dose is reduced to between 1/4-1/3 when GFR is < 10 ml /min.

- Anticonvulsants:

- Phenyton and valproic acid are highly protein-bound and the binding declines in proportion to the G.F.R.
Neither of them is dialyzable. They are used in the usual dosage.
- Also carbamazepine is used in the usual dosage.
- All anticonvulsants other than Na⁺ valproate and vigabatrin are potent inducers of cytochrome P 450.

5- Antihistaminics:

- Both terfenadine and prochlorperazine are used in usual dosage

6- Cardiovascular drugs:

- Antiarrhythmics

- Most antiarrhythmics are used without modification e.g. lignocaine, amiodarone, flecainide, verapamil, sotalol; except digoxin which must be reduced to 0.125 mg / day depending on serum level (0.7 - 2 ng /ml), and ventricular response

- Digoxin is not dialyzable
- Quinidine can be used in the usual dosage.

- Antiangina:

- Nitrates given in the usual dose
- Ca⁺⁺ channel blockers are given in the usual dose
- Atenolol is dialyzable, requires supplemental 1/2 dose after dialysis, unlike other beta blockers propranolol, metoprolol, oxprenolol, pindolol.

- Diuretics:

- Thiazides lose their potency when GFR is < 25 ml / min
- Increasing doses of loop diuretics may be needed as GFR declines.
- All potassium sparing diuretics should be avoided in renal impairment.

- ACEI :

- All this class of drugs should be started at low dosage and the dose is increased slowly with the careful monitoring of serum creatinine and potassium.
- Avoid its combination with k⁺ sparing diuretics.
- ACEIs are dialyzable.

- losartan:

- Angiotensin II receptor blocker.
- Starting dose is 25 mg daily (1/2 dose if GFR is < 20).

- Vasodilators:

- Alpha (1) blockers (prazosin), Ca⁺⁺ channel blockers, minoxidil are all used by the usual dosage
- Minoxidil is dialyzable

- Centrally acting agents:

- Alpha methyl dopa & clonidine are given in the usual dose

7- Endocrine drugs:

- Insulin :

- Its requirements decrease with declining renal function (acute or chronic).
- Intraperitoneal requirement is 50% of the I.V. one

- Oral hypoglycaemic agents:

- Gliclazide (Diamicron) is of choice in renal impairment with a dose range of 40-320 mg /day.

- Metformin should be avoided when GFR < 20 ml / min to avoid metformin - induced lactic acidosis (can be treated by dialysis).

- Thyroid drugs:

Thyroxine and antithyroid drugs are given in their usual doses.

- Allopurinol:

- It is metabolized to oxypurinol which is responsible for its side effects.
- When GFR < 20 ml /min, the dose should not exceed 100 mg / day.
- It is given cautiously in transplant cases, as it interferes with imuran. This may result in leukopenia. When given together, the dose of imuran should be decreased to one third.

8- Antiasthma:

B- agonists by inhalation, oral or by I.V. routes require no adjustment of the dose.

9- G.I.T drugs:

• **H₂ receptor blockers:**

- Ranitidine is the preferable drug with renal impairment.
- It interferes with creatinine secretion with consequent increase in serum creatinine.
- The dose must be halved when GFR < 10 ml / min.
- It is dialyzable, supplemental dose is needed after dialysis.
- In peritoneal dialysis, a dose of 150 mg /12 hrs is given safely.

• **Omeprazole**

- It is given in the usual dose (20 -40 mg / day).

• **Misoprostol:**

- It is a prostaglandin analogue
- It is given in a dose of 200 mg / day in renal impairment alone or with NSAIDS.

• **Bismuth :**

- It is avoided in renal impairment.

• **Prokinetic drugs:**

- loperamide, lomotil Metoclopramide and Domperidone (motilium) are given in their usual doses.

10- NSAIDs

- They suppress prostaglandin synthesis by inhibiting cyclo-oxygenase enzyme.

- Renal prostaglandins (PGE₂, PGI₂) are mainly renal vasodilators and natriuretic.
- When NSAIDs are given in cases with heart failure, nephrotic syndrome, and liver disease, they may lead to
 - (1) ↓ GFR
 - (2) fluid retention
 - (3) Hyperkalaemia
- They are not dialyzable

11- Corticosteroids and immunosuppressive agents:

- Prednisone and prednisolone are not cleared by the kidneys but the dose must be reduced in dialysis patients as uremia may reduce their clearance by the liver. Normal doses can be used in nephrotics.
- Methylprednisolone is cleared by dialysis, so it should be given after dialysis
- Azathioprine should be reduced in renal impairment to a maximum of 1mg /kg /day if GFR is < 10 ml /min
- Cyclosporin A is metabolized by the liver via cytochrome P 450

Drugs affecting cytochrome P.450.

Inhibitors

ketoconazole
Erythromycin
Oral pills
Verapamil
Amiodarone
Quinidine

Inducers

Rifampin
Phenytoin
Phenobarbitone
Depakine
Tegretol
Omeprazole

- Cyclophosphamide dose should be reduced in renal impairment

• **Melphalan :**

- is used in M.myeloma
- half the dose if GFR is < 25 ml /min.

12- Vaccines:

- Live attenuated vaccines are contraindicated in immunocompromized patients.
- Repeated doses of vaccine to produce seroconversion is usually needed e.g for HBV.

III. Clinical use of diuretics

Diuretics are of clinical value in the following conditions: (A) Arterial hypertension, (B) Congestive heart failure, (C) Liver cirrhosis and ascites, (D) Nephrotic syndrome, (E) Acute renal failure, (F) Others.

