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PEPTIC ULCER

Peptic ulcers are the areas of degeneration and necrosis of gastrointestinal mucosa exposed to acid-peptic secretions. Though they can occur at any level of the alimentary tract that is exposed to hydrochloric acid and pepsin, they occur most commonly (98-99%) in either the duodenum or the stomach in the ratio of 4:1. Each of the two main types may be acute or chronic.

Acute Peptic (Stress) Ulcers

Acute peptic ulcers or stress ulcers are multiple, small mucosal erosions, seen most commonly in the stomach but occasionally involving the duodenum.

ETIOLOGY. These ulcers occur following severe stress.

The causes are as follows:

i) Psychological stress

ii) Physiological stress as in the following:

Shock

Severe trauma

Septicaemia

Extensive burns (Curling's ulcers in the posterior aspect of the first part of the duodenum).

Intracranial lesions (Cushing's ulcers developing from hyperacidity following excessive vagal stimulation).

Drug intake (e.g. aspirin, steroids, butazolidine, indomethacin).

Local irritants (e.g. alcohol, smoking, coffee etc).

PATHOGENESIS.

It is not clear how the mucosal erosions occur in stress ulcers because actual hypersecretion of gastric acid is demonstrable in only Cushing's ulcers occurring from intracranial conditions such as due to brain trauma, intracranial surgery and brain tumours. In all other etiologic factors, gastric acid secretion is normal or below normal. In these conditions, the possible hypotheses for genesis of stress ulcers are as under:

1. Ischaemic hypoxic injury to the mucosal cells.

2. Depletion of the gastric mucus 'barrier' rendering the mucosa susceptible to attack by acid-peptic secretions.

Chronic Peptic Ulcers (Gastric and Duodenal Ulcers) If not specified, chronic peptic ulcers would mean gastric and duodenal ulcers, the two major forms of 'peptic ulcer disease' of the upper GI tract in which the acid-pepsin secretions are implicated in their pathogenesis. Peptic ulcers are common in the present-

day life of the industrialised and civilised world. Gastric and duodenal ulcers represent two distinct diseases as far as their etiology, pathogenesis and clinical features are concerned. However, morphological findings in both are similar and quite diagnostic.

ETIOLOGY.

The immediate cause of peptic ulcer disease is disturbance in normal protective mucosal 'barrier' by acidpepsin, resulting in digestion of the mucosa. However, in contrast to duodenal ulcers, the patients of gastric ulcer have low-to-normal gastric acid secretions, though true achlorhydria in response to stimulants never occurs in benign gastric ulcer. Besides, 10-20% patients of gastric ulcer may have coexistent duodenal ulcer as well. Thus, the etiology of peptic ulcers possibly may not be explained on the basis of a single factor but is multifactorial. These factors are discussed below but the first two—H. pylori gastritis and NSAIDs-induced injury are considered most important.

1. Helicobacter pylori gastritis. About 15-20% cases infected with H. pylori in the antrum develop duodenal ulcer in their life time while gastric colonisation by H. pylori never develops ulceration and remain asymptomatic. H. pylori can be identified in mucosal samples by histologic examination, culture and serology.

2. NSAIDs-induced mucosal injury. Non-steroidal antiinflammatory drugs are most commonly used medications in the developed countries and are responsible for direct toxicity, endothelial damage and epithelial injury to both gastric as well as duodenal mucosa.

3. Acid-pepsin secretions. There is conclusive evidence that some level of acid-pepsin secretion is essential for the development of duodenal as well as gastric ulcer. Peptic ulcers never occur in association with pernicious anaemia in which there are no acid and pepsin-secreting parietal and chief cells respectively.

4. Gastritis. Some degree of gastritis is always present in the region of gastric ulcer, though it is not clear whether it is the cause or the effect of ulcer. Besides, the population distribution pattern of gastric ulcer is similar to that of chronic gastritis.

5. Other local irritants. Pyloric antrum and lesser curvature of the stomach are the sites most exposed for longer periods to local irritants and thus are the common sites for occurrence of gastric ulcers. Some of the local irritating substances implicated in the etiology of peptic ulcers are heavily spiced foods, alcohol, cigarette smoking, unbuffered aspirin.

6. Dietary factors. Nutritional deficiencies have been regarded as etiologic factors in peptic ulcers e.g. occurrence of gastric ulcer in poor socioeconomic strata, higher incidence of duodenal ulcer in parts of South India. However, malnutrition does not appear to have any causative role in peptic ulceration in European countries and the U.S.

7. Psychological factors. Psychological stress, anxiety, fatigue and ulcer-type personality may exacerbate as well as predispose to peptic ulcer disease.

8. Genetic factors. People with blood group O appear to be more prone to develop peptic ulcers than those with other blood groups. Genetic influences appear to have greater role in duodenal ulcers as evidenced by their occurrence in families, monozygotic twins and association with HLA-B5 antigen.

9. Hormonal factors. Secretion of certain hormones by tumours is associated with peptic ulceration e.g. elaboration of gastrin by islet-cell tumour in Zollinger-Ellison syndrome, endocrine secretions in hyperplasia and adenomas of parathyroid glands, adrenal cortex and anterior pituitary.

10. Miscellaneous. Duodenal ulcers have been observed to occur in association with various other conditions such as alcoholic cirrhosis, chronic renal failure, hyperparathyroidism, chronic obstructive pulmonary disease, and chronic pancreatitis.

PATHOGENESIS.

Although the role of various etiologic factors just described is well known in ulcerogenesis, two most important factors in peptic ulcer are as under:

Exposure of mucosa to gastric acid and pepsin secretion.

Strong etiologic association with H. pylori infection.

There are distinct differences in the pathogenetic mechanisms involved in duodenal and gastric ulcers as under:

Duodenal ulcer.

There is conclusive evidence to support the role of high acid-pepsin secretions in the causation of duodenal ulcers. Besides this, a few other noteworthy features in the pathogenesis of duodenal ulcers are as follows:

1. There is generally hypersecretion of gastric acid into the fasting stomach at night which takes place under the influence of vagal stimulation. There is high basal as well as maximal acid output (BAO and MAO) in response to various stimuli.

