Shree H. N. Shukla Institute ofPharmaceutical Education andResearch,Rajkot

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Subject Name: Pathophysiology

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Hypertension

Hypertension is a common disease in industrialized countries and accounts for 6% of death worldwide. Epidemiologic studies have revealed that with elevation in systolic and diastolic blood pressure above normal in adults, there is a continuous increased risk of cardiovascular disease, stroke and renal disease—cardiovascular risk doubles with every 20 mmHg increase in systolic and 10 mmHg increase in diastolic blood pressure above normal levels.

Hypertension is generally classified into 2 types:

1. Primary or essential hypertension in which the cause of increase in blood pressure is unknown. Essential hypertension constitutes about 80-95% patients of hypertension.

2. Secondary hypertension, in which the increase in blood pressure is caused by diseases of the kidneys, endocrines or some other organs. Secondary hypertension comprises remaining 5-20% cases of hypertension.

According to the clinical course, both essential and secondary hypertension may be benign or malignant.

Benign hypertension is moderate elevation of blood pressure and the rise is slow over the years. About 90-95% patients of hypertension have benign hypertension.

Malignant hypertension is marked and suden increase of blood pressure to 200/140 mmHg or more in a known case of hypertension or in a previously normotensive individual; the patients develop papilloedema, retinal haemorrhages and hypertensive encephalopathy. Less than 5% of hypertensive patients develop malignant hypertension and life expectancy after diagnosis in these patients is generally less than 2 years if not treated effectively.

A. ESSENTIAL HYPERTENSION (90%)

1. Genetic factors

2. Racial and environmental factors

3. Risk factors modifying the course

B. SECONDARY HYPERTENSION (10%)

1. Renal i) Renovascular ii) renal parenchymal diseases

2. Endocrine i) Adrenocortical hyperfunction ii) Hyperparathyroidism iii) Oral contraceptives

3. Coarctation of Aorta

4. Neurogenic

Etiology and Pathogenesis

The etiology and pathogenesis of secondary hypertension that comprises less than 10% cases has been better understood, whereas the mechanism of essential hypertension that constitutes about 90% of cases remains largely obscure. In general, normal blood pressure is regulated by 2 haemodynamic forces—cardiac output and total peripheral vascular resistance. Factors which alter these two factors result in

hypertension. The role of kidney in hypertension, particularly in secondary hypertension, by elaboration of renin and subsequent formation of angiotensin II, is well established (renin-angiotensin system).

CLINICAL FEATURES

There is variable elevation of the blood pressure with headache, dizziness, palpitation and nervousness. Eye ground changes may be found but papilloedema is absent. Renal function tests and urine examination are normal in early stage. In long-standing cases, there may be mild proteinuria with some hyaline or granular casts. Rarely, renal failure and uraemia may occur.

CONGENITAL HEART DISEASE

Congenital heart disease is the abnormality of the heart present from birth. It is the most common and important form of heart disease in the early years of life and is present in about 0.5% of newborn children. The incidence is higher in premature infants. The cause of congenital heart disease is unknown in majority of cases. It is attributed to multifactorial inheritance involving genetic and environmental influences. Other factors like rubella infection to the mother during pregnancy, drugs taken by the mother and heavy alcohol drinking by the mother, have all been implicated in causing in utero foetal injury resulting in congenital malformations of the heart. CLASSIFICATION. Congenital anomalies of the heart may be either shunts (left-to-right or right-to-left), or defects causing obstructions to flow. However, complex anomalies involving combinations of shunts and obstructions are also often present.

VENTRICULAR SEPTAL DEFECT (VSD).

VSD is the most common congenital anomaly of the heart and comprises about 30% of all congenital heart diseases. The condition is recognised early in life. The smaller defects often close spontaneously, while larger defects remain patent and produce significant effects. Depending upon the location of the defect, VSD may be of the following types:

1. In 90% of cases, the defect involves membranous septum and is very close to the bundle of His.

2. The remaining 10% cases have VSD immediately below the pulmonary valve (subpulmonic), below the aortic valve (subaortic), or exist in the form of multiple defects in the muscular septum.

PATENT DUCTUS ARTERIOSUS (PDA).

