Case Studies

SUPPLEMENTARY INFORMATION TO CHAPTER 9

Case Study 9.1
A 10-year old child was brought to the OP Department with complaints of constant dribbling of thick mucus from mouth and not responding to surroundings. Clinical history revealed lack of developmental milestones since 2 years of age. The child has coarse facial features and thick mucus and skeletal deformities. Urinalysis revealed presence of heparan sulfate and dermatan sulfate. What is the probable diagnosis? What is the biochemical basis of this disorder?

Answer: Diagnosis is Hurler’s syndrome, a type of mucopolysaccharidoses (MPS-I). There is deficiency of α-L-iduronidase. This leads to defective degradation of dermatan sulfate and heparin sulfate. They accumulate in tissues and are also excreted in urine. Clinical features include progressive deterioration, hepatosplenomegaly, progressive mental retardation, coarse facial features, loss of physical skills, hearing loss (conductive hearing loss) and language problems, skeletal deformities (including disproportionate growth of trunk and extremities), etc. These children often die by 10 years of age.

Urine analysis for mucopolysaccharides is diagnostic in these patients. Urine cetyltrimethylammonium bromide test for mucopolysaccharides is positive. Absence of α-L-iduronidase is diagnostic. Treatment options are bone marrow transplantation, umbilical cord blood transplantation, before 18 months of age. There is no cure for the disease. Gene therapy trials and enzyme replacement therapies are ongoing. These options are partially beneficial.

Case Study 9.2
A newborn baby had severe abdominal distension, severe bowel cramps, and diarrhea after being fed breast milk. Urine analysis revealed the presence of reducing sugar. What is the possible defect? What is the confirmatory diagnostic test? How can it be treated?

Answer: The likely cause is lactose intolerance. Abdominal distension and bowel cramps after intake of milk is due to undigested lactose. This lactose can be ultimately excreted in urine giving a positive urine sugar Benedict’s test.

There is absence of lactase enzyme, which digests lactose. This is normally produced by cells lining small intestine. Highest levels of lactase are present shortly after birth, and this declines with age.

Hence secondary lactose intolerance in adults is common.

Lactose fermentation in the intestine produces large amounts of gas (a mixture of hydrogen, CO₂ and methane) which produces abdominal cramps, bloating and flatulence. Resultant elevated osmotic pressure can produce diarrhea. Symptoms usually appear 30 minutes – 1 hr after consuming milk or milk products in patients with secondary lactose intolerance.

Confirmatory diagnosis is made by (1) hydrogen breath test, and (2) stool acidity test. The person drinks a lactose-loaded beverage and breath is analyzed at regular intervals to measure the amount of hydrogen. Normally very little hydrogen is detectable in the breath, but undigested lactose produces high levels of hydrogen. The test takes 2–3 hrs.
The stool acidity test is used for infants and young children to measure amount of acid in stool. Undigested lactose produces lactic acid and other fatty acids that can be detected in stool sample. Glucose also may be present in stool.

In children with primary lactose intolerance, gradual introduction of small amounts of milk / milk products may help adaptation. Lactose-free, lactose-reduced milk, soy milk and other products may be beneficial. Lactase enzyme or tablets can be administered. Adults usually adapt themselves by avoiding milk and milk products.

**Case Study 9.3**

A 35-year old female presented with complaints of alternating diarrhea and constipation. She reported abdominal discomfort and bloating that were relieved by bowel movement. The episodes were worse in times of stress. She denies any blood in the stools, weight loss and anorexia. No history of fever or drug intake. Physical examination was within normal limits. She was prescribed a cellulose containing dietary supplementation to increase the bulk of stools. What is the likely diagnosis? What is the effect of the treatment modality prescribed?

*Answer*: The patient is likely suffering from irritable bowel syndrome, a gastrointestinal disorder of unknown etiology. Common symptoms include abdominal cramps or pain, bloating and flatulence. There might be alternating periods of diarrhea and constipation and passing mucus in the stools. Vomiting, blood in stools, pain that interrupt sleep, fever and weight loss are rare.

Diagnosis is made by excluding other causes. Stool bulking agents, antispasmodics, antidiarrheal agents, antidepressant drugs, serotonin receptor agonists and antagonists and chloride channel activators are used for therapy. Dietary fibers are the indigestible part of plant foods that make stool soft and enable smooth bowel movements, prevent constipation hemorrhoids and diverticulosis. Soluble fibers lower total and LDL cholesterol and help to prevent ischemic heart disease and stroke. Soluble fibers in excess can cause abdominal bloating and flatulence, dehydration and pectins can reduce absorption of cholesterol-lowering drugs like lovastatin.

Insoluble fibers present in food include cellulose, hemicelluloses, and lignins. Excess of insoluble fibers can result in excessive gas, constipation and intestinal obstruction, diarrhea in sensitive patients, and can reduce absorption of calcium, iron, copper and zinc, especially in children. Insoluble fibers consumed on empty stomach can aggravate symptoms of irritable bowel syndrome.

**SUPPLEMENTARY INFORMATION TO CHAPTER 10**

**Case Study 10.1**

A 12-year old girl presented with grossly enlarged abdomen. She gives history of frequent episodes of weakness, sweating and pallor that were eliminated by eating. Her weight was low (25 kg). The liver was enlarged, firm and spleen and kidneys were not palpable. Laboratory results revealed low blood glucose, low pH, high lactate, triglycerides, ketones and high free fatty acids. Liver biopsy showed elevated glycogen level, and enzyme assay done on biopsy specimen showed low glucose-6-phosphate levels. What is the possible diagnosis? What is the possible treatment?

*Answer*: The diagnosis is von Gierke’s disease (GSD Type I). The important biochemical features are hypoglycemia, lactic acidemia, metabolic acidosis, hyperlipidemia and hyperuricemia. Clinical features include convulsions, enlargement of liver and kidneys, doll’s face (rounded cheeks due to fat deposition), growth retardation, normal mental development, etc. Late complications include renal stones, tubular defects, hypertension, changes in skin and mucous membrane and altered platelet function leading to bleeding. Renal conditions may necessitate dialysis and transplantation.

No specific treatment is available. Primary goal of dietary therapy is to correct hypoglycemia and maintain normoglycemia. Intake of fructose and galactose is to be limited, because they are converted to lactate, and not to glucose. Nasogastric glucose infusion, parenteral nutrition and oral administration of raw cornstarch are useful options.
Case Study 10.2
A 6-year old boy presented with general weakness. There was paleness, fatigue, shortness of breath and a rapid heart rate. History revealed that he had prolonged neonatal jaundice. Results at that time were as follows – Total Bilirubin – 10.0 mg%, Conjugated bilirubin – 1.5 mg%, Unconjugated bilirubin – 8.5 mg%, AST – 30.0 U/L, ALT – 35.0 U/L, ALP – 10.0 KAU/L, LDH – 1000 U/L. Jaundice was triggered on many occasions by bacterial and viral infections as well as some antibiotics. What is the likely diagnosis?

Answer: GPD deficiency. Jaundice is hemolytic in type, kernicterus and anemia are present. Liver enzymes are normal and lactate dehydrogenase levels are very high. Hemolytic anemic in GPD deficiency is triggered on many occasions by bacterial and viral infections as well as some antibiotics.

Case Study 10.3
A 3-year old child was brought to the pediatrician for complaints of fever and cough. On examination, all systems were normal and no evidence for any genetic disorder. On the safer side, the doctor performed urine screening to rule out an inborn error of metabolism. As a surprise, Benedict’s test result came as positive! Blood glucose – 100 mg%, urine was negative for glucose as well as galactose; Bial’s test was positive. What is the likely diagnosis? What is the biochemical basis for this disease?

Answer: Essential pentosuria. See chapter for biochemical basis.

SUPPLEMENTARY INFORMATION TO CHAPTER 11

Case Study 11.1
A 2-year old child presented with liver enlargement. Investigations showed the following results: Blood sugar – 50 mg%, Uric acid – 10 mg%, Lactic acid – 15 mg%, Plasma cholesterol – 300 mg% and ketone bodies were present. What is the likely diagnosis? What is the biochemical basis of the disorder and its treatment?

Answer: Galactosemia. See chapter for details.

Case Study 11.2
A 3-year old boy is brought to the emergency department after several episodes of vomiting and lethargy. His pediatrician has been concerned about his failure to thrive and possible hepatic failure along with recurrent episodes of the vomiting and lethargy. After a careful history is taken, you observe that these episodes occur after ingestion of certain types of food, especially high in fructose. His blood sugar was checked in the emergency department and was extremely low.

1. What is the most likely diagnosis?
2. What is the biochemical basis for the clinical symptoms?
3. What is the treatment of the disorder?

Answers:
Diagnosis: Fructose intolerance.

Biochemical basis of disorder: Because of a genetic disorder, the hepatic aldolase B enzyme is defective, and functions normally in glycolysis but not in fructose metabolism. Glucose production is inhibited by elevated fructose 1-phosphate. When fructose is ingested, severe hypoglycemia results.

Treatment: Avoid dietary fructose.

Clinical correlation: Deficiency of aldolase B is an autosomal recessive disease, leading to fructose intolerance. It does not cause difficulty as long as the patient does not consume any foods with fructose or sucrose. Frequently, children with
fructose intolerance avoid candy and fruit, which should raise some eyebrows! Likewise, they usually do not have many
dental caries. However, if chronically exposed to fructose-containing foods, infants and small children may have poor
weight gain and abdominal cramping or vomiting.

**SUPPLEMENTARY INFORMATION TO CHAPTER 12**

**Case Study 12.1**

A teenage girl was brought to the hospital with complaints that she gets too tired and muscle pains. A consulting neurologist
found muscle weakness in arms and legs. Biochemical investigations revealed elevated amounts of triglycerides esterified
with primary long chain fatty acids. Muscle biopsy report showed significant number of lipid vacuoles. What is the
probable diagnosis? What is the cause of these symptoms?

**Answer:** Likely cause is carnitine deficiency. Causes of carnitine deficiency may be – (1) Inadequate intake, (2) Enzyme
deficiencies, (3) Decreased endogenous synthesis due to severe liver diseases, (4) Excess loss of carnitine due to diarrhea,
renal losses, hemodialysis, (5) Hereditary diseases, (6) Increased requirement, as in ketosis, critical illnesses like sepsis
and major burns, major surgery of GIT, and (7) Mitochondrial impairment as with certain drugs (zidovudine, valproate).

It can cause a heterogeneous group of disorders. Muscle metabolism is impaired, causing myopathy, hypoglycemia, or
cardiomyopathy. Infants typically present with hypoglycemia, and hypoketotic encephalopathy.

The symptoms of carnitine deficiency range from mild muscle cramps to severe weakness and death. Muscle, kidney
and heart are primarily affected. Muscle weakness during prolonged exercise is a predominant feature, because muscles
rely more of fatty acids as a long-term source of energy. Medium chain fatty acids, which do require carnitine, are
normally metabolized in these patients.

Causes of carnitine deficiency may be – (1) Inadequate intake, (2) Enzyme deficiencies, (3) Decreased endogenous
synthesis due to severe liver diseases, (4) Excess loss of carnitine due to diarrhea, renal losses, hemodialysis, (5) Hereditary
diseases, (6) Increased requirement, as in ketosis, critical illnesses like sepsis and major burns, major surgery of GIT, and
(7) Mitochondrial impairment as with certain drugs (zidovudine, valproate).

Diagnosis is made by very low carnitine level in plasma and muscle (1–2% of normal). Fasting ketogenesis may be
impaired if dietary intake is impaired. Fasting urinary organic acid pattern may show hypoketotic dicarboxylic aciduria
pattern. Carnitine assay in cultured fibroblast and lymphoblast will demonstrate low level. Treatment consists of dietary
L-carnitine.

**Case Study 12.2**

A 22-year old primigravid female at 36 weeks of gestation presented with nausea, vomiting, and malaise over the last
several days. On examinations she had high blood pressure (190/110 mm Hg) and yellowish discoloration of sclera.
Laboratory results revealed proteinuria, impaired liver function tests, prolonged clotting time, hyperbilirubinemia,
hypoglycemia and hypofibrinogenemia. The patient was diagnosed as acute fatty liver of pregnancy. An emergency
cesarean section was done, but hypoglycemia worsened and the patient went into coagulopathy, renal failure and hepatic
coma. What is the cause of acute fatty liver of pregnancy? What is the cause for hypoglycemia?

**Answer:** Short history of illness, hypoglycemia, liver failure, renal failure and coagulopathy are suggestive of acute
fatty liver of pregnancy. Condition usually sets in during the second half of pregnancy and closer to term, it can also
manifest in the postpartum period. Diagnosis is made incidentally with elevated liver enzymes. Patients develop jaundice,
encephalopathy, and profound hypoglycemia.

Triglycerides accumulate in liver and when chronic, can produce extensive fibrosis, cirrhosis and impaired liver
function. Fatty liver can be of two types. In the first type, elevated free fatty acids are due to mobilization from adipose
tissue or hydrolysis of lipoprotein triglycerides by lipoprotein lipase in extrahepatic tissues. VLDL does not increase as
fast to allow esterification to occur and hence triglycerides accumulate producing fatty liver. This pattern is typically seen
in starvation and high-fat diet. The second type is due to block in production of plasma lipoproteins and may be due to
(1) block in apolipoprotein synthesis, (2) block in synthesis of lipoprotein from lipid and apolipoprotein, or (3) failure in
secretory mechanism itself.

Fatty liver due to any condition except alcohol is termed as nonalcoholic steatohepatitis. Causes are obesity, diabetes
mellitus, hypertriglyceridemia, drugs and poisons, endocrine disorders and acute fatty liver of pregnancy. Women
with fatty liver of pregnancy develop defect in fatty acid oxidation due to reduced long chain 3 hydroxy acyl CoA
dehydrogenase activity. The defect is in mitochondrial processes and reduced β oxidation. There is fatty infiltration of
liver and glycogen levels are depleted. Gluconeogenesis is impaired and hypoglycemia develops.

**Case Study 12.3**

A 65-year old man presented with anemia, weight loss and passage of bulky pale stools. On examination, he had
hepatosplenomegaly. His plasma electrolytes were normal. Further laboratory tests were:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma total proteins</td>
<td>5.2 g/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.5 g/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>6.8 mg/dL</td>
</tr>
<tr>
<td>Phosphates</td>
<td>2 mg/dL</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>300 U/L</td>
</tr>
</tbody>
</table>

His fecal fat excretion was 55 g Over three days (normal less than 21 g) and his plasma 25-hydroxy cholecalciferol
was 28 nmol /L (normal 40–160).

A. What is the most probable diagnosis?

B. What will be the cause for steatorrhea and what functional analysis could be done?

C. How do you interpret low plasma albumin?

D. How do you interpret low plasma vitamin D, calcium and increased ALP values?

E. What is the cause for anemia in this patient?

**Answer**: Steatorrhea is confirmed by abnormal fecal fat excretion and the complaint of “passage of bulky pale motions”.
Xylose absorption test revealed a 5-hr urinary xylose excretion of 0.6 (normal 1.2 g). Xylose absorption test is positive in
disorders of upper half of small gut like celiac disease and tropical sprue. Plasma levels of bilirubin, ALT and GGT were
normal in this particular case. Liver function tests to be done to rule out chronic liver diseases. Vitamin B12 absorption
test will be positive in diseases of terminal ileum, e.g., regional enteritis.

Low plasma albumin is due to inadequate absorption of amino acids. Low plasma vitamin D, calcium and increased
ALP are due to decreased absorption of fat-soluble vitamins. Vitamin D deficiency leads to decreased gut calcium
absorption; this in turn, leads to low plasma calcium. This activates osteoblasts, which accounts for the increased ALP
level. Anemia is seen because excess fat in gut will interfere with absorption of iron.

**SUPPLEMENTARY INFORMATION TO CHAPTER 13**

**Case Study 13.1**

A middle aged man complained of fatigue and loss of memory of recent onset. There was vague abdominal pain. On
examination there was enlargement of the liver. Laboratory results obtained were as follows – Serum AST – 120 U/L,
ALT – 80 U/L, ALP – 68 U/L, GGT – 170 U/L, Bilirubin – 1.0 mg/dl, glucose – 60 mg/dl, uric acid – 8.0 mg/dl. CBC and
urinalysis were normal. What is the diagnosis? Interpret the biochemical data on the basis of your diagnosis.

**Answer**: The patient has alcohol related liver disease. Hypoglycemia and hyperuricemia are due to alcoholism. Alcoholism
is associated with fatty liver, hepatitis and cirrhosis. There can be acute or chronic inflammation and parenchymal
necrosis, which is often reversible.
Fatty liver is caused by impaired fatty acid oxidation and increased lipogenesis, due to changes in [NADH]/[NAD] ratio in liver. Oxidation of alcohol by alcohol dehydrogenase leads to increased NADH. This NADH can compete with other substrates like fatty acids for the respiratory chain, inhibiting their oxidation and causing increased esterification of fatty acids to form triglycerides and causing fatty liver. Oxidation of ethanol produces acetaldehyde and acetate. Increased [NADH]/[NAD] ratio also causes increased [lactate]/[pyruvate] ratio leading to elevated lactate, which decreases uric acid excretion aggravating gout.

In alcoholism, usually ALT is higher than AST (Please note that in this patient, it is not the case), GGT is high and ALP may be normal. Serum bilirubin may be high, serum proteins may be reduced, and hypoglycemia, hyperuricemia, ketosis and metabolic acidosis may be seen. Fasting hypoglycemia is due to high lactate and low pyruvate. Level of β hydroxy butyrate is elevated due to high NADH leading to ketosis. Ketoacidosis and lactic acidosis are accompanying features.

SUPPLEMENTARY INFORMATION TO CHAPTER 14

Case Study 14.1

A 63-year-old female presents to the clinic with recurrent mid-epigastric pain over the last 3 months. She reports some relief shortly after eating, but then the discomfort returns. She has tried various over-the-counter medications without relief. She also reports feeling tired and has had to increase the amount of ibuprofen needed for relief of her arthritis. She denies nausea, vomiting, and diarrhea. On examination she is found to have mild midepigastric tenderness. Blood microscopy revealed a microcytic anemia and normal white blood cell count, consistent with iron deficiency. The patient was referred to a gastroenterologist who performed an upper GI endoscopy that identified gastric ulcers. He stated that he suspected that the ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID) was the causative agent and suggested switching from ibuprofen to a coxib, such as celecoxib.

1. What is the likely biochemical etiology of the disorder?
2. Why do coxibs generally have a lower incidence of upper GI problems than other NSAIDs?
3. What is the major difference between aspirin and other NSAIDs with regard to platelet function?

Answer: Diagnosis: Gastric ulcer due to NSAID

Biochemical etiology: NSAID inhibits gastric enzyme (COX-1) required for synthesis of prostaglandins that have a protective effect on the gastric mucosa.

Decreased gastric side effects with coxibs: Traditional NSAIDs, such as ibuprofen and aspirin, inhibit both COX-1 and COX-2. The coxibs are selective inhibitors of COX-2, allowing continued production of protective prostaglandins by gastric COX-1.

Difference between aspirin and other NSAIDs: Aspirin covalently modifies platelet COX-1, thus irreversibly blocking thromboxane formation and reducing platelet function for the lifespan of the affected platelet (platelets cannot synthesize new proteins). The inhibitory action of other NSAIDs on platelet COX-1 is not covalent and is eventually reversed when the agents’ blood levels decline.

Nonsteroidal anti-inflammatory drugs (NSAIDs), also known as prostaglandin synthesis inhibitors or cyclooxygenase (COX) inhibitors, can induce upper GI irritation or ulcers. The NSAIDs include a wide variety of medications including aspirin, ibuprofen, naproxen, and indomethacin. These medications are used for pain, inflammation, dysmenorrhea, headache, arthritis, or fever. These compounds act as anti-inflammatory and antipyretic agents by inhibiting COX catalysis by prostaglandin H synthase (PGHS). PGHS has two isoenzymes:

PGHS-1 (or COX-1) is generally a basal enzyme found in various tissues including platelets and gastric mucosa; PGHS-2 (or COX-2) is an inducible enzyme typically expressed in response to cytokines and mitogens at sites of inflammation or cell proliferation.
The prothrombotic and vasoconstrictive actions of COX-1-derived thromboxane in the vasculature are opposed by an antithrombotic and vasodilative prostaglandin, prostacyclin, that originates from COX-2 in vascular endothelial cells. The COX-2 selective coxibs thus tend to decrease prostacyclin levels in the vasculature without reducing the thromboxane levels. This tendency is thought to explain the small but significant increase in cardiovascular risk that recently led to withdrawal of two coxibs from the market.

**SUPPLEMENTARY INFORMATION TO CHAPTER 15**

**Case Study 15.1**

A 6-month old infant began to vomit occasionally and ceased to gain weight. At 9 months of age he was readmitted to the hospital. Routine examination and laboratory analysis were normal. After one week, he became drowsy, had fever, pulse was elevated, and there was hepatomegaly. EEG was done and was grossly abnormal. Blood ammonia was elevated and urine contained high amount of glutamine and uracil. What is the probable diagnosis? What is the pathogenic mechanism involved?

**Answer:** Hyperammonemia in this patient may be due to urea cycle disorder. Excessive excretion of uracil and/or orotic acid results from accumulation of carbamoyl phosphate, and is due to absence of the enzyme ornithine transcarbamoylase (OTC). Glutamine is normally converted to glutamate and ammonia by the kidneys; but when the level exceeds, it is excreted in urine.

