Underwood: Chapter 5: Metabolic and Degenerative Disorders

Metabolic disorders, congenital or acquired, are well-defined abnormalities of metabolic pathways, often having considerable clinical effects. *Congenital metabolic disorders are usually the result of inherited enzyme deficiencies.*

Degenerative disorders are conditions in which tissue lose their specialised structure or function, other than those conditions in which the deterioration can be attributed to some specific disease process such as neoplasia or inflammatory reactions to infections. *Degenerative conditions are almost always acquired and are often major problems in the elderly.*

Metabolic Disorders

Inborn Errors of Metabolism

The concept of inborn errors of metabolism was formulated by Sir Archibald Garrod in 1908 as a result of his studies on a condition called alkaptonuria, a rare inherited deficiency of homogentisic acid oxidase.

Inborn errors of metabolism are single-gene defects resulting in the absence or deficiency of an enzyme or the synthesis of a defective protein. Single-gene defects occur in about 1% of all births, but the diseases caused by them show geographic variations in incidence; this is exemplified by the high incidence of thalassaemias - due to defects in haemoglobin synthesis - in Mediterranean regions.

Inborn errors of metabolism have four possible consequences:

- accumulation of an intermediate metabolite (i.e., homogentisic acid in alkaptonuria)

- deficiency of the ultimate product of metabolism (i.e., melanin in albinos)

- synthesis of an abnormal and less effective end product (i.e., hemoglobin S in sickle cell anaemia)

- failure of transport of the abnormal synthesised product (i.e., $alpha_1$-antitrypsin deficiency).

Accumulation of an intermediate metabolite may have toxic or hormonal effects. However, in some conditions the intermediate metabolite accumulates within the cells in which it has been synthesised, causing them to enlarge and compromising their function; these conditions are referred to as *storage disorders* (i.e., Gaucher's disease).

Genetic Basis

- May be inherited as autosomal or sex-linked genes

- Genes coding for abnormalities may be dominant or recessive

- Abnormal genes may be detected either directly from the presence of the gene itself or the defective product, or indirectly by virtue of its linkage with a detectable polymorphism.

Mode of transmission is either:

- *dominant* - only one abnormal copy of the paired gene (allele) is necessary for expression of the disease

- *recessive* - both copies of the paired gene are required to be abnormal for expression of the disease.

Single-gene defects inherited as an autosomal dominant are almost twice as common as autosomal recessive disorders. A minority of single-gene defects are sex-linked. Most inborn errors of *metabolism* are autosomal recessive disorders, whereas inherited disorders resulting in *structural* defects are autosomal dominant disorders; there are, however, exceptions to these general tendencies. A few inherited disorders are sex-linked; haemophilia is a notable example.

Homozygous and Heterozygous States

The two genes at an identical place (locus) on a pair of chromosomes are known as *alleles.* Individuals with identical alleles at a particular locus are said to be *homozygous.* If the alleles are not identical, the term used is *heterozygous.* Dominant genes are expressed in heterozygous individuals because only one abnormal copy of the gene is required. However, by definition, recessive genes are expressed only in homozygous individuals because both copies of the gene must be abnormal. The importance of this situation is that a parent carrying only one copy of a recessive abnormal gene (who is, therefore, heterozygous for this gene) appears to be normal. If the other parent is also heterozygous for this abnormal gene, then the disease will be inherited and expressed, on average, by 25% of their children. There is a higher incidence of homologous autosomal recessive heterozygosity in related individuals and, for that reason, there is a greater risk of inherited abnormalities in the children of closely related parents.

One problem in tracing genetic disorders through families is that the gene may show variable expression or penetrance. Although an abnormal gene is present, it may not necessarily always manifest itself and, when it does, the abnormality may be only slight.

Molecular Analysis of Genetic Disorders

The motivation to study these conditions at the genetic level of detail is twofold:

- to identify accurately the abnormality so that it can be detected for use in prenatal diagnosis and in parental counselling

- to improve our understanding of the expression of defective and normal genes.

Prenatal detection can be achieved by the molecular analysis of chorionic villus biopsies in cases known to be at risk.

Reverse Genetics

In some genetic disorders the metabolic abnormality is evident from the biochemistry of the affected individuals. For example, a deficiency of phenylalanine hydroxylase blocks conversion of phenylalanine to tyrosine, resulting in phenylketonuria. In many other genetic disorders, however, the ultimate biochemical defect is not so well characterised, but it is possible to locate and analyse the defective gene using a strategy called 'reverse genetics'. Having analysed the gene, it is then possible to predict its product by translating the base sequence of codons into the corresponding amino acids. The abnormal gene must first be located on the chromosomes by seeking *genetic linkages.*

Immediately prior to meiosis leading to the production of haploid germ cells (ova and spermatozoa) from their diploid precursors, there is a random interchange of DNA segments between the homologous paternally or maternally derived chromosomes to form new, recombinant chromosomes. The process of interchange occurs over such short lengths of DNA that only those genes lying adjacent on chromosomes are likely to remain together and be inherited through successive generations. This phenomenon is useful in reverse genetics only if the genes and their products are polymorphic; *polymorphic genes* show natural (and normal) variations in their base sequences and protein products - HLA substances are good example. This polymorphism enables the gene and its immediate neighbours to be mapped through a family and to the chromosomal level.

Restriction Fragment Length Polymorphism

Although polymorphic genes are useful for the mapping of abnormalities, it must be remembered that most of the DNA in chromosomes is redundant or anonymous; it does not encode any genes and has no phenotypic manifestations. However, because it lacks any function, this anonymous DNA tolerates a higher frequency of polymorphic variation than the DNA in which genes are encoded. In human nuclear DNA, these random polymorphic variations occur in approximately 1 in 200 base pairs. These variations are inherited and can be used to map the inheritance of neighbouring linked genes, even though the neighbouring genes may not have been fully characterised.

This polymorphism - restriction fragment length polymorphism (RFLP) - is produced by either of two mechanisms, both of which operate in all individuals:

- substitution of a single base on the DNA strand, thus abolishing a recognition site for a restriction enzyme

- presence of variable numbers of tandem repeats of base sequences, thus giving restriction fragments of corresponding variable size.

Variations in anonymous DNA are detected, not by using its polymorphic products (it has none), but by determining the variations in size of the smaller DNA fragments produced by incubation with *restriction enzymes.* These enzymes, derived from bacteria, break DNA

strands at specific points by virtue of the ability of the enzymes to recognise specific sequences of bases. By electrophoretic separation of the broken DNA strands according to their size, it is possible to detect polymorphic differences between individuals.

RFLP analysis is proving useful not only in mapping the chromosomal location of the abnormal genes of inborn metabolic errors, but also in forensic science, in cases of alleged rape or disputed paternity, because of its claimed individual uniqueness.

Polymerase Chain Reaction

The polymerase chain reaction (PCR) technique is being used increasingly for the prenatal identification of genetic polymorphism associated with congenital diseases when the precise base sequence of the polymorphic gene is known (i.e., in cystic fibrosis). The technique is specially applicable to prenatal diagnosis because it enables the abnormal gene to be amplified biochemically from only minute starting samples, even a single cell.