2. Patients of duodenal ulcer have rapid emptying of the stomach so that the food which normally buffers and neutralises the gastric acid, passes down into the small intestine, leaving the duodenal mucosa exposed to the aggressive action of gastric acid.

3. Helicobacter gastritis caused by H. pylori is seen in 95-100% cases of duodenal ulcers.

Gastric ulcer.

The pathogenesis of gastric ulcer is mainly explained on the basis of impaired gastric mucosal defenses against acid-pepsin secretions. Some other features in the pathogenesis of gastric ulcer are as follows:

1. Hyperacidity may occur in gastric ulcer due to increased serum gastrin levels in response to ingested food in an atonic stomach.

2 However, many patients of gastric ulcer have low-tonormal gastric acid levels. Ulcerogenesis in such patients is explained on the basis of damaging influence of other factors such as gastritis, bile reflux, cigarette smoke etc.

3. The normally protective gastric mucus ‘barrier’ against acid-pepsin is deranged in gastric ulcer. There is depletion in the quantity as well as quality of gastric mucus. One of the mechanisms for its depletion is colonisation of the gastric mucosa by H. pylori seen in 75-80% patients of gastric ulcer.

COMPLICATIONS.

Acute and subacute peptic ulcers usually heal without leaving any visible scar. However, healing of chronic, larger and deeper ulcers may result in complications. These are as follows:

1. Obstruction. Development of fibrous scar at or near the pylorus results in pyloric stenosis. In the case of healed duodenal ulcer, it causes duodenal stenosis. Healed ulcers along the lesser curvatures may produce 'hourglass' deformity due to fibrosis and contraction.

2. Haemorrhage. Minor bleeding by erosion of small blood vessels in the base of an ulcer occurs in all the ulcers and can be detected by testing the stool for occult blood. Chronic blood loss may result in iron deficiency anaemia. Severe bleeding may cause 'coffee ground' vomitus or melaena. A penetrating chronic ulcer may erode a major artery (e.g. left gastric, gastroduodenal or splenic artery) and cause a massive and severe hematemesis and sometimes death.

3. Perforation. A perforated peptic ulcer is an acute abdominal emergency. Perforation occurs more commonly in chronic duodenal ulcers than chronic gastric ulcers. Following sequelae may result:

i) On perforation the contents escape into the lesser sac or into the peritoneal cavity, causing acute peritonitis.

ii) Air escapes from the stomach and lies between the liver and the diaphragm giving the characteristic radiological appearance of air under the diaphragm.

iii) Subphrenic abscess between the liver and the diaphragm may develop due to infection.

iv) Perforation may extend to involve the adjacent organs e.g. the liver and pancreas.

4. Malignant transformation. The dictum 'cancers ulcerate but ulcers rarely cancerate' holds true for most peptic ulcers. A chronic duodenal ulcer never turns malignant, while less than 1% of chronic gastric ulcers may transform into carcinoma.

CLINICAL FEATURES.

Peptic ulcers are remitting and relapsing lesions. Their chronic and recurrent behaviour is summed up the saying: 'once a peptic ulcer patient, always a peptic ulcer patient.' The two major forms of chronic peptic ulcers show variations in clinical features which are as follows:

1. Age. The peak incidence of duodenal ulcer is in 5th decade while that for gastric ulcer is a decade later.

2. People at risk. Duodenal ulcer occurs more commonly in people faced with more stress and strain of life (e.g. executives, leaders), while gastric ulcer is seen more often in labouring groups.

3. Periodicity. The attacks in gastric ulcers last from 2-6 weeks, with interval of freedom from 1-6 months. The attacks of duodenal ulcer, are classically worsened by 'work, worry and weather.'

4. Pain. In gastric ulcer, epigastric pain occurs immediately or within 2 hours after food and never occurs at night. In duodenal ulcer, pain is severe, occurs late at night ('hunger pain') and is usually relieved by food.

5. Vomiting. Vomiting which relieves the pain is a conspicuous feature in patients of gastric ulcer. Duodenal ulcer patients rarely have vomiting but instead get heart-burn (retrosternal pain) and 'water brash' (burning fluid into the mouth).

6. Haematemesis and melaena. Haematemesis and melaena occur in gastric ulcers in the ratio of 60:40, while in duodenal ulcers in the ratio of 40:60. Both may occur together more commonly in duodenal ulcer than in gastric ulcer patients.

7. Appetite. The gastric ulcer patients, though have good appetite but are afraid to eat, while duodenal ulcer patients have very good appetite.

8. Diet. Patients of gastric ulcer commonly get used to a bland diet consisting of milk, eggs etc and avoid taking fried foods, curries and heavily spiced foods. In contrast, duodenal ulcer patients usually take all kinds of diets.

9. Weight. Loss of weight is a common finding in gastric ulcer patients while patients of duodenal ulcer tend to gain weight due to frequent ingestion of milk to avoid pain.

10. Deep tenderness. Deep tenderness is demonstrable in both types of peptic ulcers. In the case of gastric ulcer it is in the midline of the epigastrium, while in the duodenal ulcer it is in the right hypochondrium.

Inflammatory bowel diseases

The term 'inflammatory bowel disease (IBD)' is commonly used to include 2 idiopathic bowel diseases having many similarities but the conditions usually have distinctive morphological appearance. These 2 conditions are Crohn's disease (regional enteritis) and ulcerative colitis:

1. Crohn's disease or Regional enteritis is an idiopathic chronic ulcerative IBD, characterised by transmural, noncaseating granulomatous inflammation, affecting most commonly the segment of terminal ileum and/or colon, though any part of the gastrointestinal tract may be involved.

2. Ulcerative colitis is an idiopathic form of acute and chronic ulcero-inflammatory colitis affecting chiefly the mucosa and submucosa of the rectum and descending colon, though sometimes it may involve the entire length of the large bowel.