The ductus arteriosus is a normal vascular connection between the aorta and the bifurcation of the pulmonary artery. Normally, the ductus closes functionally within the first or second day of life. Its persistence after 3 months of age is considered abnormal. The cause for patency of ductus arteriosus is not known but possibly it is due to continued synthesis of PGE2 after birth which keeps it patent as evidenced by association of PDA with respiratory distress syndrome in infants and pharmacologic closure of PDA with administration of indomethacin to suppress PGE2 synthesis. PDA constitutes about 10% of congenital malformations of the heart and great vessels. In about 90% of cases, it occurs as an isolated defect, while in the remaining cases it may be associated with other anomalies like VSD, coarctation of aorta and pulmonary or aortic stenosis. A patent ductus may be upto 2 cm in length and upto 1 cm in diameter.

COARCTATION OF AORTA. The word ‘coarctation’ means contracted or compressed. Coarctation of aorta is localised narrowing in any part of aorta, but the constriction is more often just distal to ductus arteriosus

(postductal or adult), or occasionally proximal to the ductus arteriosus (preductal or infantile type) in the region of transverse aorta.

Angina pectoris

Angina pectoris is a clinical syndrome of IHD resulting from transient myocardial ischaemia. It is characterised by paroxysmal pain in the substernal or precordial region of the chest which is aggravated by an increase in the demand of the heart and relieved by a decrease in the work of the heart. Often, the pain radiates to the left arm, neck, jaw or right arm. It is more common in men past 5th decade of life. There are 3 overlapping clinical patterns of angina pectoris with some differences in their pathogenesis:

i) Stable or typical angina

ii) Prinzmetal's variant angina

iii) Unstable or crescendo angina STABLE OR

TYPICAL ANGINA.

This is the most common pattern. Stable or typical angina is characterised by attacks of pain following physical exertion or emotional excitement and is relieved by rest. The pathogenesis of condition lies in chronic stenosing coronary atherosclerosis that cannot perfuse the myocardium adequately when the workload on the heart increases. During the attacks, there is depression of ST segment in the ECG due to poor perfusion of the subendocardial region of the left ventricle but there is no elevation of enzymes in the blood as there is no irreversible myocardial injury.

PRINZMETAL'S VARIANT ANGINA.

This pattern of angina is characterised by pain at rest and has no relationship with physical activity. The exact pathogenesis of Prinzmetal's angina is not known. It may occur due to sudden vasospasm of a coronary trunk induced by coronary atherosclerosis, or may be due to release of humoral vasoconstrictors by mast cells in the coronary adventitia. ECG shows ST segment elevation due to transmural ischaemia. These patients respond well to vasodilators like nitroglycerin.

UNSTABLE OR CRESCENDO ANGINA.

Also referred to as 'pre-infarction angina' or 'acute coronary insufficiency', this is the most serious pattern of angina. It is characterised by more frequent onset of pain of prolonged duration and occurring often at rest. It is thus indicative of an impending acute myocardial infarction. Distinction between unstable angina and acute MI is made by ST segment changes on ECG— acute MI characterised by ST segment elevation while unstable angina may have non-ST segment elevation MI. Multiple factors are involved in the pathogenesis of unstable angina which include: stenosing coronary atherosclerosis, complicated coronary plaques (e.g. superimposed thrombosis, haemorrhage, rupture, ulceration etc), platelet thrombi over atherosclerotic plaques and vasospasm of coronary arteries. More often, the lesions lie in a branch of the major coronary trunk so that collaterals prevent infarction.

ACUTE MYOCARDIAL INFARCTION

Acute myocardial infarction (MI) is the most important and feared consequence of coronary artery disease. Many patients may die within the first few hours of the onset, while remainder suffer from effects of impaired cardiac function. A significant factor that may prevent or diminish the myocardial damage is the development of collateral circulation through anastomotic channels over a period of time. A regular and well-planned exercise programme encourages good collateral circulation and improved cardiac performance.

INCIDENCE. In developed countries, acute MI accounts for 10-25% of all deaths. Due to the dominant etiologic role of coronary atherosclerosis in acute MI, the incidence of acute MI correlates well with the incidence of atherosclerosis in a geographic area.

Age.

Acute MI may virtually occur at all ages, though the incidence is higher in the elderly. About 5% of heart attacks occur in young people under the age of 40 years, particularly in those with major risk factors to develop atherosclerosis like hypertension, diabetes mellitus, cigarette smoking and dyslipidaemia with familial hypercholesterolaemia.