The PCR technique has wide applications in molecular medicine. It is a method of specifically amplifying predetermined segments of DNA from a small sample. The specificity is determine by *primers,* short DNA sequences complementary to the known flanking regions of the DNA segment being sought. The amplification is achieved by using a type of *DNA polymerase* enzyme that can withstand the cyclical heating of the reaction mixture necessary to separate the DNA strands and then cooling to permit DNA synthesis. The reaction mixture must also contain free *nucleotides* for incorporation into the newly synthesised DNA segments. Within a few hours the DNA segment, if present in the starting sample, will have been amplified about 1 million-fold. Its identity can be confirmed by gel electrophoresis to determine its size, and by absorption on to a special film (Southern blotting), where it can be probed to verify that it has the appropriate nucleotide sequence for the polymorphic gene.

Phenylketonuria

This autosomal recessive disorder affects approximately 1 in 10.000 infants. It is due to a deficiency of phenylalanine hydroxylase, an enzyme responsible for the conversion of phenylalanine to tyrosine.

Testing is done by analysing a drop of blood, dried on to filter paper, for phenylalanine (Guthrie test). If phenylketonuria is not tested for in this way and the affected infant's diet contains usual amounts of phenylalanine, then the disorder manifests itself with skin and hair depigmentation, fits and mental retardation. Treatment involves a low phenylalanine diet until the child is at least 8 years old. When affected females themselves become pregnant, the special diet must be resumed to avoid the toxic metabolites damaging the developing fetus.

Alkaptonuria

This rare autosomal recessive deficiency of homogentisic acid oxidase is a good example of an inborn metabolic error that does not produce serious effects until adult life. The condition is sometimes recognised from the observation that the patient's urine darkens on standing, the sweat may also be black! Homogentisic acid accumulates in connective tissues,

principally cartilage, where the darkening is called *ochronosis.* This accumulation causes joint damage. The underlying condition cannot be treated; treatment is symptomatic only.

Homocystinuria

It is an autosomal recessive disorder. It is characterised by a deficiency of cystathionine synthetase, an enzyme required for the conversion of homcystine via homocysteine to cystathionine. Homocysteine and methionine, its precursor, accumulate in the blood. Homocystine also accumulates, interfering with the cross-linking of collagen and elastic fibres. The ultimate effect resembles Marfan's syndrome, but with the addition of mental retardation and fits.

Storage Disorders

Inborn metabolic defects result in storage disorders if an enzyme deficiency prevents the normal conversion of a macromolecule (i.e., glycogen or gangliosides) into its smaller subunits (i.e., glucose or fatty acids). The macromolecules accumulates within the cells that normally harbour it, swelling their cytoplasm and causing organ enlargement and deformities. This situation is harmful because the swelling of cells often impairs their function, or that of their immediate neighbours due to pressure effects, and because of conditions resulting from deficiency of the smaller subunits (i.e., hypoglycaemia in the case of glycogen storage disorders).

Disorders of Cell Membrane Transport

Inborn metabolic errors can lead to impairment of the specific transport of substances across cell membranes. Examples include:

- cystic fibrosis - affecting exocrine secretions

- cystinuria - affecting renal tubules and resulting in renal stones

- disaccharide deficiency - preventing absorption of lactose, maltose and sucrose from the gut

- nephrogenic diabetes insipidus - due to insensitivity of renal tubules to ADH.

Cystic Fibrosis (Mucoviscidosis)

Cystic fibrosis, formerly also called fibrocystic disease of the pancreas, is the commonest serious inherited metabolic disorder; it is, however, much commoner in Caucasians than in other races. The autosomal recessive abnormal gene is carried by approximately 1 in 20 Caucasians and the condition affects approximately 1 in 2000 births. The defective gene has been localised to chromosome 7 and ultimately results in abnormal water and electrolyte transport across cell membranes.

Clinicopathological Features

Abnormal mucous secretions. The abnormal mucus plugs exocrine ducts, causing parenchymal damage to the affected organs. The clinical manifestations are:

- meconium ileus in neonates

- failure to thrive in infancy

- recurrent bronchopulmonary infections

- bronchiectasis

- chronic pancreatitis, sometimes accompanied by diabetes mellitus due to islet damage

- malabsorption due to defective pancreatic secretions

- infertility in males.

Diagnosis

It is confirmed by measuring the sodium concentration in the sweat; in affected children it is usually greater than 70 mmol/l.

Treatment

Treatment includes vigorous physiotherapy to drain the abnormal secretions from the respiratory passages, and oral replacement of pancreatic enzymes.

Porphyrias

The porphyrias, transmitted as autosomal dominant disorders, are due to defective synthesis of haem, an iron-porphyrin complex, the oxygen-carrying moiety of haemoglobin. Haem is synthesised from 5-aminolaevulinic acid. The different types of porphyrin accumulate due to inherited defects in this synthetic pathway.

Clinicopathological Features

- acute abdominal pain

- acute psychiatric disturbance

- peripheral neuropathy

- photosensitivity (only in some porphyrias)

- hepatic damage (only in some porphyrias).

The pain and psychiatric disturbances are episodic. During the acute attacks, the patient's urine contains excess 5-aminolaevulinic acid and porphobilinogen. These can be detected by adding an equal volume of Ehrlich's reagent (paradimethyl aminobenzaldehyde in hydrochloric acid) and two volumes of chloroform; after shaking, the chloroform separates out and any colour remaining in the aqueous layer denotes a positive test.

Acute attacks of porphyria can be precipitated by some drugs, alcohol and abnormal changes (i.e., during the menstrual cycle). The most frequently incriminated drugs include barbiturates, sulphonamides, oral contraceptives and anticonvulsants.

The skin lesions are characterised by severe blistering, exacerbated by light exposure, and subsequent scarring. This photosensitivity is a distressing feature, but it has led to the beneficial use of injected porphyrins in the treatment of tumours by phototherapy with laser light.

Disorders of Connective Tissue Metabolism

Affect collagen or elastic tissue:

- osteogenesis imperfecta

- Marfan's syndrome

- Ehlers-Danlos syndrome

- pseudoxanthoma elasticum

- cutis laxa.

Osteogenesis Imperfecta

There is an inborn error of type I collagen synthesis. Type I collagen is most abundant in bone, so the principal manifestation is skeletal weakness resulting in deformities and a susceptibility to fractures. The other names are 'fragilitas ossium' and 'brittle bone disease'. The teeth are also affected and the sclerae are abnormally thin, causing them to appear blue. It occurs in dominantly and recessively inherited forms with varying degrees of severity.

Marfan's Syndrome

It is a combination of unusually tall stature, long arm span, dislocation of the lenses, aortic and mitral valve incompetence, and weakness of the aortic media predisposing to dissecting aneurysms. Recent evidence suggests a defect of fibrillin, a constituent of elastic fibres.

Acquired Metabolic Disorders

Diabetes Mellitus

- Multifactorial aetiology: genetic and environmental factors

- Relative or absolute insufficiency of insulin, causing hyperglycaemia

- Insulin-dependent and non-insulin-dependent groups

- Long-term complications include atheroma, renal damage, microangiopathy, neuropathy.