(A) Arterial hypertension:

- Despite the introduction of new hypotensive drugs as ACEIs and calcium channel blockers, diuretics remain the corner stone in the treatment of hypertension.
- Their B.P. lowering effect is pronounced in the elderly, those with systolic hypertension, those with low renin states and those with volume dependent hypertension.
- Thiazide diuretics are more effective antihypertensives than are the loop diuretics except in renal impairment.
- They are useful as second antihypertensive agents.
- They are essential in overcoming Na⁺-retaining effect of other vasodilators as minoxidil.
- Mechanisms of their antihypertensive action:
 - (1) Normalization of enhanced intracellular Na⁺, and Ca⁺⁺ concentration.
 - (2) Decrease vascular response to vasoconstrictor agents as angiotensin II and noradrenaline.
 - (3) Increase formation of vasodilator prostaglandins.
 - (4) Decrease endogenous digitalis-like Natriuretic hormone which is vasopressor.
 - (5) Potassium channel opening effect in resistance arteries.

(B) Treatment of congestive heart failure:

- In cases with acute myocardial infarction or chronic heart failure, loop diuretics have immediate action in reducing pulmonary wedge pressure, decreasing cardiac index and increasing systemic vascular resistance. Left ventricular end diastolic pressure is decreased due to decreased preload.
- Metolazone (a thiazide diuretic) is effective in inducing diuresis in loop diuretic resistant cases. If the case is resistant to the combined loop and thiazide diuretic then continuous infusion of frusemide becomes successful.

(C) Diuretic in liver cirrhosis and ascites:

Aldosterone antagonists are more frequently used because of the high blood level of aldosterone in these cases. If the response is not satisfactory loop diuretics may be added.

In cirrhotic patients diuretics are used to treat ascites and to decrease portal hypertension.

(D) Diuretic treatment of nephrotic edema:

If the GFR is within normal, thiazide diuretics with or without aldosterone antagonists may be used.

When renal function is impaired, thiazides will be ineffective and loop diuretic are indicated. Furosemide (Lasix) is given orally in a variable dose according to the response. The dose may be increased up to 120 mg/d. If there is no response, the drug may be given intravenously and a thiazide as metolazone (Metinix) may be added.

If the response is still poor, salt free human albumin and I.V. loop diuretic are indicated.

In cases of severe intractable oedema not responding to the above mentioned measures, ultrafiltration (using haemodialysis machine) and I.V. human albumin may be useful.

The resistance to loop diuretics in renal failure is due to pharmacokinetic and pharmacodynamic causes.

a) Pharmacokinetic causes:

This is mainly due to the decrease in drug delivery to loop of Henle as a result of:

- Decrease renal perfusion
- Decrease volume of distribution
- Decrease diuretic secretion in tubule resulting from the competition with organic acids.
- Binding of diuretic to filtered albumin.

b) Pharmacodynamic causes

This is mainly due to the decrease in the number of functioning nephrons with a consequent decrease in Na filtered load .

Loop diuretics in hemodialysis patients may have a role - by large doses - in controlling the fluid balance in selected patients.

(E) Diuretics in Acute Renal Failure (ARF)

(1) Mannitol:

- Its infusion during early stages of AFR may prevent the loss of renal function. Yet, this statement is still debatable.
- The probable mechanisms of actions:
 - 1- Increase intratubular flow rate which prevent obstruction by debris, and proteins.
 - 2- Decrease endothelial and epithelial cell swelling.
 - 3- Protect mitochondrial function.

4- Decrease O₂ free radicals.

5- Renal V.D. (due to increase in prostaglandin, and decrease in renin)

(2) loop diuretics:

- Debatable
- Its use with renal dose dopamine in incipient ARF is the treatment of choice in many centers, although this approach is still empirical.
- Possible mechanisms :
 - (1) Decrease transport activity of loop of Henle.
 - (2) Remove obstructing casts.
 - (3) renal V.D. by increasing prostaglandin.

(F) Other indications of diuretics:

- (1) glaucoma
- (2) urine alkalinization
- (3) Calcium nephrolithiasis
- (4) Treatment of hypercalcaemia
- (5) Treatment of toxicity of aspirin and phenobarbitone.

KIDNEY AND THE HEART

This issue could be discussed by covering the following items:

- 1- Effects of cardio-vascular diseases on the kidney.
- 2- Effects of renal diseases on the heart.
- 3- Diseases affecting both organs.
- 4- Cardiac drug modification in renal diseases.

Effects of Cardiovascular Diseases on the Kidney

The following are some of the effects on the kidney which may be induced by cardiovascular diseases.

1- Heart failure, affects the kidney through the backward and the forward failure effects.

a- systemic venous congestion

This results in an increase in the capillary pressure, transudation into interstitial spaces with decrease in effective circulating volume. This will be aggravated by the presence of forward failure and decrease in perfusion of the vital organs including the kidney.

The result is oliguria; and in severe cases it may lead to prerenal failure. Increase in right atrial pressure and systemic congestion will increase secretion of ANP.

b- Decreased cardiac output.

This results in a decrease in the renal perfusion with:

- Renal vasoconstriction
- Increased secretion of renin, angiotensin, aldosterone with consequent salt and water retention.
- Increased secretion of ADH with consequent water retention.

2- Infective endocarditis: This may result in glomerulonephritis, embolic renal disease and renal impairment.