Sex.

Males throughout their life are at a significantly higher risk of developing acute MI as compared to females. Women during reproductive period have remarkably low incidence of acute MI, probably due to the protective influence of oestrogen. The use of oral contraceptives is associated with high risk of developing acute MI. After menopause, this sex difference gradually declines but the incidence of disease among women never reaches that among men of the same age.

ETIOPATHOGENESIS. The etiologic role of severe coronary atherosclerosis (more than 75% compromise of lumen) of one or more of the three major coronary arterial trunks in the pathogenesis of about 90% cases of acute MI is well documented by autopsy studies as well as by coronary angiographic studies. A few notable features in the development of acute MI are as under:

1. Myocardial ischaemia.

Myocardial ischaemia is brought about by one or more of the following mechanisms: i) Diminised coronary blood flow e.g. in coronary artery disease, shock. ii) Increased myocardial demand e.g. in exercise, emotions. iii) Hypertrophy of the heart without simultaneous increase of coronary blood flow e.g. in hypertension, valvular heart disease.

2. Role of platelets. Rupture of an atherosclerotic plaque exposes the subendothelial collagen to platelets which undergo aggregation, activation and release reaction. These events contribute to the build-up of the platelet mass that may give rise to emboli or initiate thrombosis.

3. Acute plaque rupture. In general, slowly-developing coronary ischaemia from stenosing coronary atherosclerosis of high-grade may not cause acute MI but continue to produce episodes of angina pectoris. But acute complications in coronary atherosclerotic plaques in the form of superimposed coronary thrombosis due to plaque rupture and plaque haemorrhage is frequently encountered in cases of acute MI: i) Superimposed coronary thrombosis due to disruption of plaque is seen in about half the cases of acute MI. Infusion of intracoronary fibrinolysins in the first half an hour of development of acute MI in such cases restores blood flow in the blocked

vessel in majority of cases. ii) Intramural haemorrhage is found in about one-third cases of acute MI. Plaque haemorrhage and thrombosis may occur together in some cases.

4. Non-atherosclerotic causes. About 10% cases of acute MI are caused by non-atherosclerotic factors such as coronary vasospasm, arteritis, coronary ostial stenosis, embolism, thrombotic diseases, trauma and outside compression as already described.

5. Transmural versus subendocardial infarcts. There are some differences in the pathogenesis of the transmural infarcts involving the full thickness of ventricular wall and the subendocardial (laminar) infarcts affecting the inner subendocardial one-third to half.

LOCATION OF INFARCTS.

Infarcts are most frequently located in the left ventricle. Right ventricle is less susceptible to infarction due to its thin wall, having less metabolic requirements and is thus adequately nourished by the thebesian vessels. Atrial infarcts, whenever present, are more often in the right atrium, usually accompanying the infarct of the left ventricle. Left atrium is relatively protected from infarction because it is supplied by the oxygenated blood in the left atrial chamber.

TYPES OF INFARCTS.

Infarcts have been classified in a number of ways by the physicians and the pathologists:

1. According to the anatomic region of the left ventricle involved, they are called anterior, posterior (inferior), lateral, septal and circumferential, and their combinations like anterolateral, posterolateral (or inferolateral) and anteroseptal.

2. According to the degree of thickness of the ventricular wall involved, infarcts are of two types. i) Full-thickness or transmural, when they involve the entire thickness of the ventricular wall. ii) Subendocardial or laminar, when they occupy the inner subendocardial half of the myocardium.

3. According to the age of infarcts, they are of two types: i) Newly-formed infarcts called as acute, recent or fresh. ii) Advanced infarcts called as old, healed or organised.

COMPLICATIONS

1. Arrhythmias
2. Congestive heart failure
3. Cardiogenic shock
4. Mural thrombosis and thromboembolism
5. Rupture
6. Cardiac aneurysm
7. Pericarditis
8. Postmyocardial infarction syndrome.

