Many pre- or subclinical stages occur in the DM patient before clinical diagnosis can be done:

1. Stage 1: the cell mass and function of β cells is normal but individuals who carry genetic susceptibility alleles to type 1 suffer exposure to an environmental stimulus triggering islets inflammation (insulitis). The release of sequestered or altered self antigens explains in part the later development of islet Autoantibodies that mark the recognition of stage 2.
2. Stage 2: serological evidence of humoral and cell-mediated autoimmunity indicated by the appearance of different types of autoantibody as islet cell cytoplasmic autoantibody (ICA), glutamic acid decarboxylase autoantibody (GADA), insulinoma-2 associated autoantibody (IA-2A) or insulin autoantibody (IAA). This occurs without any clinical metabolic signs. However, during this stage, there can be a 50% decline in β cells mass without detectable abnormalities by any form of glucose tolerance testing.
3. Stage 3: The earliest functional β cells abnormalities which manifestation by the intravenous glucose tolerance test (IVGTT) which decrease.
4. Stage 4: intolerance to oral glucose challenges appears as indicated by oral glucose tolerance test (OGTT).
5. Stage 5: after 1-2 years of glucose intolerance upon oral testing, atypical history of polyuria, polydipsia, polyphagia with weight lose impaired visual acuity, tingling or numbness in the hands or feet resulting from sensory nerve changes are identified. Finally by a true hyperglycemia a full diagnosis can be done. If diabetes is undiagnosed or untreated, failure to metabolize glucose will result in the breakdown of fat, leading to ketonemia and ketoacidosis, which may be accompanied by nausea and hyperventilation before life-threatening ketoacidotic coma

Lecture No. 7

Inflammatory bowel disease

It is a chronic inflammatory disease of gastrointestinal tract due to immune response to the commensal microflora in the lumen of basal consistent and may be divided into two major groups:

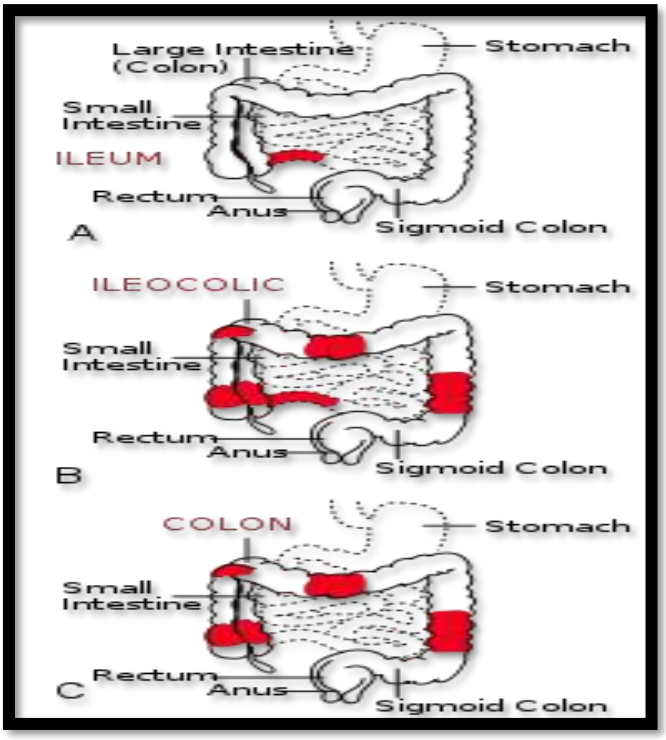
- Crohn's disease
- Ulcerative colitis

Crohn's disease also known as granulomatous colitis and regional enteritis, it is classified as a type of inflammatory bowel disease, in which the body immune system attacks the gastrointestinal tract, causing a transmural inflammation, that may affect any part of the

gastrointestinal tract from mouth to anus. It is onset patient between 15-30 year, males and females are equally affected.

Most gastroenterologists categorize the presenting disease by the affected areas:

- ***Ileocolic Crohn's diseases*,** which affect both the ileum (the last part of the small intestine that connect to the large intestine) and the large intestine, accounts for 50% of cases.
- ***Crohn's ileitis*,** affecting the ileum only, accounts for 30% of cases.
- ***Crohn's colitis*,** affecting the large intestine, accounts for the remaining 20% of cases and may be difficult to distinguish from ulcerative colitis.