3- Cardiogenic shock: This may result in either pre-renal failure or acute tubular necrosis; according to the severity and the duration of the condition.

4- Atrial fibrillation may lead to thromboembolic disease involving the kidney.

5- Hypertension may result in nephrosclerosis.

6- Dissecting aortic aneurysm may extend to affect the renal vessels with consequent ischaemic renal disease.

Effects of the Kidney on the Cardiovascular System

- 1- Hyperlipidaemia may complicate renal disease as nephrotic syndrome and chronic renal failure. This may play a major role in the pathogenesis of systemic atherosclerosis and coronary artery disease.
- 2- Renal hypertension may perpetuate atherosclerosis, coronary artery disease and may lead to hypertensive heart failure.
- 3- Hypervolaemia of renal failure may result in pulmonary oedema.
- 4- Hypovolaemia of nephrotic syndrome may result in postural hypotension.
- 5- Deep vein thrombosis as a known complication of nephrotic syndrome which may result in pulmonary embolism.
- 6- Chronic renal failure may result in pericarditis, uraemic cardiomyopathy, pulmonary oedema or coronary artery disease.
- 7- Anaemia due to renal failure may result in heart failure and anginal pain.
- 8- Electrolyte and acid-base disorders resulting from renal diseases may have cardiac manifestations as arrhythmia and intractable heart failure.

Diseases Affecting Both Organs

Many diseases may affect the heart and kidney such as:

- 1- Viral infection which may cause myocarditis and interstitial nephritis.
- 2- Parasitic diseases as schistosoma that may lead to corpulmonale and schistosomal nephropathy.
- 3- Autoimmune diseases as SLE which may cause cardiomyopathy and lupus nephritis.
- 4- Systemic vasculitis that may affect the heart and the kidney.
- 5- Systemic amyloidosis that may lead to cardiomyopathy and nephropathy.
- 6- Metabolic diseases as diabetes mellitus and hyperparathyroidism may affect both systems.
- 7- Toxic substances as NSAIDS heavy metals as lead may affect both systems.

Modification of cardiac drugs in renal disease

See the chapter on drugs and kidney (Page 383).

Suggested Readings:

- Leschke M, et al: Coronary heart disease in patients with end-stage kidney failure. Dtsch Med Wochenschr, 133 : 31-32, 967-82, 1997.
- Bellomo R, et al: The kidney in heart failure. Kidney Int Suppl, 66 : S58-61, 1998.

KIDNEY AND THE LUNG

The interaction between the kidney and the lung is enormous. The following are examples of this relationship:

- 1- Renal disease may result in pulmonary disease such as:
 - Hypercoagulable state in nephrotic syndrome that may be complicated by DVT which may result in pulmonary embolism.
 - Pulmonary oedema may complicate fluid overload or severe hypertension secondary to a renal disease as acute nephritis and chronic renal failure.
- 2- Pulmonary disease may be complicated with renal disease such as:
 - Bacterial pneumonia and upper respiratory infection may lead to acute nephritis.
 - Pulmonary TB and empyema may lead to renal amyloidosis.
- 3- A systemic disease may effect both organs as SLE, Good pasture's syndrome and cryoglobulinaemia.

RENAL DISEASES IN THE ELDERLY

As a result of improvement of quality of medical service and nutritional status, there is an increase of longevity with a consequent increase in elderly population.

Kidney wise, there are structural and functional changes which take place in the kidney with age. These changes have an impact on the management of these patients.

The renal structural and functional changes with aging are as the following:

1- Structural changes:

Macroscopically, there is a reported decrease in the kidney size which may reach up to 20-40% (on comparing ages of 30 to 90 years). This reduction in renal mass is most probably related to the reduction in body mass.

Microscopically, with age the following microscopic findings could be observed:

- There is an increasing reduction in the number of glomeruli and there is an increase in glomerular sclerosis. Also, there is an increase in the GBM thickness.
- Renal tubules show an irregular thickening of the basement membrane especially in the DCT. The overall tubular mass is decreased. The interstitium may show areas of tubular atrophy and interstitial fibrosis.

- The renal vessels may show intimal thickening and reduplication of the elastic lamina.
- These structural renal changes may start as early as the age of 30 years.

2- Functional changes:

There is an age-related reduction in both renal plasma flow and glomerular filtration rate. The renal plasma flow declines at approximately 10% per decade from about the age of 30 years.

The renal plasma flow decreases by 10ml/min every decade of life and the glomerular filtration rate declines with age at a decremental rate of 0.75 ml/min/year. The cortical blood flow is reduced to a greater extent than the medullary flow.

As there is a reduction in muscle mass and body weight with age, the reduction in GFR is not associated with comparable changes in serum creatinine because of the decrease in endogenous creatinine production. So, for proper assessment of the kidney function in elderly, creatinine clearance with 24 hours urine collection is mandatory. Equations relying on body weight for calculation of GFR are misleading in the elderly.

Tubular function seems to be little influenced by age, although it is recognized that the ability to concentrate and dilute urine is impaired. In addition, there is a reduction in the ability of the nephron to conserve sodium.

Glomerular Diseases in The Elderly:

Some forms, particularly membranous nephropathy, may be more common in elderly. This may be linked to the increased incidence of malignancy among this group of patients.

Elderly patients often have multiple pathology such as hypertension, diabetes and atherosclerotic changes. Any of these may be a cause or associated with primary glomerular disease.