Diabetes mellitus is a group of diseases characterised by impaired glucose homeostasis resulting from a relative or absolute insufficiency of insulin. Insulin insufficiency causes hyperglycaemia and glycosuria.

The aetiology is multifactorial; although the disorder is acquired, there is an element of genetic predisposition. It is subclassified into primary and secondary types. Primary is much more common.

Primary Diabetes Mellitus

It is subdivided into:

- insulin-dependent (IDDM)

- non-insulin-dependent (NIDDM).

Juvenile-onset diabetes, usually manifesting itself before the age of 20 years, is almost always of IDDM type. There is an inherited predisposition associated with HLA-DR3 and HLA-DR4. There is reliable evidence that the initiating event is viral infection of the insulin-producing beta-cells precipitating their immune destruction.

DM developing in adults (over 25 years of age) is most likely to be NIDDM type. It is associated with an acquired resistance to insulin. There is no HLA association, but there is a family tendency to develop the disease. The affected patients are often, but not always, obese.

Secondary Diabetes Mellitus

DM may be secondary to:

- chronic pancreatitis
- haemochromatosis
- acromegaly
- Cushing's syndrome.

Complications of Diabetes Mellitus

Good control of blood sugar levels reduces the risk of complications:

- accelerated development of atheroma

- glomerular damage leading to nephrotic syndrome and renal failure

- microangiopathy, causing nerve damage and retinal damage

- increased susceptibility to infections

- catarcts

- diabetic ketoacidosis

- hyperosmolar diabetic coma.

To this list should be added hypoglycaemia which is a frequent and troublesome complication of insulin therapy in IDDM.

There are two possible biochemical explanations for the tissue damage that results from long-term DM:

- *Glycosylation.* The high blood sugar encourages binding of glucose to many proteins; this can be irreversible. This glycosylation often impairs the function of the proteins. The level of glycosylated haemoglobin is commonly used as a way of monitoring blood sugar control.

- *Polyol pathway.* Tissues containing aldose reductase (i.e., nerves, kidneys and the lenses of the eyes) are able to metabolise the high glucose levels into sorbitol and fructose. The products of this polyol pathway accumulate in the affected tissues, causing osmotic swelling and cell damage.

Gout

- Multifactorial disorder characterised by high blood uric acid levels

- Urate crystal deposition causes skin nodules (tophi), joint damage, renal damage and stones.

Gout is a common disorder resulting from high blood uric acid levels. Uric acid is a breakdown product of the body's purine (nucleic acid) metabolism, but a small proportion comes from the diet. Most uric acid is excreted by the kidneys. In the blood, most uric acid is in the form of monosodium urate. In patients with gout, the monosodium urate concentration may be very high, forming a supersaturated solution, thus risking urate crystal deposition in tissues causing:

- tophi (subcutaneous nodular deposits of urate crystals)

- synovitis and arthritis

- renal disease and calculi.

Gout occurs more commonly in men than in women, and is rare before puberty. A rare form of gout in children - *Lesch-Nyhan syndrome* - is due to a complete deficiency of the enzyme HGPRT (hypoxanthine guanine phospho-ribosyl transferase) and is associated with mental deficiency and a bizarre tendency to self-mutilation.

Aetiology

Like DM, the aetiology of gout is multifactorial. There is a genetic component, but the operation of other factors justifies the inclusion of gout under the heading of acquired disorders. Aetiological factors include:

- gender (male>female)

- family history

- diet (meat, alcohol)

- socio-economic status (high>low)

- body size (large>small).

Gout can be subdivided into *primary gout*, due to some genetic abnormality of purine metabolism, or *secondary gout*, due to increased liberation of nucleic acids from necrotic tissue or decreased urinary excretion of uric acid.

Clinicopathological Features

The clinical features of gout are due to urate crystal deposition in various tissues. In joints, a painful acute arthritis results from phagocytosis of the crystals by neutrophil polymorphs, in turn causing release of lysosomal enzymes along with the indigestible crystals, thus accelerating and perpetuating a cyclical inflammatory reaction. The first metatarsophalangeal joint is affected typically.

Water and Electrolyte Balance

Water and electrolyte homeostasis is tightly controlled by various hormones, including antidiuretic hormone (ADH), aldosterone and atrial natriuretic peptide, acting upon selective re-absorption in the renal tubules. The process is influenced by the dietary intake of water and electrolytes and the adjustments necessary to cope with disease or adverse environmental conditions.

Water Homeostasis

Water is constantly lost from the body - in urine, in faeces, in exhaled gas from the lungs, and from the skin. The replenishment of body water is controlled by a combination of the satisfaction of the sensation of thirst and the regulation of the renal tubular reabsorption of water mediated by ADH.

Water Retention

May occur in patients with extensive oedema or if there is inappropriate production of ADH (i.e., as occurs with some lung tumours). Water overload can be caused iatrogenically by excessive parenteral infusion of fluids in patients with impaired renal function; this can be avoided by carefully monitoring fluid input and output.

Dehydration

It results from either excessive water loss or inadequate intake or a combination of both.

Excessive water loss can be due to:

- vomiting and diarrhoea

- extensive burns

excessive sweating (fever, exercise, hot climates)

- diabetes insipidus (failure to produce ADH)

- nephrogenic diabetes insipidus (renal tubular insensitivity to ADH)

- diuresis (i.e., osmotic loss accompanying the glycosuria of diabetes mellitus).

Dehydration is recognised clinically by a dry mouth, inelastic skin and, in extreme cases, sunken eyes. The blood hematocrit will be elevated, causing an increase in whole blood viscosity. This results in sluggish circulation and consequent impairment of the function of many organs.

The plasma sodium and urea concentrations are typically elevated, reflecting haemoconcentration and impaired renal function.

Sodium and Potassium Homeostasis

- Sodium may be retained excessively by the body due to action of inappropriately high levels of mineralocorticoid hormones acting on renal tubule reabsorption

- Sodium may be lost excessively in urine, due to impaired renal tubular reabsorption, or in sweat

- Potassium may accumulate excessively in the body if there is extensive tissue necrosis or renal failure

- High serum potassium level is a medical emergency because of risk of cardiac arrest

- Potassium may be lost excessively in severe vomiting and diarrhoea.

Hypernatraemia

May occur in conditions (renal failure, Cushing's syndrome, Conn's syndrome) in which there is excessive mineralocorticoid (aldosterone) production acting on renal tubular reabsorption; Conn's syndrome, due to an adrenal adenoma of the zona glomerulosa cells, is a typical example. The increased total body sodium content may be concealed by a commensurate increase in body water content in an attempt to sustain a normal plasma osmolarity; the serum sodium concentration may therefore underestimate the increase in total body sodium.

Hyponatraemia

It is a logical consequence of impaired renal tubular reabsorption of sodium. It may happen in Addison's disease and excessive diuretic therapy. This occurs in Addison's disease of the adrenal glands due to loss of the aldosterone-producing zona glomerulosa cortical cells. Sodium is the electrolyte most likely to be lost selectively in severe sweating in hot climates or during physical exertion such as marathon running; the syndrome of 'heat exhaustion' is due mainly to a combination of dehydration and hyponatraemia. Falsely low sodium concentrations may be found in hyperlipidemic states; the sodium concentration in the aqueous phase of the serum is actually normal but the lipid contributes to the total volume of serum assayed.