Ornithine transcarbamoylase (OTC) deficiency is inherited as X-linked dominant condition and the disease is more severe in males. Women respond well to treatment, but they have risk for hyperammonemia during delivery and postpartum period. Drugs like valproate and corticosteroids increase the risk. Other causes of urea cycle disorders are carbamoyl phosphate I deficiency (characterized by severe hyperammonemia in the newborn period), argininosuccinic acid synthetase deficiency (leading to citrullinemia, which is also characterized by severe hyperammonemia), argininosuccinic acid lyase deficiency (leading to argininosuccinic aciduria, with rapid onset hyperammonemia in neonatal period) and arginase deficiency (leading to hyperargininemia, which is the least severe). NAG synthase (NAGS) deficiency mimics CPSI deficiency.

Clinical symptoms of urea cycle disorders are lethargy, anorexia, hyperventilation or hypoventilation, hypothermia, seizures and coma. Hyperammonemia may be triggered by illness or stress, which along with a normal anion gap, is the classical hallmark of urea cycle disorder. Plasma amino acid analysis is a useful diagnostic test. In the first four disorders, arginine levels will be low but in hyperargininemia, levels may be 5–7 fold elevated. Plasma citrulline is elevated in proximal urea cycle disorders, while urine orotate is elevated in CPSI and NAGS deficiency, but not in OTC deficiency. Definitive diagnosis depends on enzyme assay from liver biopsy specimen and genetic analysis. Differential diagnosis includes viral infections of the liver and organic acidurias; in both these conditions hyperammonemia is seen. However, there is alteration of anion gap, especially in organic acidurias.

Treatment includes dialysis to reduce ammonia levels, intravenous arginine chloride and nitrogen scavenger drugs (phenyl acetate, benzoate) to activate alternative pathways for ammonia excretion, and protein restricted diet. Chronic therapy includes protein restricted diet, phenyl butyrate, arginine, citrulline supplements, and if necessary, liver transplantation. Genetic counseling and prenatal diagnosis are advised. Extended newborn screening programs help to identify urea cycle disorders.

**SUPPLEMENTARY INFORMATION TO CHAPTER 16**

**Case Study 16.1**

A 36-year old woman reported with a dull pain in the left flank which was radiating towards left leg. She reports fever and inability to pass urine for the last few days. Similar history of illness was reported in the last 6 months. She was anemic
and abdomen was tender. Routine urinalysis revealed presence of RBC, pus cells, WBC casts, characteristic hexagonal crystals and amino acids. What is the probable cause? What is the pathogenesis of the condition?

**Answer:** The likely cause is cystinuria. Cystinuria is characterized by build-up of cystine stones or crystals in kidneys and bladder. Patients with cystinuria cannot properly reabsorb cystine into their bloodstream and the amino acid accumulates in their urine. As urine becomes more concentrated, excess cystine forms crystals that can lodge in bladder or kidneys. Cystine can also combine with calcium to form larger stones. They can block passage of urine and this can also lead to infections.

Symptoms are recurrent nephrolithiasis (staghorn calculi) and obstruction. This can produce severe, sudden onset of flank pain, blood in urine, infection which can produce fever, WBC in urine and in advanced cases, renal failure.

The disease is inherited as autosomal recessive. Diagnostic tests are sodium nitroprusside test; cystine stones are detected by X-rays as they are radioopaque or by CT of kidneys. Traditionally intravenous pyelogram (IVP) was used. Microscopy reveals flat hexagonal crystals of cystine.

Treatment is aimed at eliminating stones and preventing new stones. Dietary sodium and protein restriction increases cystine excretion. Urine alkalinization improves cystine solubility. Severe cases need surgical intervention.

In the condition cystinosis, excess cystine crystals accumulate in eyes and kidneys. This is a lysosomal storage disorder and is also inherited as autosomal recessive condition. There is mutation in the gene CTNS which codes for the protein cystinosin, the lysosomal cystine transporter. Symptoms include excessive urination, followed by poor growth, photophobia and renal failure by age 6. Cystinosis is the common cause of renal Fanconi syndrome. There is loss of large amounts of salt and other minerals in urine. Definitive diagnosis is by measurement of WBC cystine levels. The drug cysteamine is used to clear cystine. Replenishment of lost fluid and electrolytes, as well as high doses of Vitamin D and phosphorus is needed.

**Case Study 16.2**

An adolescent girl presents with subluxation of lens and mental retardation. On examination, she is tall and thin with elongated limbs. Mild scoliosis was present with pectus excavatum and genu valgum. One of her sisters had similar complaints. What is the likely disorder? What is the basis of the disease?

**Answer:** Likely cause is homocystinuria. Different causes are there of which classical homocystinuria is due to the deficiency of enzyme, CBS. It is inherited as an autosomal recessive condition. Common clinical features are failure to thrive, developmental delay, ectopia lentis (subluxation of lens), severe myopia, iridodonesis, astigmatism, glaucoma, cataracts, retinal detachment and optic atrophy during infancy and early childhood. Progressive mental retardation may be there, but in some individuals intelligence may be normal. Skeletal abnormalities may resemble Marfan syndrome. Generalized osteoporosis may be present. Thromboembolic episodes involving large and small vessels, especially those of the brain, are common and may be seen at any age. Elevated homocysteine level (hyperhomocysteinemia) is an independent risk factor for coronary artery disease, cerebrovascular diseases, peripheral arterial disorders as well as deep vein thrombosis. During pregnancy, it can lead to neural tube defects in embryo and pre-eclampsia in pregnant mother.

Diagnosis is by amino acid screen in urine and blood (homocysteine and methionine are elevated, cystine will be low), liver biopsy and enzyme assay, skeletal X-ray, skin fibroblast enzyme assay, standard ophthalmic testing and genetic testing. Treatment with high doses of pyridoxine, folic acid, B12 and betaine reduces homocysteine levels.

**Case Study 16.3**

A six-year old boy was brought to the pediatric department. He had mental and physical retardation, knock-knees, arched feet, dislocated lenses and sparse hair. Routine blood and urine examinations were within normal limits. Urine was positive for ninhydrin test and cyanide-nitroprusside test. The patient was treated for 2 weeks with high doses of pyridoxine, when urine abnormality was reversed.
A. What is your provisional diagnosis?
B. What will be the blood level of methionine, cysteine and homocysteine in this patient?
C. Which enzyme is defective in this patient?
D. What is coenzyme required for this enzyme?
E. What is the fate of cystathionine in the body?
F. Why pyridoxine is effective in this case?
G. What are the conditions in which urine ninhydrin test (generalized aminoaciduria) will be positive? What is the principle of this test?
H. What are the conditions in which cyanide-nitroprusside test will be positive? What is the principle of this test?
I. What are the nutrient deficiencies, in which homocystinuria is observed?

**SUPPLEMENTARY INFORMATION TO CHAPTER 17**

**Case Study 17.1**

Patient presented at 3 months of age with excessive irritability, abnormal posturing since birth and delayed developmental milestones. There is history of sibling death at Day 15 of life. The clinician reported abnormal urine odor. Laboratory analysis revealed ketonuria and metabolic acidosis. HPLC analysis of amino acid showed elevated leucine, isoleucine and valine. Child died immediately afterwards. Patient 2 presented at Day 12 with metabolic acidosis, abnormal urine odor, ketonuria and hepatosplenomegaly. Blood and urine studies revealed elevated levels of valine, isoleucine and leucine. Aggressive treatment was started including branched chain amino acid restricted diet and supplementation. Patient has survived until 3 years of age, without any episode of exacerbation afterwards. Levels of leucine, isoleucine and valine came down to normal level. What is the diagnosis? What is the significant difference between the two patients?

**Answer:** The diagnosis is maple syrup urine disease. In the case of the first patient (Patient 1), diagnosis was delayed and hence treatment could not be instituted and the baby died. But in the second case (Patient 2) diagnosis and treatment was started early in life and outcome was better. These two case studies indicate the importance of early diagnosis and treatment in MSUD.

**SUPPLEMENTARY INFORMATION TO CHAPTER 18**

**Case Study 18.1**

A 2-month old baby was brought by her parents to the pediatrician. She had pale skin, blonde hair and pink iris. The baby was otherwise healthy, was feeding well but was unable to fix the gaze. Ophthalmic examination showed absence of pigment in the retina. Two siblings had complete albinism, but parents were normal. What is the defect in this patient? What is the molecular basis of the condition?

**Answer:** Oculocutaneous albinism has autosomal recessive inheritance. There is defect in synthesis of melanin, and results in pale skin, blonde hair and pink iris as seen in this patient. Visual impairment is also typical of this condition. Other symptoms include strabismus, photophobia, nystagmus, refractive errors and functional blindness. The disease does not affect life span.

Albinism can be tyrosinase positive or negative. In tyrosinase positive type, enzyme is present but the melanocytes are unable to produce melanin due to a variety of reasons. In tyrosinase negative type, enzyme is absent or non-functional. In oculocutaneous type, skin, eyes and hair lack melanin, whereas in ocular albinism, only eyes lack melanin. Ocular albinism may have X-linked inheritance and hence may be more common in male offspring. The other type has equal chances in both male and female.

Genetic testing confirms diagnosis. Treatment involves protecting skin and eyes from direct sunlight.
Case Study 18.2
A 1-year-old girl is brought to the hospital OP and mother reports that the baby was not achieving the normal milestones for a baby of her age. She also reports an unusual odor to her urine and some areas of hypopigmentation on her skin and hair. On exam, the girl is noted to have some muscle hypotonia and microcephaly. The urine collected is found to have a “mousy” odor. What is the most likely diagnosis? What is the biochemical basis of the hypopigmented skin and hair?

Answer: Likely Diagnosis: Phenylketonuria (PKU) Biochemical basis of hypopigmentation: Phenylalanine is competitive inhibitor of tyrosinase (key enzyme in melanin synthesis)

Clinical correlation: The most common deficiency is in phenylalanine hydroxylase (autosomal recessive) resulting in the classic picture of PKU. Deficiency of dihydropteridine reductase and 6-pyruvoyl-tetrahydropterin synthase, enzymes necessary for the biosynthesis of tetrahydrobiopterin will also cause PKU. If unrecognized, the child will develop profound mental retardation and impairment of cerebral function.

Treatment consists of dietary modifications with limitation of phenylalanine intake and supplementation of tyrosine. The diagnosis of PKU and initiation of diet modification needs to be implemented prior to 3 weeks of age to prevent mental retardation.

Case Study 18.3
A 50-year old man with two-year history of refractory hypertension and occasional panic attacks reported to the clinic with sudden episode of pounding headache. There was excessive sweating. He had similar attacks earlier. Family history is positive for hypertension. On examination, BP was 170/90 mm Hg and pulse was 72/min. Weight was 80 kg. He was taking beta blockers. Other examination findings were unremarkable. 24 hr VMA was elevated (12.0 mg/day). What is the probable diagnosis?

Answer: Patient is suffering from pheochromocytoma, a catecholamine-producing tumor of sympathetic or parasympathetic nervous system. Catecholamines are degraded by two enzymes, COMT and MAO and the final product is VMA, vanillylmandelic acid. This is increased in pheochromocytoma (and paraganglioma, another similar tumor).

Pheochromocytoma usually is seen around the age of 40, though it can set in at any time. The “rule of ten” for pheochromocytoma states that 10% are bilateral, 10% are extra-adrenal, and 10% are malignant. Up to 25% may be familial. It may be part of a syndrome known as multiple endocrine neoplasia (MEN). Common laboratory investigations are 24 hr urinary VMA, metanephrine (total and fractionated), and plasma metanephrines.

Clinical features are varied, but the classic triad of symptoms is episodes of palpitations, headaches and profuse sweating. Both benign and malignant pheochromocytomas can recur (after surgery) and hence long-term follow up is important. Recurrence rate is also 10%.

SUPPLEMENTARY INFORMATION TO CHAPTER 21
Case Study 21.1
A man aged 20 years presented in a hospital with complaints of passing red colored urine and abdomen pain. History revealed that one week ago, he had very high fever, which was diagnosed as malaria. He was treated with Chloroquine tablets when malarial fever subsided, yesterday he took Primaquine tablet, as advised by the physician as a prophylactic measure against recurrence of malaria. On examination, he was pale, had tachycardia and mild splenomegaly. The laboratory findings were—

Blood hemoglobin: 9 g/dl
RBC count: 3 million/cu.mm
Reticulocyte count: 8%
Morphology: nucleated RBCs in peripheral blood serum total bilirubin: 4 mg/dl
Conjugated bilirubin: 0.4 mg/dl
Haptoglobin: 15 mg/dl (normal: 100–200 mg)
Urine blood: ++
Urine urobilinogen: Present.

A. What is the diagnosis?
B. Which enzyme is defective in this patient?
C. What points in the history suggested that diagnosis?
D. What are the common causes for acute hemolytic crisis?
E. What is the relevance of HMP shunt pathway in RBCs?
F. What is the biochemical explanation for this hemolysis?
G. Enzyme deficiency did not produce any disease in the patient till this time, but now he has an acute condition, explain.
H. What is the mode of inheritance in this condition?
I. What is the geographical distribution of this condition? Why?
J. What is haptoglobin? What is the half-life of haptoglobin? The lowering of haptoglobin indicates what?

Guidance to Answers
Acute Intermittent Porphyria.

Case Study 21.2
A 24-year old girl was brought to the casualty complaining of severe abdominal colic. She was also showing symptoms of behavioral disorder. The patient was kept under observation. When the patient became agitated, she was given a mild sedative containing barbiturates. Her condition worsened. The drug was not repeated and the consultant requested for a fresh urine sample to be sent to the Biochemistry laboratory for special tests.
A. What is the likely explanation for the disorders?
B. What are the tests to be done in urine to arrive at a diagnosis?
C. Explain the biochemical basis of the disorder.

Guidance to Answers
Acute Intermittent Porphyria.

SUPPLEMENTARY INFORMATION TO CHAPTER 22

Case Study 22.1
A 55-year old man was treated in the ICU with intravenous nitroprusside for hypertensive crisis for 48 hours. BP was restored, but he had a burning sensation in his throat and mouth, followed by nausea and vomiting, excessive sweating, agitation and dyspnea. There was a sweet almond smell in his breath and arterial blood gas analysis revealed severe metabolic acidosis. What is the likely condition? How is it treated? What is the pathogenesis?

Answer: Patient is most probably suffering from cyanide poisoning. Cyanide inhibits mitochondrial cytochrome oxidase, blocks the electron transport chain and prevents oxygen utilization. Lactic acidosis is secondary to anaerobic metabolism. Cellular oxygen metabolism is impaired and can produce death within minutes. Nitroprusside therapy, which is the drug of choice for hypertensive emergency, on prolonged usage can produce cyanide poisoning. Hence, in clinical practice, nitroprusside is used only for short term.

Causes for cyanide poisoning include smoke inhalation from residential or industrial fires, metal trades, mining, electroplating, jewelry manufacture and X-ray film recovery. It can occur during fumigation of ships, warehouses, etc. and are also used commonly as suicidal agents, especially by terrorists and health care and laboratory workers. Cyanide
affects all body tissues and attaches to many metalloenzymes, rendering them inactive. Chronic consumption of cyanide containing foods can lead to ataxia and optic neuropath, subacute blindness, etc.

Treatment includes administration of cyanide antidote kit (CAK) or hydroxocobalamin (Cyanokit); essentially these contain amyl nitrite pearls, sodium nitrite and sodium thiosulfate, increasing oxygen concentration in inspired air and sodium bicarbonate therapy. Amyl and sodium nitrites induce methemoglobin formation, it combines with cyanide and reduces its toxicity. Sodium thiosulfate converts cyanide to thiocyanate and which is excreted in urine. Hydroxocobalamin combines with cyanide to form cyanocobalamin which is excreted through urine. Sodium bicarbonate reduces lactic acidosis.

Case Study 22.2

An elderly couple was brought to the emergency department on a cold winter morning by their son with complaints of altered behavior, headaches, confusion, fatigue and nausea. History revealed that they were kept warm on two nights by the fire of a furnace in their home. Both patients were afebrile, had normal vital signs and had an oxygen saturation of 99%. The lips were very red. Carboxyhemoglobin levels were elevated. What is the likely condition? What is the pathogenesis involved?

Answer: They are probably suffering from carbon monoxide poisoning, due to exposure to carbon monoxide (CO) from the fire of the furnace in a closed room. Symptoms of headache, confusion, fatigue, nausea and red lips are suggestive of CO poisoning. High carboxyhemoglobin level confirms the diagnosis.

CO poisoning is one of the most common fatal poisons causing death by inhalation. It can result from combustion of carbon containing materials, like automobile exhaust, smoke inhalation in fire, accidental exposure to improperly vented gas heater, etc. (Tobacco smoke can lead to increased CO but not to the extent to produce poisoning).

CO can bind hemoglobin with very high avidity and reduces oxygen delivery to tissues. It can inhibit mitochondrial respiration and produce direct toxic effects on the brain. Diagnosis is confirmed by elevated arterial or venous carboxyhemoglobin levels. Treatment includes removing the patient from the source immediately, and in certain cases, hyperbaric oxygen therapy may be needed.

Case Study 22.3

A 14-year old girl was admitted to the emergency room with complaints of fever and recurrent pain in her arms and legs. Her laboratory data were as follows – Hemoglobin – 7.5 gm/dl, Hematocrit – 9.0%, Serum iron- 11 μg/dl, Serum albumin – 4.5 gm/dl. Blood smear showed target cells, poikilocytes, hypochromasia, sickle red cells, nucleated RBC, and Howell-Jolly bodies. Hb electrophoresis showed a slow moving band. What is the probable diagnosis? What is the pathogenesis of the disease?

Answer: The patient is suffering from sickle cell disease. Sickle cell disease (SCD) and its variants are genetic disorder of mutant hemoglobin. The molecular defect, a mutation in 6th position of β chain of globin chain converting adenine to thymine, changes normal adult hemoglobin (HbA) to sickle hemoglobin (HbS) and leads to sickle cell anemia. The charge at this site gets altered and leads to polymerization of hemoglobin under conditions of hypoxia. HbS is slow moving on electrophoresis.

After recurrent episodes of such sickling, membrane damage occurs and the cells are no longer capable of regaining their biconcave shape upon reoxygenation, and they become irreversibly sickled cells (ISCs). 5–50% of RBC may remain in this state, depending upon severity. These cells can block blood flow in small capillaries causing tissue anoxia, pain and infarction. Thrombotic coagulopathy ensues which adds to the complexity of the disease.

Clinical features of SCD include pain and anemia, and may manifest early in childhood. During childhood and adolescence, growth retardation, delayed sexual development, and lack of weight are seen. Anemia is chronic and hemolytic in type, and may be accompanied by aplastic crisis. Other common features are (1) Splenomegaly, (2) pneumococcal
infections, (3) vaso-occlusive crisis, (4) acute chest syndrome (chest pain, fever, tachypnea, leukocytosis, pulmonary infiltrates), (5) CNS effects, (6) chronic hemolysis (jaundice, bile stones), (7) repeated infarctions of joints, bones and growth plates, (8) pulmonary hypertension, (9) renal failure preceded by proteinuria, (10) paraorbital facial infarction leading to ptosis and loss of vision, (11) leg ulcers which are characterized by delayed healing, and (12) priapism and impotence. Pregnancy is a special problem and is associated with abortion, placenta previa, abruption placentae, placental infarction, and low birth weight babies.

Case Study 22.4

A 7-year old girl was brought to the pediatrician by her parents. At the age of 3 years, she was in the 10th percentile of growth for height and weight, and her hemoglobin was 5.8 gm/dl. Following further analysis, she was diagnosed to have β thalassemia major. Over the next 4 years, she was hospitalized every 1–2 months for packed RBC transfusions. Currently, her hemoglobin is 10.0 gm/dl and serum iron is 180 mg/dl. What is the biochemical basis of the disease?

**Answer:** Thalassemias are a group of inherited, microcytic hemolytic anemias where there is defect in hemoglobin synthesis. Symptoms result from anemia, hemolysis, splenomegaly, bone marrow hyperplasia and consequent to treatment, iron overload. Diagnosis is by genetic testing and Hb quantitative analysis. Treatment includes transfusions, splenectomy, chelation and stem cell transplantation.

Thalassemias may be α or β, depending on the globin chain which is not synthesized. Alpha (0) thalassemia is associated with lack of production of α chain and is incompatible with life, child dies in utero. Alpha (+) thalassemia is due to reduced production of α chain and is seen in areas where malaria is endemic, and mainly in Asian, African and Mediterranean lineages.

β thalassemia is caused by point mutations which result in premature chain termination or defective transcription and reduced or absent synthesis of β chain. It is one of the most common genetic disorders worldwide and is also common in malaria endemic areas. β thalassemia major is due to homozygous states (homozygous β0 and β+) and β thalassemia minor is due to heterozygous state (heterozygous β0 and β+).

Diagnosis is made by amount of HbF and HbA1, in homozygous states HbA1 is very low (0–10%) and HbF is very high (90–96%) and in heterozygous state, HBA1 is 80–95%, HbF is 1–5% and HbA2 is 4–8%. Other studies include iron studies (iron, transferrin and ferritin) to exclude iron deficiency anemia, bone marrow examination to exclude certain causes of microcytic anemia and prenatal diagnosis.

Case Study 22.5

A child, born to consanguinous parents, presents with anemia and splenomegaly.

A. What are the possible causes?
B. How will you investigate the child?
C. How will you explain the nature of inheritance?
D. What are the chances of other children being affected?
E. Suggest possible lines of management.