However, individual affected by the disease rarely fall outside these three classification, being affected in other parts of the gastrointestinal tract such as the stomach and esophagus. Crohns disease may also be categorized by the behavior of disease as it progresses. There are three categories of disease presentation in Crohns disease:

- ***Stricturing disease:*** narrowing of the bowel which may lead to bowel obstruction or changes in the caliber of the feces.
- ***Penetrating disease:*** creates abnormal passageways (fistulae) between the bowel and other structures such as the skin.
- ***Inflammatory disease:*** cause inflammation without causing stricture or fistulae.

Causes

- **Genetic factor:** many studies that is suggested relationship between genetic and Crohns disease such as mutation in gene nucleotide-binding oligomerisation domain 2 (NOD2 gene) on chromosome 16.
- **Environmental factor:** by diet, smoking, drugs, hormonal contraception.
- **Immune system:** abnormalities in immune system causes Crohns disease and the inflammation that is occur in this disease causes activation of T_H1 by an overproduction of IL-12 by macrophages and of IFN-γ by T lymphocytes.
- **Microbes:** there are many bacteria causes of Crohns disease such as Mycobacterium ovum, Yersinia spp and Listeria spp.

Clinical Features

A. Gastrointestinal Features

- Abdominal pain.
- Diarrhea may be bloody or may not be bloody, is different according to the part of the small intestine or large intestine, in ileitis large-volume watery feces, while, in colitis small volume semisolid or watery feces.
- Vomiting &nausea.
- Perianal discomfort (itching around the anus).
- Aphthousof mouth (ulceration of mouth).

B. Systemic Features

- In children causes growth failure, acute myelogenous leukemia in blood (myeloid) and lymphoma (cancer of lymph).
- In adult causes weight loss.

Ulcerative colitis

Ulcerative colitis is confined to the colon and affects the mucosal layer only and causing a continuous inflammation. It is result of immune response to commensal microflora with T_H2 profile, through there is an increase of the T_H2 cytokine IL- 5. Favouring a T_H2 pattern is the fact that ulcerative colitis is associated with the production of various autoantibodies, such as perinuclear anti-neutrophil cytoplasmic antibody (PANCA) and anti- tropomyosin.

Clinical Features

- The clinical presentation of ulcerative colitis depends on the extent of the disease process. Patients usually present with diarrhea mixed with blood [Relapsing rectal bleeding] and mucus, of gradual onset.
- They also may have signs of weight loss, and blood on rectal examination.
- The disease is usually accompanied with different degrees of abdominal pain, from mild discomfort to severely painful cramp [**Tenesmus**].

Diagnosis

1. In both inflammatory bowel diseases, the key diagnostic procedures are radiologic, endoscopic and histologic.
2. In Crohn's disease, typical laboratory findings include anemia (chronic disease, iron deficiency, vitamin B12 deficiency, folate deficiency), leukocytosis, thrombocytosis, elevation of the sedimentation rate, hypoalbuminaemia and electrolyte imbalance in the presence of severe diarrhea. The measurement of C-reactive protein appears to be of use in monitoring the progress of the disease.
   In the setting of supportive findings through imaging or endoscopy, the measurement of certain serum antibodies can further strengthen the diagnosis of Crohn disease and even help differentiate it from UC, but they should not be used by themselves as diagnostic tests. It has been shown that up to 68% of patients with Crohn disease are seropositive for antibodies targeting microbial antigens, such as anti–Saccharomyces cerevisiae antibody (up to 16% of patients with UC are seropositive).
3. While, in ulcerative colitis, the laboratory findings are mostly non-specific, reflecting blood loss and inflammation, and include anemia, leukocytosis, elevated sedimentation rate and C-reactive protein levels. Seventy percent of patients with ulcerative colitis, but not with Crohn's disease, have been reported to have in their sera an anti-neutrophil cytoplasmic antibody (ANCA) that give a characteristic perinuclear staining (PANCA) that can also be seen in primary sclerosing cholangitis.
4. General stool examination for occult blood.

Table 14.6 Some differences between ulcerative colitis and Crohn's disease.

	Ulcerative colitis	Crohn's disease
Disease site	Colon	Any part of gastrointestinal tract
Inflammation	Mucosal	Transmural, granulomatous
Cytokine profile	T_{H2}	T_{H1}
ANCA positivity	50–80%	5–20%

Helicobacter pylori associated Chronic Gastritis & Mucosa-Associated Lymphoid Tissue Lymphoma (MALT)

Gastritis is a histological term that describes stomach inflammation resulting from toxic exposures, infection, idiopathic inflammation, and autoimmunity. The most common cause of gastritis is **H pylori infection**. Other causes include acid reflux, prolonged use of

nonsteroidal anti-inflammatory drugs (NSAIDS), alcohol use, and tobacco use, all of which can irritate the lining of the stomach. Severe illness and radiation therapy can also cause gastritis

Erosive gastritis is most commonly caused by alcohol use, tobacco use, and prolonged use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDS). Severe illness and consumption of caustic substances have also been associated with the development of erosive gastritis. The most common cause of chronic, **nonerosive gastritis** is a stomach infection caused by Helicobacter pylori (H pylori), a type of bacteria found in up to half of all people in industrialized nations.