Hyperkalaemia

Extensive tissue necrosis can liberate large quantities of potassium into the plasma, causing the concentration to reach dangerously high levels. The commonest cause is renal failure causing decreased urinary potassium excretion. There are other causes (renal failure, acidosis, extensive tissue necrosis). Severe hyperkalaemia (> c.6.5 mmol/l) is a serious medical emergency demanding prompt treatment because of the risk of cardiac arrest. Moderate hyperkalaemia is relatively asymptomatic, emphasising the importance of regular biochemical monitoring to avoid fatal complications.

Hypokalaemia

It has many causes (vomiting, diarrhoea, diuretic therapy, alkalosis, Cushing's syndrome, Conn's syndrome). It is often accompanied by a metabolic alkalosis due to hydrogen ion shift into the intracellular compartment. Clinically, it presents with muscular weakness and cardiac dysrhythmias.

Vomiting and diarrhoea result in combined loss of water, sodium and potassium. Superimposed on this may be alkalosis from vomiting due to loss of hydrogen ions, or acidosis from diarrhoea due to loss of alkaline intestinal secretions.

Calcium Homeostasis

Serum calcium levels are regulated by the vitamin D metabolite - 1,25-dihidroxyvitamin D - and by parathyroid hormone (PTH). The precise role of calčitonin in man is uncertain, but it has a serum-calcium-lowering effect when administered to patients with hypercalcaemia; however, patients with the calcitonin-producing medullary carcinoma do not present with hypocalcaemia.

Hypercalcaemia

Acute hypercalcaemia causes fits, vomiting and polyuria. Persistent hypercalcaemia additionally results in 'metastatic' calcification of tissues. Causes of hypercalcaemia include:

- primary hyperparathyroidism

- hypervitaminosis D

- extensive skeletal metastases

- PTH-like secretion from tumours.

Hypocalcaemia

It causes neuromuscular hypersensitivity manifested by *tetany*. This can be corrected rapidly by giving calcium gluconate intravenously. The commonest cause of acute hypocalcaemia is accidental damage to or removal of parathyroid glands during thyroid surgery. Low serum calcium levels resulting from renal disease or intestinal malabsorption are rapidly corrected, in a patient with intact parathyroid glands, by stimulation of PTH secretion. This eventually causes hyperplasia of the parathyroid glands (secondary hyperparathyroidism) and weakening of the skeleton due to excessive osteoclastic resorption under the influence of PTH.

Tetany also results from respiratory alkalosis, often in patients with hysterical hyperventilation who excessively eliminate carbon dioxide, due to a reduction in the ionised calcium concentration as the pH rises.

Acid-Base Homeostasis

- Body has an innate tendency to acidification

- Buffers (bicarbonate/carbonic acid, proteins) have limited capacity

- Acidosis or alkalosis may be due to respiratory or metabolic causes

- Body attempts to restore pH by varying rate of respiration or by adjusting renal tubular function.

Metabolic pathways are intolerant of pH deviation. The extracellular pH is tightly controlled at an approximate value of 7.4, but the intracellular pH is marginally lower and varies within an even narrower range. Acidic deviation outside the normal plasma pH range is sensed by chemoreceptors at the carotid bifurcations (carotid bodies), in the aortic arch and in the medulla of the brain.

The body has an innate tendency towards acidification due to production of:

- carbon dioxide from aerobic respiration

- lactic acid from glycolysis

- fatty acids from lipolysis.

This acidific tendency is counteracted by basic (alkaline) buffers (bicarbonate, proteins) in the first instance, but these have limited capacity. Acid-base balance in the plasma is ultimately regulated by:

- elimination of carbon dioxide by exhalation

- renal excretion of hydrogen ions

- metabolism of fatty and lactic acids

- replenishment of bicarbonate ions.

Acidosis and Alkalosis

There are four possible combinations:

- respiratory acidosis

- metabolic acidosis

- respiratory alkalosis

- metabolic alkalosis.

Respiratory Acidosis

May be acute (asthma, pneumonia, respiratory impairment) or chronic (emphysema). It can be corrected by increased renal tubular reabsorption of bicarbonate ions (which are alkaline) or by increased urinary loss of hydrogen ions (which are acidic). By either mechanism, the pH is not corrected as promptly as it can be in metabolic acidosis by immediate stimulation of hyperventilation.

Metabolic Acidosis

May be acute (diabetic ketoacidosis, cardiac arrest) or chronic (renal failure). It stimulates hyperventilation, often with deep sighing respiratory excursions (Kussmaul respiration), in order to blow off carbon dioxide and thereby maintain the equilibrium of the bicarbonate/carbonic acid ratio, restoring the pH to neutrality.

Respiratory Alkalosis

May be acute (hysterical hyperventilation) or chronic (diffuse pulmonary fibrosis). It is always due to hyperventilation, causing excessive elimination of carbon dioxide. There is limited scope for correction by increasing the urinary loss of bicarbonate ions.

Metabolic Alkalosis

May be acute (excess bicarbonate administration) or chronic (persistent vomiting). It is more difficult to correct naturally because the vitally important hypoxic drive to respiration overrides the extent to which carbon dioxide can be conserved by hypoventilation.

Pathology of Malnutrition

It may be a consequence or a cause of disease. Diseases and conditions commonly complicated by malnutrition include:

- anorexia nervosa

- carcinoma of the oesophagus and stomach

- post-operative states

- senile dementia.

It may be:

- protein-energy malnutrition

- vitamin deficiencies

- a combination of both.

Protein-Energy Malnutrition

- Kwashiorkor: severe wasting is concealed by oedema

- Marasmus: severe wasting

- Both may be complicated by infections, parasitic infestations and vitamin deficiencies

- Cachexia: profound wasting often occurring terminally in cancer patients.

Protein-energy malnutrition results from the frequent combination of insufficient protein, carbohydrate and fat in the diet. Carbohydrate and fat together account for approximately 90% of the energy content of a typical healthy diet. Protein alone cannot replace the necessary energy yield from fats and carbohydrates.

Protein-energy malnutrition frequently co-exists with infections. The infections may exacerbate the deficiency, thus exposing the malnourished state, or they may complicate the deficiency because of impaired body defence mechanisms. In children prolonged malnutrition leads to stunted development due to retardation of linear growth. A shorter period of malnutrition produces body wasting.

Malnutrition in Children

- Kwashiorkor

- marasmus.

Kwashiorkor

It is characterised by oedema which may be very extensive and so belie the extreme wasting of the underlying tissues. The skin is scaly and the hair loses its natural colour. The condition often develops when a child is weaned off breast milk, but without the compensation of adequate dietary protein.

The serum albumin is low and this accounts for the oedema due to reduced plasma oncotic pressure. Hypokalaemia and hyponatraemia are common. The liver is enlarged due to severe fatty change; this occurs because the lack of protein thwarts the production of lipoprotein.

Marasmus

It is characterised by severe emaciation rather than oedema. The skin is wrinkled and head hair is lost. The serum albumin is usually within the normal range, but hypokalaemia and hyponatraemia are common.