**Guidance to Answers:** Hemoglobinopathy.

Case Study 22.6

A 68-year-old female in a hypertensive crisis is being treated in the intensive care unit (ICU) with intravenous nitroprusside for 48 hours. The patient’s blood pressure was brought back down to normal levels; however, she was complaining of a burning sensation in her throat and mouth followed by nausea and vomiting, diaphoresis, agitation, and dyspnea. An arterial blood gas revealed a significant metabolic acidosis. A serum test suggests a metabolite of nitroprusside, thiocyanate, is at toxic levels.
1. What is the likely cause of her symptoms?
2. What is the biochemical mechanism of this problem?
3. What is the treatment for this condition?

Answer: Diagnosis: Cyanide poisoning from toxic dose of nitroprusside.

Biochemical mechanism: Cyanide inhibits mitochondrial cytochrome oxidase, blocking electron transport and preventing oxygen utilization. Lactic acidosis results secondary to anaerobic metabolism.

Treatment: Supportive therapy, oxygen, and antidotal therapy with sodium nitrite, and sodium thiosulfate.

Clinical correlation: Malignant hypertension is diagnosed when there is elevated blood pressure (systolic levels of 220 mm Hg and/or diastolic blood pressures exceeding 120 mm Hg). The symptoms may include severe headache, neurological deficits, chest pain, or heart failure. Hypertensive emergencies require immediate lowering of the blood pressure to lower levels.

One hazard of abruptly lowering the blood pressure is causing hypotension and subsequent ischemia to the brain or heart. Sodium nitroprusside induces a smooth fall in blood pressure. One side effect of sodium nitroprusside is that its metabolite is thiocyanate, and with prolonged use, cyanide poisoning may result, which inhibits the electron transport chain. Thus, in clinical practice, short-term nitroprusside is used.

Causes for cyanide poisoning include smoke inhalation from residential or industrial fires, metal trades, mining, electroplating, jewelry manufacture and X-ray film recovery. It can occur during fumigation of ships, warehouses, etc. and are also used commonly as suicidal agents, especially by terrorists and health care and laboratory workers. Cyanide affects all body tissues and attaches to many metalloenzymes, rendering them inactive.

Treatment includes administration of amyl nitrite, sodium nitrite and sodium thiosulfate, increasing oxygen concentration in inspired air and sodium bicarbonate therapy. Amyl and sodium nitrites induce methemoglobin formation, it combines with cyanide and reduces its toxicity. Sodium thiosulfate converts cyanide to thiocyanate which is excreted in urine. Hydroxocobalamin combines with cyanide to form cyanocobalamin which is excreted through urine. Sodium bicarbonate reduces lactic acidosis.

SUPPLEMENTARY INFORMATION TO CHAPTER 23

Case Study 23.1

A 51-year-old male presents to the emergency center with chest pain. He states that he has had chest discomfort or pressure intermittently over the last year especially with increased activity. He describes the chest pain as a pressure behind his breastbone that spreads to the left side of his neck. Unlike previous episodes, he was lying down, watching television. The chest pain lasted approximately 15 minutes then subsided on its own. He also noticed that he was nauseated and sweating during the pain episode. He has no medical problems that he is aware of and has not been to a physician for several years. On examination, he is in no acute distress with normal vital signs. His lungs were clear to auscultation bilaterally, and his heart had a regular rate and rhythm with no murmurs. An electrocardiogram (ECG) revealed ST segment elevation and peaked T waves in leads II, III, and aVF. Serum troponin I and T levels are elevated. What is the most likely diagnosis? What biochemical shuttle may be active to produce more adenosine triphosphate (ATP) per glucose molecule?

Likely diagnosis: Acute myocardial infarction.

Clinical correlation: Patient’s symptoms in this case are very typical of myocardial infarction, that is, chest pressure or chest pain, often radiating to the neck or to the left arm. The pain is usually described as deep and “squeezing chest pain.” Cardiac muscle is perfused by coronary arteries with very little redundant or shared circulation; thus, occlusion of one coronary artery usually leads to ischemia or necrosis of the corresponding cardiac muscle. Laboratory confirmation of myocardial infarction (death of cardiac muscle) includes ECG showing elevation of the ST segment and/or increase of
the cardiac enzymes. When there is insufficient oxygen available for the cardiac muscle, then the glycolytic pathway must be used, which leads to a very small amount of ATP per glucose molecule.

**Case Study 23.2**

A patient presented with acute chest pain of half hour duration. The biochemical analysis reports are as follows: Blood Glucose – 350 mg%, Serum cholesterol – 288 mg%, SGOT – 55 U/L, SGPT – 15 U/L. CPK and LDH were elevated. Give your provisional diagnosis. What are the other markers which can be estimated in this case?

*Answer:* Myocardial infarction. Cardiac troponins, myoglobin.

**Case Study 23.3**

A 40-year-old obese female presents to the emergency center with complaints of worsening nausea, vomiting, and abdominal pain. Her pain is located in the midepigastric area and right upper quadrant. Her pain is presently constant and sharp in nature but previously was intermittent and cramping only after eating “greasy” foods. On examination, she has a temperature of 37.8° C with otherwise normal vital signs. She has significant midepigastric and right upper-quadrant tenderness. Some guarding is present. Her abdomen is otherwise soft with no distention and active bowel sounds. Laboratory values were normal except for increased liver function tests, white blood cell count, and serum amylase. Ultrasound of the gallbladder revealed numerous gallstones and a thickening of the gallbladder wall. What is the most likely diagnosis? What is the role of amylase in digestion?

*Answer:* Diagnosis: Gallstone pancreatitis.  
*Role of amylase:* Enzyme for carbohydrate metabolism, used to digest glycogen and starch.

Acute pancreatitis is an inflammatory process in which pancreatic enzymes are activated and cause autodigestion of the gland. In the United States, alcohol use is the most common cause, and episodes are often precipitated by binge drinking. The next most common cause is biliary tract disease, usually passage of a gallstone into the common bile duct. Hypertriglyceridemia is also a common cause, and that occurs when serum triglyceride levels are greater than 1000 mg/dL, as is seen in patients with familial dyslipidemias or diabetes. When patients appear to have “idiopathic” pancreatitis, that is, no gallstones are seen on ultrasound, and no other predisposing factors can be found, biliary tract disease is still the most likely cause: either biliary sludge (microlithiasis), or sphincter of Oddi dysfunction. Abdominal pain is the cardinal symptom of pancreatitis, and it is often severe, typically in the upper abdomen with radiation to the back. The pain is often relieved by sitting up and bending forward and is exacerbated by food. Patients also commonly have nausea and vomiting, also precipitated by oral intake. The treatment includes nothing by mouth, intravenous hydration, pain control, and monitoring for complications.

**Case Study 23.4**

A healthy 10-year old boy interested in sports started complaining of muscle cramps and weakness of lower limbs after the sports. On examination, he had mild wasting of the lower limb muscles. History revealed that his mother had a younger brother, who had a similar illness to which he succumbed around the age of 20. Laboratory investigations revealed that creatinine in urine and CK in blood are elevated.

A. What is the most probable cause?  
B. What are the investigations to be done?  
C. How does history give a clue in this case?  
D. What is the prognosis?  
E. Explain the nature of inheritance in this case.

*Guidance to Answers:* X-linked muscular dystrophy.
Case Study 23.5

A 29-year old pregnant woman, while waiting in the clinic for results of glucose tolerance test, complained of severe abdominal pain. A doctor was called to the laboratory, to see the patient. Doctor suspected acute pancreatitis, and requested the laboratory to assay serum amylase and lipase. The technician performed the tests, using the plasma remaining from her glucose tolerance test. The serum amylase value was 180 U/L (normal 50–120); but her lipase value was normal. In the meanwhile, patient felt comfortable. But, the discrepancy in the laboratory results caused confusion in diagnosis. So doctor requested a repeat analysis. A fresh blood sample was taken for the tests. This time, her serum amylase and lipase were found to be normal.

A. Explain the discrepancy in the amylase results.
B. Do you think serum amylase value will come down to normal levels within a few hours?
C. What are conditions in which serum amylase is increased?
D. What are the advantages of lipase estimation?

Guidance to Answers: In the first analysis, serum amylase was tested on serum samples taken for blood sugar estimation. For blood sugar estimation, fluoride is added (chapter 24). Fluoride will activate amylase (chapter 23).

SUPPLEMENTARY INFORMATION TO CHAPTER 24

Case Study 24.1

A known diabetic patient on insulin was brought to the hospital in a semiconscious state. He was sweating profusely and had tremors of hands. His BP was 100/60 mm of Hg.

A. What is the possible diagnosis?
B. What are the investigations to be done urgently?
C. During the treatment, what special precaution should be taken?

Answers: The possibility is hypoglycemia due to excessive dose of insulin. Investigations to be done and treatment policies are discussed in chapter 24 of the textbook.

Case Study 24.2

A 45-year old obese male had a tooth infection. Prior to extraction he was advised to have a routine blood and urine examination. The results were:

- Total WBC count 35,000/cmm
- Differential count: P70, L20, E7, M2, B1
- ESR: 45 mm/hr
- Urine albumin: trace
- Urine sugar: orange precipitate
- Urine ketone bodies: nil
- Urine bile salts: nil
- Urine bile pigments: nil.

A. What are the further investigations to be done in this patient? Explain the rationale behind each test.
B. When the diagnosis is confirmed and treatment started, how will you monitor the patient?
C. What are the possible complications that can be avoided by proper monitoring of the patient?
**Case Study 24.3**

A 30-year old woman during her second pregnancy had a glucose tolerance test and the results are—Fasting glucose level: 125 mg/dl
1 hr glucose level: 210 mg/dl
2 hr value: 170 mg/dl.
A. Plot a GTT graph with these results.
B. Comment on the GTT results.
C. What will be the result of Benedict's test with the urine sample collected along with each blood sample?
D. How will you follow up the patient?
E. What is the importance of assessing the glucose tolerance in a pregnant lady?
F. How do you rule out lactosuria in this case?

*Guidance to Answers:* Gestational diabetes mellitus.

---

**Case Study 24.4**

A comatose patient with tremors admitted in the hospital. His blood glucose level was 300 mg/dl. His urine was positive for both Rothera’s test and Benedict’s test.
A. What is the diagnosis?
B. What are the lines of treatment?
C. During the treatment, what special precaution should be taken?

*Guidance to Answers:* Diabetic ketoacidosis.

---

**Case Study 24.5**

An apparently healthy man, on a routine check up, was found to have fasting blood sugar of 80 mg/dl, and urine showed no abnormal constituents. After a heavy breakfast of one-and-half hours, his blood sugar was 140 mg/dl and urine sample at that time was positive for Benedict’s test.
A. What is the diagnosis?
B. How do you further investigate?
C. What is the line of treatment?
D. What is the course of this disease?

*Guidance to Answers:* Renal glycosuria. Normal renal threshold for glucose is 180 mg/dl.

---

**Case Study 24.6**

A 50-year old business executive fainted in the middle of a meeting. He was rushed to the emergency room of the nearest hospital in a semiconscious state. On examination he was found to be sweating profusely and BP was found to be 90/50mm Hg.
A. Suggest two possible causes.
B. Enumerate the laboratory tests to be done urgently to arrive at a diagnosis.
C. Indicate the abnormal findings expected.
Guidance to Answers:
1. Hypoglycemia
2. Acute myocardial infarction. A blood sugar estimation will clinch the diagnosis.

Case Study 24.7
A known diabetic patient was admitted in a semicomatose state. He had cellulitis on the right foot. The laboratory results on a blood sample drawn at the time of admission was—
Blood glucose: 384 mg/dl
Blood urea: 80 mg/dl
Serum creatinine: 2 mg/dl
Serum sodium: 134 mmol/L
Serum potassium: 5.8 mmol/L
Serum bicarbonate: 18 mmol/L
Serum chloride: 98 mmol/L
Glycohemoglobin: 18% (normal 5–9% of total Hb)
Urine glucose: positive
Urine ketone bodies: positive.
A. What is the most probable cause?
B. What is the biochemical explanation for this condition?
C. Calculate the anion gap and osmolality of plasma.

Guidance to Answers: Uncontrolled diabetes mellitus with ketoacidosis

Case Study 24.8
A 40-year old male was brought to the emergency room complaining of dizziness and weakness. History revealed that he had skipped breakfast. Random blood sugar value was 40 mg%. What is the probable diagnosis?

Answer: Patient has hypoglycemia, probably due to fasting. Under physiological conditions, brain derives fuel from glucose.

Hypoglycemia is considered when blood glucose falls to below 60 mg%. Symptoms begin at this concentration of glucose; brain symptoms appear when glucose level falls below 50 mg%. CNS symptoms include behavioral changes, confusion, fatigue, seizures, loss of consciousness, and if severe and prolonged, death.

Spontaneous hypoglycemia may be (1) fasting, and (2) postprandial. Fasting hypoglycemia may be subacute or chronic and usually presents with neuroglycopenia. Postprandial hypoglycemia is usually acute and symptoms of neurogenic autonomic discharge like sweating, palpitations, anxiety and tremulousness are seen.

There are many causes for hypoglycemia. Fasting hypoglycemia may be due to drugs (e.g., insulin), critical illness (hepatic, renal and cardiac, sepsis), endocrine problems, insulinoma, endogenous hyperinsulinism, other β cell disorders, autoimmune disorders and certain inborn errors of metabolism. Postprandial hypoglycemia may be due to alimentary (post-gastrectomy), noninsulinoma pancreaticogenous hyperinsulinism, galactosemia, hereditary fructose intolerance and idiopathic.

Treatment of hypoglycemia is oral glucose (I/V glucose, S/C or I/M glucagon if oral intake is not possible).

Case Study 24.9
During a factory strike, one leader went on “fast till death”, who took only water for the next 15 days. When his condition deteriorated, he was admitted in a hospital. Blood levels of sugar and amino acids were found to be decreased; urine had ketone bodies, urinary nonprotein nitrogen was increased.
Case Studies

A. The brain consumes 65% of the total circulating glucose daily. How does it obtain its energy during starvation?
B. Can brain utilize ketone bodies to meet part of its energy requirement?
C. How starvation triggers gluconeogenesis and lipolysis?
D. What is the fate of amino nitrogen generated in the liver during the process of gluconeogenesis?
E. What are the sources of two nitrogen atoms in urea molecule?
F. Why does ketoadidosis develop in this patient?
G. What happens to “branched chain amino acids” in the initial phases of starvation?
H. What happens to alanine in the initial phases of starvation?
I. Is the patient in positive or negative nitrogen balance? Why?

Answers: Details on starvation ketoadidosis are given in chapter 24 of the textbook.

Case Study 24.10
A person is brought to the emergency department in a comatose state. The following test results were obtained – Blood sugar – 400 mg%, Benedict’s test (Urine) – Red precipitate, Rothera’s test (Urine) – Positive, Serum bicarbonate – 12 mEq/L, Plasma pH – 7.14. What is your probable diagnosis?

Answer: Diabetic ketoacidosis (DKA)

Case Study 24.11
A person is brought to the emergency department in a comatose state. The following test results were obtained – Blood sugar – 40 mg%, Benedict’s test (Urine) – Negative, Rothera’s test (Urine) – Negative, Serum bicarbonate – 12 mEq/L, Plasma pH – 7.14. What is your probable diagnosis?

Answer: Starvation ketosis

Case Study 24.12
A 19-year old with 4 years history of juvenile diabetes mellitus was brought to the emergency department in state of coma. The following laboratory results were obtained – Blood sugar – 1300 mg%, Plasma pH – 7.1, pCO₂ – 13 mm Hg, Pulse rate – 120/min, Respiratory rate – 28/min. What is your probable diagnosis? What is the pathophysiology of the above condition?

Answer: Diabetic ketoacidosis (DKA)

Case Study 24.13
A 55-year old man with long standing diabetes mellitus presented with fever, pruritis, delirium and low urine output. His blood urea level was 135 mg% and urea clearance was 35 ml/min. What is the most likely diagnosis?

Answer: Diabetic nephropathy

Case Study 24.14
A 52-year old woman with a medical history of hepatitis B, hyperlipidemia, hypertension and anemia, presented to the medicine department for a routine visit. Laboratory tests 3 months previously had revealed an impaired fasting glucose concentration of 118 mg/dL [reference interval, 70–110 mg/dL]. Therefore, a hemoglobin HbA1c analysis was performed. The initial HbA1c evaluation by HPLC showed an HbA1c value of 12.8% (reference interval, 4.0%–5.5.0%).

What are the various types of methods used for measuring HbA1c? How do Hb variants interfere with each of these HbA1c methods? What actions should be taken when a spurious HbA1c result is present?
**Answer:** In an effort to determine if the unusual HbA1c result was due to potential hemoglobinopathies, Hb variant analysis was done and presence of HbS and HbF identified. In this particular case, increased HbF caused the abnormal HbA1c value. HbA1c assays can be divided into methods that use molecular charge (HPLC and electrophoresis) and methods that use molecular structure (immunoassays). Hb variants (or their glycated forms) may interfere with HbA1c assays based on HPLC and electrophoresis by coeluting/comigrating with Hb A and/or HbA1c. When a spurious HbA1c result is obtained, the possibility of interference by Hb variants should be considered. Fructosamine and daily testing of glucose may be used to monitor glycemic control. These alternative tests may also be used for patients who have an altered erythrocyte life span and changes in the degree of glycation. HbA1c testing cannot be used for these individuals.

**Case Study 24.16**

A 40-year old man presented with complaints of frequent episodes of dizziness and numbness in legs. On examination, he is obese, leads a sedentary life style, has a BP of 200/120 mm Hg, has fasting hyperglycemia, hyperinsulinemia, dyslipidemia and glucose intolerance. What is the diagnosis? What is the pathogenesis involved?

**Answer:** The patient has “insulin resistance syndrome” or metabolic syndrome. Metabolic syndrome is multi-factorial in origin; there are 6 major factors involved, abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance (with or without the presence of glucose intolerance), proinflammatory state and prothrombotic state.

The defect may be due to – (1) Prereceptor pathology – mutations in insulin molecule, anti-insulin antibodies, (2) receptor defects – decreased number of receptors, reduced insulin binding, insulin receptor mutations, insulin receptor blocking antibodies, (3) post-receptor defects – defective signal transduction, mutations in GLUT4, (4) combination of defects, (5) Other pathologies – Werner syndrome, ataxia telangiectasia, lipodystrophic states, etc. (6) increased production of insulin antagonists, and (7) glucose intolerance.

Other laboratory tests helpful are apoB, hs-CRP, fibrinogen, uric acid, urine microalbumin and liver function tests. Treatment includes treating insulin resistance, lipid abnormalities, prothrombotic state, hypertension, impaired fasting glucose and lifestyle modifications. Diet and exercise are the keystones to the clinical management.

**Case Study 24.17**

A 30-year old woman during her second pregnancy had a glucose tolerance test and the results are—

Fasting glucose level: 125 mg/dl
1 hr glucose level: 210 mg/dl
2 hr value: 170 mg/dl.

**A.** Plot a GTT graph with these results.
**B.** Comment on the GTT results.
**C.** What will be the result of Benedict’s test with the urine sample collected along with each blood sample?
**D.** How will you follow up the patient?
**E.** What is the importance of assessing the glucose tolerance in a pregnant lady?
**F.** How do you rule out lactosuria in this case?

**Answer:** Gestational diabetes mellitus.

**Case Study 24.18**

An apparently healthy man, on a routine check up, was found to have fasting blood sugar of 80 mg/dl, and urine showed no abnormal constituents. After a heavy breakfast of one-and-half hours, his blood sugar was 140 mg/dl and urine sample at that time was positive for Benedict’s test.

**A.** What is the diagnosis?
**B.** How do you further investigate?
C. What is the line of treatment?
D. What is the course of this disease?

*Answer:* Renal glycosuria. Normal renal threshold for glucose is 180 mg/dl.

**Case Study 24.19**

A 60-year old man presented with complaints of frequent episodes of dizziness and numbness in legs. On examination, he is obese, leads a sedentary lifestyle, has a BP of 200/120 mm Hg, has fasting hyperglycemia, hyperinsulinemia, dyslipidemia and glucose intolerance. What is the diagnosis? What is the pathogenesis involved?

*Answer:* The patient has “insulin resistance syndrome” or metabolic syndrome. NCEP/ATP III guidelines for the diagnosis of metabolic syndrome include: (1) Waist circumference more than 102 cm in men and 88 cm in women, (2) Fasting triglycerides more than 150 mg/dl, (3) BP more than 130/85 mm Hg, (4) HDL-C <40 mg/dl in men and HDL-C < 50 mg/dl in women, and (5) fasting glucose level > 110 mg/dl. A diagnosis is made when 3 or more of these criteria are met.

Metabolic syndrome is multi-factorial in origin; there are 6 major factors involved, abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance (with or without the presence of glucose intolerance), proinflammatory state and prothrombotic state.

The defect may be due to – (1) Prereceptor pathology – mutations in insulin molecule, anti-insulin antibodies, (2) receptor defects – decreased number of receptors, reduced insulin binding, insulin receptor mutations, insulin receptor blocking antibodies, (3) postreceptor defects – defective signal transduction, mutations in GLUT4, (4) combination of defects, (5) Other pathologies – Werner syndrome, ataxia telangiectasia, leprechaunism, lipodystrophic states, etc. (6) aging, (7) increased production of insulin antagonists, (8) drugs including insulin, (9) HIV and (10) glucose intolerance.

Other laboratory tests are apoB, hs-CRP, fibrinogen, uric acid, urine microalbumin and liver function tests. Treatment includes treating insulin resistance, lipid abnormalities, prothrombotic state, hypertension, impaired fasting glucose and lifestyle modifications. Diet and exercise are the keystones to the clinical management.