Asthma

Asthma is a disease of airways that is characterised by increased responsiveness of the tracheobronchial tree to a variety of stimuli resulting in widespread spasmodic narrowing of the air passages which may be

relieved spontaneously or by therapy. Asthma is an episodic disease manifested clinically by paroxysms of dyspnoea, cough and wheezing. However, a severe and unremitting form of the disease termed status asthmaticus may prove fatal. Bronchial asthma is common and prevalent worldwide; in the United States about 4% of population is reported to suffer from this disease. It occurs at all ages but nearly 50% of cases develop it before the age of 10 years. In adults, both sexes are affected equally but in children there is 2:1 malefemale ratio.

ETIOPATHOGENESIS AND TYPES.

Based on the stimuli initiating bronchial asthma, two broad etiologic types are traditionally described: extrinsic (allergic, atopic) and intrinsic (idiosyncratic, non-atopic) asthma. A third type is a mixed pattern in which the features do not fit clearly into either of the two main types.

1. Extrinsic (atopic, allergic) asthma.

This is the most common type of asthma. It usually begins in childhood or in early adult life. Most patients of this type of asthma have personal and/or family history of preceding allergic diseases such as rhinitis, urticaria or infantile eczema. Hypersensitivity to various extrinsic antigenic substances or 'allergens' is usually present in these cases. Most of these allergens cause ill-effects by inhalation e.g. house dust, pollens, animal danders, moulds etc.

Occupational asthma stimulated by fumes, gases and organic and chemical dusts is a variant of extrinsic asthma. There are increased levels of IgE in the serum and positive skin test with the specific offending inhaled antigen representing an IgE-mediated type I hypersensitivity reaction which includes an 'acute immediate response' and a 'late phase reaction': Acute immediate response is initiated by IgE-sensitised mast cells (tissue counterparts of circulating basophils) on the mucosal surface. Mast cells on degranulation release mediators like histamine, leukotrienes, prostaglandins, platelet activating factor and chemotactic factors for eosinophils and neutrophils. The net effects of these mediators are bronchoconstriction, oedema, mucus hypersecretion and accumulation of eosinophils and neutrophils.

Late phase reaction follows the acute immediate response and is responsible for the prolonged manifestations of asthma. It is caused by excessive mobilisation of blood leucocytes that include basophils besides eosinophils and neutrophils. These result in further release of mediators which accentuate the above-mentioned effects. In addition, inflammatory injury is caused by neutrophils and by major basic protein (MBP) of eosinophils.

2. Intrinsic (idiosyncratic, non-atopic) asthma. This type of asthma develops later in adult life with negative personal or family history of allergy, negative skin test and normal serum levels of IgE. Most of these patients develop typical symptom-complex after an upper respiratory tract infection by viruses. Associated nasal polypi and chronic bronchitis are commonly present. There are no recognisable allergens but about 10% of patients become hypersensitive to drugs, most notably to small doses of aspirin (aspirin-sensitive asthma).

3. Mixed type. Many patients do not clearly fit into either of the above two categories and have mixed features of both. Those patients who develop asthma in early life have strong allergic component, while those who develop the disease late tend to be non-allergic. Either type of asthma can be precipitated by cold, exercise and emotional stress.

CLINICAL FEATURES.

Asthmatic patients suffer from episodes of acute exacerbations interspersed with symptomfree periods. Characteristic clinical features are paroxysms of dyspnoea, cough and wheezing. Most attacks typically last for a few minutes to hours. When attacks occur continuously it may result in more serious condition called status asthmaticus. The clinical diagnosis is supported by demonstration of circulation eosinophilia and sputum demonstration of Curschmann's spirals and Charcot-Leyden crystals. More chronic cases may develop cor pulmonale.

Chronic obstructive airways diseases

Chronic obstructive pulmonary disease (COPD) or chronic obstructive airway disease (COAD) are commonly used clinical terms for a group of pathological conditions in which there is chronic, partial or complete, obstruction to the airflow at any level from trachea to the smallest airways resulting in functional disability of the lungs i.e. they are diffuse lung diseases. The following 4 entities are included in COPD:

I. Chronic bronchitis
II. Emphysema
III. Bronchial asthma
IV. Bronchiectasis

Chronic bronchitis and emphysema are quite common and often occur together. Now, small airways disease involving inflammation of small bronchi and bronchioles (bronchiolitis) has also been added to the group of COPD.