Cachexia

It is a state of severe debilitation associated with profound weight loss. It is seen in malnutrition (marasmus is akin to cachexia), but the term is most widely associated with the profound weight loss suffered by patients with cancer. When the Tumour involves the gastrointestinal tract, the explanation for the cachexia is often obvious. However, weight loss can be a very early manifestation of cancer and is a particularly common feature of carcinoma of the lung; in this instance, it may be due to factors causing increased protein catabolism because the patient's food intake may be still within normal limits. Among several factors postulated to be responsible for the increased catabolic state in cachexia is *tumour necrosis factor*, a peptide secreted by tumour tissue.

Vitamin Deficiencies

- Multiple vitamin deficiencies may occur in severe malnutrition

- Each vitamin deficiency is associated with specific consequences.

Deficiencies of vitamins - so named by Casimir Funk (1884-1967) because he believed (mistakenly) that they were all vital amines - produce more specific abnormalities than those encountered in protein-energy malnutrition. This is because of their involvement in specific metabolic pathways.

Thiamine (B_1) Deficiency

Thiamine deficiency impairs glycolytic metabolism and affects the nervous system and the heart. The classical deficiency state is called *beri-beri* (from the Sinhalese word 'beri' meaning weakness). This state is characterised by peripheral neuropathy and, in some cases, cardiac failure.

Alcoholism is often associated with an inadequate diet. Alcoholics with thiamine deficiency can develop two CNS syndromes:

- *Korsakoff's psychosis* - characterised by confusion, confabulation and amnesia

- *Wernicke's encephalopathy* - characterised by confusion, nystagmus and aphasia.

Folate and Vitamin B_{12} Deficiency

Folate and cobalamin are essential for DNA synthesis. Deficiency of either impairs cellular regeneration; the effects are seen most severely in haemopoietic tissues, resulting in megaloblastic changes and macrocytic anaemia. In addition, cobalamin deficiency also causes subacute combined degeneration of the spinal cord.

Folate deficiency may result from:

- dietary insufficiency (principal source is fresh vegetables)

- intestinal malabsorption (i.e., coeliac disease)

- increased utilisation (i.e., pregnancy, tumour growth)

- anti-folate drugs (i.e., methotrexate).

Cobalamin deficiency may result from:

- autoimmune gastritis resulting in loss of intrinsic factor, thus causing pernicious anaemia

- surgical removal of the stomach (i.e., gastric cancer)

- disease of the terminal ileum, the site of absorption (i.e., Crohn's disease)

- blind loops of bowel in which there is bacterial overgrowth

- infestation with *Diphyllobothrium latum,* a parasitic worm.

Vitamin C Deficiency

It is now most common in elderly people and in chronic alcoholics whose diet is often lacking in fresh fruit and vegetables. Ascorbic acid is essential principally for collagen synthesis: it is necessary for the production of chondroitin sulphate and hydroxyproline from proline. Minor degrees of deficiency may be responsible for lassitude and an unusual susceptibility to bruising. Severe deficiency causes *scurvy,* a condition characterised by swollen, bleeding gums, hyperkeratosis of hair follicles, and petechial skin haemorrhages.

Vitamin D Deficiency

It is derived either from the diet (milk, fish, etc.) as ergocalciferol (D_2) or from the action of UV light on 7-dehydrocholesterol (D_3) to form cholecalciferol in the skin. The intermediate precursors are activated by hydroxylation sequentially in the liver and kidneys to give 1.25-dihydroxy-cholecalciferol, a steroid hormone. Hydroxylation in the kidney is stimulated by parathyroid hormone and hypocalcaemia. An apparent deficiency can therefore result from:

- lack of dietary vitamin D with inadequate sunlight

- intestinal malabsorption of fat (vitamin D is fat soluble)

- impaired hydroxylation due to hepatic or renal disease.

People with deeply pigmented skin (i.e., negroes) rely more heavily on dietary vitamin D when they migrate to countries that enjoy less sunlight than do their native lands.

Vitamin D is vital for normal calcium homeostasis. Its action resembles that of parathyroid hormone, ultimately causing elevation of the serum calcium concentration. It does so by:

- promotion of absorption of calcium (and phosphate to a lesser extent) from the gut

- increased osteoclastic resorption of bone and mobilisation of calcium.

In children, lack of vitamin D impairs mineralisation of the growing skeleton, thus causing *rickets.* In adults, vitamin D deficiency results in *osteomalacia.* However, the pathogenesis of ricketts and osteomalacia is identical; the two conditions are different clinical manifestations of vitamin D deficiency occurring at different stages of skeletal development.

Vitamin K Deficiency

Vitamin K is essential for the synthesis of blood-clotting factors. It is involved in the carboxylation of glutamic acid residues on factors II, VII, IX and X. The principal dietary sources are vegetables, leguminous plants and liver. Deficiency may result from:

- lack of dietary vitamin K

- intestinal malabsorption of fat (vitamin K is fat soluble).

The commonest situation leading to dietary insufficiency is found in neonates on breast milk deficient in vitamin K.

Bruising and abnormal bleeding tendency are the clinical manifestations of vitamin K deficiency. This occurs not only in the circumstances outlined above, but also in patients with liver failure in whom there is impaired hepatic synthesis of the vitamin K-dependent clotting factors; this can be corrected by giving large doses of vitamin K. It is essential to check the prothrombin time before performing a liver biopsy or any surgery on a patient with suspected liver disease.

Trace Elements and Disease

Trace elements are those present at an arbitrarily defined low concentration in a given situation. Some are of vital importance despite the meagre quantities found in the human body.

Mercury

The average human body contains only 13 mg of mercury. The safe daily intake is < 50 microg.

Mercury has been used in dental amalgams for filling tooth cavities since 1818. Although doubts have been expressed about its safety, metallic mercury and mercury-containing dental amalgams are insoluble in saliva and are, therefore, not absorbed to an appreciable extent. Dentists must, of course, exercise caution in the handling of mercury to minimise the risk of cumulative occupational exposure.

Mercury is neurotoxic. Chronic poisoning also results in a characteristic blue line on the gums. Perhaps the best known (but fictitious) case is that of the Mad Hatter in *Alice in Wonderland;* hatmakers used mercuric nitrate for making felt out of animal fur! In the 1950s at Minamata, Japan, there was serious water pollution with methyl mercury causing at least 50 deaths and many more cases of permanent disability.

Mercury was a popular, though ineffectual, remedy for syphilis; this gave rise to the adage 'A night with Venus; a lifetime on Mercury'! More recently, pharmaceutical preparations containing mercury were advocated for treating childhood ailments such as measles, teething and diarrhoea. One such preparation containing calomel (mercurous chloride) was sold as a teething powder. It was not until 1942 that it was first suggested to

be the cause of 'pink disease', a distressing condition affecting infants and young children, formerly of unknown aetiology.

Lead

The human body contains approximately 120 mg of lead and the daily intake should not exceed 500 microg. In the UK the old lead piping in water supplies is the main source, as well as tetra-ethyl and tetra-methyl lead added to petrol as anti-knocking agents.