---

**SUPPLEMENTARY INFORMATION TO CHAPTER 25**

**Case Study 25.1**

A 48-year old male presented to OP with concerns about heart disease. Family history shows that his father died of a heart attack at the age of 46, and his elder brother also had a heart attack at the same age. The patient reports that he gets chest pain occasionally with ambulation and is not able to climb stairs without significant chest pain and shortness of breath. His plasma cholesterol level was 450 mg%. What is the possible diagnosis?

*Answer:* The patient might be suffering from familial hypercholesterolemia (FH). It is an autosomal dominant condition where total cholesterol and LDL-C show severe elevation. Sometimes, as in this patient, it is also a moderate elevation. It carries a risk premature CAD and hence early detection and treatment are important. Exercise, dietary adjustments and weight loss are the initial steps, but if they fail, drugs may be needed.

FH is due to a defect in LDL receptor. LDL receptor activity may be completely absent or up to 25% activity may be present. There are three types; in the first type LDL receptor is absent, in the second type there is mutation in the terminal region so that binding is affected and in the third type, there is mutation in the C-terminal region so that endocytosis is affected. Cholesterol synthesis continues even when plasma cholesterol is very high in these patients.

In children with FH, typically cholesterol levels may be above 600 mg%, and LDL-C may be 200 – 400 mg%. Foam cell formation, plaque cell formation and premature CAD are typical features. Cholesterol may accumulate in other areas, leading to xanthelasma and variety of xanthomas. Corneal arcus and valvular abnormalities are seen secondary to cholesterol deposition.
The condition may be homozygous (which is a rare condition, with an incidence of 1 in 1 million) or heterozygous (which is much more common, with an incidence of 1 in 500 persons). Men are more prone to develop CAD than women. Symptoms appear later in heterozygotes. An LDL-C higher than 200 mg% in a patient less than 20 years is suggestive of heterozygous FH.

Case Study 25.2

A 48-year-old male presents to the clinic because of concerns about heart disease. He reports that his father died from a heart attack at age 46, and his older brother has also had a heart attack at age 46 but survived and is on medications for elevated cholesterol. The patient reports chest pain occasionally with ambulation around his house and is not able to climb stairs without significant chest pain and shortness of breath. The physical exam is normal, and the physician orders an electrocardiogram (ECG), exercise stress test, and blood work. The patient’s cholesterol result comes back as 400 mg/dL (normal 200).

What is the possible diagnosis?

Answer: The patient might be suffering from familial hypercholesterolemia (FH). An LDL-C higher than 200 mg% in a patient less than 20 years is suggestive of heterozygous FH. It is an autosomal dominant condition where total cholesterol and LDL-C show severe elevation. Sometimes, it is also a moderate elevation. It carries a risk premature CAD and hence early detection and treatment are important. Exercise, dietary adjustments and weight loss are the initial steps, but if they fail, drugs may be needed. FH is due to a defect in LDL receptor. LDL receptor activity may be completely absent or up to 25% activity may be present. There are three types; in the first type LDL receptor is absent, in the second type there is mutation in the terminal region so that binding is affected and in the third type, there is mutation in the C-terminal region so that endocytosis is affected. Cholesterol synthesis continues even when plasma cholesterol is very high in these patients.

The physician prescribes medication, which he states is directed at the rate limiting step of cholesterol biosynthesis. What is the rate-limiting step of cholesterol metabolism? What is the class of medication prescribed?

Rate-limiting step: The enzyme hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase) catalyzes an early rate-limiting step in cholesterol biosynthesis. Likely medication: HMG-CoA reductase inhibitor, otherwise known as “statin” medications.

Clinical correlation: Hyperlipidemia is one of the most treatable risk factors of atherosclerotic vascular disease. In particular, the level of the low-density lipoprotein (LDL) correlates with the pathogenesis of atherosclerosis. Exercise, dietary adjustments, and weight loss are the initial therapy of hyperlipidemia. If these are not sufficient, then pharmacologic therapy is required. The exact LDL targets depend on the patient’s risk of cardiovascular disease. For example, if an individual has had a cardiovascular event previously (heart attack or stroke), the LDL target is 100 mg/dL; 1 to 2 risk factors without prior events =130 mg/dL; and no risk factors =160 mg/dL.

In children with FH, typically cholesterol levels may be above 600 mg%, and LDL-C may be 200 – 400 mg%. Foam cell formation, plaque cell formation and premature CAD are typical features. Cholesterol may accumulate in other areas, leading to xanthelasma and variety of xanthomas. Corneal arcus and valvular abnormalities are seen secondary to cholesterol deposition.

The condition may be homozygous (which is a rare condition, with an incidence of 1 in 1 million) or heterozygous (which is much more common, with an incidence of 1 in 500 persons). Men are more prone to develop CAD than women. Symptoms appear later in heterozygotes.

SUPPLEMENTARY INFORMATION TO CHAPTER 26

Case Study 26.1

A 25-year old patient was admitted in a hospital with severe abdominal pain. He had similar attacks of pain during the last 2 years. X-ray showed the presence of gallstones. The laboratory values were—RBCs: 3 million/cu mm; Reticulocytes: 15%; Hemoglobin: 8 g/dl; Serum total bilirubin: 2.5 mg/dl; Urine urobilinogen: positive.
Case Study 26.2

A 40-year old woman admitted with recurrent pain in the abdomen, developed jaundice two days after admission. History revealed that the pain often aggravated after intake of fatty food. The patient was also complaining of itching. A routine urine examination showed the presence of bile pigments and bile salts, but urobilinogen was absent.

A. What is the most likely cause?
B. Explain the findings in urine?
C. What is the type of jaundice?
D. Which are the blood tests to be done in this patient?
E. If the patient is to have surgery, which liver function test must be done prior to surgery? Explain.

Guidance to Answers: Obstructive jaundice due to cholelithiasis.

Case Study 26.3

A 25-year old woman, with 12 weeks pregnancy, was admitted to hospital complaining acute abdominal pain of 4-hour duration. The pain was of sudden onset. It radiated to the back. Patient was febrile but not jaundiced. Her plasma electrolyte values were normal. Plasma amylase was 3100 U/L (normal <300 U/L). Alkaline phosphatase and SGPT were mildly increased.

A. What is the provisional diagnosis? Acute pancreatitis. (See also Chapter 15, under trypsin). Differential diagnosis included small gut obstruction, perforated gastric ulcer and ruptured ectopic pregnancy.
B. What are the causes for acute pancreatitis? Biliary tract disease and alcoholism are the commonest causes. 30% of plasma amylase is cleared by renal excretion; so mild hyperamylasemia is seen in renal insufficiency.
C. Follow up of the patient: She was treated conservatively. An obstetric examination ruled out the possibility of ruptured ectopic pregnancy. Next day, the plasma amylase was 1220 U/L, and the third day, it was 550 U/L. She was discharged from the hospital after 5 days.
D. Three weeks later, a cholecystogram revealed small stones in her gallbladder. What is the final diagnosis? Acute pancreatitis, secondary to cholelithiasis.
E. What is the cause for abnormal LFT values? Due to ascending cholangitis.

Case Study 26.4

A 65-year old man presented with anemia, weight loss and passage of bulky pale stools. On examination, he had hepatosplenomegaly. His plasma electrolytes were normal. Further laboratory tests were:

Plasma, total proteins : 5.2 g / L
Question and Guidance to Answers

A. What is the most probable diagnosis? Steatorrhea is confirmed by abnormal fecal fat excretion and the complaint of "passage of bulky pale motions".

B. What will be the cause for steatorrhea and what functional analysis could be done? Xylose absorption test revealed a 5-hr urinary xylose excretion of 0.6 (normal 1.2 g). Xylose absorption test is positive in disorders of upper half of small gut like celiac disease and tropical sprue. Plasma levels of bilirubin, ALT and GGT were normal in this particular case. Liver function tests to be done to rule out chronic liver diseases. Vitamin B12 absorption test will be positive in diseases of terminal ileum, e.g., regional enteritis.

C. How do you interpret low plasma albumin? Due to inadequate absorption of amino acids.

D. How do you interpret low plasma vitamin D, calcium and increased ALP values? Due to decreased absorption of fat-soluble vitamins. Vitamin D deficiency leads to decreased gut calcium absorption; this in turn, leads to low plasma calcium. This activates osteoblasts, which accounts for the increased ALP level (Chapter 36 and 39).

E. What is the cause for anemia in this patient? Excess fat in gut will interfere with absorption of iron.

Case Study 26.5

A lady, 45 years of age, was admitted with loss of appetite and vomiting. In the outpatient department, one house surgeon thought that her sclera is mildly yellowish, but the opinion was otherwise by another house surgeon. She was admitted. On examination she had mild fever and mild tenderness over right hypochondrium. Her clinical laboratory data revealed:

- Serum bilirubin: 2.5 mg%
- Conjugated bilirubin: 0.1 mg%
- Serum alkaline phosphatase: 200 U/L
- AST (SGOT): 60 units
- ALT (SGPT): 76 units
- Urine bile pigments negative
- Urine bile salts negative.

A. Give the most probable diagnosis.
B. What are the causes of that disease?
C. What are the normal values for ALP, AST and ALT?

Guidance to Answers: Hepatic (viral) jaundice.

Case Study 26.6

A 14-year old boy, who was a resident of a boarding school, was admitted to the hospital. He was ill looking and frankly jaundiced. On the day prior to the development of jaundice, he noticed that his urine was dark and frothy. The laboratory analysis values were:

- Plasma, total proteins: 7.7 g/dl
  - albumin: 4.4 g/dl
  - alkaline phosphatase: 150 U/L
  - alanine transaminase: 4000 U/L
- Plasma, bilirubin: 4 mg/dl
- Urine, bilirubin: ++
Questions and Guidance to Answers:
A. What is the most probable diagnosis? Jaundice, associated with very high plasma levels of ALT and normal ALP are the typical findings of acute infective hepatitis.
B. What further tests do you suggest? Serum antibodies against hepatitis A and hepatitis B surface antigen are to be tested. In this particular case, HAV antibody was positive. HAV is usually transmitted by oral route and is common in boarding schools.

Case Study 26.7
A 70-year old man with advanced carcinoma of colon showed the following liver function tests:
Total proteins : 6.4 g/dl
Albumin : 3.5 g/dl
Alkaline phosphatase : 725 U/L
Alanine transaminase : 78 U/L
Bilirubin, total : 3.8 mg/dl
Bilirubin, conjugated : 2.0 mg/dl
Urine, bile salts positive

Questions and Guidance to Answers:
A. Comment on the type of liver disease. Very high plasma ALP and moderately increased ALT indicate cholestatic liver pathology.
B. Interpret each laboratory data. Very high ALP = obstruction of intrahepatic bile ducts. Normal bilirubin = no obstruction of large bile ducts; excretory capacity of liver is intact. Mild increase in ALT = lesion is slowly expanding and destroying hepatocytes. Normal albumin = functional liver tissue is adequate; lesion has not affected the whole liver. Urine bile salt indicates obstructive lesion.
C. Diagnosis is secondary deposits in lymph nodes, obstructing the bile flow.

Case Study 26.8
A 21-year-old healthy male college student went to celebrate his birthday with some friends at a bar. His friends convinced him to have his first beer since he just turned 21. After consuming the beer, he began to experience intense, worsening abdominal pain that was nonspecific in location and described as cramping. Nausea and vomiting then ensued and he was taken to the ER.
Upon arrival to the ER, he was found to be very anxious with hallucinations. He was noted to be hypertensive, tachycardic, and diaphoretic. Peripheral neuropathy was also noticed on examination. Initial laboratory test revealed a normal CBC, drug screen, and EtOH level. Serum and urine aminolevulinic acid (ALA) and porphobilinogen (PBG) were both found to be elevated.
What is the likely diagnosis?
What is the underlying biochemical problem?
Diagnosis: Porphyria (likely acute intermittent porphyria)
Biochemical problem: Enzymatic deficiency in heme biosynthetic pathway
Clinical correlation: Patients often are asymptomatic unless exposed to factors that increase production of porphyrrias (drugs, alcohol, sunlight). Erythropoietic varieties primarily present with photosensitivity.
Hepatic porphyrias present with primarily neurovisceral symptoms such as: abdominal pain, nausea and vomiting, tachycardia and hypertension, peripheral neuropathy, and mental symptoms (hallucinations, anxiety, seizures).
Diagnosis is confirmed with elevated levels of ALA and PBG in the urine and serum. Treatment is supportive with avoidance of triggers in the future.
**Case Study 26.9**

The following are the biochemical values in a patient. What is your probable diagnosis?

- Serum bilirubin: 13.0 mg%
- Conjugated bilirubin: 6.0 mg%
- Unconjugated bilirubin: 7.0 mg%
- Serum alkaline phosphatase: 280 IU/L
- SGOT: 250 U/L
- SGPT: 370 U/L
- Urine bile salts: Negative, bile pigments: Positive (+++), Urobilinogen: Positive
- Feces stercobilinogen: Positive

*Answer:* Hepatocellular jaundice

**Case Study 26.10**

Comment on the following laboratory results obtained in a patient and give your probable diagnosis.

- Serum bilirubin: 9.0 mg%
- Conjugated bilirubin: 7.5 mg%
- Unconjugated bilirubin: 1.5 mg%
- SGOT: 80 U/L
- SGPT: 90 U/L
- ALP: 140 KA Units
- Urine bile salts: Positive (++), Bile Pigments: Positive (++), Urobilinogen: Negative
- Feces stercobilinogen: Negative

*Answer:* Obstructive jaundice. Causes are discussed in the text.

**Case Study 26.11**

Comment on the following laboratory results and give your provisional diagnosis.

- Serum bilirubin: 9.0 mg%
- Conjugated bilirubin: 0.5 mg%
- Unconjugated bilirubin: 8.5 mg%
- SGOT: 26 U/L
- SGPT: 30 U/L
- ALP: 8 KA Units
- Urine bile salts: Negative, Bile Pigments: Negative, Urobilinogen: Positive (+++), Feces stercobilinogen: Positive (+++)

*Answer:* Hemolytic jaundice. Causes are discussed in the text.

**Case Study 26.12**

A 42-year old obese lady presented with intolerance to fatty food and pain in the right abdominal region. On examination her eyes were yellowish and stools had clay colored appearance. The doctor ordered some laboratory tests. The results obtained were as follows –

- Serum bilirubin: 25.0 mg%
SGOT – 35 U/L
SGPT – 40 U/L
ALP – 400 IU/L

What is the probable diagnosis?

*Answer:* Obstructive jaundice due to gallstones.

**Case Study 26.13**

A newborn baby presented with yellowish discoloration of skin and conjunctiva after 3 days of birth. The neonatologist advised phototherapy. The child became normal. What is the type of jaundice? What are the tests to be done in this child? Why did phototherapy benefit the child? What are the other types of jaundice that may be seen in a newborn baby?

*Answer:* Hemolytic disease of the newborn. See text for description on the congenital types of jaundice.

**SUPPLEMENTARY INFORMATION TO CHAPTER 27**

**Case Study 27.1**

A 50-year old patient was admitted for treatment of pneumonia. He had poorly controlled diabetes mellitus and on admission blood urea was 140 mg/dl and serum creatinine was 2.8 mg/dl. He received 2.0 L fluid, but blood urea rose to 160 mg/dl and serum creatinine to 3.0 mg/dl. Urine output which was initially good dropped to 500 ml over a 24 hr period. Next day, he developed shortness of breath and lower extremity edema. Blood urea rose to 300 mg/dl and serum creatinine to 6.3 mg/dl. He failed to respond to diuretics. What is the probable diagnosis?

*Answer:* The patient is suffering from acute renal failure (ARF), also referred to as acute kidney injury (AKI). A brief history of illness, rising urea and creatinine values, oliguria, edema and failed response to diuretics all point towards diagnosis. Retention of nitrogenous waste products, oliguria, electrolyte and acid base disturbances are clinical features of ARF. There are many causes for ARF and they are usually classified as prerenal, intrinsinc and postrenal causes. Risk factors for ARF include hypertension, congestive heart failure, diabetes, multiple myeloma, chronic infection and myeloproliferative diseases.

Laboratory investigations include blood urea (or BUN, blood urea nitrogen), serum creatinine, myoglobin, free hemoglobin, uric acid, serum electrolytes (hyponatremia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypermagnesemia and metabolic acidosis are seen in ARF), serological tests for antinuclear antibodies (ANA), hepatitis, antistreptolysin – O (ASO), and complements, urine analysis (casts, myoglobin, hemoglobin, proteins, RBC and WBC or their casts, eosinophils, uric acid, calcium oxalate crystals) and urine electrolytes. Renal biopsy is indicated in patients in whom prerenal and postrenal causes have been ruled out and cause for intrinsinc ARF is unclear.

**Case Study 27.2**

A 50-year old man was admitted with loss of appetite, nausea, vomiting, difficulty of breathing and fatigue. History revealed that he had similar symptoms 5 years back and was diagnosed with hypertension and kidney failure. On examination, temperature was 36.8°C, respiratory rate was 22/min, pulse rate 64/min, BP was 170/100 mm Hg, marked pallor was present, chest and lungs showed bilateral basal rales, abdomen was soft, flat and tender. No other abnormality was detected. Patient was an occasional alcoholic, and a chronic smoker.

Laboratory investigations showed – Blood urea – 65 mg/dl, serum creatinine – 2.4 mg/dl, serum calcium 6.4 mg/dl, serum potassium 4.9 mg/dl, and serum sodium 139 mmol/L. Urine examination results were as follows – Color – Straw colored, pH 5.0, specific gravity 1.020, appearance was turbid, volume 650 ml/24 hrs, albumin 3+, sugar negative, pus cells 1-3/ HPF, RBC – 1-2/ HPF, and epithelial cells rare. What is the probable diagnosis?
**Answer:** The patient is suffering from chronic renal failure (CRF), also known as chronic kidney disease (CKD). The past history of hypertension and kidney failure goes against the diagnosis of ARF. There are 5 stages for CKD, (1) Stage 1 – Normal GFR, persistent albuminuria, known structural or hereditary kidney disease, (2) Stage 2 – GFR 60 – 89 ml/min/1.73 m², (3) Stage 3 – GFR 30 – 59 ml/min/1.73 m², (4) Stage 4 – GFR 15 – 29 ml/min/1.73 m², and (5) Stage 5 – GFR < 15 ml/min/1.73 m².

CKD can arise due to glomerulopathies which may be (1) primary glomerular diseases - focal and segmental glomerulosclerosis, membranoproliferative glomerulonephritis, IgA nephropathy, membranous nephropathy and (2) secondary glomerular diseases - diabetic nephropathy, amyloidosis, postinfectious causes, HIV associated nephropathies, collagen vascular diseases, sickle cell nephropathy, etc. Other causes are tubulointerstitial nephritis (drugs, heavy metals, analgesics, pyelonephritis, idiopathic), hereditary diseases (polycystic kidney disease, medullary cystic disease, Alport’s syndrome), obstructive nephropathies (prostate diseases, nephrolithiasis, tumors) and vascular diseases (hypertension, renal artery stenosis). The most common cause in diabetic nephropathy followed by hypertensive nephroangiosclerosis.

Decreased renal function interferes with kidneys’ ability to maintain fluid and electrolyte balance. The ability to concentrate urine declines early and is followed by inability to excrete phosphate, acids and potassium. In advanced stages, urine cannot be diluted and urine osmolality is “fixed”. Plasma levels of urea and creatinine are elevated rapidly, and abnormalities of calcium, phosphate, PTH, vitamin D, and renal osteodystrophy are seen. Moderate acidosis is seen. Anemia is normochromic-normocytic in nature. CKD is rarely reversible and leads to progressive decline in renal function.

Diagnostic tests are electrolytes, blood urea nitrogen (BUN) or blood urea, creatinine, phosphate, calcium, CBC and urinalysis. The definitive diagnostic tool is renal biopsy, but is not recommended when ultrasound indicates small, fibrotic kidneys.

Treatment includes (1) Control of underlying diseases, (2) Restriction of dietary protein, phosphate and potassium, (3) Vitamin D supplements, (4) Treatment of anemia and heart failure, and (5) Dialysis for severe decrease in renal function.

**Case Study 27.3**

A 55-year old hypertensive complains of dry, painful eyes and xerostomia for a few weeks. On examination, he was afebrile, BP 140 / 94 mm Hg, PR – 80/min. Facial and lower limb edema was present. Investigation results are as follows – Fasting blood sugar – 280 mg/dl, urine reducing sugars – Benedict’s test red precipitate, urine proteins - ++++, serum albumin – 2.0 gm/dl, serum cholesterol – 280 mg/dl, serum creatinine – 2.0 mg/dl, blood urea – 120 mg/dl. Serum immunoglobulins were normal, tests for hepatitis antigens were negative, culture for bacteria and fungi revealed no growth and serum and urinary electrophoresis were negative. What is the possible diagnosis?

**Answer:** Proteinuria, hypoalbuminemia and hypercholesterolemia along with acute renal failure and edema are the classical presentation of nephrotic syndrome (nephrosis). Patient has diabetes mellitus and hypertension, and these may have caused nephrotic syndrome. Confirmation of diagnosis can be done by renal biopsy. Hypercoagulable state, hypovitaminosis D and immunodeficiency are associated features seen.

Causes of nephrotic syndrome are – (1) Primary – minimal change nephropathy, focal glomerulosclerosis, membranous nephropathy, hereditary nephropathies, and (2) Secondary – Diabetes mellitus, lupus erythematosus, amyloidosis, paraproteinemia, viral infections like hepatitis B, C, HIV, etc. pre-eclampsia, vasculitis, drugs.