ETIOPATHOGENESIS.

1. Genetic factors.

2. Immunologic factors.

3. Exogenous factors-microbes, psychological, smoking, oral contraceptives.

CROHN'S DISEASE.

Crohn's disease may involve any portion of the gastrointestinal tract but affects most commonly 15-25 cm of the terminal ileum which may extend into the caecum and sometimes into the ascending colon.

ULCERATIVE COLITIS.

Classically, ulcerative colitis begins in the rectum, and in continuity extends upwards into the sigmoid colon, descending colon, transverse colon, and sometimes may involve the entire colon. The colonic contents may rarely backflow into the terminal ileum in continuity, causing 'back-wash ileitis' in about 10% of cases.

COMPLICATIONS.

Crohn's disease:

1. Malabsorption due to impaired absorption of fat, vitamin B12, proteins and electrolytes from the diseased small bowel.

2. Fistula formation may occur in long-standing cases. These may be internal fistulae between the loops of the intestine, or external fistulae such as enterocutaneous, rectal and anal fistulae.

3. Stricture formation may occur in chronic cases due to extensive fibrosis in the affected bowel wall.

4. Development of malignancy in the small intestine as a late complication of Crohn's disease is rarer than that in ulcerative colitis, but lymphoma may develop more often in Crohn's disease than adenocarcinoma (seen in some long-standing cases of ulcerative colitis).

Ulcerative colitis:

1. Toxic megacolon (Fulminant colitis) is the acute fulminating colitis in which the affected colon is thin-walled and dilated and is prone to perforation and faecal peritonitis. There is deep penetration of the inflammatory cell infiltrate into muscle layer which is disrupted.

2. Perianal fistula formation may occur rarely.

3. Carcinoma may develop in long-standing cases of ulcerative colitis of more than 10 years' duration.

4. Stricture formation almost never occurs in ulcerative colitis

JAUNDICE

Jaundice or icterus refers to the yellow pigmentation of the skin or sclerae by bilirubin (page 42). Bilirubin pigment has high affinity for elastic tissue and hence jaundice is particularly noticeable in tissues rich in elastin content. Jaundice is the result of elevated levels of bilirubin in the blood termed hyperbilirubinaemia. Normal serum bilirubin concentration ranges from 0.3-1.3 mg/dl, about 80% of which is unconjugated. Jaundice becomes clinically evident when the total serum bilirubin exceeds 2 mg/dl.

A rise of serum bilirubin between the normal and 2 mg/dl is generally not accompanied by visible jaundice and is called latent jaundice. Before considering the features and types of jaundice, it is essential to review the normal bilirubin metabolism.

ETIOLOGY

1. Increased bilirubin production

2. Decreased hepatic uptake

3. Decreased hepatic conjugation

4. Decreased excretion of bilirubin into bile

Pathophysiologic Classification of Jaundice.

I. PREDOMINANTLY UNCONJUGATED HYPERBILIRUBINAEMIA

1. Increased bilirubin production (Haemolytic, acholuric or prehepatic jaundice)

• Intra- and extravascular haemolysis

• Ineffective erythropoiesis

2. Decreased hepatic uptake

• Drugs

• Prolonged starvation

• Sepsis

3. Decreased bilirubin conjugation

• Hereditary disorders (e.g. Gilbert's syndrome, Crigler-Najjar syndrome)

• Acquired defects (e.g. drugs, hepatitis, cirrhosis)

• Neonatal jaundice

II. PREDOMINANTLY CONJUGATED HYPERBILIRUBINAEMIA (CHOLESTASIS)

1. Intrahepatic cholestasis (Impaired hepatic excretion)

• Hereditary disorders or 'pure cholestasis' (e.g. Dubin-Johnson syndrome, Rotor's syndrome, fibrocystic disease of pancreas, benign familial recurrent cholestasis, intrahepatic atresia, cholestatic jaundice of pregnancy)

• Acquired disorders or 'hepatocellular cholestasis' (e.g. viral hepatitis, drugs, alcohol-induced injury, sepsis, cirrhosis)

2. Extrahepatic cholestasis (Extrahepatic biliary obstruction)

• Mechanical obstruction (e.g. gallstones, inflammatory strictures, carcinoma head of pancreas, tumours of bile ducts, sclerosing cholangitis, congenital atresia of extrahepatic ducts).

VIRAL HEPATITIS

The term viral hepatitis is used to describe infection of the liver caused by hepatotropic viruses. Currently there are 5 main varieties of these viruses and a sixth poorlycharacterised virus, causing distinct types of viral hepatitis:

Hepatitis A virus (HAV), causing a faecally-spread selflimiting disease.

Hepatitis B virus (HBV), causing a parenterally transmitted disease that may become chronic.

Hepatitis C virus (HCV), previously termed non-A, non-B (NANB) hepatitis virus involved chiefly in transfusionrelated hepatitis.

Hepatitis delta virus (HDV) which is sometimes associated as superinfection with hepatitis B infection.

Hepatitis E virus (HEV), causing water-borne infection.

Hepatitis G virus (HGV), is a recently discovered transfusion-transmitted hepatotropic virus but is not known to cause hepatitis.

CLINICOPATHOLOGIC SPECTRUM

Among the various etiologic types of hepatitis, evidence linking HBV and HCV infection with the spectrum of clinicopathologic changes is stronger than with other hepatotropic viruses. The typical pathologic changes of hepatitis by major hepatotropic viruses are virtually similar. HAV and HEV, however, do not have a carrier stage nor cause chronic hepatitis. The various clinical patterns and pathologic consequences of different hepatotropic viruses can be considered under the following headings:

i) Carrier state

ii) Asymptomatic infection

iii) Acute hepatitis

iv) Chronic hepatitis

v) Fulminant hepatitis (Submassive to massive necrosis) All these human hepatitis viruses are RNA viruses except HBV which is a DNA virus.