Toxic effects include central and peripheral nervous system damage, renal damage and sideroblastic anaemia.

Aluminium

It is used therapeutically in the form of aluminium hydroxide as an antacid. It is also used in cooking utensils, from which it can be leached under acid conditions. Aluminium powder has also been used for the treatment of pneumoconiosis, a chronic lung disorder due to the inhalation of toxic or allergenic dust.

It has been incriminated in the development of skeletal abnormalities and encephalopathy in patients on regular haemodialysis for chronic renal failure. It was found deposited on mineralisation fronts in the skeleton, where it may interfere with bone turnover. Dialysis encephalopathy, first reported in 1972, is characterised by progressive dementia, epileptic fits and tremors. In 1976, dialysis encephalopathy was shown to be associated with an abnormally high aluminium concentration in brain tissue obtained from autopsies on affected patients.

It may be involved in the aetiology of Alzheimer's disease.

Copper

It is essential for the function of several enzymes (i.e., superoxide dismutase), though copper deficiency appears to be rare.

Wilson's disease is the most important disorder of copper metabolism. This is inherited as an autosomal recessive condition in which copper accumulates in the liver, basal ganglia of the brain, kidney and eyes. The brown ring of copper deposition around the corneal limbus - the Kayser-Fleischer ring - is absolutely diagnostic. Serum caeruloplasmin levels are usually low. In the liver, the copper accumulation is associated with chronic hepatitis frequently culminating in cirrhosis. It is absolutely vital to consider the diagnosis in any patient presenting with chronic liver disease and neurological signs. D-penicillamine, a chelating agent, has revolutionised the treatment, but it is to little avail if the liver and brain have already been irreversibly damaged.

Iodine

The human body contains only 15-20 mg of iodine, most of which is in the thyroid gland. Iodine is almost unique among elements in having just one known role in the human body: it is essential for the synthesis of thyroxine.

Ingestion of modestly excessive quantities of iodine (as potassium iodide, for example) has no serious adverse consequences. Indeed, large stocks of potassium iodide tablets are kept in the vicinity of nuclear power stations for use in the event of accidental release of radioactive iodine, a cause of thyroid cancer. The potassium iodide competes with the smaller amounts of radioactive iodine for uptake by the thyroid gland.

Iodine deficiency results in goitre. It was prevalent in regions where the water and solid food lacked an adequate iodine content, usually in mountainous regions (hence, for example, 'Derbyshire neck'). Iodine deficiency during pregnancy causes cretinism in neonates, characterised by mental retardation and stunted growth.

Oedema and Serous Effusions

- Oedema is excess water in tissues

- Oedema and serous effusions have similar pathogenesis

- May be due to increased vascular permeability, venous or lymphatic obstruction, or reduced plasma oncotic pressure.

Oedema is an excess of fluid in the intercellular compartment of a tissue. A serous effusion is an excess of fluid in a serous or coelomic cavity (i.e., peritoneal cavity, pleural cavity). The main ingredient of the fluid is always water.

Clinical Features

Oedema is recognised clinically by diffuse swelling of the affected tissue. If the oedema is subcutaneous, the affected area shows pitting; i.e., if the skin is indented firmly with the fingers, an impression of the fingers is left transiently on the surface.

Pathogenesis

Oedema and serous effusions are due to either:

- excessive leakage of fluid from blood vessels into the extravascular spaces

- impaired reabsorption of fluid from tissues or serous cavities.

Oedema is classified into four pathogenetic categories:

- inflammatory: due to increased vascular permeability

- venous: due to increased intravenous pressure

- lymphatic: due to obstruction of lymphatic drainage

- hypoalbuminaemic: due to reduced plasma oncotic pressure.

Serous effusions can be attributable to any of the above causes, but in addition there is another important diagnostic category: neoplastic effusions due to primary or secondary neoplasms involving serous cavities.

Inflammatory Oedema

Oedema is a feature of acute inflammation. In acutely inflamed tissues there is increased vascular (mainly venular) permeability due to the separation of endothelial cells under the influence of chemical mediators. Fluid with a high protein content leaks out of the permeable vessels into the inflamed tissue. This is beneficial, because the proteins in the oedema fluid assist in defeating the cause of the inflammation. For example:

- albumin increases the oncotic pressure of the extravascular fluid, causing water to be imbibed, thus diluting any toxins

- fibrinogen polymerises to form a fibrin mesh which helps to contain the damage

- immunoglobulins and complement specifically destroy bacteria or neutralise toxins.

Venous Oedema

Oedema results from increased intravenous pressure because this pressure opposes the plasma oncotic pressure, largely due to the presence of albumin, that draws fluid back into the circulation at the venous end of capillary beds. Increased intravenous pressure results from either *heart failure* or impairment of blood flow due to *venous obstruction* by a thrombus or extrinsic compression. The affected tissues are often intensely congested due to engorgement by venous blood under increased pressure. In heart failure, there is also *pulmonary congestion with oedema* and so-called *passive venous congestion of the liver.*

Venous oedema is seen most commonly in dependent parts of the body, notably the legs; indeed, it is not unusual for mild degrees of venous oedema to occur at the ankles and feet of normal people who have sat in aircraft on long intercontinental flights - immobilisation impairs venous return. The fluid in venous oedema has a low protein content.

Oedema of just one leg is almost always due to venous obstruction by a thrombus. This is a common complication of immobilisation following major surgery or trauma. Bilateral leg oedema, if due to venous causes (there may be other explanations), is more likely to be due to heart failure rather than venous obstruction. In either case it is a serious manifestation prompting immediate attention to the underlying condition.

Lymphatic Oedema

Some fluid normally leaves capillary beds and drains into adjacent lymphatic channels to return eventually to the circulation through the thoracic duct. If the lymphatic channels are obstructed, the fluid remains trapped in the tissues and oedema results.

Causes of lymphatic oedema include blockage of lymphatic flow by filarial parasites or by tumour metastases, or as a complication of surgical removal of lymph nodes. Blockage of inguinal lymphatics by filarial parasites frequently causes gross oedema of the legs and, in males, the scrotum; the resulting deformity is called *elephantiasis.* Blockage of lymphatic drainage from the small intestine, usually because of tumour involvement, causes *malabsorption* of fats and fat-soluble substances. Blockage of lymphatic drainage at the level of the thoracic duct, or at least close to it, causes *chylous effusions* in the pleural and peritoneal cavities; the fluid is densely opalescent due to the presence of numerous tiny fat globules (chyle).

Hypoalbuminemic Oedema

A low plasma albumin concentration results in oedema because of the reduction in plasma oncotic pressure; thus, fluid cannot be drawn back into the venous end of capillary beds and it remains in the tissues. Causes of hypoalbuminaemia are:

- protein malnutrition (as in kwashiorkor)

- liver failure (reduced albumin synthesis)

- nephrotic syndrome (excessive albumin loss in urine)

- protein-losing enteropathy (a variety of diseases are responsible).

Hypoalbuminaemia as the cause of oedema can be verified easily by measuring the albumin concentration in serum.

Ascites and Pleural Effusions

Ascites is an excess of fluid in the peritoneal cavity. It is one of the five general causes of a distended abdomen: fluid, fat, faeces (constipation or obstruction), fetus, flatus.