CHRONIC BRONCHITIS Chronic bronchitis is a common condition defined clinically as persistent cough with expectoration on most days for at least three months of the year for two or more consecutive years. The cough is caused by oversecretion of mucus. In spite of its name, chronic inflammation of the bronchi is not a prominent feature. The condition is more common in middle-aged males than females; approximately 20% of adult men and 5% of adult women have chronic bronchitis, but only a minority of them develop serious disabling COPD or cor pulmonale. Quite frequently, chronic bronchitis is associated with emphysema.

ETIOPATHOGENESIS.

The two most important etiologic factors responsible for majority of cases of chronic bronchitis are: cigarette smoking and atmospheric pollution. Other contributory factors are occupation, infection, familial and genetic factors.

1. Smoking. The most commonly identified factor implicated in causation of chronic bronchitis and in emphysema is heavy smoking. Heavy cigarette smokers have 4 to 10 times higher proneness to develop chronic bronchitis. Prolonged cigarette smoking appears to act on the lungs in a number of ways:
   i) It impairs ciliary movement.
   ii) It inhibits the function of alveolar macrophages.
   iii) It leads to hypertrophy and hyperplasia of mucussecreting glands.
   iv) It causes considerable obstruction of small airways.

v) It stimulates the vagus and causes bronchoconstriction.

2. Atmospheric pollution. The incidence of chronic bronchitis is higher in industrialised urban areas where air is polluted. Some of the atmospheric pollutants which increase the risk of developing chronic bronchitis are sulfur dioxide, nitrogen dioxide, particulate dust and toxic fumes.

3. Occupation. Workers engaged in certain occupations such as in cotton mills (byssinosis), plastic factories etc. are exposed to various organic or inorganic dusts which contribute to disabling chronic bronchitis in such individuals.

4. Infection. Bacterial, viral and mycoplasmal infections do not initiate chronic bronchitis but usually occur secondary to bronchitis. Cigarette smoke, however, predisposes to infection responsible for acute exacerbation in chronic bronchitis.

5. Familial and genetic factors. There appears to be a poorly-defined familial tendency and genetic predisposition to develop disabling chronic bronchitis. However, it is more likely that nonsmoker family members who remain in the air-pollution of home are significantly exposed to smoke (passive smoking) and hence have increased blood levels of carbon monoxide.

CLINICAL FEATURES

1. Persistent cough with copious expectoration of long duration; initially beginning in a heavy smoker with 'morning catarrh' or 'throat clearing' which worsens in winter.

2. Recurrent respiratory infections are common.

3. Dyspnoea is generally not prominent at rest but is more on exertion.

4. Patients are called 'blue bloaters' due to cyanosis and oedema.

5. Features of right heart failure (cor pulmonale) are common.

6. Chest X-ray shows enlarged heart with prominent vessels.

EMPHYSEMA

The WHO has defined pulmonary emphysema as combination of permanent dilatation of air spaces distal to the terminal bronchioles and the destruction of the walls of dilated air spaces. Thus, emphysema is defined morphologically, while chronic bronchitis is defined clinically. Since the two conditions coexist frequently and show considerable overlap in their clinical features, it is usual to label patients as 'predominant emphysema' and 'predominant bronchitis'.

CLASSIFICATION.

As mentioned in the beginning of this chapter, a lobule is composed of about 5 acini distal to a terminal bronchiole and that an acinus consists of 3 to 5 generations of respiratory bronchioles and a variable number of alveolar ducts and alveolar sacs (page 461). As per WHO definition of pulmonary emphysema, it is classified according to the portion of the acinus involved, into 5 types: centriacinar, panacinar (panlobular), para-septal (distal acinar), irregular (para-cicatricial) and mixed (unclassified) emphysema. A number of other conditions to which the term 'emphysema' is loosely applied are, in fact, examples of 'overinflation'.

ETIOPATHOGENESIS.

The commonest form of COPD is the combination of chronic bronchitis and pulmonary emphysema. Chronic bronchitis, however, does not always lead to emphysema norall cases of emphysema have changes of chronic bronchitis. The association of the two conditions is principally linked to the common etiologic factors— most importantly tobacco smoke and air pollutants. Other less significant contributory factors are occupational exposure, infection and somewhat poorly-understood familial and genetic influences. All these factors have already been discussed above.