Acute Hepatitis

The most common consequence of all hepatotropic viruses is acute inflammatory involvement of the entire liver. In general, type A, B, C, D and E run similar clinical course and show identical pathologic findings. Clinically, acute hepatitis is categorised into 4 phases: incubation period, pre-icteric phase, icteric phase and posticteric phase.

1. Incubation period: It varies among different hepatotropic viruses: for hepatitis A it is about 4 weeks (15-45 days); for hepatitis B the average is 10 weeks (30-180 days); for hepatitis D about 6 weeks (30-50 days); for hepatitis C the mean incubation period is about 7 weeks (20-90 days), and for hepatitis E it is 2-8 weeks (15-60 days). The patient remains asymptomatic during incubation period but the infectivity is highest during the last days of incubation period.

2. Pre-icteric phase: This phase is marked by prodromal constitutional symptoms that include anorexia, nausea, vomiting, fatigue, malaise, distaste for smoking, arthralgia and headache. There may be low-grade fever preceding the onset of jaundice, especially in hepatitis A. The earliest laboratory evidence of hepatocellular injury in pre-icteric phase is the elevation of transaminases.

3. Icteric phase: The prodromal period is heralded by the onset of clinical jaundice and the constitutional symptoms diminish. Other features include dark-coloured urine due to bilirubinuria, clay-coloured stools due to cholestasis, pruritus as a result of elevated serum bile acids, loss of weight and abdominal discomfort due to enlarged, tender liver. The diagnosis is based on deranged liver function tests (e.g. elevated levels of serum bilirubin, transaminases and alkaline phosphatase; prolonged prothrombin time and hyperglobulinaemia) and serologic detection of hepatitis antigens and antibodies.

4. Post-icteric phase: The icteric phase lasting for about 1 to 4 weeks is usually followed by clinical and biochemical recovery in 2 to 12 weeks. The recovery phase is more prolonged in hepatitis B and hepatitis C. Up to 1% cases of acute hepatitis may develop severe form of the disease (fulminant hepatitis); and 5-10% of cases progress on to chronic hepatitis.

Chronic Hepatitis

Chronic hepatitis is defined as continuing or relapsing hepatic disease for more than 6 months with symptoms along with biochemical, serologic and histopathologic evidence of inflammation and necrosis.

Majority of cases of chronic hepatitis are the result of infection with hepatotropic viruses—hepatitis B, hepatitis C and combined hepatitis B and hepatitis D infection.

However, some non-viral causes of chronic hepatitis include: Wilson's disease, α-1-antitrypsin deficiency, chronic alcoholism, drug-induced injury and autoimmune diseases.

The last named gives rise to autoimmune or lupoid hepatitis which is characterised by positive serum autoantibodies (e.g. antinuclear, anti-smooth muscle and anti-mitochondrial) and a positive LE cell test but negative for serologic markers of viral hepatitis.

CLINICAL FEATURES.

The clinical features of chronic hepatitis are quite variable ranging from mild disease to fullblown picture of cirrhosis.

i) Mild chronic hepatitis shows only slight but persistent elevation of transaminases ('transaminitis') with fatigue, malaise and loss of appetite.
ii) Other cases may show mild hepatomegaly, hepatic tenderness and mild splenomegaly.
iii) Laboratory findings may reveal prolonged prothrombin time, hyperbilirubinaemia, hyperglobulinaemia and markedly elevated alkaline phosphatase.
iv) Systemic features of circulating immune complexes due to HBV and HCV infection may produce features of immune complex vasculitis, glomerulonephritis and cryoglobulinaemia in a proportion of cases.

Alcoholic liver disease

The term used to describe the spectrum of liver injury associated with acute and chronic alcoholism. There are three sequential stages in alcoholic liver disease: alcoholic steatosis (fatty liver), alcoholic hepatitis and alcoholic cirrhosis.

ETHANOL METABOLISM.

One gram of alcohol gives 7 calories. But alcohol cannot be stored in the body and must undergo obligatory oxidation, chiefly in the liver. Thus, these empty calories make no contribution to nutrition other than to give energy. Ethanol after ingestion and absorption from the small bowel circulates through the liver where about 90% of it is oxidised to acetate by a two-step enzymatic process involving two enzymes: alcohol dehydrogenase (ADH) present in the cytosol, and acetaldehyde dehydrogenase (ALDH) in the mitochondria of hepatocytes. The remaining 10% of ethanol is oxidised elsewhere in the body.

First step: Ethanol is catabolised to acetaldehyde in the liver by the following three pathways, one major and two minor:

i) In the cytosol, by the major rate-limiting pathway of alcohol dehydrogenase (ADH).
ii) In the smooth endoplasmic reticulum, via microsomal P-450 oxidases (also called microsomal ethanol oxidising system, MEOS), where only part of ethanol is metabolised.
iii) In the peroxisomes, minor pathway via catalase such as H2O2.

Acetaldehyde is toxic and may cause membrane damage and cell necrosis. Simultaneously, the cofactor nicotinamideadenine dinucleotide (NAD) which is a hydrogen acceptor, is reduced to NADH. Second step:

The second step occurs in the mitochondria where acetaldehyde is converted to acetate with ALDH acting as a co-enzyme. Most of the acetate on leaving the liver is finally oxidised to carbon dioxide and water, or converted by the citric acid cycle to other compounds including fatty acids. Simultaneously, the same cofactor, NAD, is reduced to NADH resulting in increased NADH: NAD redox ratio which is the basic biochemical alteration occurring during ethanol metabolism. A close estimate of NADH:NAD ratio is measured by the ratio of its oxidised and reduced metabolites in the form of lactate-pyruvate ratio and β -hydroxy butyrate-acetoacetate ratio.

RISK FACTORS FOR ALCOHOLIC LIVER DISEASE.