Tubulointerstitial diseases in the Elderly:

Patients are more at the risk of having tubulointerstitial nephritis than younger patients are. This is most probably due to:-

- Elderly use drugs more commonly than young; especially NSAIDS.
- Diminished drug clearance, due to decreased GFR.
- Presence of co-morbid conditions, making them more vulnerable to drug nephrotoxicity (as DM, heart failure).

Renovascular Disease:

Elderly are the main victims of renovascular hypertension and ischaemic nephropathy.

End-stage renal disease in the Elderly:

Dialysis:

There is a growing trend that there should be no age limit for the acceptance to dialysis therapy so far the patient could benefit from treatment. This decision should be taken after careful consideration of the patient's general and psychological health as well as his or her family circumstances.

Haemodialysis is always confronted with the following difficulties:

- Vascular access problems.
- Cardiac insufficiency and vascular instability during dialysis.
- Tolerance of interdialysis fluid gain is always poor.

However, in view of the availability of advanced dialysis facilities and experienced physicians and nursing staff, many elderly patients can achieve a satisfactory degree of rehabilitation by haemodialysis.

Peritoneal dialysis is always well tolerated by elderly patients.

Transplantation:

Elderly are less tolerable to immunosuppression and corticosteroid therapy.

Previous cerebrovascular disease seems to be of particular poor prognostic significance.

If there is no comorbid condition, transplantation is still the best therapeutic option with better patient survival.

Suggested Readings:

- Lindeman RD, Tobin J, Shock NW: Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 1985; 33 : 278-285.
- Abrass CK: Glomerulonephritis in the elderly. *Am J Nephrol* 1985; 5 : 409-418.
- Lamy PP: Renal effects of nonsteroidal antiinflammatory drugs: Heightened risk in the elderly? *J Am Geriatr Soc* 1986; 34 : 361-367.
- Kasiske BL: Relationship between vascular disease and age-associated changes in the human kidney. *Kidney Int* 1987; 31 : 1153 : 1159.
- Gourtsagiannis N, Prassopoulos P, Cavouras D, Pantelidis N: The thickness of the renal parenchyma decreases with age: A CT study of 360 patients. *AJR* 1990; 155 : 541-544.
- Röhrich B, Asmus G, Von Herrath D, Schaefer K: Is it worth performing kidney replacement therapy on patients aged over 80? *Nephrol Dial Transplant.* 1996; 11 : 2412-2413.
- A. Davison. Renal diseases in elderly. *Nephron* 1998, 80 : 6-16.

KIDNEY AND PREGNANCY

This chapter on kidney and pregnancy will shed the light on the following items:

- 1- Renal physiological changes during pregnancy
- 2- Renal alterations in Toxemia of pregnancy
- 3- Obstetric-related acute renal failure
- 4- Some specific renal diseases in relation to pregnancy.

1- Renal Physiologic changes during pregnancy:

- The blood pressure decreases in early phases of normal pregnancy due to the reduction in systemic vascular resistance. As pregnancy approaches full term, these changes become attenuated and blood pressure returns towards normal.
- There is extracellular fluid volume expansion as a result of augmentation in renal tubular salt and water reabsorption induced by the excess oestrogen and aldosterone and fall in blood pressure.
- There is increase in the cardiac output and in the renal perfusion.
- GFR increases in the first trimester and reaches a peak (about 50% above the non pregnancy level) and serum creatinine decreases to about 0.3-0.5 mg/dl by the beginning of second trimester
- GFR returns towards baseline during 9th month of gestation.

2- Toxaemia Of Pregnancy (Preeclampsia and Eclampsia)

Definition:

Preeclampsia is characterized with gradual onset of hypertension, proteinuria and edema which usually manifest after the 20th week of gestation. In severe cases, this may progress to a convulsive phase which is then called eclampsia.

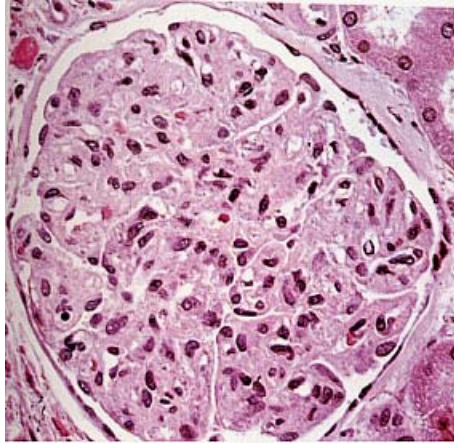
Incidence: 5-10% of all pregnancies are complicated with toxemia.

Pathogenesis:

There is a uteroplacental ischemia due to vasoconstriction of the placental vessels. This is mediated by abnormal prostaglandin metabolism which results in the increase in thromboxane level and activation of coagulation system. This leads to obliteration of the placental vessels by platelets and fibrin. Ischemic placental degeneration occurs, this may result in the release of thromboplastins into the systemic circulation leading to fibrin deposition in the kidney and other organs.

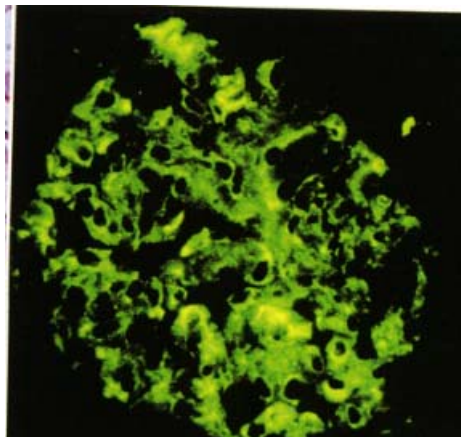
Renal pathology:

Glomeruli show swelling and ballooning of the endothelial and mesangial cells leading to the narrowing of the glomerular capillary lumens (Fig. 15.4a). This characteristic ballooning of endothelial cells may be related to fibrin deposition (Fig. 15.4b) and is called glomerular endotheliosis.