CLINICAL FEATURES

1. There is long history of slowly increasing severe exertional dyspnoea.

2. Patient is quite distressed with obvious use of accessory muscles of respiration.

3. Chest is barrel-shaped and hyperresonant.

4. Cough occurs late after dyspnoea starts and is associated with scanty mucoid sputum.

5. Recurrent respiratory infections are not frequent.

6. Patients are called 'pink puffers' as they remain well oxygenated and have tachypnoea.

7. Weight loss is common.

8. Features of right heart failure (cor pulmonale) and hypercapneic respiratory failure are the usual terminal events.

9. Chest X-ray shows small heart with hyperinflated lungs.

BRONCHIECTASIS

Bronchiectasis is defined as abnormal and irreversible dilatation of the bronchi and bronchioles (greater than 2 mm in diameter) developing secondary to inflammatory weakening of the bronchial walls. The most characteristic clinical manifestation of bronchiectasis is persistent cough with expectoration of copious amounts of foul-smelling, purulent sputum. Post-infectious cases commonly develop in childhood and in early adult life.

ETIOPATHOGENESIS.

The origin of inflammatory destructive process of bronchial walls is nearly always a result of two basic mechanisms: endobronchial obstruction and infection. Endobronchial obstruction by foreign body, neoplastic growth or enlarged lymph nodes causes resorption of air distal to the obstruction with consequent atelectasis and retention of secretions. Infection may be secondary to local obstruction and impaired systemic defense mechanism promoting bacterial growth, or infection may be a primary event i.e. bronchiectasis developing in suppurative necrotising pneumonia.

These 2 mechanisms—endobronchial obstruction and infection, are seen in a number of clinical settings as under: 1. Hereditary and congenital factors. Several hereditary and congenital factors may result secondarily in diffuse bronchiectasis:

i) Congenital bronchiectasis caused by developmental defect of the bronchial system.

ii) Cystic fibrosis, a generalised defect of exocrine gland secretions, results in obstruction, infection and bronchiectasis.

iii) Hereditary immune deficiency diseases are often associated with high incidence of bronchiectasis.

iv) Immotile cilia syndrome that includes Kartagener's syndrome (bronchiectasis, situs inversus and sinusitis) is characterised by ultrastructural changes in the microtubules causing immotility of cilia of the respiratory tract epithelium, sperms and other cells.

v) Atopic bronchial asthma patients have often positive family history of allergic diseases and may rarely develop diffuse bronchiectasis.

2. Obstruction.
Post-obstructive bronchiectasis, unlike the congenital-hereditary forms, is of the localised variety, usually confined to one part of the bronchial system. The causes of endobronchial obstruction include foreign bodies, endobronchial tumours, compression by enlarged hilar lymph nodes and post-inflammatory scarring (e.g. in healed tuberculosis) all of which favour the development of postobstructive bronchiectasis.

3. As secondary complication. Necrotising pneumonias such as in staphylococcal suppurative pneumonia and tuberculosis may develop bronchiectasis as a complication.

CLINICAL FEATURES.

The clinical manifestations of bronchiectasis typically consist of chronic cough with foulsmelling sputum production, haemoptysis and recurrent pneumonia. Sinusitis is a common accompaniment of diffuse bronchiectasis. Late complications occurring in cases uncontrolled for years include development of clubbing of the fingers, metastatic abscesses (often to the brain), amyloidosis and cor pulmonale.

Acute and chronic renal failure

Acute renal failure (ARF) is a syndrome characterised by rapid onset of renal dysfunction, chiefly oliguria or anuria, and sudden increase in metabolic waste-products (urea and creatinine) in the blood with consequent development of uraemia.

ETIOPATHOGENESIS. The causes of ARF may be classified as pre-renal, intra-renal and post-renal in nature.
1. Pre-renal causes. Pre-renal diseases are those which cause sudden decrease in blood flow to the nephron. Renal ischaemia ultimately results in functional disorders or depression of GFR, or both. These causes include inadequate cardiac output and hypovolaemia or vascular disease causing reduced perfusion of the kidneys.

2. Intra-renal causes. Intra-renal disease is characterised by disease of renal tissue itself. These include vascular disease of the arteries and arterioles within the kidney, diseases of glomeruli, acute tubular necrosis due to ischaemia, or the effect of a nephrotoxin, acute tubulointerstitial nephritis and pyelonephritis.