Serous effusions may be divided into *transudates* and *exudates* by their protein content. Transudates have a protein concentration of less than 2 g/100 ml, whereas the concentration in exudates is higher. Involvement by tumour is the most important cause of an exudate.

Degenerative Disorders

Tissue Degenerations

- Calcification: *dystrophic* in previously damaged tissues; *metastatic* due to hypercalcaemia

- Elastosis: due to collagen degeneration in, i.e., light-damaged skin

- Sclerosis: non-specific term describing hardening of a tissue frequently due to collagen deposition

- Brown atrophy: senile shrinkage of an organ accompanied by lipofuscin accumulation.

Calcification

Precipitates of calcium salts are normally found only in bones, otoliths and teeth. In disease states, however, tissues can become hardened by deposits of calcium salts; this process is called calcification. It may be:

- dystrophic

- 'metastatic' (meaning widespread).

Dystrophic Calcification

Calcification is said to be dystrophic if it occurs in tissue already affected by disease. In these cases the serum calcium is normal. The calcification is due to local precipitation of insoluble calcium salts. Common examples are:

- atheromatous plaques

- congenitally bicuspid aortic valves

- calcification of mitral valve ring

- old tuberculous lesions

- fat necrosis

- breast lesions

- calcinosis cutis.

A bicuspid aortic valve can function quite normally, but when it becomes calcified, a common event in the elderly, the valve cusps become thick and rigid; this causes stenosis, incompetence and, ultimately, cardiac failure. The biochemical basis of dystrophic

calcification is uncertain except in the instance of fat necrosis, a common result of trauma to adipose tissue or of acute pancreatitis; the liberated fatty acids bind calcium to form insoluble calcium soaps sometimes causing hypocalcaemia and tetany.

A few tumours contain minute concentric lamellated calcified bodies. These are called *psammoma bodies* and are commonly found in:

- meningiomas

- papillary carcinoma of thyroid

- papillary ovarian carcinoma.

Psammoma bodies assist the histopathologist in correctly identifying the type of tumour, but their pathogenesis is unknown.

'Metastatic' Calcification

It is much less common than dystrophic calcification and occurs as a result of hypercalcaemia. Calcification may be widespread and occurs in otherwise normal tissues. Frequent causes are:

- hyperparathyroidism

- hypercalcaemia of malignancy.

In hyperparathyroidism, an adenoma or, less often, a diffuse hyperplasia of the parathyroid glands secretes excess quantities of parathyroid hormone; this liberates calcium from the bone, resulting in hypercalcaemia. In some patients with malignant neoplasms, hypercalcaemia results from either the secretion of a parathyroid hormone-like substance or extensive bone erosion due to skeletal metastases.

In this condition the calcium salts are precipitated on to connective tissue fibres (i.e., collagen, elastin).

Elastosis

Elastosis is an excess of elastic tissue or of collagen altered in such a way that it acquires some of the properties of elastic tissue. It is a common finding in breast cancers and is associated with the presence of oestrogen receptors in the tumour cells and a probability that the patient will benefit from endocrine therapy. Elastosis of the dermis is common in light-exposed skin, particularly of the face; paradoxically, it is associated with a loss of elasticity and accounts for the wrinkles inflicted by age.

Sclerosis

It is a hardening or thickening of tissues. It has many causes and is a manifestation of many diseases. A frequent feature is the presence of excessive amounts of collagen in the affected tissue. Examples include:

- systemic sclerosis (scleroderma)

- multiple sclerosis (of the CNS)

- atherosclerosis or arteriosclerosis

- nephrosclerosis.

It is invariably associated with impaired function of the affected tissue. In systemic sclerosis the process restricts peristaltic movement of the gut, and in nephrosclerosis, a common sequel of renal injury from a variety of causes, renal failure may develop.

Intracellular Degenerative Changes

Two common are:

- fatty change

- brown atrophy.

Fatty Change

Sub-lethal cellular injury commonly leads to the accumulation of fat droplets in the cytoplasm. This is seen most severely in the liver when there is interference with the normal metabolism of fat. The fat droplets are often so large that they compress the nucleus and distort the cell. Organs affected are enlarged, pale, and have a greasy consistency. Fatty change is induced intentionally in the liver of geese for the production of *pate de foie gras.*

Brown Atrophy

Many body organs in the elderly are reduced in size and are abnormally brown; this condition is 'brown atrophy'. The heart and liver are affected commonly. The atrophy is due to senile involution. The brown appearance is due to excessive amounts of lipofuscin, a granular brown intracellular pigment, often referred to as 'wear-and-tear' pigment because of its supposed association with excessive usage of an organ. The mere presence of excess lipofuscin does not appear to interfere with the function of the affected organ.

Amyloid

- Extracellular material with affinity for Congo red or Sirius red dyes

- Composed of immunoglobulin light chains, serum amyloid protein A, peptide hormones, pre-albumin, etc.

- Systemic amyloidosis may be due to a plasma cell neoplasma (i.e., myeloma) or to a chronic inflammatory disorder

- Localised amyloid deposits occur in some peptide-hormone-producing tumours

- Amyloid often impairs the function of the organ in which it is deposited

- Heart failure and nephrotoxic syndrome are common complications.

Amyloid (meaning starch-like from the Greek 'amylon') is the name given to a group of proteins or glycoproteins which, when deposited in tissues, share the following properties:

- beta-pleated sheet molecular configuration with an affinity for certain dyes (i.e., Congo or Sirius red)

- fibrillar ultrastructure

- presence of a glycoprotein of the pentraxin family (amyloid P protein)

- extracellular location, often on basement membranes

- resistance to removal by natural processes

- a tendency to cause the affected tissue to become hardened and waxy.

Small asymptomatic deposits of amyloid are not uncommon in the spleen, brain, heart and joints of elderly people.

Classification of Amyloid

It can be classified according to:

- chemical composition

- tissue distribution

- aetiology.

The tissue distribution and aetiology may be combined to evolve a clinical classification.

Clinically amyloidosis presents with organ involvement which is either:

- systemic

- localised.

Systemic Amyloidosis

The material is deposited in a wide variety of organs; virtually no organ is exempt. Clinical features suggesting amyloidosis include generalised diffuse organ enlargement (i.e., hepatomegaly, splenomegaly, macroglossia) and evidence of organ dysfunction (i.e., heart failure, proteinuria).

Systemic amyloidosis is further classified according to its aetiology:

- myeloma-associated

- reactive (secondary)

- senile

- haemodialysis-associated

- hereditary.

Myeloma-Associated Amyloidosis

The amyloid substance in myeloma-associated amyloidosis is *AL amyloid* immunoglobulin light chains.

A *myeloma* is a plasma tumour, often multiple, arising in bone marrow and causing extensive bone erosion. It produces excessive quantities of immunoglobulin of a single class (i.e., IgG) with a uniform light chain (i.e., kappa). The light chain forms the amyloid material. The amyloid is deposited in many organs - heart, liver, kidneys, spleen, etc. - but shows a predilection for the connective tissues within these organs.