Treatment is based on treating protein loss, edema, hyperlipidemia, hypercoagulable state, associated nutritional deficiencies and protection from infections. Prognosis depends on cause, person’s age and type and degree of renal damage caused at the time of initiating treatment.

**Case Study 27.4**

A 10-year old boy was referred to the nephrologist with the following laboratory results—

**Blood urea** : 75 mg/dl  
**Serum creatinine** : 3.2 mg/dl
Case Studies

Serum sodium : 125 mmol/L
Serum potassium : 5.2 mmol/L
Urine protein : 4 g/L.

A. Give your impressions regarding the laboratory results.
B. What additional tests are to be done in this patient?
C. How will you assess the glomerular filtration rate (GFR) in this patient?
D. What is protein creatinine ratio?
E. What is the simple test by which you can determine the 24-hour excretion of proteins in urine?

Guidance to Answers: Nephrotic syndrome progressing to renal failure.

Case Study 27.5

A boy of 5 years who had pyoderma (skin infection) was found to have edema on the face and decreased urine output. The biochemical parameters are:
Serum albumin: 1.5 g/dl
Blood urea: 95 mg/dl
Serum creatinine: 2 mg/dl
Serum uric acid: 9 mg/dl
Serum phosphate: 6 mg/dl
Urine: albumin ++++
Urine RBC ++
Urine volume for 24 hours: 300 ml

Guidance to Answers: Acute glomerulonephritis. It is due to antibodies produced against certain bacteria cross reacting with kidney tissues, leading to severe decrease in kidney functions. See Chapter 28 for explanation for edema formation.

Case Study 27.6

The following laboratory results are those of a 70-year old woman:
Serum sodium : 124 mmol/L
Serum potassium : 3.6 mmol/L
Serum bicarbonate : 12 mmol/L
Blood urea : 200 mg/dL
Serum creatinine : 4 mg/dL
Serum calcium : 6 mg/dL
Serum phosphate : 8 mg/dL
Serum albumin : 3.1 g/dL
Alkaline phosphatase : 90 U/L

Questions and Guidance to Answers:
A. What is the most probable diagnosis? Increase in blood urea and creatinin indicates renal failure.
B. Interpret the calcium and phosphate values (see Chapter 39). The commonest cause of hyper-phosphatemia is renal failure. In this particular case, it indicates a severe degree of renal insufficiency. Phosphorus interferes with calcium absorption, resulting in hypocalcemia and renal osteodystrophy.

Case Study 27.7

A 60-year old male with history of hypertension and hyperlipidemia since 10 years, presents with oliguria since 10 days. He had undergone an aortogram three weeks back. He had bluish discoloration of toes on right foot. The laboratory analysis values were:
Hemoglobin : 11.2 g/dL
Total lymphocyte count : 11,200/cu.mm.
Platelet : 120,000/cu.mm
Urine : Protein ++
Microscopy : 2–3 RBCs
Blood urea : 160 mg/dl
Serum creatinine : 8.2 mg/dl

Questions and Guidance to Answers:
A. What is the most probable diagnosis? Patient has oliguria; urea and creatinine levels are increased; urine contains proteins; so it is a clear picture of acute glomerulonephritis. One of the complications of aortogram is thrombosis in renal artery and lower part of aorta. That would explain the acute onset of oliguria and infarction of toes.
B. What further tests do you suggest? (See kidney function tests).

Case Study 27.8
A fifteen years old girl presents with bilateral leg edema, arthralgia and purpuric spots on the lower limbs. The laboratory analysis values were:
Hemoglobin : 11.2 g/dl
Platelets : 180,000/cu.mm
Total count : 9600/cu.mm
ESR : 40 mm/hr
Serum creatinine : 4 mg/dl
Urine, proteins : +++
Urine, microscopy : 30–35 RBCs per field

Questions and Guidance to Answers:
A. What is the most probable diagnosis? Henoch-Schonlein Purpura. It is an autoimmune disease, where antibodies are produced against patient’s own platelets.
B. What further tests do you suggest? (See chapter 27 for renal function tests).

Case Study 27.9
A fifteen years old girl presents with bilateral leg edema, arthralgia and purpuric spots on the lower limbs. The laboratory analysis values were:
Hemoglobin : 11.2 g/dL
Platelets : 180,000 /cu.mm
Total Count : 9600 /cu.mm
ESR : 40 mm/hr
Serum, creatinine : 4 mg/dL
Urine, proteins : +++
Urine, microscopy : 30-35 RBCs per field
A. What is the most probable diagnosis?
B. What further tests do you suggest?

Answer: Henoch-Schonlein Purpura.
**SUPPLEMENTARY INFORMATION TO CHAPTER 28**

**Case Study 28.1**

A severe form of obstructive lung disease starting with dyspnea and leading to emphysema was found in several members of the same family. Blood analysis of the surviving members of the family revealed abnormally low concentration of alpha 1 antitrypsin. What is the basis of this condition?

*Answer:* Emphysema, a lung disease characterized by destruction of alveolar walls, has many causes including airway infections, cigarette smoking, air pollution and hereditary origin. Deficiency of alpha 1 antitrypsin leads to development of emphysema. Alpha 1 antitrypsin makes up most of the proteins in α1 globulin band during serum protein electrophoresis.

Lungs contain a natural enzyme called neutrophil elastase that digests damaged aging cells and bacteria and promotes healing of lung tissue. Being non-specific, it can attack lung tissue itself; but alpha 1 antitrypsin protects against this process by destroying excess amount of this enzyme. Absence of alpha 1 antitrypsin can lead to destruction of lung tissue and emphysema.

Clinical features of alpha 1 antitrypsin deficiency include shortness of breath, reduced exercise tolerance, wheezing, weight loss, recurrent respiratory infections, fatigue, tachycardia and in advanced cases, difficulty in breathing, hacking cough, barrel-shaped chest, etc. Smoking exacerbates the condition. About 10% of patients can have liver damage.

Diagnosis is by estimation of alpha 1 antitrypsin levels, arterial blood gas analysis, chest X-ray, CT scan of chest, pulmonary function tests and genetic testing. Treatment involves supplementation of alpha 1 antitrypsin and antioxidants.

**Case Study 28.2**

A male child, born to a normal young couple, was found to develop hemorrhagic tendency quite early in life. History revealed that the mother was the only daughter of a family who did not have any male offspring during the past 2 generations.

A. What are the possible causes?
B. How will you explain the nature of inheritance?
C. What is the advice to be given to the parents regarding bringing up the son and having another child.

*Guidance to Answers:* Hemophilia.

**SUPPLEMENTARY INFORMATION TO CHAPTER 29**

1. A patient was operated for intestinal obstruction. He had continuous gastric aspiration for the past 3 days. The arterial blood gas results of this postoperative patient are given below—
   - pH: 7.54
   - PCO₂: 45 mm of Hg
   - Plasma bicarbonate: 36 mmol/L
   - Serum sodium: 130 mmol/L
   - Serum potassium: 2.8 mmol/L
   - Serum chloride: 90 mmol/L.

A. What are the abnormalities noted?
B. What is the significance of serum potassium in relation to acid-base status?
C. Calculate and comment on the anion gap.
D. What is the significance of measuring urine chloride level in this patient?

*Guidance to Answers:* Metabolic alkalosis with hypokalemia.
2. The following are the blood gas results of a patient who has been on a respirator for the past week—

3. pH : 7.5  
   \( pCO_2 \) : 24 mm of Hg  
   \( pO_2 \) : 88 mm of Hg  
   Plasma bicarbonate: 18 mmol/L.

A. What is the acid-base status of the patient?  
B. Explain the nature of the disturbance and the alteration in each parameter.  
C. What is the nature of the compensatory change?

**Guidance to Answers:** Respiratory alkalosis.

4. The following results were obtained by blood gas analysis on the arterial blood of a patient admitted in an unconscious state with suspected barbiturate poisoning—

   pH: 7.24  
   \( pCO_2 \) : 60 mm of Hg  
   \( HCO_3^- \) : 27 mmol/L.

A. What is the nature of acid-base disturbance? Explain.  
B. Why barbiturates cause acid-base disturbance?  
C. What will be the nature of compensation?  
D. What are the enzyme levels that are likely to be elevated in this patient?  
E. Define the term base deficit.  
F. What is the effect of barbiturates on heme synthesis?

**Guidance to Answers:** Respiratory acidosis (For Answer for F, see Chapter 21).

4. One early morning, mother discovered that her 19-year old boy is unconscious. He was brought to the hospital. The mother gave the history that the boy was on treatment for epilepsy.

A. What is the effect of an overdose of anti-epileptic drugs?  
B. What is the nature of acid-base imbalance that can occur in this case?  
C. How is it compensated?  
D. Name an anti-convulsant drug, which is an enzyme inhibitor.

**Guidance to Answers:** Respiratory acidosis.

5. The laboratory results of a 6-year old boy are as follows:

   pH: 7.31  
   \( pO_2 \) : 94 mm of Hg  
   \( pCO_2 \) : 35 mm of Hg  
   Plasma bicarbonate: 20 mmol/L  
   Sodium: 138 mmol/L  
   Potassium: 3 mmol/L  
   Chloride: 112 mmol/L.

A: What is the nature of acid-base balance?  
B. Calculate the anion gap.  
C. Explain the abnormalities in electrolyte levels.

**Guidance to Answers:** Hyperchloremic acidosis.

6. The laboratory results of a patient with chronic obstructive pulmonary disease (COPD) are:

   pH : 7.26  
   \( pCO_2 \) : 65 mm of Hg  
   \( pO_2 \) : 60 mm of Hg  
   Bicarbonate: 36 mmol/L.
A. What is the nature of the disturbance?
B. How is it compensated?
C. What are the major buffer systems of plasma?
D. Explain the role of hemoglobin in buffering.

Guidance to Answers: Chronic respiratory acidosis.

7. Interpret the data and give the type of acid base disturbance. Blood pH – 7.12, pCO₂ – 80 mm Hg, Plasma bicarbonate – 26 mEq/L, H₂CO₃ – 20.7 mEq/L. What are the causes for the condition?

Answer: Respiratory acidosis.

8. A patient was operated for intestinal obstruction and had continuous gastric aspiration for 3 days. Blood pH – 7.55, pCO₂ – 50 mm Hg, Plasma bicarbonate – 30 mEq/L, Serum sodium – 130 mmol/L, Serum potassium – 2.9 mmol/L, Serum chloride – 95 mmol/L. Comment on the obtained values. What is the significance of potassium in acid base status assessment? Why is chloride measured in this patient? Calculate and comment on the anion gap.

Answer: Metabolic alkalosis.

9. Interpret the data and give the type of acid base disturbance. Blood pH – 7.54, pCO₂ – 20 mm Hg, Plasma bicarbonate – 26 mEq/L, H₂CO₃ – 0.7 mEq/L. What are the causes for the condition?

Answer: Respiratory alkalosis.

SUPPLEMENTARY INFORMATION TO CHAPTER 36

Case Study 36.1

A 6-year old child was brought to the hospital with complaints of slow growth and pain in bones. On examination he was anemic, had frontal bossing, bowing of legs and swelling of costochondral junction. Lab results were: Serum calcium - 8.2 mg/dl, serum phosphorus - 2.8 mg/dl and serum ALP-720 U/L. What is the likely diagnosis?

Interpretation – Rickets.

Tests: Vitamin D, Calcium

Vitamin D functions as both a vitamin and a prohormone. Low levels of vitamin D are associated with increased mortality; excess as well as deficiency of vitamin D causes premature aging. Low vitamin D levels are associated with osteomalacia, rickets, falls and low bone mineral density. Lower vitamin D levels also seem to be correlated with some cancers, bronchial asthma, heart palpitations, multiple sclerosis, infections and neurodegenerative diseases. Serum 25 hydroxy vitamin D levels also have to be maintained for bone and overall health.

Case Study 36.2

Serum sample collected from a 10-year old boy with stunted growth gave the following results:

Serum calcium: 8.2 mg/dl
Serum phosphorus: 2.8 mg/dl
Serum alkaline phosphatase: 720 U/L.

A. What are the biochemical abnormalities seen in the results?
B. What is the possible cause?
C. What are the other investigations to be done?
D. Explain the biochemical basis for the management.

Guidance to Answers: Vitamin D deficiency.
**Case Study 36.3**

A 40-year old woman, grossly overweight, presented with the complaint of cramps and spasms of both hands. On examination, she was found to be severely depressed with positive Trousseau’s and Chavostek’s signs. Six months prior to admission, she had thyroidectomy for Grave’s disease. The present biochemical findings:

- **Serum creatinine**: 1.1 mg/dL
- **Serum calcium**: 4 mg/dL
- **Serum phosphate**: 6 mg/dL
- **Alkaline phosphatase**: 65 U/L
- **Serum albumin**: 3.9 g/dL

**Questions and Guidance to Answers:**

A. What are the differential diagnosis? Vitamin D deficiency or hypoparathyroidism. See Chapters 36 and 39.

B. What will be the laboratory findings in renal failure and in hypoparathyroidism? In renal failure, high plasma creatinine and high phosphate are found. Hypocalcemia associated with high plasma phosphate occurs in renal failure and hypoparathyroidism. A low plasma calcium and hypophosphatemia is seen in secondary hyperparathyroidism (vitamin D deficiency).

C. How do you interpret the alkaline phosphatase? A high plasma ALP indicates increased osteoblastic activity. Hypocalcemia of vitamin D deficiency is associated with high ALP levels.

D. What laboratory tests will give a definite diagnosis? 25-hydroxy cholecalciferol was normal in this patient. This excluded vitamin D deficiency. Renal failure was excluded by normal plasma creatinine. Blood gas analysis revealed normal values, which excluded alkalosis, as the cause of neuromuscular hyperexcitability. So Trousseau’s sign was due to hypocalcemia, secondary to hypoparathyroidism.

E. What is the final diagnosis? Hypoparathyroidism, as a complication of accidental removal of parathyroid tissue during thyroid surgery.

**SUPPLEMENTARY INFORMATION TO CHAPTER 37**

**Clinical Case 37.1**

A 40-year old man was brought to the emergency department in an extremely confused and disoriented state. He had unsteady gait and abnormal irregular eye movements. There is no history of any other medical problem in the past. The patient was a chronic alcoholic and was a heavy drinker. Blood levels of alcohol were high, urine drug screen was negative and blood pyruvate and lactate levels were high. What is the likely cause of the symptoms?

*Answer:* The most likely diagnosis is Wernicke-Korsakoff syndrome due to thiamine deficiency associated with chronic alcoholism. Thiamine deficiency is generally uncommon except in alcoholics and is a result of nutritional deficiencies and malabsorption. Symptoms include confusion, apathy, indifference, speech problems, hallucinations, agitation, visual impairment, nystagmus, ataxia, postural hypotension, tachycardia, and syncope.

Human beings cannot synthesize thiamine and it needs to be obtained from the diet. Thiamine pyrophosphate is an important co-enzyme mediating oxidative decarboxylation and transketolase reaction of HMP shunt pathway. Deficiency of thiamine will decrease formation of acetyl CoA from pyruvate and cause depression of TCA cycle and subsequently of oxidative phosphorylation. Blood lactate and pyruvate levels are elevated.

Laboratory studies include electrolytes, serum thiamine levels, erythrocyte transketolase level, arterial blood gas analysis, urine drug screen and liver enzymes. Wernicke’s encephalopathy is a medical emergency and requires parenteral thiamine therapy. Early treatment can reverse neurological symptoms.
Clinical Case 37.2
A 59-year-old male is brought to the emergency department after a family member found him extremely confused and disoriented, with an unsteady gait. The patient has been known in the past to be a heavy drinker. He has no known medical problems. On examination, he is afebrile with a normal blood pressure. He is extremely disoriented and agitated. Horizontal rapid eye movement on lateral gaze is noted bilaterally. His gait is very unsteady. The urine drug screen was negative and he had a positive blood alcohol level. The emergency room physician administers thiamine. What is the most likely diagnosis? What is importance of thiamine in biochemical reactions?

Answer: Wernicke-Korsakoff syndrome (thiamine deficiency) often associated with chronic alcoholics.

Importance of thiamine: It is used as a cofactor in enzymatic reactions involving the transfer of an aldehyde group. Without thiamine, individuals can develop dementia, macrocytic anemia (folate deficiency), liver disease, depression, cardiomyopathy, and pancreatitis.

Thiamine deficiency is uncommon except in alcoholics as a result of nutritional deficiencies and malabsorption. The classic clinical triad of dementia, ataxia (difficulty with walking), and eye findings may be seen, but more commonly, only forgetfulness is noted. Sometimes, thiamine deficiency can lead to vague symptoms such as leg numbness or tingling. Other manifestations include beri beri, leading to a high cardiac output, heart failure and vasodilation. Affected patients often feel warm and flushed.

Clinical Case 37.3
A 65-year old chronic smoker and alcoholic suffered from painful swallowing, insomnia, epigastric discomfort and recurrent diarrhea. On examination, he had disorientation, stomatitis, glossitis, esophagitis and exfoliative dermatitis. Laboratory measurements revealed leukocytosis, elevated ALT, AST and GGT and there was ultrasound evidence of fatty liver. Treatment with 500 mg daily nicotinamide was started when rashes improved and other symptoms were reduced. He restricted alcohol and smoking and increased consumption of other B complex vitamins and food sources of B complex vitamins. What is the likely condition? What is the pathophysiology of the findings?

Answer: Diarrhea, dementia and dermatitis (3 Ds) are typical features of niacin deficiency, pellagra. Chronic alcoholics are prone to multiple vitamin deficiencies, which are seen in this patient. Fatty liver is also due to chronic alcoholism. Treatment with multivitamins resulted in amelioration of the symptoms. A balanced diet including all B complex vitamins is needed.

Niacin in large doses can also lower LDL cholesterol and triglycerides, and increase HDL cholesterol level.

SUPPLEMENTARY INFORMATION TO CHAPTER 38

Case Study 38.1
A 45-year old man presented with loss of appetite, fatigue, muscle weakness and emotional disturbances. Physical examination showed enlarged liver that was firm and nodular, mild jaundice and smell of alcohol in breath. Hematological examination showed macrocytic anemia, and bone marrow showed presence of megaloblasts. Serum folate was reduced and Vitamin B12 and iron were normal. What is the cause of megaloblastic anemia in this patient?

Answer: Megaloblastic anemia can be due to different causes, like Vitamin B12 deficiency, folate deficiency, genetic defects in these vitamins or defects in DNA synthesis. Alcoholics are at particular risk for folate deficiency because of poor nutrition and defective absorption.

Folate is needed for one carbon metabolism, purine and pyrimidine synthesis, DNA and RNA replication, methionine synthesis, conversion of serine to glycine, and in various other transmethylation reactions.
Causes for folate deficiency are: (1) Dietary deficiency due to anorexia, alcoholism, patients who do not eat fresh fruits and vegetables, overcooking, etc. (2) Impaired absorption, due to celiac disease and tropical sprue, small bowel resection, etc. (3) Impaired metabolism and inability to utilize absorbed folate, as with use of antimetabolites like methotrexate and trimethoprim, hypothyroidism, alcoholism, etc. (4) Increased requirement as in pregnancy, lactation, infancy, malignancies, chronic hemolytic anemias, concurrent infections, etc. (5) Increased excretion and loss and (6) Increased destruction. Treatment is by folate supplementation. Vitamin B12 deficiency, if present, should be corrected, otherwise neuropathy can develop.

Strict vegetarian diet and lack of supplementation of cobalamin are the common causes for Vitamin B12 deficiency. Absence of intrinsic factor, pernicious anemia, gastrectomy, pancreatic insufficiency, helicobacter pylori, fish tapeworm infestation, decreased ileal absorption, Crohn’s disease and surgical resection can also produce B12 deficiency.

Symptoms are megaloblastic anemia, fatigue, weakness, palpitations, vertigo, tachycardia, sore, beefy-red tongue, weight loss and diarrhea which are common for both folate and B12 deficiencies. In addition, neurological symptoms are common for B12 deficiency, these include numbness, paresthesia, weakness, ataxia, abnormal reflexes and diminished vibratory sensation. Treatment includes supplementation of folate and vitamin B12.

**Case Study 38.2**

A 60-year old woman presented with complaints of weight loss, general ill health, weakness, generalized body aches, numbness and paresthesia in legs, reduced appetite and abdominal discomfort for 8 months. There is no past history of any significant illness. On examination, patient was pale, moderate jaundice, tongue was beefy red and fissured, and nails were brittle. Mild tachycardia was present and BP was normal.

Peripheral smear showed macrocytic anemia with presence of anisopoikilocytosis, ovalocytes, basophilic stippling, occasional Howell-Jolly bodies, and a moderate number of hypersegmented neutrophils. Platelet count and WBC counts were also reduced. Folate levels were normal and Vitamin B12 was low. Bilirubin was high but liver enzymes were normal. Schilling test results were as follows – Part I (before intrinsic factor) – 2% (Normal >7.5%) and Part II (after intrinsic factor) – 8%.

What is the likely diagnosis? Interpret the laboratory data.

*Answer:* The likely cause is Vitamin B12 deficiency which has produced moderate hemolytic anemia and neurological features. She has pancytopenia. Blood smear reports show features of hemolytic anemia. Since liver enzymes are normal, cause for jaundice is not a liver problem. Folate is normal and B12 levels are low, confirming a diagnosis of B12 deficiency. Results of Schilling test indicate pernicious anemia, which is due to lack of intrinsic factor in gastric secretions. It is probably due to gastric atrophy in this patient.