Symptoms

The signs and symptoms of gastritis vary among individuals. If infection with H pylori bacteria is the cause, symptoms will remain as long as the infection is untreated. H. pylori is uniquely adapted to the acidic environment of the stomach through its ability to metabolize urea to ammonia, which provides a buffered microenvironment that allows prolonged asymptomatic colonization.

Some people with gastritis have no symptoms at all, while others may have burning abdominal pain, Loss of appetite, nausea with or without vomiting.

In some cases, gastritis can be life threatening, with symptoms including**:**

- Bloody stool (blood may be red, black, or tarry in texture)
- Severe abdominal pain
- Vomiting blood or black material (resembling coffee grounds)

Although acute infection can cause abdominal pain and dyspepsia, there is typically no clinical recognition of acute infection. Rather, the burden of H. pylori results from chronic infection of the stomach.The development of peptic ulcer disease and adenocarcinoma caused by chronic H. pylori infection correlates with the anatomical distribution of inflammation. When H. pylori chronic gastritis affects the antrum predominantly, there is an association with duodenal ulcers, increased serum gastrin levels and excess acid production, and no gastric mucosal atrophy. However, when H. pylori affects the body and the antrum in a confluent or patchy manner, intestinal metaplasia develops, oxyntic mucosa atrophies, and acid production decreases. This latter type of H. pylori chronic gastritis is associated with gastric ulcerations and increased risk for adenocarcinoma and mucosa-associated lymphoreticular tissue (MALT) B-cell lymphoma. Although eradication of H. pylori can reverse the mucosal atrophy and restore acid production in this setting, mucosal restoration occurs only in a minority of patients and does not necessarily reverse the intestinal metaplasia.

Immune pathophysiology

Although there are many pieces of evidence to support immune mechanisms for the persistence of HP infection in the stomach, data suggest that pro-regulatory effects of H.

pylori infection, including local IL-10 production, increases in regulatory T cells (Tregs) in the gastric mucosa and increased antigen-presenting cell (APC) phagocytosis of apoptotic cells all contribute to persistence of chronic H. pylori gastritis.

Diagnosis

Active disease can be diagnosed with endoscopic biopsy, which has high sensitivity and specificity, while simultaneously assessing peptic and malignant complications. Noninvasive testing for *H. pylori* infection includes serum antibody detection (best used in highly endemic areas to predict active infection), urea breath testing (limited by expense and possible false-positive results), and fecal antigen testing (which has potential advantages in the setting of intestinal metaplasia and after antibiotic treatment).

Lecture No. 8

Autoimmune Hepatitis

Autoimmune hepatitis(AIH) is a progressive inflammation of the liver that has been identified by a number of different names, including **autoimmune chronic active hepatitis (CAH), idiopathic chronic active hepatitis** and **lupoid hepatitis**. The reason for this inflammation is not certain, but it is associated with an abnormality of the body immune system. It is a rare condition characterized by active inflammation, liver cell necrosis and fibrosis, which may lead to hepatic failure, cirrhosis and ultimately death.The disease affects young to middle-aged women, many of whom (60%) are associated with other autoimmune diseases, such as diabetes mellitus, thyroiditis, rheumatoid arthritis, ulcerative colitis crohns disease and glomerulonephritis.

Pathophysiology

Evidence suggests that liver injury in a patient with autoimmune hepatitis is the result of a cell-mediated immunological attack. This attack is directed against genetically predisposed hepatocytes. Aberrant display of human leukocyte antigen (HLA) class II on the surface of hepatocytes (normally not expressed on liver cells), facilitates the presentation of normal liver cell membrane constituents as autoantigenic peptides to $CD4^{+}$T cells.

Causes

It is not clear why autoimmune hepatitis develops. Researchers suspect that some people inherit a genetic disposition that could make them more likely to develop it. Sometimes drugs (e.g., interferon) or viral infections (e.g., acute hepatitis A or B, Epstein-Barr virus infection) have been suggested to play a role in triggering AIH, possibly through molecular mimicry and cross-reactivity between their epitopes and liver antigens, trigger the development of the disease.

Symptoms

The clinical features of AIH can be quite variable. About 25% of individuals are asymptomatic and are diagnosed only after abnormal liver function tests are found