All those who indulge in alcohol abuse do not develop liver damage. The incidence of cirrhosis among alcoholics at autopsy is about 10-15%. Why some individuals are predisposed to alcoholic cirrhosis is not clearly known, but a few risk factors have been implicated. These are as under:

1. Drinking patterns. Most epidemiologic studies have attributed alcoholic cirrhosis to chronic alcoholism. Available evidence suggests that chronic and excessive consumption of alcohol invariably leads to fatty liver in >90% of chronic alcoholics, progression to alcoholic hepatitis in 10-20% cases, and eventually to alcoholic cirrhosis in more than 10 years. It is generally agreed that continued daily imbibing of 60-80 gm of ethanol in any type of alcoholic beverage for at least 10 years is likely to result in alcoholic cirrhosis. Liver injury is related to the quantity of ethanol contained in alcoholic beverage consumed and its duration, but not related to the type of alcoholic beverage consumed. Ethanol content in an alcoholic beverage is given on the label of the container, but in general, it s about 4-6% in beer, 10-12% in wine, and about 40-50% in brandy, whisky and scotch. Intermittent drinking for long duration is less harmful since the liver is given chance to recover.

2. Gender. Women have increased susceptibility to develop advanced alcoholic liver disease with much lesser alcohol intake (20-40 g/day). This gender difference in disease progression is unclear but is probably linked to effects of oestrogen.

3. Malnutrition. Absolute or relative malnutrition of proteins and vitamins is regarded as a contributory factor in the evolution of cirrhosis. The combination of chronic alcohol ingestion and impaired nutrition leads to alcoholic liver disease and not malnutrition per se. It appears that calories derived from alcohol displace other nutrients leading to malnutrition and deficiency of vitamins in alcoholics. Additional factors contributing to malnutrition in alcoholics are chronic gastritis and pancreatitis. The evidence in favour of synergistic effect of malnutrition in chronic alcoholism comes from clinical and morphologic improvement in cases of alcoholic cirrhosis on treatment with protein-rich diets.

4. Infections. Intercurrent bacterial infections are common in cirrhotic patients and may accelerate the course of the disease. Lesions similar to alcoholic cirrhosis may develop in non-alcoholic patients who have had viral infections in the past.

5. Genetic factors. The rate of ethanol metabolism is under genetic control. It is chiefly related to altered rates of elimination of ethanol due to genetic polymorphism for the two main enzyme systems, MEOS (microsomal P-450 oxidases) and alcohol dehydrogenase (ADH). Various HLA histocompatibility

types have been associated with susceptibility of different populations to alcoholic liver damage but no single genotype has been identified yet.

6. Hepatitis C infection. Concurrent infection with HCV is an important risk factor for progression of alcoholic liver disease. HCV infection in chronic alcoholic leads to development of alcoholic liver disease with much less alcohol consumption (20-50 g/day), disease progression at a younger age, having greater severity, and increased risk to develop cirrhosis and hepatocellular carcinoma, and overall poorer survival.

PATHOGENESIS.

Exact pathogenesis of alcoholic liver injury is yet unclear as to why only some chronic alcoholics develop the complete sequence of changes in the liver while others don't. However, knowledge and understanding of the ethanol metabolism has resulted in discarding the old concept of liver injury due to malnutrition. Instead, now it is known that ethanol and its metabolites are responsible for ill-effects on the liver in a susceptible chronic alcoholic having above-mentioned risk factors.

1. Direct hepatotoxicity by ethanol. There is evidence to suggest that ethanol ingestion for a period of 8-10 days regularly may cause direct hepatotoxic effect on the liver and produce fatty change. Ethanol is directly toxic to microtubules, mitochondria and membrane of hepatocytes.

2. Hepatotoxicity by ethanol metabolites. The major hepatotoxic effects of ethanol are exerted by its metabolites, chiefly acetaldehyde. Acetaldehyde levels in blood are elevated in chronic alcoholics. Acetaldehyde produces hepatotoxicity by production of two adducts:

i) Production of protein-aldehyde adducts which are extremely toxic and can cause cytoskeletal and membrane damage and bring about hepatocellular necrosis.

ii) Formation of malon-di-aldehyde-acetaldehyde (MAA) adducts which produce autoantibodies and initiate autoimmune response. Theses adducts have also a role in hepatic fibrogenesis due to peroxisome proliferator-activated receptor (PPAR)-γ on hepatocytes.

3. Oxidative stress. Oxidation of ethanol by the cytochrome450 oxidases (MEOS) leads to generation of free radicals which causes oxidative damage to the membranes and proteins.

4. Immunological mechanism. Cell-mediated immunity is impaired in alcoholic liver disease. Ethanol causes direct immunologic attack on hepatocytes. In a proportion of cases, alcohol-related liver cell injury continues unabated despite cessation of alcohol consumption which is attributed to immunologic mechanisms. Immunological mechanism may also explain the genesis of Mallory's alcoholic hyalin though more favoured hypothesis for its origin is the aggregation of intermediate filaments of prekeratin type due to alcoholinduced disorganisation of cytoskeleton.

5. Inflammation. Chronic ethanol ingestion is not only injurious to hepatocytes but also damages the intestinal cells. The injured intestinal cells elaborate endotoxins which release proinflammatory cytokines, chiefly tumour necrosis factor-α, IL-1, IL-6 and TGF-β. These cytokines and endotoxinaemia produce apoptosis and necrosis of hepatocytes and initiate inflammatory reaction in the alcohol damaged liver.

6. Fibrogenesis. Main event facilitating hepatic fibrogenesis is activation of stellate cells by various stimuli: i) by damaged hepatocytes, ii) by malon-di-aldehyde-acetaldehyde adducts, iii) by activated Kupffer cells, and iv) direct stimulation by acetaldehyde. All forms of collagen are increased and there is increased transformation of fat-storing lto cells into myofibroblasts and fibrocytes.

7. Increased redox ratio. Marked increase in the NADH:NAD redox ratio in the hepatocytes results in increased redox ratio of lactate-pyruvate, leading to lactic acidosis. This altered redox potential has been implicated in a number of metabolic consequences such as in fatty liver, collagen formation, occurrence of gout, impaired gluconeogenesis and altered steroid metabolism.