Other causes of pernicious anemia are genetic causes, autoimmune disorders and thyroid disease, gastrectomy and other surgeries, pancreatic insufficiency, Zollinger–Ellison syndrome, tapeworm infestation and a variety of drugs. Treatment includes supplementation of large doses of Vitamin B12. In elderly patients and in long-standing cases, neurological symptoms may become irreversible.

**Case Study 38.3**

A 32-year old female is being treated with methotrexate for a recently diagnosed choriocarcinoma of the ovary, and presents with complaints of oral mucosal ulcers. Five weeks ago the affected ovary was surgically removed. The patient has been taking methotrexate for 2 weeks. On examination, patient was afebrile but appeared ill. Several mucosal ulcers were seen in her mouth. The patient also had some upper abdominal tenderness. Her platelet count was decreased at 60,000/mm$^3$ (normal 150,000 to 450,000/mm$^3$). What is the most likely etiology of her symptoms? What is the biochemical explanation of her symptoms? What part of the cell cycle does methotrexate act on?
Answer: Likely cause of symptoms: Side effects of methotrexate (antimetabolite chemotherapy) affecting rapidly dividing cells such as oral mucosa. Folate antagonists inhibit dihydrofolate reductase (tetrahydrofolate needed for purine synthesis).

Case Study 38.4
A 47-year-old female is brought to the emergency department with complaints of malaise, vomiting and fatigue. The patient reveals alcohol abuse for the last 10 years. She has been to rehab on several occasions for alcoholism but has not been able to stop drinking. She denies cough, fever, chills, upper respiratory symptoms. She reports feeling hungry. On physical examination, she appears malnourished but in no distress. Her physical exam is normal. Her blood count revealed a normal white blood cell count but also showed anemia with large red blood cells. Other tests were normal. What is the most likely cause of her anemia? What is the molecular basis for the large erythrocytes?

Cause of anemia: Folic acid deficiency.

Molecular basis of macrocytosis: Abnormal proliferation of erythroid precursors in the bone marrow, since folate deficiency encumbers the maturation of these cells by inhibition of deoxyribonucleic acid (DNA) synthesis.

Case Study 38.5
A 38-year-old vegetarian female presented to her doctor with fatigue and tingling/numbness in her extremities (bilateral). The symptoms were gradually getting worse over the last year. She reported frequent episodes of diarrhea and weight loss. On examination, she was pale with tachycardia. Her tongue was beefy red. Neurological examination revealed numbness in all extremities with decreased vibration senses. The CBC demonstrated megaloblastic anemia. What is the most likely diagnosis? What is the most likely underlying problem for this patient? What are the two most common causes of megaloblastic anemia and how would this patient’s history and examination differentiate the two?

Diagnosis: Cobalamin (vitamin B12) deficiency.

Underlying problem: Lack of cobalamin intake. Patients with folate deficiency have similar hematologic and GI findings but do not have the neurologic symptoms as with cobalamin deficiency. Treatment consists of identifying/treating the underlying cause of deficiency and replacement of cobalamin and folate.

Case Study 38.6
A 45-year old man presented with loss of appetite, fatigue, muscle weakness and emotional disturbances. Physical examination showed enlarged liver that was firm and nodular, mild jaundice and smell of alcohol in breath. Hematological examination showed macrocytic anemia, and bone marrow showed presence of megaloblasts. Serum folate was reduced and Vitamin B12 and iron were normal. What is the cause of megaloblastic anemia in this patient?

Megaloblastic anemia can be due to different causes, like vitamin B12 deficiency, folate deficiency, genetic defects in utilization of these vitamins or defects in DNA synthesis. Alcoholics are at particular risk for folate deficiency because of poor nutrition and defective absorption.

Folate is needed for one carbon metabolism, purine and pyrimidine synthesis, DNA and RNA replication, methionine synthesis, conversion of serine to glycine, and in various other transmethylation reactions.

Vegetarian diet without milk and lack of supplementation of cobalamin are the common causes for Vitamin B12 deficiency. Absence of intrinsic factor, pernicious anemia, gastrectomy, pancreatic insufficiency, Helicobacter pylori, fish tapeworm infestation, decreased ileal absorption, Crohn’s disease and surgical resection can also produce B12 deficiency.

Symptoms are megaloblastic anemia, fatigue, weakness, palpitations, vertigo, tachycardia, sore, beefy-red tongue, weight loss and diarrhea which are common for both folate and B12 deficiencies. In addition, neurological symptoms are common for B12 deficiency, these include numbness, paresthesia, weakness, ataxia, abnormal reflexes and diminished vibratory sensation. Treatment includes supplementation of folate and vitamin B12.
Case Study 38.7
A pale, slightly jaundiced man of 56 years, with an unsteady gait, was admitted from a nursing home for investigation of possible liver disease. Examination revealed a beefy red tongue, slightly enlarged liver and a palpable spleen. There was also loss of vibration sense and loss of co-ordination in lower extremities. His hemoglobin concentration was 7.5 g/dl (normal 13-16). Results of his liver function tests are shown below:

- Total protein: 6.9 g/dL
- Albumin: 3.9 g/dL
- Alkaline phosphatase: 105 U/L
- Bilirubin: 2.2 mg/dL
- ALT: 35 U/L
- LDH: 1680 U/L
- GGT: 30 U/L

Questions and Guidance to Answers:
A. What are the differential diagnosis? Provisional diagnosis was hemolytic anemia; but the possibilities of pernicious anemia and liver diseases were also considered.
B. In this patient, total LDH level was very high. Further, the electrophoretic pattern showed predominance of LDH-1 and LDH-2. How do you interpret LDH iso-enzyme pattern? The LDH iso-enzyme pattern, along with normal levels of plasma ALT and ALP suggested that there was no liver cell damage (Chapter 26).
C. How is LDH iso-enzymes distributed in tissues? The plasma levels of these fractions depend on the tissue of origin (See Chapter 23). To summarize, Cardiac muscle produces LDH 2; Liver cells, LDH5; Kidney LDH 1-2; Skeletal muscle LDH5; RBC, LDH 1-2.
D. How do you further investigate?
E. A blood film revealed macrocytic anemia and bone marrow biopsy showed megaloblastic picture. Schilling test revealed abnormality. What is Schilling test? (See under vitamin B12).
F. What is the final diagnosis? Vitamin B12 deficiency.
G. How do you interpret the high plasma bilirubin and LDH levels? Due to destruction of abnormal red cell precursors in the bone marrow and spleen.

SUPPLEMENTARY INFORMATION TO CHAPTER 39
Case Study 39.1
A 45-year old female reported to the emergency department with severe pain in the left flank radiating towards lower leg and back. The patient was in acute distress. History revealed that she had recurrent urinary tract infections in the past and several similar episodes of pain. She also had weakness, fatigue and bone pains for the last two months. Physical examination was normal except for tenderness in the left kidney region. Laboratory investigations showed normal CBC, high calcium and low phosphorus. Urine was cloudy and had plenty of pus cells. She was admitted and treated for renal colic. What is the likely cause for renal colic in this patient? What is the pathogenesis of the findings?

Answer: The patient is suffering from hyperparathyroidism, overactivity of parathyroid glands, which results in elevated parathyroid hormone (PTH). PTH, in turn, regulated calcium and phosphorus level. Hyperparathyroidism may be (1) Primary – Due to hyperfunction of parathyroid and may be due to adenoma, hyperplasia or carcinoma, (2) Secondary – Reaction of parathyroid to hypocalcemia due to chronic renal failure, Vitamin D deficiency, etc. and (3) Tertiary – Hyperplasia of parathyroid and loss of response to serum calcium.

Clinical features are (1) recurrent nephrolithiasis, (2) peptic ulcers, (3) mental changes, (4) extensive bone resorption, (5) neuromuscular manifestations like proximal muscle weakness, easy fatigability, and muscle atrophy may be seen rarely and (6) gastrointestinal symptoms are vague abdominal pain, and disorders of stomach and pancreas.
Laboratory tests include hypercalcemia, abnormally low phosphate, elevated PTH and elevated alkaline phosphatase (ALP may not be elevated in all cases). Parathyroid immunoassay is the current gold standard of diagnosis.

**Case Study 39.2**

A 36-year old female was on treatment with I\textsuperscript{131} (radioactive iodine) for hyperthyroidism. Two months later, she developed severe carpopedal spasm and plasma calcium was 6.0 mg/dl. Laboratory results also revealed normal fT3, fT4 and TSH and low PTH. What is the possible diagnosis? What is the cause of hypocalcemia in this patient?

*Answer*: The patient is suffering from hypoparathyroidism, due to decreased activity of PTH. Treatment with I\textsuperscript{131} has led to persistent hypoparathyroidism in this patient. Carpopedal spasm is due to hypocalcemia and can be treated by calcium and vitamin D supplementation.

**Causes of hypoparathyroidism are** – (1) Primary – which is permanent and irreversible, could be congenital or acquired, (2) Iatrogenic – Excision of all 4 parathyroid glands, as during surgery of thyroid or other neck surgeries, extensive irradiation of face, neck or mediastinum, parathyroidectomy, (3) Autoimmune hypoparathyroidism, (4) Congenital, (5) Metal overload conditions like hemochromatosis and thalassemia, (6) Wilson’s disease, (7) hypomagnesemia, (8) Neonatal hypoparathyroidism, and (9) Pseudohypoparathyroidism – due to resistance to PTH.

Clinical features are paresthesias, irritability, fatigue, anxiety, mood swings, personality disturbances, seizures, hoarseness of voice, wheezing and dyspnea, muscle cramps, biliary colic, electrolyte disturbances (hypomagnesemia, hypokalemia and alkalosis) and tetany with positive Chvostek’s sign and Trousseau sign. Hypocalcemia can produce a variety of associated features like extra pyramidal choreothetotic syndromes, spastic paraplegia, ataxia, etc. papilledema, emotional disturbances, cataracts, abnormal dentition, dry, puffy skin and effects on heart including congestive heart failure.

**Case Study 39.3**

A 54-year old grossly overweight woman presented with complaints of cramps and spasms of both hands. She was depressed and had positive Trosseau’s and Chovstek’s signs. Past medical history revealed history of thyroidectomy for Grave’s disease. The laboratory results obtained were as follows –

- Serum creatinine – 1.0 mg%, Serum calcium – 4.1 mg%, Serum phosphate – 5.9 mg%, ALP – 60 IU/L, Serum albumin – 4.0 gm%.

Comment on the laboratory results and give your likely diagnosis. What additional tests are to be done to come to a conclusive diagnosis?

*Answer*: Hypocalcemia due to accidental removal of parathyroid glands. Please see details under Clinical Case Study 39.4 also.

**Case Study 39.4**

A 42-year old female presented to the clinic with complaints of vague abdominal discomfort, weakness and fatigue, and bone pain. She had frequent urinary tract infections and had several episodes of kidney stones. Her physical examination was within normal limits. The patient had a normal complete blood count (CBC), but electrolytes revealed a significantly elevated calcium level and low phosphorus level. What is the most likely diagnosis?

*Answer*: Diagnosis: Hyperparathyroidism, leading to hypercalcemia and hyperphosphatemia.

**Biochemical mechanism**: Elevated parathyroid hormone level acts by binding its receptor to activate the adenylate cyclase/protein kinase signaling system. Primary hyperparathyroidism, usually because of a solitary parathyroid adenoma, is the most likely cause when hypercalcemia is discovered in an otherwise asymptomatic patient. Hypercalcemia may be the presentation of intoxication with vitamin D, or calcium-containing antacids, genetic conditions like familial hypocalciuric
Hypercalcemia and hyperparathyroidism as part of a multiple endocrine neoplasia syndrome are uncommon. Most patients have no symptoms with mild hypercalcemia below 12.0 mg/dL, except polyuria. With levels above 13 mg/dL, patients begin developing neurological symptoms (lethargy, stupor, coma, psychosis), gastrointestinal symptoms (anorexia, nausea, peptic ulcer disease), kidney problems (polyuria, nephrolithiasis), and musculoskeletal complaints (myalgias, weakness.) The symptoms of hyperparathyroidism can be summarized as: stones (kidney), moans (abdominal pain), groans (myalgias), bones (bone pain), and psychiatric overtones. Diagnosis can be established by finding hypercalcemia and hypophosphatemia, with elevated PTH levels. Symptomatic patients can be treated with parathyroidectomy.

**Case Study 39.5**

A 9-year old girl presented with muscle pain and cramps, tingling of hands and feet, stiffness, recurrent carpopedal spasms, and titanic posturing of both hands and feet. She was a strict vegetarian with no milk or milk products. Other siblings are normal.

On examination, no symptoms of rickets or short stature, BP was normal and general examination was normal. Trousseau’s sign was positive. Calcium level was 6.5 mg/dl. What is the diagnosis? What are the causes for the disease? What other investigations are needed to come to a confirmatory diagnosis?

**Answer**: Muscle pain and cramps, stiffness, tingling of hands and feet, carpopedal spasm and positive Trousseau’s sign are indicative of hypocalcemia. Two common causes for hypocalcemic tetany are hypoparathyroidism or chronic renal failure. Abnormal renal function tests, arterial blood gases, hemogram and urine calcium/creatinine ratio would point towards a renal cause for hypocalcemia. High serum alkaline phosphatase and low parathyroid hormones would indicate hypoparathyroidism. Antimicrosomal antibody may be elevated in the latter state. Hypoparathyroidism may be due to parathyroid aplasia or hypoplasia, parathyroid hormone gene mutations, autoimmune parathyroiditis, hemosiderosis, Wilson’s disease, or accidental removal during thyroid surgery.

Causes of hypocalcemia are many, a few important causes are listed below. (1) Secondary to hypoalbuminemia, hypomagnesemia, hyperphosphatemia, etc., (2) Medications, (3) Surgical effects, (4) PTH deficiency or resistance, (5) Vitamin D deficiency or resistance, (6) Multifactorial – Acute pancreatitis, rhabdomyolysis, sepsis, toxic shock syndrome, malignancies, hepatic and renal insufficiencies, infiltrative diseases like sarcoidosis, tuberculosis, etc. and (7) Enhanced protein binding and anion chelation. Maternal hypovitaminosis D can present with hypocalcemia in the neonate. The risk is higher in preterm infants, maternal diabetes and perinatal asphyxia.

Additional tests include electrolytes (magnesium, phosphate and other electrolytes), renal function tests (urea and creatinine), arterial blood gases, liver function tests (albumin, coagulation studies and other liver function tests), PTH and Vitamin D levels. Cardiac assessment may be necessary to rule out cardiac effects of hypocalcemia.

**Case Study 39.6**

A 10-year old girl presented with excessive tiredness, poor appetite, inability to concentrate and tingling sensations. On examination, there was pallor. Laboratory examination revealed decrease in hemoglobin, ferritin and MCV. Total iron binding capacity (TIBC), transferrin and RDW were increased. What is the likely diagnosis?

**Answer**: The symptoms are suggestive of iron deficiency anemia, the commonest deficiency disease prevalent worldwide. Iron requirements are high during infancy, childhood, adolescence and last two trimesters of pregnancy. Iron is a critical element in the functioning of cells, but free iron is highly toxic. Ferritin and hemosiderin are storage forms of iron.

Laboratory indices of iron deficiency are lowered serum iron, low ferritin level, and high total iron binding capacity (TIBC). Other tests include complete blood count (CBC) where MCV and MCHC are reduced, peripheral smear, soluble transferrin receptor protein (TRP), stool for hemoglobin, hemoglobin electrophoresis and urine for hemoglobin and hemosiderin.

Treatment includes iron (oral or parenteral) and red cell transfusion, as necessary.
Case Study 39.7

A 19-year old female reported with complaints of generalized weakness, lethargy, loss of appetite and inability to do routine work for the past few months. She gives history of excessive bleeding during menstruation from the past six months. She also gives history of breathlessness and palpitation while climbing stairs, light-headedness and leg cramps. There is no history of fever, drug intake or abdominal discomfort.

On examination, she had tachycardia, pale gums and nail beds, and tongue was swollen. Hemoglobin was 8.0 gm/dl and iron was 32 mg/dl. What is the cause of anemia in this patient?

Answer: The symptoms are suggestive of iron deficiency anemia (See discussion of the previous case).

Case Study 39.8

A 76-year old woman was admitted with anorexia, weight loss and anemia and diagnosed to have carcinoma of the colon. Biochemical results were as follows – Serum sodium – 123 mmol/L, Potassium – 3.8 mmol/L, Chloride – 88 mmol/L, Bicarbonate – 21 mmol/L. Serum osmolality was 247 mOsm/kg and urine osmolality was 176 mOsm/kg. Urea and creatinine were normal. What is the probable diagnosis?

Answer: The patient has dilutional hyponatremia. Normal urea and creatinine exclude significant sodium depletion and absence of edema exclude increase in total body sodium. The results are classical of “syndrome of inappropriate ADH secretion” (SIADH), due to secretion of AVP is response to nonosmotic stimuli. Hyponatremia is the most common electrolyte disturbance, and there is marked presence of hyponatremia in hospitalized patients (30% of patients in ICUs may have hyponatremia).

Common causes of hyponatremia are diuretic use, diarrhea, heart failure and renal diseases. Clinical features are headache, confusion, stupor, seizures and coma may be seen in severe cases. Hypovolemic hyponatremia can be due to renal causes (acute or chronic renal failure, salt-losing nephropathy, diuretics, etc.) or extrarenal causes (excessive fluid losses, cerebral salt-losing syndrome, prolonged exercise, etc.). Other types of hyponatremia are euvolemic hyponatremia (seen in patients who are taking excess fluids), hypervolemic hyponatremia (renal causes like acute and chronic renal failure, hepatic cirrhosis, congestive heart failure, and nephrotic syndrome), redistributive hyponatremia (seen in hyperglycemia or mannitol therapy) and pseudohyponatremia (hypertriglyceridemia, multiple myeloma).

Case Study 39.9

A 76-year old man with depression and very severe incapacitating disease was admitted to the emergency department. He was clinically dehydrated, skin was lax and lips and tongue were dry and shriveled looking. PR – 104/min, BP – 95/65 mm Hg. Biochemical results were – Sodium – 162 mmol/L, Potassium – 3.7 mmol/L, Chloride – 132 mmol/L, Bicarbonate – 17 mmol/L. Blood urea was 90 mg/dl, serum creatinine 1.8 mg/dl. Interpret the findings.

Answer: The patient possibly has prerenal uremia and severe hypernatremia. Patient might be suffering from water deprivation. Serum potassium is normal. It is important to exclude nonketotic diabetic coma and blood glucose and ketones should be estimated for this purpose.

Hypernatremia also may be hypovolemic, euvolemic and hypervolemic. Causes are: (1) Hypovolemic – GI losses, skin losses, renal losses, (2) Euvolemic – Extra-renal losses from respiratory tract, skin, renal losses, etc. and (3) Hypervolemic – Hypertonic fluid administration, mineralocorticoid excess. Hypernatremia may be seen in elderly, post-operative patients and those on tube feeds or parenteral nutrition.

Case Study 39.10

A 55-year old man was brought to the emergency with severe multiple injuries in a road traffic accident and crush injuries, fractures of the legs and scalp lacerations. He was conscious and breathing spontaneously. PR – 130/min, BP – 60/40
mm Hg. Laboratory results were as follows – Sodium – 142 mmol/L, Potassium – 7.9 mmol/L, Chloride – 110 mmol/L, Blood urea – 40 mg/dl, and serum creatinine – 1.2 mg/dl. Interpret the laboratory data. What is the basis of the changes?

*Answer:* Patient has severe hyperkalemia due to release of potassium from the damaged tissues. Clinical features are neuromuscular; muscle weakness, cardiac toxicity, and may produce ventricular fibrillation and asystole.

Causes are: (1) Pseudohyperkalemia – Hemolysis, thrombocytosis, leukocytosis, excessivemultipleapplication during blood draw, (2) Redistribution – Acidosis, insulin deficiency, beta blockers, acute digoxin intoxication, succinylcholine, arginine HCl, hyperkalemic periodic paralysis, (3) Excessive endogenous potassium load – Hemolysis, rhabdomyolysis, internal hemorrhage, (4) Excessive exogenous potassium load – parenteral therapy, excess in diet, potassium supplements, salt substitutes, (5) Diminished potassium excretion – decreased GFR, decreased mineralocorticoids, defect in tubular secretion, drugs etc. Usually there are many simultaneous factors causing hyperkalemia.

**Case Study 39.11**

A 65-year old female complaining of severe diarrhea over the past few days presented to the clinic. Her physical examination revealed dry mucous membranes, postural hypotension was present. PR – 140/min. Laboratory results were as follows: Sodium – 132 mmol/L, potassium – 2.7 mmol/L, chloride – 90 mmol/L, pCO₂ – 31 mm Hg, blood urea and creatinine were normal. Interpret the findings.

*Answer:* There is hypokalemia due to severe diarrhea. Diarrhea has also produced loss of fluid and sodium chloride. Main cause of hypokalemia in this patient is extracellular volume depletion (ECVD) which has also induced metabolic alkalosis (contraction alkalosis).

Hypokalemia (decrease in serum potassium) is caused by deficit of potassium stores or abnormal movement into cells. Common causes are excess losses from kidneys and GI tract. Clinical features of hypokalemia are muscle weakness, polyuria and cardiac hyperexcitability. Hypokalemia is also common among hospitalized patients.

Causes are: (1) Renal losses – Renal tubular acidosis, adrenal steroid excess, Bartter syndrome, Gitelman’s syndrome, Liddle syndrome, renal potassium wasting, hypomagnesemia, leukemia, (2) GI losses – Vomiting, diarrhea, enemas and laxatives, prolonged gastric suction, (3) Drugs like diuretics, theophylline, aminoglycosides, etc., (4) Transcellular shift – Insulin, α adrenergic antagonists, thyrotoxicosis, (5) Malnutrition and decreased dietary intake, and (6) Pseudohypokalemia.