(Fig. 15.4a)

H & E stained kidney section (X 360) of a case with preeclamptic toxemia of pregnancy. It shows minimal increase in cellularity and occlusion or extreme narrowing of capillary lumina. The glomerulus appears uniformly "Solid"



(Fig. 15.4b)

The same case examined by immunofluorescence microscopy (X 260), it shows deposits of fibrinogen along the capillary walls and in the mesangium.

Electron microscopy shows widening of the glomerular basement membrane by fibrin deposits.

Immunofluorescence microscopy shows deposits which are mainly of fibrinogen along the capillary walls and the mesangium (Fig. 15.4b).

After termination of pregnancy, these changes resolve within 2-3 weeks.

In severe preeclampsia, there may be extensive glomerular deposition of fibrin and platelets which may be associated with cortical necrosis or delayed and incomplete recovery of renal damage.

Management:

- Close monitoring of pregnancy
- Use of prophylactic low dose aspirin in high risk patients.
Category of patients at risk of toxemia of pregnancy includes:
 - Diabetics
 - Hypertensives
 - Those with laboratory risk factors such as hyperuricaemia and hypocalciuria. These are due to increased tubular reabsorption of uric acid and calcium.
- Patients prone to develop toxemia of pregnancy characteristically demonstrate increased blood pressure response to infusion of angiotensin II at as early as 24th week of pregnancy. Also, in these patients there is exaggerated blood pressure response to changes in posture with more increase in supine position. In these patients, the percentage of development of hypertension or preeclampsia is 45% while only 5% of non responders develop these complications.
- The definitive treatment of toxemia of pregnancy is the delivery of the fetus and placenta. The only reason to delay delivery in established preeclampsia is evidence of fetal immaturity. In this setting bed rest in lateral recumbent position and antihypertensive agents should be used until delivery is safely performed. However, delivery should not be delayed if there are signs indicating that the mother is at risk of progression to eclampsia. These include uncontrollable hypertension, visual disturbance, seizures, HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count) or D.I.C.
- We have to use safe antihypertensive drugs during pregnancy including α methyl dopa, atenolol, and hydralazine
- ACEI and diuretics are contraindicated during pregnancy.

3- Obstetric-Related Acute Renal Failure:

Acute renal failure can occur during pregnancy in a variety of situations similar to those causing sudden renal dysfunction in nonpregnant patients. However, pathology peculiar to pregnancy must always be considered.

Acute fatty liver of pregnancy can be complicated by renal failure and its early recognition with prompt treatment reduces fetal and maternal mortality rates. Hemolytic-uremic syndrome is also associated with high morbidity and mortality rates.

- Treatment of sudden acute renal failure resembles that in non pregnant populations and aims at retarding the appearance of uremic syndrome, acid-base and electrolyte disturbances and volume problems (i.e. overhydration when the patient is oliguric and dehydration during the polyuric phase).
- Infection problems should be taken seriously.
- Some of the problems can be dealt with judicious conservative management, but if such an approach is unsuccessful, dialysis must be used promptly.
- Urea, creatinine and a variety of metabolic waste products cross the placenta. Then, "prophylactic" dialysis could be more compelling in a pregnant woman with an immature fetus and in whom temporization is desired.
- The method of dialysis (peritoneal or hemodialysis) should be dictated by facilities available and by clinical circumstances.
- Peritoneal dialysis is effective and safe as long as the catheter is inserted high in the abdomen under direct vision through a small incision. It probably minimizes the rapid metabolic perturbation which occurs with haemodialysis and provides another route for drug administration.
- Controlled anticoagulation with heparin during hemodialysis should be similar to that used in non pregnant patients.
- Great care should be given to avoid significant volume shifts during hemodialysis to avoid impairment of uteroplacental blood flow.
- Early delivery (as dictated by fetal maturity) should be undertaken.
- Blood losses at or after delivery should be corrected.
- The neonate can be subject to rapid dehydration because of increased concentrations of urea and other solutes within the fetal circulation which precipitates an osmotic diuresis shortly after birth.
- Once the patient has recovered from acute renal failure, she should have no difficulty in conceiving or carrying another pregnancy to term.