8. Retention of liver cell water and proteins. Alcohol is inhibitory to secretion of newly-synthesised proteins by the liver leading to their retention in the hepatocytes. Water is simultaneously retained in the cell in proportion to the protein and results in swelling of hepatocytes resulting in hepatomegaly in alcoholics.

9. Hypoxia. Chronic ingestion of alcohol results in increased oxygen demand by the liver resulting in a hypoxic state which causes hepatocellular necrosis in centrilobular zone (zone 3). Redox changes are also more marked in zone 3. 10. Increased liver fat. In chronic alcoholism, there is rise in the amount of fat available to the liver which could be from exogenous (dietary) sources, excess mobilisation from adipose tissue or increased lipid synthesis by the liver itself. This may account for lipid accumulation in the hepatocytes.

LABORATORY DIAGNOSIS.

1. Elevated transaminases: increase in SGOT (AST) is more than that of SGPT (ALT).

2. Rise in serum γ-glutamyl transpeptidase (γ-GT).

3. Elevation in serum alkaline phosphatase.

4. Hyperbilirubinaemia.

5. Hypoproteinaemia with reversal of albumin-globulin ratio.

6. Prolonged prothrombin time and partial thromboplastin time.

7. Anaemia.

8. Neutrophilic leucocytosis in alcoholic hepatitis and in secondary infections.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown cause. Though the most prominent manifestation of RA is inflammatory arthritis of the peripheral joints, usually with a symmetrical distribution, its systemic manifestations include haematologic, pulmonary, neurological and cardiovascular abnormalities.

RA is a common disease having peak incidence in 3rd to 4th decades of life, with 3-5 times higher preponderance in females. The condition has high association with HLA-DR4 and HLA-DR1 and familial aggregation. The onset of disease is insidious, beginning with prodrome of fatigue, weakness, joint stiffness, vague arthralgias and myalgias. This is followed by pain and swelling of joints usually in symmetrical fashion, especially involving joints of hands, wrists and feet. Unlike migratory polyarthritis of rheumatic fever, RA usually persists in the involved joint.

Approximately 20% of patients develop rheumatoid nodules located over the extensor surfaces of the elbows and fingers. About 80% of cases are seropositive for rheumatoid factor (RF). However, RF titres are elevated in certain unrelated diseases too such as in: viral hepatitis, cirrhosis, sarcoidosis and leprosy.

Advanced cases show characteristic radiologic abnormalities such as narrowing of joint space and ulnar deviation of the fingers and radial deviation of the wrist. Other laboratory findings include mild normocytic and normochromic anaemia, elevated ESR, mild leucocytosis and hypergammaglobulinaemia. Extra-articular manifestations infrequently produce symptoms, but when present complicate the diagnosis.

ETIOPATHOGENESIS. Present concept on etiology and pathogenesis proposes that RA occurs in an immunogenetically predisposed individual to the effect of microbial agents acting as trigger antigen. The role of superantigens which are produced by several microorganisms with capacity to bind to HLADR molecules (MHC-II region) has also emerged. I. Immunologic derangements. A number of observations in patients and experimental animals indicate the role of immune processes, particularly autoimmune phenomenon, in the development of RA. These include the following:

1. Detection of circulating autoantibody called rheumatoid factor (RF) against Fc portion of autologous IgG in about 80% cases of RA. RF antibodies are heterogeneous and consist of IgM and IgG class.

2. The presence of antigen-antibody complexes (IgG-RF complexes) in the circulation as well as in the synovial fluid.

3. The presence of other autoantibodies such as antinuclear factor (ANF), antibodies to collagen type II, and antibodies to cytoskeleton.

4. Antigenicity of proteoglycans of human articular cartilage.

5. The presence of γ-globulin, particularly IgG and IgM, in the synovial fluid.

6. Association of RA with amyloidosis.

7. Activation of cell-mediated immunity as observed by presence of numerous inflammatory cells in the synovium, chiefly CD4+ T lymphocytes and some macrophages.

II. Trigger events. Though the above hypothesis of a possible role of autoimmunity in the etiology and pathogenesis of RA is generally widely accepted, controversy continues as regards the trigger events which initiate the destruction of articular cartilage.

Various possibilities which have been suggested are as follows:

1. The existence of an infectious agent such as mycoplasma, Epstein-Barr virus (EBV), cytomegalovirus (CMV) or rubella virus, either locally in the synovial fluid or systemic infection some time prior to the attack of RA.

2. The possible role of HLA-DR4 and HLA-DR1 in initiation of immunologic damage. The proposed events in immunopathogenesis of RA are as under:

In response to antigenic exposure (e.g. infectious agent) in a genetically predisposed individual (HLA-DR), CD4+ Tcells are activated.

These cells elaborate cytokines, the important ones being tumour necrosis factor (TNF)-α, interferon (IF)-γ , interleukin (IL)-1 and IL-6.

These cytokines activate endothelial cells, B lymphocytes and macrophages.

Activation of B-cells releases IgM antibody against IgG (i.e. anti-IgG); this molecule is termed rheumatoid factor (RF). IgG and IgM immune complexes trigger inflammatory damage to the synovium, small blood vessels and collagen.

Activated endothelial cells express adhesion molecules which stimulate collection of inflammatory cells.

Activation of macrophages releases more cytokines which cause damage to joint tissues and vascularisation of cartilage termed pannus formation.

Eventually damage and destruction of bone and cartilage are followed by fibrosis and ankylosis producing joint deformities.

There are a few variant forms of RA:

1. Juvenile RA found in adolescent patients under 16 years of age is characterised by acute onset of fever and predominant involvement of knees and ankles. Pathologic changes are similar but RF is rarely present.

2. Felty's syndrome consists of polyarticular RA associated with splenomegaly and hypersplenism and consequent haematologic derangements.

3. Ankylosing spondylitis or rheumatoid spondylitis is rheumatoid involvement of the spine, particularly sacroiliac joints, in young male patients. The condition has a strong HLA-B27 association and may have associated inflammatory diseases such as inflammatory bowel disease, anterior uveitis and Reiter's syndrome.