3. Post-renal causes. Post-renal disease is characteristically caused by obstruction to the flow of urine anywhere along the renal tract distal to the opening of the collecting ducts. This may be caused by a mass

within the lumen or from wall of the tract, or from external compression anywhere along the lower urinary tract—ureter, bladder neck or urethra. It is important to note that ARF originating in pre- and post-renal disease, such as by renal ischaemia or renal infection, eventually leads to intra-renal disease. Thus, fullblown ARF reflects some degree of nephron damage.

CLINICAL FEATURES.

The clinical features will depend to a large extent on the underlying cause of ARF and on the stage of the disease at which the patient presents. However, one of the following three major patterns usually emerge:

1. Syndrome of acute nephritis. This is most frequently associated with acute post-streptococcal glomerulonephritis and rapidly progressive glomerulonephritis. Renal dysfunction results from extensive proliferation of epithelial cells in the glomeruli with consequent mild increase in glomerular permeability and decrease in GFR. The characteristic features are: mild proteinuria, haematuria, oedema and mild hypertension. Fluid retention in acute nephritis syndrome appears to be due to both diminished GFR and increased salt and water reabsorption in distal nephron.

2. Syndrome accompanying tubular pathology. When the ARF is caused by destruction of the tubular cells of the nephron as occurs in acute tubular necrosis, the disease typically progresses through 3 characteristic stages from oliguria to diuresis to recovery.

i) Oliguric phase: The initial oliguric phase lasting on an average from 7 to 10 days is characterised by urinary output of less than 400 ml per day. The decline in formation of the urine leads to accumulation of waste products of protein metabolism in the blood and resultant azotaemia, metabolic acidosis, hyperkalaemia, hypernatraemia and hypervolaemia due to secondary effects of circulatory overload and pulmonary oedema. The specific gravity of the urine is low but the concentration of sodium in urine tends to be elevated.

ii) Diuretic phase: With the onset of healing of tubules, there is improvement in urinary output. This is believed to occur due to drawing of water and sodium by preceding high levels of creatinine and urea as they move through the nephron so as to be excreted. Since tubular cells have not regained normal functional capacity, the urine is of low or fixed specific gravity.

iii) Phase of recovery: Full recovery with healing of tubular epithelial cells occurs in about half the cases, while others terminate in death. The process of healing may take up to one year with restoration of normal tubular function.

3. Pre-renal syndrome. The ARF occurring secondary to disorders in which neither the glomerulus nor the tubules are damaged, results in pre-renal syndrome. Typically, this pattern is seen in marginal ischaemia caused by renal arterial obstruction, hypovolaemia, hypotension or cardiac insufficiency. Due to depressed renal blood flow, there is decrease in GFR causing oliguria, azotaemia (elevation of BUN and creatinine) and possible fluid retention and oedema. Since the tubular cells are functioning normally, the nephron retains its ability to concentrate the glomerular filtrate according to the adaptive needs.

Chronic Renal Failure (CRF)

Chronic renal failure is a syndrome characterised by progressive and irreversible deterioration of renal function due to slow destruction of renal parenchyma, eventually terminating in death when sufficient

number of nephrons have been damaged. Acidosis is the major problem in CRF with development of biochemical azotaemia and clinical uraemia syndrome.

ETIOPATHOGENESIS.

All chronic nephropathies can lead to CRF. The diseases leading to CRF can generally be classified into two major groups: those causing glomerular pathology, and those causing tubulointerstitial pathology. Though this classification is useful to facilitate study, the disease rarely remains confined to either glomeruli or tubulointerstitial tissue alone. In the final stage of CRF, all parts of the nephron are involved.

1. Diseases causing glomerular pathology. A number of glomerular diseases associated with CRF have their pathogenesis in immune mechanisms. Glomerular destruction results in changes in filtration process and leads to development of the nephrotic syndrome characterised by proteinuria, hypoalbuminaemia and oedema. The important examples of chronic glomerular diseases causing CRF are covered under two headings: primary and systemic.

i) Primary glomerular pathology: The major cause of CRF is chronic glomerulonephritis, usually initiated by various types of glomerulonephritis such as membranous glomerulo nephritis, membranoproliferative glomerulonephritis, lipoid nephrosis (minimal change disease) and anti-glomerular basement membrane nephritis. ii) Systemic glomerular pathology: Certain conditions originate outside the renal system but induce changes in the nephrons secondarily. Major examples of this type are systemic lupus erythematosus, serum sickness nephritis and diabetic nephropathy.