**Case Study 39.12**

A 3-year old boy was brought to the clinic for chronic productive cough not responding to antibiotics. There was no history of fever, but there was abdominal distension, difficulty to pass stool, and emesis in infancy. History revealed that the child frequently passed bulky, foul-smelling stools. No diarrhea was present. He had many relatives with chronic lung and “stomach” problems and some had died at a young age.

On examination, child was ill-appearing, slender and in moderate distress. Lung examination and chest X-ray revealed poor air movement in base of lungs, bilateral and coarse ronchi throughout lungs and bronchopneumonia. A quantitative pilocarpine iontophoresis sweat test was done and serum chloride was 70 mEq/L. Repeat testing after a few days yielded same results. What is the diagnosis? What is the mechanism involved?

*Answer:* The most probable diagnosis is cystic fibrosis, a disease with defective chloride ion channels of exocrine glands in acinar cells of pancreas, sweat glands and mucous glands of respiratory, digestive and reproductive tracts. There is mutation in the CFTR gene; more than 1400 mutations have been identified and 230 mutations are associated with clinical features. CFTR Δ508 mutation accounts for 70% of cases.

Clinical findings are: (1) Lungs – Thickening of mucus and depletion of periciliary liquid leading to adhesion of mucus to airway surface; infections of airways, (2) GI tract – Damage to exocrine pancreas and destruction of pancreas, desiccated intestinal intraluminal contents, obstruction of small and large intestines, thickened biliary secretions, focal
biliary cirrhosis, bile duct proliferation, chronic cholecystitis, cholelithiasis, (3) Sweat gland – Normal volumes of sweat with defective chloride content is hallmark of CF.

Laboratory findings are (1) Hypoxemia and in advanced cases, chronic compensated respiratory acidosis. Pulmonary function shows mixed obstructive and restrictive pattern. (2) Elevated chloride in sweat on two tests on different days is diagnostic. Normal sweat chloride level does not rule out diagnosis of CF. (3) DNA analysis (PCR test).

**Case Study 39.13**

A 70-year old woman was admitted with anorexia, weight loss and anemia and diagnosed to have carcinoma of the colon. Biochemical results were serum sodium–123 mmol/L, potassium–3.8 mmol/L, chloride–88 mmol/L, bicarbonate 21–mmol/L. Serum osmolality was 247 mOsm/kg and urine osmolality was 176 mOsm/kg. Urea and creatinine were normal. What is the probable diagnosis?

*Answer:* The patient has dilutional hyponatremia. Normal urea and creatinine exclude significant sodium depletion and absence of edema exclude increase in total body sodium. The results are classical of “syndrome of inappropriate ADH secretion” (SIADH), due to secretion of AVP in response to nonosmotic stimuli. Hyponatremia is the most common electrolyte disturbance, and there is marked presence of hyponatremia in hospitalized patients (30% of patients in ICUs may have hyponatremia).

Common causes of hyponatremia are diuretic use, diarrhea, heart failure and renal diseases. Clinical features are headache, confusion, stupor, seizures and coma may be seen in severe cases. Hypovolemic hyponatremia can be due to renal causes (acute or chronic renal failure, salt-losing nephropathy, diuretics, etc.) or extrarenal causes (excessive fluid losses, cerebral salt-losing syndrome, prolonged exercise, etc.). Other types of hyponatremia are euvolemic hyponatremia (seen in patients who are taking excess fluids), hypervolemic hyponatremia (renal causes like acute and chronic renal failure, hepatic cirrhosis, congestive heart failure, and nephrotic syndrome), redistributive hyponatremia (seen in hyperglycemia or mannitol therapy) and pseudohyponatremia (hypertriglyceridemia, multiple myeloma).

**Case Study 39.14**

A 70-year old man with depression and weakness was admitted to the emergency department. He was clinically dehydrated, skin was lax and lips and tongue were dry and shriveled looking. Pulse–104/min, BP 95/65 mm Hg, serum sodium–162 mmol/L, potassium–3.7 mmol/L, chloride–132 mmol/L, bicarbonate–17 mmol/L, blood urea–90 mg/dl, and serum creatinine–1.8 mg/dl. Interpret the findings.

*Answer:* The patient possibly has prerenal uremia and severe hypernatremia. Patient might be suffering from water deprivation. Serum potassium is normal. It is important to exclude nonketotic diabetic coma and blood glucose and ketones should be estimated for this purpose.

Hypernatremia also may be hypovolemic, euvolemic and hypervolemic. Causes are: (1) Hypovolemic – GI losses, skin losses, renal losses, (2) Euvolemic – Extra-renal losses from respiratory tract, skin, renal losses, etc., and (3) Hypervolemic – Hypertonic fluid administration, mineralocorticoid excess. Hypernatremia may be seen in elderly, post-operative patients and those on tube feeds or parenteral nutrition.

**Case Study 39.15**

A 55-year old man was brought to the emergency with severe multiple injuries in a road traffic accident and crush injuries, fractures of the legs and scalp lacerations. He was conscious and breathing spontaneously. Pulse–130/min, BP–60/40 mm Hg, serum sodium–142 mmol/L, potassium–7.9 mmol/L, chloride–110 mmol/L, blood urea–40 mg/dl, and serum creatinine–1.2 mg/dl. Interpret the laboratory data. What is the basis of the changes?

*Answer:* Patient has severe hyperkalemia due to release of potassium from the damaged tissues. Clinical features are neuromuscular; muscle weakness, cardiac toxicity, and may produce ventricular fibrillation and asystole.
Causes are: (1) Pseudohyperkalemia – Hemolysis, thrombocytosis, leukocytosis, excessive tourniquet application during blood draw, (2) Redistribution – Acidosis, insulin deficiency, beta blockers, acute digoxin intoxication, succinylcholine, arginine HCl, hyperkalemic periodic paralysis, (3) excessive endogenous potassium load – Hemolysis, rhabdomyolysis, internal hemorrhage, (4) excessive exogenous potassium load – parenteral therapy, excess in diet, potassium supplements, salt substitutes, (5) Diminished potassium excretion – decreased GFR, decreased mineralocorticoids, defect in tubular secretion, drugs, etc. Usually there are many simultaneous factors causing hyperkalemia.

SUPPLEMENTARY INFORMATION TO CHAPTER 40

Case Study 40.1
A 2-year old boy was brought to the hospital. He was eating poorly for the last one month, had intermittent diarrhea, and had become irritable and apathetic. On examination, he was underweight for height and small for age. He was pale, weak, skin was flaky, hair was brittle, abdomen was distended, liver was moderately enlarged and generalized edema was present. Laboratory tests were as follows – Hemoglobin – 6.5 gm/dl, Total protein – 4.0 gm/dl, Albumin – 1.8 gm/dl. What is the probable diagnosis?

**Answer:** The child is suffering from protein energy malnutrition (kwashiorkor). This is a severe form of childhood malnutrition characterized by edema, irritability, anorexia, ulcerating dermatitis, enlarged liver with fatty infiltrates and when well advanced, there may be inadequate growth, lack of stamina, loss of muscle tissue, increased susceptibility of infections, vomiting, diarrhea, anorexia and edema. Eventually there is stupor, coma and death.

The condition may develop when mother weans the child from breast milk and replaces the diet with food rich in carbohydrates, and deficient in proteins. Along with protein deficiency, micronutrient and antioxidant deficiencies, like iron, folate, iodine, selenium, vitamin C, glutathione, albumin, vitamin E and PUFA, may play an important role. Treatment includes treatment of dehydration, antibiotics, a diet providing adequate proteins, vitamins, minerals and electrolytes.

Case Study 40.2
An 8-month old girl was brought to the clinic in an irritable state. Weight was much lower than expected, mid arm circumference and triceps thickness were very low for age. Creatinine-height index was low and serum albumin was normal. The mother tells that she had stopped breastfeeding at the age of 6 months and was now giving only formula milk (which was diluted). What is the probable diagnosis?

**Answer:** The child is suffering from nutritional marasmus, a type of protein energy malnutrition (PEM). There is inadequate intake of proteins and calories leading to emaciation. Low body weight, diminished skin fold thickness, and reduced arm muscle circumference reflect loss of fat and catabolism of proteins from the body. All available fat stores have been exhausted due to starvation.

PEM might be (1) primary (due to lack of food) or (2) secondary, due to disorders affecting GI function, wasting diseases like AIDS, cancer, renal failure, or conditions that increase metabolic demands like infections, hyperthyroidism, burns, trauma, etc. Edematous PEM is kwashiorkor and non-edematous PEM is marasmus. Another type is known as marasmic-kwashiorkor PEM.

All organs are affected in malnutrition. Dietary proteins, energy and micronutrients become deficient. Weight loss, immunodeficiency, neurological changes, fatty degeneration and other effects are seen. Laboratory tests include CBC, measures of protein nutritional status assessment like serum albumin, retinol-binding protein, prealbumin, transferrin, creatinine and BUN levels, serum electrolytes, blood glucose, urinalysis and culture and arterial blood gases (often metabolic acidosis is present). If child has history of abnormal stools, stool specimens should be checked for ova and parasites.
Best treatment is oral balanced diet, if child can take oral feeds. Severe PEM or prolonged starvation requires treatment in a hospital with controlled diet.

**SUPPLEMENTARY INFORMATION TO CHAPTER 41**

**Case Study 41.1**

A 20-year-old female was brought to the emergency department with nausea, vomiting, and complaining of abdominal pain. She had been under a lot of stress with final examinations. In her hostel room, her friends noticed an empty bottle of acetaminophen near the bed with numerous pills lying on the ground. On arrival to the emergency department, the patient was found distressed with vomiting. Laboratory tests revealed hypokalemia and elevated liver enzymes. Her white blood cell count was normal. Her acetaminophen blood level was above 200 femto g/ml. The emergency department physician gave a gastric lavage and then prescribed oral N-acetylcysteine.

**Answer:** Overdose concentrations are the result of deliberate ingestion, as in this clinical case, or accidental ingestion, often involving either a child who finds a bottle of acetaminophen and consumes its contents or a disoriented elderly person who loses track of how many tablets have been consumed. Liver cell necrosis takes place, with clinical manifestations of nausea and vomiting, diarrhea, abdominal pain, and shock.

Acetaminophen is metabolized via the cytochrome P450 enzymes into a deleterious product N-acetyl benzoquinoneimine, which destroys proteins, lipids, RNA and DNA. Because the liver has high levels of cytochrome P450 enzymes, it is the major organ affected by acetaminophen overdose. Normally acetaminophen is cleared by conjugation with either glucuronic acid or sulfate followed by excretion. The antidote of toxicity is N-acetylcysteine which helps to facilitate glutathione synthesis. Glutathione is used to conjugate and thereby detoxify the toxic metabolite.

**SUPPLEMENTARY INFORMATION TO CHAPTER 42**

**Case Study 42.1**

A 3-year old girl was brought to the emergency department. She was cold and clammy and was breathing rapidly. She was obviously confused and lethargic. Her mother had indicated that she had accidentally ingested automobile antifreeze while playing in the garage. Following GI lavage and activated charcoal administration, a nasogastric tube for ethanol was administered. What is the likely cause?

**Answer:** This is a case of ethylene glycol poisoning. Ethylene glycol is the major ingredient of radiator fluid products. It is used to increase boiling point and decrease freezing point of radiator fluid. Thus, overheating and freezing of the fluid is reduced, depending upon season.

Ethylene glycol is a relatively nontoxic compound before it is metabolized. However, ethylene glycol is sequentially converted to glycoaldehyde, glycolate, glyoxylic acid and finally to oxalate. Glycolate can produce acidosis and hyperventilation. Calcium oxalate crystals can form and accumulate in blood and other tissues and hypocalcemia can occur. Thus symptoms include severe anion gap metabolic acidosis, tachypnea, confusion, convulsions, and coma, oxalate crystalluria and renal failure.

Laboratory investigations are: (1) Ethylene glycol levels in blood, (2) Serum osmolality, (3) Serum electrolytes, (4) Serum calcium, (5) Arterial blood gas analysis, and (6) Urinalysis, calcium oxalate crystals may be seen.
**SUPPLEMENTARY INFORMATION TO CHAPTER 43**

**Case Study 43.1**

A 45-year old male presented with severe pain of right toe. Patient was normal until early in the morning when he woke up with severe right big toe pain. Patient does not give any history of injury and/or pain in any joints previously. He had been binge drinking the previous night. The patient is hypertensive, diabetic, is a chronic alcoholic and had renal stones for which he had undergone nephrectomy a few years back.

*Answer:* On examination, he had fever and was in distress due to the pain. The right big toe was swollen, warm, red and very tender. Synovial fluid analysis revealed needle-shaped crystals that were negatively birefringent under polarizing microscopy. Serum uric acid level was 10.9 mg/dl, 24-hour urinary uric acid excretion was 530 mg/dl. Random blood sugar was 150 mg/dl. Other tests were normal. What is the likely diagnosis? What is the pathophysiological mechanism?

The likely diagnosis is gouty arthritis. The pain in big toe is precipitated by alcohol intake, which is a typical feature of gouty arthritis. Serum uric acid and synovial fluid analysis results are confirmatory.

Gout most often affects middle-aged to elderly men and post-menopausal women, and is characterized by hyperuricemia. Monosodium urate crystals are deposited in joints and connective tissues, and there is risk of uric acid nephrolithiasis. At acidic pH of urine, the crystals aggregate to form stones, which can cause obstruction. Acute gouty arthritis can be triggered by trauma, stress, vascular occlusions, surgery, drugs and purine-rich food including alcohol. Tophi around joints limit motion and cause deformities.

Hyperuricemia can be due to increased production or reduced excretion of uric acid or a combination of these two. Treatment includes treatment of acute attack with NSAIDs and steroids, prevention of recurrent attacks with colchicines and NSAIDs, prevention of further deposition of gouty crystals and reducing tophi by lowering serum uric acid levels, and treatment of co-existing diseases like hypertension, hyperlipidemia, diabetes mellitus and obesity.

With early diagnosis, patients can lead a normal life. Gout is more aggressive when initial symptoms appear before the age of 30. Nonadherence, alcoholism and under treatment by the physician are the common reasons for patients not improving to treatment.

**Case Study 43.2**

A 3-year old girl presented with megaloblastic anemia and failure to thrive. Obstetric history was uneventful. Anemia was present, which did not improve despite blood transfusions. There was no response to B12, folate and pyridoxine therapy.

Urinalysis revealed presence of a crystalline sediment, which was identified to be orotic acid. Very high levels of orotate (above 1.0 gm/day were excreted, normal being < 1.4 mg/day). Enzyme assays were done and showed deficiency of orotate phosphoribosyl transferase (OPRTase). What is the likely condition? What is the pathogenesis of the findings?

*Answer:* The likely condition is orotic aciduria. There is excessive excretion of orotic acid. The enzyme deficient may be OPRTase or orotidylate decarboxylase. It can also be secondary to OTC deficiency. Clinical findings appear in the first year of life and include growth failure, developmental retardation and megaloblastic anemia, refractory to vitamin B12 and folic acid.

Lack of CTP, UTP, and TMP as a result of enzyme inhibition decreases nucleic acid synthesis and decreases RBC production leading to megaloblastic anemia, physical and mental retardation.

Diagnosis is made by severe megaloblastic anemia with normal B12 and folate levels and no evidence of transcobalamin II deficiency. Elevated orotic acid and RBC enzyme assay (transferase) confirms the diagnosis. Treatment is to administer uridine, which will synthesize UTP, CTP and TMP reducing the symptoms and also produces feedback inhibition of orotic acid production.
Case Study 43.3

One evening, a smart 40-year old male business executive entertained a party in which much food and alcohol had been consumed. In the next early morning, he woke up with excruciating pain in ankle. He was admitted in the hospital. On examination, he had fever. His ankle joint was swollen, and red, felt hot to touch, and was very tender and stiff. No other joints were involved. Lymph glands were normal, not tender. Routine peripheral smear revealed mild granulocytosis. The laboratory data were—

Blood glucose: 130 mg/dl
Blood urea: 38 mg/dl
Serum creatinine: 1 mg/dl
Serum uric acid: 10 mg/dl.

Urine pH was found to be 6.2.

A. What is the most probable diagnosis?
B. Which part of the case history and laboratory data helped you to reach this diagnosis?
C. What is the origin and fate of uric acid?
D. What are the causes for primary and secondary hyperuricemia?
E. What is the cause for gout? Explain the pathogenesis.
F. Which type of food will precipitate an attack of gout?
G. What is the short-term and long-term treatment for gout?
H. What is the biochemical basis for such a treatment policy?
I. An inborn error of purine metabolism will affect male children only. Name the condition, and name the enzyme defect.
J. Uric acid is the end product of which metabolism?
K. Urea is the end product of which metabolism?
L. Creatinine is the end product of which metabolism?
M. Explain the mild increase in blood sugar.
N. There was mild granulocytosis, but no lymphadenopathy of local glands in this patient. Explain.

Guidance to Answers: Gout classically afflicts the big toe, but other joints may also sometimes be affected.

Case Study 43.4

A 40-year old male presented with severe pain, redness and swelling of the base of the first metatarsophalangeal joint in the night after a bout of alcohol consumption. The patient was in usual state of health until early in the morning when he woke up with severe pain in his right big toe. The patient denies any trauma to the toe and no previous history of such pain in other joints. On examination, he had mild fever 38.2°C. The right big toe was swollen, warm, red, and exquisitely tender. Serum uric acid was 9.7 mg/dl. What is the likely diagnosis? What is the pathogenesis of the condition? How would you make a definite diagnosis?

Diagnosis: Gouty arthritis.

Pathophysiology: Elevated levels of uric acid are detectable in the blood and urine, resulting in precipitation of urate crystals in the joints. Synovial fluid will reveal needle-shaped crystals of monosodium urate that are negatively birefringent under polarizing microscopy will confirm the diagnosis. Formation of urate crystals in the big toe, is thought to be associated with the decreased temperature of the extremities that aids in urate crystal formation when levels exceed solubility.
Case Study 43.5

A 4-year old boy presented with hypotonia, developmental delay, irritability and self-mutilating behavior. On examination, there was testicular atrophy and hematuria. The serum uric acid level was 10.0 mg/dl. What is the likely diagnosis? What is the biochemical basis of the condition?

Diagnosis: Lesch Nyhan syndrome.

See text for details about biochemical basis.

SUPPLEMENTARY INFORMATION TO CHAPTER 49

Case Study 49.1

A 4-year old boy was brought to the hospital. His mother was concerned that he was walking in an awkward manner, fell over frequently, and had difficulty in climbing stairs. Family history revealed a maternal uncle who died due to muscular dystrophy at the age of 19. Clinical examination showed muscle weakness in shoulder and pelvic girdles and enlargement of calf muscles. A tentative diagnosis of Duchenne muscular dystrophy was made. What is the defect in this condition?

Answer: Duchenne muscular dystrophy (DMD) is due to mutations in DMD gene. The gene encodes a protein known as dystrophin. All muscular dystrophies are progressive in nature and many are genetically inherited. Dystrophin acts as a link between actin in the cytoskeleton and the extracellular matrix and helps anchor the muscle fiber to the extracellular matrix. Dystrophin and its isoforms are found in skeletal muscles, smooth muscles and brain.

Patients usually present in the 3rd – 5th year of life with motor delay or abnormal gait, difficulty in running, getting up from ground, frequent falls, etc. Proximal muscles are affected first (quadriceps, shoulder girdle) and progresses to upper extremities and there may be pseudohypertrophy of calf muscles (fibro-fatty replacement of degenerating muscle tissue). Cardiac defects include cardiomyopathy and rhythm changes. Respiratory involvement by 16–18 years include scoliosis (which impairs pulmonary functions), respiratory failure (due to progressive failure of intercostals muscles), hypercapnia and severe respiratory infections.

Laboratory analysis reveals elevated serum CK (10 – 100 times above normal), AST, ALT and LDH. Muscle biopsy (shows deficient dystrophin), electromyography and PCR can be used for confirmatory diagnosis.

SUPPLEMENTARY INFORMATION TO CHAPTER 50

Case Study 50.1

A 25-year old woman working in a rural school suddenly began to pass profuse watery stools almost continuously. Immediately she started to vomit and her general condition deteriorated. She was rushed to the hospital and on admission, she was cyanotic, skin turgor was poor, BP was 70/50 mm Hg and pulse was rapid and weak. The stool sample was taken for culture and treatment was started immediately. What is the diagnosis? What is the basis of clinical findings?

Answer: The patient is suffering from cholera, an acute diarrheal disease that can result in rapidly progressive dehydration and death within a few hours. It is caused by the bacteria, *Vibrio cholerae*. People are infected when they consume contaminated food or water. Patients present with watery diarrhea and vomiting, with no fever. Diagnosis is confirmed by identifying bacteria is stool sample. Treatment includes replacing lost fluids and giving antibiotics.

Certain toxins produced by the bacteria (choleragen) leads to activation of the enzyme, adenyl cyclase, converting cAMP to ATP. The activated protein leads to continuous activation of protein kinase A which opens a chloride channel (CFTR channel) and inhibits Na+ - H+ exchanger. The net effect is inhibition of absorptive sodium transport system in intestinal villus cells and activation of secretory chloride channel transport in crypt cells. This leads to accumulation of sodium chloride in lumen; water moves passively to maintain osmolality and watery diarrhea results. Unless replaced, this leads to shock (due to fluid depletion) and acidosis (due to loss of bicarbonate).