GOUT AND GOUTY ARTHRITIS

Gout is a disorder of purine metabolism manifested by the following features, occurring singly or in combination:

1. Increased serum uric acid concentration (hyperuricaemia).

2. Recurrent attacks of characteristic type of acute arthritis in which crystals of monosodium urate monohydrate may be demonstrable in the leucocytes present in the synovial fluid.

3. Aggregated deposits of monosodium urate monohydrate (tophi) in and around the joints of the extremities.

4. Renal disease involving interstitial tissue and blood vessels.

5. Uric acid nephrolithiasis.

The disease usually begins in 3rd decade of life and affects men more often than women. A family history of gout is present in a fairly large proportion of cases indicating role of inheritance in hyperuricaemia.

Clinically, the natural history of gout comprises 4 stages: asymptomatic hyperuricaemia, acute gouty arthritis, asymptomatic intervals of intercritical periods, and chronic tophaceous stage. In addition, gout nephropathy and urate nephrolithiasis may occur.

TYPES AND PATHOGENESIS.

The fundamental biochemical hallmark of gout is hyperuricaemia. A serum uric acid level in excess of 7 mg/dl, which represents the upper limit of solubility of monosodium urate in serum at 37°C at blood pH,

is associated with increased risk of development of gout. Thus, pathogenesis of gout is pathogenesis of hyperuricaemia. Hyperuricaemia and gout may be classified into 2 types: metabolic and renal, each of which may be primary or secondary. Primary refers to cases in which the underlying biochemical defect causing hyperuricaemia is not known, while secondary denotes cases with known causes of hyperuricaemia.

1. Hyperuricaemia of metabolic origin. This group comprises about 10% cases of gout which are characterised by overproduction of uric acid. There is either an accelerated rate of purine biosynthesis de novo, or an increased turnover of nucleic acids. The causes of primary metabolic gout include a number of specific enzyme defects in purine metabolism which may be either of unknown cause or are inborn errors of metabolism. The secondary metabolic gout is due to either increased purine biosynthesis or a deficiency of glucose-6phosphatase.

2. Hyperuricaemia of renal origin. About 90% cases of gout are the result of reduced renal excretion of uric acid. Altered renal excretion could be due to reduced glomerular filtration of uric acid, enhanced tubular reabsorption or decreased secretion. The causes of gout of renal origin include diuretic therapy, drug-induced (e.g. aspirin, pyrazinamide, nicotinic acid, ethambutol and ethanol), adrenal insufficiency, starvation, diabetic ketosis, and disorders of parathyroid and thyroid. Renal disease per se rarely causes secondary hyperuricaemia such as in polycystic kidney disease and leads to urate nephropathy.

Osteoporosis

Osteoporosis or osteopenia is a common clinical syndrome involving multiple bones in which there is quantitative reduction of bone tissue mass but the bone tissue mass is otherwise normal. This reduction in bone mass results in fragile skeleton which is associated with increased risk of fractures and consequent pain and deformity. The condition is particularly common in elderly people and more frequent in postmenopausal women.

The condition may remain asymptomatic or may cause only backache. However, more extensive involvement is associated with fractures, particularly of distal radius, femoral neck and vertebral bodies. Osteoporosis may be difficult to distinguish radiologically from other osteopenias such as osteomalacia, osteogenesis imperfecta, osteitis fibrosa of hyperparathyroidism, renal osteodystrophy and multiple myeloma. Radiologic evidence becomes apparent only after more than 30% of bone mass has been lost. Levels of serum calcium, inorganic phosphorus and alkaline phosphatase are usually within normal limits.

PATHOGENESIS.

Osteoporosis is conventionally classified into 2 major groups: primary and secondary.

Primary osteoporosis

It results primarily from osteopenia without an underlying disease or medication. Primary osteoporosis is further subdivided into 2 types: idiopathic type found in the young and juveniles and is less frequent, and involutional type seen in postmenopausal women and aging individuals and is more common. The exact mechanism of primary osteoporosis is not known but there is a suggestion that it is the result of an excessive osteoclastic resorption and slow bone formation. A number of risk factors have been attributed to cause this imbalance between bone resorption and bone formation.

These include the following:

1. Genetic factors—more marked in whites and Asians than blacks.

2. Sex—more frequent in females than in males.

3. Reduced physical activity—as in old age.

4. Deficiency of sex hormones—oestrogen deficiency in women as in postmenopausal osteoporosis and androgen deficiency in men. 5. Combined deficiency of calcitonin and oestrogen.

6. Hyperparathyroidism.

7. Deficiency of vitamin D.

8. Local factors—which may stimulate osteoclastic resorption or slow osteoblastic bone formation.

Secondary osteoporosis

It is attributed to a number of factors and conditions (e.g. immobilisation, chronic anaemia, acromegaly, hepatic disease, hyperparathyroidism, hypogonadism, thyrotoxicosis and starvation), or as an effect of medication (e.g. hypercortisonism, administration of anticonvulsant drugs and large dose of heparin).

MORPHOLOGIC FEATURES.

Except disuse or immobilisation osteoporosis which is localised to the affected limb, other forms of osteoporosis have systemic skeletal distribution.

Most commonly encountered osteoporotic fractures are: vertebral crush fracture, femoral neck fracture and wrist fracture. There is enlargement of the medullary cavity and thinning of the cortex. Histologically, osteoporosis may be active or inactive type. Active osteoporosis is characterised by increased bone resorption and formation i.e. accelerated turnover. There is increase in the number of osteoclasts with increased resorptive surface as well as increased quantity of osteoid with increased osteoblastic surfaces.

The width of osteoid seams is normal. Inactive osteoporosis has the features of minimal bone formation and reduced resorptive activity i.e. reduced turnover. Histological changes of inactive osteoporosis include decreased number of osteoclasts with decreased resorptive surfaces, and normal or reduced amount of osteoid with decreased osteoblastic surface. The width of osteoid seams is usually reduced or may be normal.

cancer

INTRODUCTION.