4- Specific kidney diseases and pregnancy

Renal disease	Effects and outcome
Chronic glomerulonephritis	Usually no adverse effect in the absence of hypertension. One view is that glomerulonephritis is adversely affected by the coagulation changes of pregnancy. Urinary tract infections may occur more frequently
IgA nephropathy	Risks as uncontrolled and/or sudden escalating hypertension and worsening of renal function
Pyelonephritis	Bacteriuria in pregnancy can lead to exacerbation. Multiple organ system derangements may ensue, including adult respiratory distress syndrome
Reflux nephropathy	Risks of sudden escalating hypertension and worsening of renal function
Urolithiasis	Infections can be more frequent, but ureteral dilatation and stasis do not seem to affect natural history. Limited data on lithotripsy, thus best avoided.
Polycystic disease	Functional impairment and hypertension are usually minimal in childbearing years
Diabetic nephropathy	Usually no adverse effect on the renal lesion, but there is increased frequency of infection, oedema, and/or pre-eclampsia
Systemic lupus erythematosus	Controversial; prognosis most favorable if disease is in remission >6 months prior to conception. Steroid dosage should be increased postpartum
Polyarteritis nodosa	Fetal prognosis is dismal and maternal death often occurs
Scleroderma	If onset during pregnancy then there can be a rapid overall deterioration. Reactivation of quiescent scleroderma may occur postpartum
Previous urinary tract surgery	Might be associated with other malformations of the urogenital tract. Urinary tract infection is common during pregnancy. Renal function may undergo reversible decrease. No significant obstructive problem but Caesarean section often needed for abnormal presentation and/or to avoid disruption of the continence mechanism if an artificial sphincter is present
After nephrectomy, solitary kidney and pelvic kidney	Might be associated with other malformations of the urogenital tract. Pregnancy is well tolerated. Dystocia rarely occurs with pelvic kidney.
Wegener's granulomatosis	Limited information. Proteinuria (\pm hypertension) is common from early in pregnancy. Immunosuppressives are safe but cytotoxic drugs are better avoided
Renal artery stenosis	May present as chronic hypertension or as recurrent isolated pre-eclampsia. If diagnosed then transluminal angioplasty can be undertaken in pregnancy if appropriate.

Pregnancy In Dialysis Patients:

- These patients are usually infertile but contraception should not be neglected.
- The live birth outcome at best is 36%. Realistically, these women should not take any health risks.
- Early diagnosis of pregnancy in dialysis patients is difficult because the symptoms of early pregnancy may look like uremic symptoms, urine pregnancy test is unreliable. So if pregnancy is suspected ultrasound is the method of choice.

Pregnancy in kidney transplant patients

- Is not free of risk to both foetus and the mother.
- Neonatal problems in offsprings of renal transplant patients include
 - Pre-term delivery, offspring is always small for gestational age
 - Respiratory distress syndrome is more common
 - Lymphoid-thymic hypoplasia is more common
 - Adrenocortical insufficiency is more common
 - CMV, HBV and HCV hepatitis are more common.
 - Congenital anomalies.
- Criteria for the reduction of post transplant pregnancy risks are the following:
 - 1- Pregnancy occurring 1 1/2-2 years post-transplant.
 - 2- Patients with reasonable graft function
 - Serum creatinine < 2 mg/dl
 - Preferably < 1.5 mg/dl
 - 3- Patients with no recent episode of rejection
 - 4- Normotensives or those using minimal antihypertensive drugs
 - 5- Patients with minimal or no proteinuria
 - 6- Patients with normal graft ultrasound
 - 7- Patients with Prednisone < 15 mg/day, Azathioprine < 2 mg/kg/day, and Cyclosporine within the therapeutic window.

Important remarks:

- In perinatal period, steroid dose should be augmented to cover the stress of labour and to prevent precipitation of rejection.
- Breast feeding should be discouraged.
- Great care should be taken to the graft function during the 3 months postpartum.

Suggested Readings:

- Marwah D, et al: Renal disease in pregnancy. *Curr Opin Nephrol Hypertens*, 5 : 2, 147-50, 1996.

- Jungers P, et al: Pregnancy in renal diseases. *Kidney Int*, 52 : 4, 871-85, 1997.

- Bernheim J: Hypertension in pregnancy (clinical conference). *Nephron*, 76 : 3, 254-63, 1997.

- Suzuki S, et al: Postpartum renal lesions in women with pre-eclampsia. *Nephrol Dial Transplant*, 12 : 12, 2488-93, 1997.

- Hussey MJ, et al: Obstetric care for renal allograft recipients or for women treated with hemodialysis or peritoneal dialysis during pregnancy. *Adv Ren Replace Ther*, 5 : 1, 3-13, 1998.

- Hou S, et al: Management of the pregnant dialysis patient. *Adv Ren Replace Ther*, 5 : 1, 24-30, 1998.

- Schmidt RJ: Fertility and contraception in end-stage renal disease. *Adv Ren Replace Ther*, 5 : 1, 38-44, 1998.

- Paller MS: Hypertension in pregnancy. *J Am Soc Nephrol*, 9 : 2, 314-21, 1998.

ENVIRONMENTALLY-INDUCED KIDNEY DISEASES

The extent of the contribution of environment in causing renal disease is unknown. This is largely due to the following: 1- The fact that multiple environmental factors could be working together, 2- Difficulty in confirming and quantifying the exposure to a certain environmental toxin; and 3- The lack of specific clinical or pathologic presentation of different environmental toxin.

In the USA, 19% of patients with end stage renal failure have disease of unknown cause and in 30 per cent of those presenting with glomerulonephritis the aetiology is unrecognized, possibly environmental toxins are responsible at least in part for these cases.

The kidney is more prone to environmental toxins for the following reasons:

- 1- The kidney is the principal organ for excretion of different toxins;
- 2- High renal blood flow;
- 3- Extensive surface of endothelial contact with toxins;
- 4- Positive intraglomerular hydrostatic pressure;
- 5- The medullary counter-current multiplier system leading to more accumulation of toxic agents and their metabolites in the renal medulla.

The environmentally-induced renal injury may be tubulo-interstitial, glomerular or combined. Tubulo-interstitial lesions may be in the form of acute tubular necrosis (such as exposure to high concentration of mercury) or chronic tubulointerstitial nephritis (such as chronic exposure to low doses of lead). Glomerular lesions may be due to direct toxicity (such as deposition of gold in basement membrane and silica in the mesangium) or immunologically-induced (for example immune complex disease in chronic exposure to hydrocarbons).