The cholera toxin can also enhance intestinal secretion via prostaglandins and neural histamine receptors.
Case Study 51.1
A 40-year old male complains that his face has coarse features. On examination, his height was above normal. He has large nose, large tongue, and frontal bossing of his forehead. His hands are enlarged with soft tissue swelling, and his heel pad is thickened. What is the most likely diagnosis? What is the biochemical mechanism of this disorder?

Answer: Diagnosis: Acromegaly.

Biochemical mechanism: Acromegaly is a disorder with excessive growth hormone (GH), usually due to a nonmalignant anterior pituitary tumor. When increased, GH occurs prior to bone growth plate closure, gigantism may result; after the bone growth plates close, the patients usually develop coarse features and large hands and feet. In normal persons, an oral glucose load (75 g) will cause decreased GH secretion within 1–2 hours. The diagnosis is confirmed by demonstrating the failure of GH suppression by glucose. Increased GH will cause diabetes mellitus and hypertension. In 30% cases, cardiac arrhythmias, cardiomyopathy and left ventricular hypertrophy, etc. may be seen. The primary therapy is surgical removal of the tumor. Further, somatostatin analogues or dopamine agonists are used.

Case Study 52.1
A 45-year old man presented with vague symptoms of weakness, fatigue, and extreme lethargy from the past few months. He reports that he developed tanning of skin all over the body and is losing weight in spite of normal appetite. Nausea and abdominal pain were present. He had low BP and fainted on two occasions. On examination, BP was 100/60 mm Hg and pulse was 66/minute. Skin was bronze colored. No other abnormalities were seen. The doctor suspected an endocrine disorder. Laboratory assessment showed low blood and urine cortisol level. What is the probable diagnosis? What further tests are needed to confirm the diagnosis? What is the pathogenic mechanism involved?

Answer: The probable diagnosis is Addison’s disease, also known as chronic adrenal insufficiency or hypocortisolism. Adrenal steroid hormone production (glucocorticoids and mineralocorticoids) is reduced. It may be primary adrenal insufficiency (commonly due to an autoimmune process or due to tuberculosis, adrenoleukodystrophy, bilateral hemorrhage, tumor metastasis, HIV, CMV, amyloidosis, sarcoidosis, genetic defect, etc.) or secondary adrenal insufficiency (due to lack of ACTH, cortisol is low and aldosterone will be normal).

Clinical features are chronic worsening fatigue, muscle weakness, loss of appetite, weight loss, nausea, vomiting, diarrhea, postural hypotension, skin changes, irritability, depression, craving for salty food, hypoglycemia (more severe in children) and irregular menstruation in women. Acute adrenal insufficiency or Addisonian crisis may be seen and symptoms are sudden penetrating pain in lower back, abdomen or legs, severe vomiting and diarrhea, dehydration, low BP and loss of consciousness. These may be precipitated by an illness and may be fatal if untreated.

Laboratory assessment includes urine and blood cortisol, ACTH stimulation test, CRH stimulation test and estimation of serum electrolytes (Na, Cl, HCO₃ are reduced and K may be high). During Addisonian crisis, ACTH and cortisol will be low, glucose and Na will also be low and K may be high. Diagnosis may be achieved by ACTH stimulation test once the crisis is treated.

Case Study 52.2
A 42-year old woman presented with symptoms of fatigue, weakness, lethargy, decreased concentration and decreased memory over 2 years. She had gained about 18 kg weight over the last 3 months with central distribution of fat and neck obesity. Her physical examination showed Cushingoid appearance with body weight of 100 kg, palmar erythema and
hirsutism. Blood cortisol levels were also very high. Dexamethasone suppression test was consistent with Cushing’s disease. What is the defect in Cushing’s disease? How is it different from Cushing syndrome?

Answer: Cushing syndrome is due to long-term exposure to excessive glucocorticoids and may be due to excessive administration of exogenous glucocorticoids. Cushing’s disease is due to excessive secretion of ACTH and may be due to pituitary adenoma. Cushing syndrome might be due to Cushing’s disease, ectopic ACTH secreting tumors and primary adrenal neoplasms.

Symptoms are: (1) upper body obesity, rounded face, increased fat around neck, thinning arms and legs, typical “moon” face, “buffalo hump” (adipose tissue deposition in interscapular area), “truncal” obesity, (2) thin and fragile skin, purplish skin stretch marks, (3) fatigue, muscle weakness, (4) high BP, (5) hyperglycemia, (6) weak bones, (7) hirsutism in women, (8) increased thirst and urination, and (9) opportunistic bacterial infections.

Diagnostic tests are: (1) 24-hr urine free cortisol level – High, (2) Midnight plasma cortisol and late-night salivary cortisol – Midnight suppression does not occur, as is normally seen, (3) Low dose dexamethasone suppression test, (4) Plasma ACTH – Low level, (5) CRH test, (6) CRH stimulation test, and (7) High dose dexamethasone suppression test.

Case Study 52.3

A female baby with ambiguous genitalia was brought to the pediatrician. The child was referred to an endocrinologist. He suggested some laboratory tests and asked the parents to bring the two elder siblings (boys) to him during the next visit.

A. What is the most likely cause?
B. What are the laboratory tests to be done in this case?
C. Explain the metabolic defect.
D. What is the possible treatment?
E. Explain the rationale for examining the elder children.

Guidance to Answers: Adrenogenital syndrome.

Case Study 52.4

A 42-year old woman presented with symptoms of fatigue, weakness, lethargy, decreased concentration and decreased memory over 2 years. She had gained about 18 kg weight over the last 3 months with central distribution of fat and neck obesity. Her physical examination showed Cushingoid appearance with body weight of 100 kg, high BP, palmar erythema and hirsutism. Blood cortisol levels were also very high. Dexamethasone suppression test was consistent with Cushing’s disease. What is the defect in Cushing’s disease?

Answer: Symptoms are: (1) upper body obesity, rounded face, increased fat around neck, thinning arms and legs, typical “moon” face, “buffalo hump” (adipose tissue deposition in interscapular area), “truncal” obesity, (2) thin and fragile skin, purplish skin stretch marks, (3) fatigue, muscle weakness, (4) high BP, (5) hyperglycemia, (6) weak bones, (7) hirsutism in women, (8) increased thirst and urination, and (9) opportunistic bacterial infections.

Diagnostic tests are: (1) 24-hr urine free cortisol level – High, (2) Midnight plasma cortisol and late-night salivary cortisol – Midnight suppression does not occur, as is normally seen, (3) Low dose dexamethasone suppression test, (4) Plasma ACTH – Low level, (5) CRH test, (6) CRH stimulation test, and (7) High dose dexamethasone suppression test.

SUPPLEMENTARY INFORMATION TO CHAPTER 53

Case Study 53.1

A 34 year old female presented to the clinic with complaints of tiredness, nervousness, anxiety and palpitations. She lost nearly 10 kg weight in the last 3 months and had diarrhea of the same duration. Other complaints were change in hair
Case Studies

A 53-year old female presented with complaints of swelling in the neck region. She had gained 12 kg weight in the last one year, had shortness of breath, and was easily fatigued. There is family history of thyroid disease. Laboratory results were as follows – Total cholesterol – 325 mg/dl, fT4 – 0.5 pmol/L (Normal 5 – 15), TSH – 8.3 µIU/ml (Elevated). TPOAb and TgAb were done and were both elevated. What is the diagnosis? What is the pathology involved?

Answer: The diagnosis is Hashimoto’s thyroiditis, an autoimmune disease caused by gradual destruction of thyroid gland and subsequent hypothyroidism. The cause is a combination of genetic and environmental factors. The cellular and humoral responses involved are evidenced by the presence of the autoantibodies, TPOAb, TgAb and TSHRAb.

The common symptoms are: (1) dermatological changes like dry skin, decreased sweating, thinning of epidermis, hyperkeratosis, myxedema, puffy face, pallor, retarded nail growth, dry hair, alopecia, etc., (2) constipation and weight gain, (3) decreased libido, (4) menstrual irregularities, (5) reduced myocardial contractility and heart rate, (6) cool extremities, (7) impaired memory and other intellectual functions like concentration, cerebellar ataxia, dementia, psychosis, coma, and (8) hoarse voice and clumsy speech. Diagnosis is by low fT4, high TSH, low or normal T3 and presence of autoantibodies. Thyroid replacement therapy is beneficial in most patients.

Hypothyroidism is a very common clinical condition. It is more common in women than in men and there is increased incidence with age. Other causes for hypothyroidism are: (1) Primary, where the defect is in thyroid gland itself, (2) Secondary, due to pituitary diseases, and (3) Transient, due to silent thyroiditis including postpartum thyroiditis, subacute thyroiditis, withdrawal of thyroxine treatment and after radio-iodine treatment for Graves’ disease. Lifelong thyroid replacement therapy is needed in most cases.

Case Study 53.3

A 50-year old lady school teacher complains of hoarseness of voice and feeling of tiredness. She also admitted that she has started putting on weight and feeling comfortable in warm weather. After the initial examination by the local doctor she was referred to the endocrinologist.

A. What is the most probable cause?
B. What are the laboratory investigations to be done in this patient?
C. How will you interpret the abnormal results to arrive at a diagnosis?
D. What are the techniques available for hormone assay?
E. Is there any role for dynamic tests in this patient?
F. Enumerate the physiological parameters that are likely to be altered in this patient.

*Guidance to Answers*: Hypothyroidism.

**Case Study 53.4**

The laboratory results of a 50-year old school teacher are given below—
Random blood glucose: 95 mg/dl
Blood cholesterol: 285 mg/dl
Plasma T4: 4 microgram/dl (normal range: 5 to 12); Plasma T3: 70 ng/dl (normal, 120 to 190 ng/ml), Plasma TSH: 6 mIU/ml (normal, 0.5 to 4.5 mIU/ml).

A. How will you interpret the results to arrive at a diagnosis?
B. Why TSH has increased while T4 is lowered?
C. What are the other physiological changes observed in this patient?
D. Which of the laboratory results is crucial in making the diagnosis?

*Guidance to Answers*: Hypothyroidism.

**Case Study 53.5**

A 49-year old female had the following base-line laboratory results:
TSH: 8 mU/L (normal 0.3–4.0)
T4: 34 nanomol/L (normal 65–150).

Three weeks after treatment with thyroxine, her repeat laboratory tests values were:
TSH: 7.8 mU/L
T4: 92 nmol/L.

A. What is the original diagnosis?
B. Is the treatment satisfactory?
C. Why her TSH value still elevated?

*Guidance to Answers*: Hypothyroidism. Treatment is satisfactory as shown by the T4 values. It will take 6 weeks of thyroxin treatment for TSH values to come down to normal levels.

**Case Study 53.6**

A 50-year old female presents to the clinic complaining of feeling tired all the time. She has cold intolerance and constipation. On examination, she is afebrile and appears in good health. She has an enlarged, nontender swelling on her neck. Her reflexes are diminished, and her skin is dry. What is the most likely diagnosis? What laboratory test would you need to confirm the diagnosis? What is the treatment of choice?

*Answer*: Diagnosis: Hypothyroidism

*Laboratory tests*: TSH and free T4

*Treatment*: Thyroid hormone replacement. Hypothyroidism is quite common in older adults. It may induce coma or pericardial effusion. The most common etiology is primary hypothyroidism, or failure of the thyroid gland to produce sufficient thyroid hormone. The diagnosis is established by an elevated TSH and decreased T4.
Case Study 53.7

A 17-year-old lean female was referred to the endocrinology clinic. She had intermittent palpitations and tremor. On examination, the patient had tachycardia (100 beats/min). She had a small diffuse goiter without retrosternal extension or bruit. Auscultation of the precordium revealed murmurs in systole and diastole consistent with mixed aortic valve disease. An echocardiogram had demonstrated a bicuspid aortic valve with good flow and minor regurgitation.

Biochemically, the patient had TSH <0.03 mIU/L (reference interval, 0.3–5.6 mIU/L) and an increased concentration of free thyroid hormone (FT4 = 43 pmol/L) (reference interval, 7.5–21.1 pmol/L). Her total calcium (9.08 mg/dL and phosphate 3.9 mg/dL) were both within their reference intervals. The serum albumin concentration was 4.1 g/dl (reference interval, 3.5–5.0 g/dL), and the magnesium concentration was 0.71 mmol/L (reference interval, 0.74–1.00 mmol/L). Her thyroid peroxidase antibodies was 582 IU/L (reference interval, 0–60 IU/L) and TSH receptor antibodies was 6.9 U/L (reference interval, 0–1.5 U/L). Thyroid imaging revealed a diffusely enlarged thyroid gland, with no visible parathyroid tissue apparent on ultrasound and MRI evaluations. What is the diagnosis? What effect does thyrotoxicosis have on serum calcium? What other endocrine disorders affect serum calcium?

Diagnosis: Graves’ disease; hyperthyroidism. Graves’ disease is an autoimmune process in which circulating immunoglobulins bind to the TSH receptor on the thyroid follicular cells and stimulate thyroid hormone production. The diagnosis is confirmed by increased thyroid stimulating IgG antibodies.

SUPPLEMENTARY INFORMATION TO CHAPTER 55

Case Study 55.1

A 45-year old man presented with severe back pain and weakness. He had lost 7 kg in the last 3 months. Loss of appetite is present. No history of fever or any other medical problem. However, he reports extreme fatigue, body pain and complains that he is unable to do any work. X-ray of skull revealed punched out lesions. Bone marrow biopsy was done and it showed plasma cells in excess. Serum electrophoresis was ordered on the basis of clinical features. It showed an abnormal band between β globulin and γ globulin. Urine was positive for Bence Jones Proteins (BJP). What is the probable diagnosis? What is the significance of laboratory findings in this patient?

Answer: The patient is suffering from multiple myeloma. Multiple myeloma represents a malignant proliferation of plasma cells, from a single clone of cells. Multiple myeloma can produce varied symptoms including bone pain or fracture, soft tissue masses, lytic lesions in the skeleton, renal failure, spinal cord compression, susceptibility to infections, anemia, leukopenia, thrombocytopenia, hypercalcemia, occasionally clotting abnormalities, neurological problems, manifestations of hyperviscosity, amyloidosis, etc.

The classic triad of multiple myeloma is marrow plasmacytosis (>10%), lytic bone lesions and serum and/or urine M component. Diagnosis is confirmed by (1) Electrophoresis – Monoclonal antibodies seen as M band (myeloma band) are seen as a sharp spike. (2) Bone marrow shows a large number of malignant plasma cells. (3) X-ray skull shows punched out lesions. (4) Hypercalcemia and hypercalciuria are seen. (5) Proteinuria is seen as a rule and in 20–50% of patients it is seen as Bence Jones protein which is excreted in urine. (6) β microglobulin is increased in patients with renal failure. (7) Serum free light chains – These are superior to urine tests and are detected in multiple myeloma and related plasma cell dyscrasias.

In most patients with multiple myeloma, myeloma cells also secrete excessive amounts of light chains of Ig. The excess light chains are either κ or λ. Sometimes they are excreted as a dimer. In normal conditions, they are not excreted in urine. Free light chains can also be detected in serum. These are alternative to urine Bence Jones proteins. They are also present as κ or λ; their ratio is also sometimes measured.
**SUPPLEMENTARY INFORMATION TO CHAPTER 56**

**Case Study 56.1**

A 32-year old man presented with complaints of chills and breathing difficulty. He had lost 12 kg weight since last few months. On examination, he had multiple enlarged lymph nodes. Several nodules were present on the skin of chest and arms. Body temperature was 40°C, respiratory rate was 40 breaths/min and respiration was shallow. Chest radiograph showed diffuse pneumonia. Sputum was positive for *Pneumocystis carinii* infection and skin biopsy was positive for Kaposi’s sarcoma. What is the possible diagnosis? What are the laboratory tests to be done in this patient? What is the biochemical basis?

**Answer:** Patient is suffering from acquired immunodeficiency syndrome (AIDS); there is collapse of immune system leading to a series of viral, fungal and protozoal infection which are otherwise not seen. Kaposi’s sarcoma and *Pneumocystis carinii* infection are typical features of HIV infection. HIV is transmitted by (1) Sexual contact, (2) Parenteral – as by blood transfusion or blood products, sharing of unsterilized needles, organ transplantation, contaminated fluids, etc. and (3) mother to child during pregnancy or birth, breast milk.

Infection is transmitted when virus enters blood or tissue and comes in contact with suitable host cells, classically CD4 lymphocytes. Tissues and cells which are susceptible include B lymphocytes, monocytes, macrophages, specialized macrophages like alveolar macrophages in lungs, Langerhans cells in dermis, glial cells, microglial cells and follicular dendritic cells from tonsils.

Steps in viral entry into host cells include: (1) Attachment of virus into host cells – via envelope glycoprotein gp120, (2) Cell to cell fusion – by glycoprotein gp 4 and two major co-receptors CCR5 (seen in macrophage tropic viruses) and CXR4 (seen in T cell tropic viruses), (3) Uncoating of viral envelope and entry of nuclear capsid core into cells, (4) Viral transcription – via reverse transcriptase, (5) Integration into host DNA as provirus, (6) Fate of provirus – lytic infection is initiated from time to time releasing progeny virus, which infects other cells; virus can be isolated from blood, lymphocytes, cell free plasma, serum, cervical secretions, saliva, urine and breast milk, (7) Transcription back into RNA, (8) Virion assembly, and (9) Cell lysis.

Damage caused to CD4+ lymphocytes include: (1) T4 cells increase and T4: T8 ratio reverses, (2) infected cells do not release cytokines, (3) cell mediated immune system is dampened, (4) cell mediated and humoral immunity is affected, (5) AIDS patients are unable to respond to new antigens, (6) there is polyclonal activation of B lymphocytes leading to hypergammaglobulinemia which are non-specific, (7) monocye macrophage system is affected, (8) activity of NK cells and Tc (T cytotoxic) cells are affected, (9) all these features lead to decreased immunity and patient becomes susceptible to life-threatening opportunistic infections and malignancies.

Laboratory tests include: (1) Total leukocyte and lymphocyte count - Decreased, (2) T cell subset assays – Absolute CD4+ count < 200/L, T4:T8 count reversed, (3) Platelet count - Decreased, (4) IgA and IgG – Increased, (5) Diminished cell mediated immunity as evidenced by skin tests, (6) Lymph node biopsy, (7) Demonstration of p24 antigen (p24 capture ELISA assay), (8) Detection of antibodies, (9) Screening tests – include ELISA, rapid tests (Dot blot assay, particle agglutination tests, HIV spot and comb test, fluorimetric microparticle techniques) and simple tests based on ELISA, (10) Supplemental tests – Western blot, indirect immunofluorescence test, radioimmunoprecipitation assay, (11) Demonstration of viral nucleic acid – by PCR and RT-PCR, and (12) Virus isolation.

**SUPPLEMENTARY INFORMATION TO CHAPTER 57**

**Case Study 57.1**

A three-year old girl was admitted to hospital, suffering from loss of appetite, weakness, pain and fever. Her spleen, liver and lymph nodes were enlarged. Blood parameters showed RBCs: 3 million/cu.mm; Total WBCs: more than 1 lakh/cu.mm. Blood smear showed large number of lymphoblasts. The diagnosis was acute lymphoblastic leukemia. The
remission was induced by prednisone, vincristine and L-asparaginase. Allopurinol was also included in this regime. On remission, methotrexate was injected into CSF, as a prophylaxis for CNS involvement. Maintenance therapy involved the administration of 6-mercaptopurine and methotrexate, with occasional pulses of vincristine and prednisone for a further period of 1 year.

A. What is leukemia?
B. What is the difference between leukemia and multiple myeloma?
C. What is the basic difference between a normal cell and a cancer cell?
D. Explain cell cycle, cell cycle check points and oncogenes.
E. What is the mechanism of action of methotrexate?
F. What is the role of folic acid?
G. Sulfonamides interfere with folic acid metabolism in bacteria, but not in human beings, why?
H. What are the mechanisms of action of prednisone, vincristine, asparaginase and mercaptopurine?
I. What is the basis of including allopurinol in the treatment regime?

Case Study 57.2

A 30-year old woman presented to the clinic with concerns over a recently detected right breast lump. Mammograph evidences were suggestive of breast cancer. On further questioning, her sister was also diagnosed with breast cancer at the age of 35. Mother passed away at the age of 40 years due to ovarian cancer, and a maternal aunt had breast and ovarian cancer. What is the gene likely to be involved? What is the likely mechanism of the cancer gene?

Answer: There is familial breast/ovarian cancer trait in this family. Cancer can occur in a person due to somatic mutation, which may not be inherited. In this family, it is likely that there is a germline mutation. There are two classes of genes associated with cancer, oncogenes (which cause cancer) and tumor suppressor genes (which protect against cancer).

Familial breast/ovarian cancer occurs commonly due to mutations in BRCA1/BRCA2 genes which are tumor suppressor genes. Point mutations can lead to truncated protein products or nonfunctional proteins and deletions can sometimes lead to loss of entire gene or chromosome arm leading to loss of heterozygosity (LOH), a hallmark of cancer. Epigenetic gene silencing by DNA hypermethylation can also be carcinogenetic.

In the case of breast/ovarian cancer families, there are a number of hotspot mutations which might be causative, including BRCA1 185delAG mutation, BRCA1 5382insC mutation, etc. These and other mutations can be identified by a number of mutation detection techniques (SSCP, CSGE, dHPLC, PTT, DNA sequencing, etc.). Presence of germline mutation in BRCA1/BRCA2 genes is a strong indication of development of cancer in future generations as well.