In some cases, myeloma-associated amyloidosis is called *primary amyloidosis* because of the absence of any clinically obvious myeloma. However, in these cases it is due to a clinically occult plasma cell tumour, with little bone erosion to declare itself, and is accompanied by the presence of a monoclonal immunoglobulin band on serum electrophoresis; this is referred to as a benign *monoclonal gammopathy*.

Amyloidosis is a serious complication of myeloma, making a further contribution to the ill-health of the patient.

Reactive (Secondary) Amyloidosis

The amyloid substance in reactive or secondary amyloidosis is *AA amyloid* - derived from serum amyloid protein A.

Serum amyloid protein A is an acute phase reactant protein, one of several so called because the serum concentrations rise in response to the presence of a variety of diseases.

Predisposing cause is invariably a chronic inflammatory disorder:

- rheumatoid arthritis

- bronchiectasis

- osteomyelitis.

It has a predilection for liver, spleen and kidneys.

Senile Amyloidosis

Minute deposits of amyloid, usually derived from serum pre-albumin, may be found in the heart and in the walls of blood vessels in many organs of elderly people.

Haemodialysis-Associated Amyloidosis

The clinical manifestations include arthropathy and carpal tunnel syndrome. In a few cases there is much more excessive involvement of other organs. The amyloid material deposited in the affected tissues appears to be *$beta_2$-microglobulin.*

Hereditary and Familial Amyloidosis

They are rare and include:

- familial Mediterranean fever

- Portuguese nephropathy

- neuropathic forms.

Localised Amyloidosis

Amyloid material is often found in the stroma of tumours producing peptide hormones. It is particularly characteristic of medullary carcinoma of the thyroid, a tumour of the calcitonin-producing interfollicular C cells. In this instance, the amyloid contains calcitonin-precursor molecules arranged in a beta-pleated sheet configuration.

Localised deposits of amyloid may be found, without any obvious predisposing cause, in virtually any organ; this is, however, a rare occurrence. The skin, lungs and urinary tract seem to be the most frequent sites.

Cerebral amyloid is found in Alzheimer's disease and in the brain of elderly people in:

- neuritic (senile) plaques

- the walls of small arteries (amyloid angiopathy).

Clinical Effects and Diagnosis

- nephrotic syndrome, eventually renal failure

- hepatosplenomegaly

- cardiac failure due to restricted myocardial movement

- macroglossia

- purpura

- carpal tunnel syndrome

- factor X deficiency (in AL amyloid).

As the kidneys are often involved and the amyloid is deposited in glomerular basement membranes, altering their filtration properties, the patients often have proteinuria; in severe cases the proteinuria can result in nephrotic syndrome. Various organs are enlarged (liver, spleen). The diagnosis is best confirmed by biopsy of the rectal mucosa, commonly involved in cases of systemic amyloidosis. When examined using one fixed and one rotating polarising filter in the light path on either side of the section, the red colour changes to green (dichroism); this is very specific for amyloid.

Pathology of the Bed Rest

- Prolonged bed rest exposes patient to increased risk of predictable pathological complications

- Complications due to immobilisation

- Impaired circulation due to direct skin pressure or immobility predisposes to decubitus ulcers and venous thrombosis respectively

- Disuse atrophy affects bones and muscles

- Gravitational congestion predisposes to hypostatic pneumonia.

Most complications can be prevented by careful nursing and active physiotherapy.

Decubitus Ulcers (Bed Sores)

They occur over pressure points, such as the sacrum and heels in a patient lying supine. They are due to ischaemic necrosis of the skin caused by compression of the vascular network. Emaciated patients are especially liable to develop decubitus ulcers because there is less subcutaneous fat to diffuse the pressure over bony prominences.

The skin first appears gangrenous and then sloughs to expose a raw base of connective tissue. The resulting ulcer frequently becomes infected and may lead to septicaemia.

They can be prevented by regularly turning the patient and by using special mattresses.

Venous Thrombosis

Venous return from the legs results from the movement of the surrounding muscles combined with the effect of valves. Immobilised patient commonly develop deep leg vein thrombosis because of venous stasis; this has two consequences:

- venous oedema of the leg

- risk of pulmonary embolism.

The latter is an ominous event causing either pulmonary infarction or even sudden death.

Leg vein thrombosis can be prevented by anticoagulation in cases at risk and by physiotherapy.

Osteoporosis and Muscle Wasting

Osteoporosis is a condition in which there is a reduction in bone mass. It weakens the skeleton and liberates much calcium, leading to hypercalciuria and a risk of renal stone formation.

Hypostatic Pneumonia

Patients lying supine in bed have a reduced respiratory excursion and, if severely ill, may have reduced cough reflexes. Furthermore, the posterior regions of the lungs become congested with blood and alveolar oedema can occur. These events combine to predispose the patient to develop a form of bronchopneumonia known as hypostatic pneumonia.

Pathology of Ageing

- All sexually-reproducing organisms have a finite lifespan

- Multifactorial process (intrinsic and extrinsic factors), often accelerated by disease

- Elderly patients often respond atypically to disease

- Elderly patients commonly have multiple diseases and organ failure.

Even individual cells from a multicellular organism are limited to a finite number of mitotic divisions; this limit is known as the *Hayflick limit.* Only those cells transformed by some mutagenic agent can be regarded ar immortal.

Ageing is a multifactorial process. In addition to the innate restriction on the number of mitotic divisions of which a cell is capable, there are other factors. *Mutational errors of cellular metabolism,* even though they may be non-lethal to the cell harbouring them, may have a cumulative deleterious effect on the biochemical homeostasis of the whole body. Non-replicating cells (i.e., cardiac myocytes, neurones) gradually accumulate *waste products of metabolism* of which lipofuscin, a brown pigment, is the most noticeable. Finally, *immune failure* leads to increased susceptibility to infections and to an increased incidence of autoimmune disease in the elderly.

Some disorders, atheroma for example, are so common in the elderly that one is perhaps reluctant to regard them as a disease in this setting. This reluctance may be justified; disease is a state of ill-health or disability ('dis-ease') and not just the presence of lesions of which the patient is unaware. Most important, however, is the fact that all cells have a finite lifespan and it is the cumulative effect of this process in the multicellular individual that determines the pace at which ageing occurs. This effect is independent of any disease.

Two classes of factor contribute to the ageing process:

- intrinsic

- extrinsic.

Progeria

It is a rare congenital disorder characterised by premature ageing. Affected individuals show a remarkable accelerated development of baldness, cataracts and atheroma. The wizened facial appearance by the time the patients reach their teens is particularly striking.

Response of the Aged to Disease

The elderly individual often shows impaired responses to disease.

Multiple Pathology in the Elderly

- atheroma affecting large and medium-size arteries, causing weakening of their walls and partial or even complete occlusion of the lumen

- osteoarthrosis (osteoarthritis), causing relative immobility if it affects the main weight-bearing joints

- hypertension, causing heart failure and impairment of renal function

- cerebral atrophy, causing senile dementia and therefore an inability to communicate clearly.

Senile Involution

Brown atrophy, sclerosis of glomeruli in the kidney, adipose replacement of lymph nodes, elastosis of the skin, and senile osteoporosis.