Environmental chemicals with nephrotoxicity includes solvents, hydrocarbons, heavy metals and fungal toxins. Other environmental nephrotoxins include physical agents (e.g. radiation injury) and biological (e.g. parasite as bilharziasis and malaria).

Volatile Hydrocarbons (Organic Solvents) As Environmental Nephrotoxins

Types of exposure include:

- Ingestion or inhalation of carbon tetrachloride;

- Intentional sniffing of cleaning fluid (toluene-containing glues, trichloroethylene, 1,1,1,-trichloroethane);
- Suicide attempts by ingestion of tetralin;
- Occupational exposure (inhalation of trichloroethylene, diesel fuel and toluene, paints, glue, degreasing solvents);
- Washing hands and hair with diesel fuel;
- Domestic solvent inhalation.

Kidney lesions induced by organic solvents include:

- Acute tubular necrosis owing to exposure to high doses of organic solvent;
- Chronic tubulo-interstitial nephritis as a consequence of acute exposure;
- Glomerulonephritis owing to chronic exposure with possibly genetic predisposition, which may result in either anti-GBM glomerulonephritis, membranous glomerulonephritis or proliferative glomerulonephritis.
- Clinically, renal lesions may present as acute renal failure, chronic renal failure or nephrotic syndrome; and neoplasia especially renal cell carcinoma.

Heavy Metals As Environmental Nephrotoxins

These include lead, cadmium, mercury, uranium and arsenic. Moreover, addition, therapeutic forms of gold, bismuth and platinum can cause nephrotoxicity. Silicon, beryllium, lithium, barium and selenium are not heavy metals (specific gravity <5) but may cause nephrotoxicity.

Lead nephrotoxicity:

Prior to the industrial revolution the normal total body burden of lead was 2mg. In a typical modern industrialized society, it is now about 200 mg. About 10-15 per cent of ingested and 40 per cent of inhaled lead is absorbed.

Exposure:

- a) Occupational: metal smelting workers, miners, storage battery workers, pottery makers, automanufacturers, ship builders, paint manufacturers and painting industry.
- b) Household: lead-glazed pottery, moonshine whisky, lead added to aphrodisiacs, herbal and folk medicines.
- c) Others: retained bullet, leaded gasoline.

Acute lead nephropathy:

This may manifest as acute renal failure with Fanconi syndrome and systemic disease including abdominal colic, anorexia, vomiting, constipation, anaemia, peripheral neuropathy and encephalopathy.

Lead containing inclusion bodies will be detected in renal tubular cells, urine, liver, neural tissue and osteoblasts.

Good responses can be achieved by chelation therapy (EDTA, BAL and Penicillamine).

Chronic lead nephropathy:

Histologically, it will appear as a slowly progressive tubulointerstitial nephritis. Clinically, this manifests as chronic renal failure, hypertension, hyperuricaemia and gout. These manifestations are associated with others, including gastrointestinal, haematologic and neurologic. The diagnosis is confirmed with the detection of an abnormal body lead level >80 ug/L and positive EDTA lead chelation test. In the hypertensive gouty patient with chronic renal failure and without stone disease, chelation test may detect an unrecognized lead exposure.

Chronic lead nephropathy, especially if diagnosed and treated early could be arrested or its progression is retarded.

Ca Na₂ EDTA is given in combination with BAL for symptomatic cases.

Cadmium nephropathy:

Source of exposure: Cadmium is a component of metal alloys, in the manufacture of electrical conductors, electroplating storage batteries, aircraft industries, as a by-product of iron smelting, as a pigment, in ceramics, glass, in plastic stabilizer, in photographic developer, rubber or dental prosthetics. Also, the burning of coal, oil and cigarettes.

Cadmium toxicity: The acute absorption of as little as 10 mg of dust or fumes will cause severe gastrointestinal symptoms; and 12 hours later, pulmonary oedema. Chronic low dose exposure will cause emphysema, anosmia and renal disease. Early renal manifestations are those of adult Fanconi syndrome, tubular proteinuria and renal tubular acidosis. Urinary calculi are detected in 40 per cent of cases. In late phases chronic renal failure appears.

Treatment: Ca Na₂ EDTA is of little value after cadmium has fixed in tissues. Vitamin D and calcium may be of help for bone disease, but may aggravate renal disease (by more stone formation).

Mercury nephrotoxicity:

Mercury toxicity depends on its chemical form and route of administration. Elemental mercury is harmless when ingested but when its vapour is inhaled will be very toxic. Environmentally, mercury is either organic

or inorganic salt. Toxicity is usually caused by methyl, ethyl, or phenoxyethyl organic salts and the chloride salt.

Acute mercury nephrotoxicity will manifest as acute renal failure due to acute tubular necrosis associated with erosive gastritis, haematemesis and melena.

Chronic mercury nephrotoxicity will manifest as tubulo-interstitial nephritis or nephrotic syndrome (due to membranous nephropathy or nil-change disease or less commonly anti-GBM disease) which is associated with neurologic deficits.

Treatment: Acute toxicity is treated with BAL and chronic toxicity by removal from the source of exposure.

Arsenic nephrotoxicity:

Elemental arsenic is not toxic, but the pentavalent, trivalent salts and arsine gas (Arsine) are very toxic.