2. Diseases causing tubulointerstitial pathology. Damage to tubulointerstitial tissues results in alterations in reabsorption and secretion of important constituents leading to excretion of large volumes of dilute urine. Tubulointerstitial diseases can be categorised according to initiating etiology into 4 groups: vascular, infectious, toxic and obstructive.

i) Vascular causes: Long-standing primary or essential hypertension produces characteristic changes in renal arteries and arterioles referred to as nephrosclerosis. Nephrosclerosis causes progressive renal vascular occlusion terminating in ischaemia and necrosis of renal tissue.

ii) Infectious causes: A good example of chronic renal infection causing CRF is chronic pyelonephritis. The chronicity of process results in progressive damage to increasing number of nephrons leading to CRF.

iii) Toxic causes: Some toxic substances induce slow tubular injury, eventually culminating in CRF. The most common example is intake of high doses of analgesics such as phenacetin, aspirin and acetaminophen (chronic analgesic nephritis). Other substances that can cause CRF after prolonged exposure are lead, cadmium and uranium.

iv) Obstructive causes: Chronic obstruction in the urinary tract leads to progressive damage to the nephron due to fluid backpressure. The examples of this type of chronic injury are stones, blood clots, tumours, strictures and enlarged prostate.

CLINICAL FEATURES.

Clinical manifestations of fullblown CRF culminating in uraemic syndrome are described under 2 main headings: primary (renal) uraemic manifestations and secondary (systemic or extra-renal) uraemic manifestations.

A. Primary uraemic (renal) manifestations. Primary symptoms of uraemia develop when there is slow and progressive deterioration of renal function. The resulting imbalances cause the following manifestations:

1. Metabolic acidosis. As a result of renal dysfunction, acidbase balance is progressively lost. Excess of hydrogen ions occurs, while bicarbonate level declines in the blood, resulting in metabolic acidosis. The clinical symptoms of metabolic acidosis include: compensatory Kussmaul breathing, hyperkalaemia and hypercalcaemia.

2. Hyperkalaemia. A decreased GFR results in excessive accumulation of potassium in the blood since potassium is normally excreted mainly in the urine. Hyperkalaemia is further worsened by metabolic acidosis. The clinical features of hyperkalaemia are: cardiac arrhythmias, weakness, nausea, intestinal colic, diarrhoea, muscular irritability and flaccid paralysis.

3. Sodium and water imbalance. As GFR declines, sodium and water cannot pass sufficiently into Bowman's capsule leading to their retention. Release of renin from juxtaglomerular apparatus further aggravates sodium and water retention. The main symptoms referable to sodium and water retention are: hypervolaemia and circulatory overload with congestive heart failure.

4. Hyperuricaemia. Decreased GFR results in excessive accumulation of uric acid in the blood. Uric acid crystals may be deposited in joints and soft tissues resulting in gout. 5. Azotaemia. The waste-products of protein metabolism fail to be excreted resulting in elevation in the blood levels of urea, creatinine, phenols and guanidines causing biochemical abnormality, azotaemia. The secondary manifestations of uraemia are related to toxic effects of these metabolic waste-products.

B. Secondary uraemic (extra-renal) manifestations. A number of extra-renal systemic manifestations develop secondarily following fluid-electrolyte and acid-base imbalances. These include the following:

1. Anaemia. Decreased production of erythropoietin by diseased kidney results in decline in erythropoiesis and anaemia. Besides, gastrointestinal bleeding may further aggravate anaemia.

2. Integumentary system. Deposit of urinary pigment such as urochrome in the skin causes sallow-yellow colour. The urea content in the sweat as well as in the plasma rises. On evaporation of the perspiration, urea remains on the facial skin as powdery 'uraemic frost'.

3. Cardiovascular system. Fluid retention secondarily causes cardiovascular symptoms such as increased workload on the heart due to the hypervolaemia and eventually congestive heart failure.

4. Respiratory system. Hypervolaemia and heart failure cause pulmonary congestion and pulmonary oedema.