The term ‘neoplasia’ means new growth; the new growth produced is called ‘neoplasm’ or ‘tumour’. However, all ‘new growths’ are not neoplasms since examples of new growth of tissues and cells also exist in the processes of embryogenesis, regeneration and repair, hyperplasia and hormonal stimulation. The proliferation and maturation of cells in normal adults is controlled as a result of which some cells proliferate throughout life (labile cells), some have limited proliferation (stable cells), while others do not replicate (permanent cells). On the other hand, neoplastic cells lose control and regulation of replication and form an abnormal mass of tissue.

Therefore, satisfactory definition of a neoplasm or tumour is ‘a mass of tissue formed as a result of abnormal, excessive, uncoordinated, autonomous and purposeless proliferation of cells even after

cessation of stimulus for growth which caused it'. The branch of science dealing with the study of neoplasms or tumours is called oncology (oncos=tumour, logos=study). Neoplasms may be 'benign' when they are slow-growing and localised without causing much difficulty to the host, or 'malignant' when they proliferate rapidly, spread throughout the body and may eventually cause death of the host. The common term used for all malignant tumours is cancer.

Hippocrates (460-377 BC) coined the term karkinos for cancer of the breast. The word 'cancer' means crab, thus reflecting the true character of cancer since 'it sticks to the part stubbornly like a crab'.

Classification of Tumours. Tissue of Origin Benign Malignant

I. TUMOURS OF ONE PARENCHYMAL CELL TYPE

A. Epithelial Tumours

1. Squamous epithelium -Squamous cell papilloma, Squamous cell (Epidermoid) carcinoma

2. Transitional epithelium -Transitional cell papilloma, Transitional cell carcinoma

3. Glandular epithelium- Adenoma, Adenocarcinoma

4. Basal cell layer skin — Basal cell carcinoma

5. Neuroectoderm Naevus- Melanoma (Melanocarcinoma)

6. Hepatocytes Liver cell -adenoma, Hepatoma (Hepatocellular carcinoma)

7. Placenta (Chorionic epithelium)- Hydatidiform mole, Choriocarcinoma

B. Non-epithelial (Mesenchymal) Tumours

1. Adipose tissue –Lipoma, Liposarcoma

2. Adult fibrous tissue –Fibroma, Fibrosarcoma

3. Embryonic fibrous tissue- Myxoma, Myxosarcoma

4. Cartilage- Chondroma, Chondrosarcoma

5. Bone- Osteoma, Osteosarcoma

6. Synovium -Benign synovioma, Synovial sarcoma

7. Smooth muscle- Leiomyoma, Leiomyosarcoma

8. Skeletal muscle- Rhabdomyoma, Rhabdomyosarcoma

9. Mesothelium — Mesothelioma

10. Blood vessels- Haemangioma, Angiosarcoma

11. Lymph vessels- Lymphangioma, Lymphangiosarcoma

12. Glomus- Glomus tumour —

13. Meninges- Meningioma, Invasive meningioma

14. Haematopoietic cells — Leukaemias

15. Lymphoid tissue- Pseudolymphoma, Malignant lymphomas

16. Nerve sheath- Neurilemmoma, Neurofibroma, Neurogenic sarcoma

17. Nerve cells- Ganglioneuroma, Neuroblastoma

II. MIXED TUMOURS

Salivary Glands -Pleomorphic adenoma, Malignant mixed salivary tumour (mixed salivary tumour)

III. TUMOURS OF MORE THAN ONE GERM CELL LAYER

Totipotent cells in gonads or in embryonal rests- Mature teratoma, Immature teratoma

CHARACTERISTICS OF TUMOURS

Majority of neoplasms can be categorised clinically and morphologically into benign and malignant on the basis of certain characteristics listed below. However, there are exceptions—a small proportion of tumours have some features suggesting innocent growth while other features point towards a more ominous behaviour. Therefore, it must be borne in mind that based characteristics of neoplasms, there is a wide variation in the degree of deviation from the normal in all the tumours. The characteristics of tumours are described under the following headings:

I. Rate of growth

II. Cancer phenotype and stem cells

III. Clinical and gross features

IV. Microscopic features

V. Local invasion (Direct spread)

VI. Metastasis (Distant spread).

Grading Cancers

It may be graded grossly and microscopically. Gross features like exophytic or fungating appearance are indicative of less malignant growth than diffusely infiltrating tumours. However, grading is largely based on 2 important histologic features: the degree of anaplasia, and the rate of growth.

Based on these features, cancers are categorised from grade I as the most differentiated, to grade III or IV as the most undifferentiated or anaplastic. Many systems of grading have been proposed but the one described by Broders for dividing squamous cell carcinoma into 4 grades depending upon the degree of differentiation is followed for other malignant tumours as well. Broders' grading is as under:

Grade I: Well-differentiated (less than 25% anaplastic cells).

Grade II: Moderately-differentiated (25-50% anaplastic cells).

Grade III: Moderately-differentiated (50-75% anaplastic cells).

Grade IV: Poorly-differentiated or anaplastic (more than 75% anaplastic cells).

EPIDEMIOLOGIC FACTORS

A) A large number of predisposing epidemiologic factors or cofactors which include a number of endogenous host factors and exogenous environmental factors.
   1. FAMILIAL AND GENETIC FACTORS
   2. RACIAL AND GEOGRAPHIC FACTORS.
   3. ENVIRONMENTAL AND CULTURAL FACTORS
   4. SEX
   5. AGE

B) Chronic non-neoplastic (pre-malignant) conditions.

1. Carcinoma in situ (intraepithelial neoplasia).

2. Some benign tumours.

3. Miscellaneous conditions

C) Role of hormones in cancer.

1. OESTROGEN

2. CONTRACEPTIVE HORMONES

3. ANABOLIC STEROIDS.

4. HORMONE-DEPENDENT TUMOURS