Exposure:

- Industry: glass, pigment, bronze plating or metal alloys.
- Wood preservation, veterinary medicine, herbicides, insecticides and rodenticides.
- Certain herbal preparations, burning of arsenic-treated wood or arsenic containing prescription medicines.
- Arsine can be released from sewage plants.

Clinical manifestations of arsenic nephrotoxicity:

- a) Acute exposure (for example arsine gas): Acute renal failure (ATN), haemolytic anemia, cardiomyopathy, encephalopathy, epigastric pain, vomiting and explosive diarrhoea. This is usually fatal and those who recover develop chronic renal failure.
- b) Chronic exposure: slowly progressive renal failure, encephalopathy, polyneuropathy, cardiomyopathy, anemia, liver cirrhosis, abdominal cramps, diarrhoea and vomiting and hyperpigmentation.

Diagnosis and treatment:

Arsenic may be detected in urine, blood, hair and nail. Treatment is with BAL, exchange transfusion or haemodialysis which should be performed within 24 hours of exposure.

Radiation injury

It may be defined as any somatic or genetic disruption of function or form caused by electromagnetic waves or accelerated particles. These could be ultraviolet radiation, microwave radiation, high intensity ultrasound and ionized radiation from natural or man made sources.

Exposure:

- a) Medical: Staff or the public may be affected by a malfunction or during repair of machinery in radiotherapy departments. Patients subjected to radiotherapy may be affected and can be a source of irradiation to others.
- b) Industrial and military: atomic weapon testing, catastrophes (such as Chernobyl reactor), industrial and laboratory exposure. This could be through ingestion or inhalation of long-lived isotopes (such as radium and plutonium).

Radiobiology of kidney tissue:

After exposure to a dose of radiation of 10 Gray (GY) or more, the renal tubular cells are reduced in number, exhibiting flattening in the tubule lining. Whole nephrons are lost over 4-18 months after exposure.

Radiation Nephrotoxicity:

- a) Immediate: decreased renal blood flow and glomerular filtration rate.
- b) Early: acute nephritis
- c) Late: chronic nephritis, obstructive uropathy, urinary fistula and fluid and electrolyte depletion.

Infective (biological) environmental risk factors

- a) Parasitic: for example malaria, schistosoma and hydatid disease.
- b) Bacterial: for example tuberculosis.
- c) Viral: for example viral hepatitis and HIV.
- d) Fungal toxins: especially ochratoxin and aflatoxin.

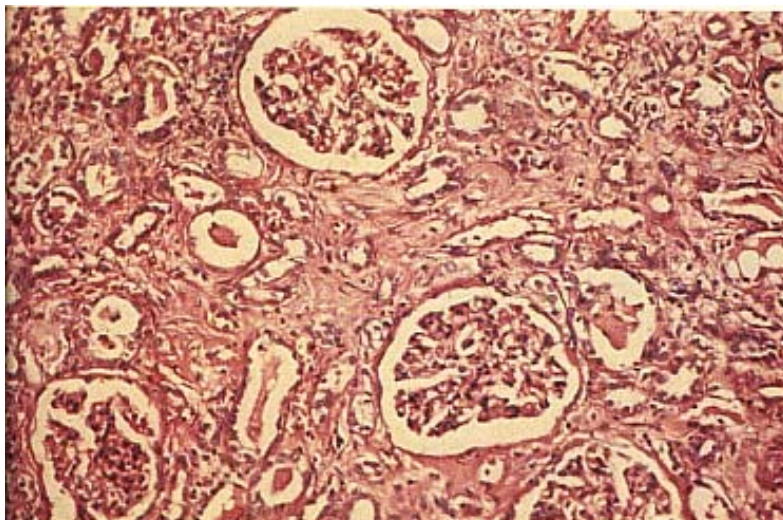
Ochratoxins arise from fungus *Aspergillus ochraceus*, discovered in the mid 1960s during a search for new toxic substances from moulds. It was discovered to be a natural contaminant of maize (Fig. 15.5), and to be the cause of porcine nephropathy in Scandinavia by 1978. It is established as grain contaminant and a cause of porcine nephropathy in Europe and USA.



(Fig.15.5)
Normal and fungus- invaded
Kernels of maize. The later,
as other fungus-
contaminated grains, could
produce nephropathy in
animals and human.

Ochratoxin nephrotoxicity

- Ochratoxins induce nephropathy and kidney tumours in rodents, dogs, pigs and birds.
- It induces endemic porcine nephropathy in central and northern European countries.
- It most probably has a major role in the aetiology of Balkan endemic nephropathy which is characterised by chronic tubulo-interstitial disease (Fig. 15.6) progressing to end stage renal failure and urethral tumours, a picture similar to porcine nephropathy.
- Recently it has been reported to be responsible for nephropathy in Tunisia and possibly in Egypt.



(Fig. 15.6)
Kidney section of case with
chronic tubulointerstitial
nephritis, most probably
produced by ochratoxycosis

Suggested Reading:

- Sobh M: Environmental pollution is increasing the incidence of chronic renal failure. *J Toxicol-Toxin Reviews*, 15 (3), 199-205, 1996.
- Maaroufi K, et al: Human nephropathy related to ochratoxin A in Tunisia. *J Toxicol-Toxin Reviews*, 15 (3), 223-237, 1996.
- Simon P: Ochratoxin and kidney disease in human. *J Toxicol-Toxin Reviews*, 15 (3), 239-249, 1996.
- Badria D: A multidisciplinary study to monitor mycotoxins in Egypt. *J Toxicol-Toxin Reviews*, 15 (3), 251-272, 1996.