

## OBJECTIVES

Know the two forms of idiopathic inflammatory bowel disease (IBD)

Describe the pathogenesis of IBD.
Compare and contrast Crohn disease and ulcerative colitis with respect
to:

1. clinical features and extraintestinal manifestations
2. pathology (gross and microscopic features) of IBD
3. complications of IBD (especially adenocarcinoma preceded by
dysplasia).

THIS LECTURE WAS PRESENTED BY DR.MAHA ARAFAH \& DR.AHMED ALHUMAIDI

IF YOU WANT TO READ THE LECTURE FROM ROBBINS

IF YOU WANT TO READ THE LECTURE FROM FIRST AID


NINJA NERD ON ULCERATIVE COLITIS "VERY DETALLED"

NINJA NERD ON CROHN'S DISEASE "VERY DETAILED"

NINJA NERD ON IBS " USMLE"

NEED NINJA NERD BOARD ? CLICK HERE

IF YOU WANT TO WATCH OSMOSIS VIDED

## Inflammatory Bowel Disease

## Definition

- It is a chronic condition resulting an inappropriate mucosal immune activation
- It has two types:

1- Crohn's disease
2- Ulcerative colitis

- Ulcerative colitis is the common inflammatory bowel disease
- Although their causes are still not clear, the two diseases probably have an immunologic hypersensitivity basis (abnormal interactions between intestinal microbiota and host immunity in genetically predisposed individuals).



## Epidemiology

Crohn's Disease

- More common in whites than blacks
- More common in Jews than non-jews
- More common in children than adults
- Smoking is a risk factor
- Majority (>75\%) of cases occur between 11 and 35 years of age
- More common in whites than blacks - Occurs between 14 and 38 years of age
- Lower incidence in smokers and other nicotine users
- Lower incidence if previous appendectomy $\mathbf{2 0}$ years
- Both Crohn's disease(CD) and ulcerative colitis (UC) are more common in females and in young adults
- The geographic distribution of IBD is highly variable
- It is most prevalent in North America, northern Europe, and Australia.
- IBD incidence worldwide is on the rise and is becoming more common in regions in which the prevalence was historically low. Previously we don't see that much of Crohn's \& ulcerative colitis in KSA , now it increased
- Hygiene hypothesis suggests that these changes in incidence are related to:
- Improved food storage conditions and decreased food contamination. Improved hygiene has resulted in inadequate development of regulatory processes that limit mucosal immune responses early in life.
- As a result, exposure of susceptible individuals to normally innocuous microbes later in life triggers inappropriate immune responses due to loss of intestinal epithelial barrier function.


## Inflammatory Bowel Disease

## Pathophysiology

The etiology of IBD (ulcerative colitis and Crohn disease) is unknown.
An idiopathic disorder
The pathophysiology of IBD is under active investigation.
Persons with IBD have a genetic predisposition for the disease.


#### Abstract

Most investigators believe that the two diseases result from a combination of 1. Defects in host interactions with intestinal microbes 2. Intestinal epithelial dysfunction 3. Aberrant mucosal immune responses. 4.Altered composition of the gut microbiome For unclear reasons, research suggests that smoking increases the risk of Crohn disease but reduces the likelihood of ulcerative colitis.




Mutations in NOD2 are seen in about 15\% of Crohn's disease patients but are also seen in a smaller percentage of the general population, so mutations in NOD2 are neither necessary nor sufficient for the development of Crohn's disease

## Clinical Note

Patient with IBS may present with Erythema Nodosum ( mentioned in this lecture) which is :
an immune-mediated panniculitis (inflammation of the subcutaneous fat) caused by a type IV (delayed-type) hypersensitivity reaction. It commonly manifests in young women as tender, erythematous nodules on the shins. The underlying etiology varies and may be associated with infection, drug exposure, inflammatory bowel disease, pregnancy, or malignancy. The lesions often self-resolve within 8 weeks without scarring. Management focuses on identifying and treating the underlying cause.

# Inflammatory Bowel Disease 

## Pathophysiology

Familial aggregation suggests a genetic predisposition, but no definite genetic markers have been identified except for the uniform presence of HLA-B27 in patients with IBD and ankylosing spondylitis.

Current evidence suggests that IBD results from the combined effects of alterations in host interactions with intestinal microbiota, intestinal epithelial dysfunction, aberrant mucosal immune responses, and altered composition of the gut microbiome.

These evidence suggest a cycle by which transepithelial flux of luminal bacterial components activates innate and adaptive immune responses. In a genetically susceptible host, the subsequent release of tumor necrosis factor alpha (TNF-a) and other immune-mediated signals direct epithelia to increase tight junction permeability, which causes further increases in the influx of luminal material.

These events may establish a self-amplifying cycle that gives rise to maladaptive and injurious immune responses.
Recent development in inflammatory bowel diseases role of T-helper 1 and 2

T-helper (Th)-l cells Accumulate in the intestinal tract of individuals with Crohn's disease (CD) and are directly associated with disease. Interferon-y is the defining cytokine produced by Thl cells and is used almost exclusively to identify Thl cells in settings of disease.

While thl cells are indicative of CD, $T$-helper (Th)- 2 cells Are more associated with UC. This Thl/Th2 paradigm, although controversial, has been recently supported by the development of an equation that can predict CD vs UC based on cell populations with 83\% accuracy.

## Deep Focus Question

What is a genetic risk factor for ulcerative colitis?
A. DRQ8
B. HLA-B27
C. DRQ4
D. ATM2
E. HLA-B14

## Deep Focus Question

## Which finding is consistent with Crohn disease?

A. Epithelial metaplasia
B. Th2 cell proliferation
C. Non-caseating granuloma
D. Epithelial erosion and ulceration

## Inflammatory Bowel Disease

## Pathophysiology

## Pathophysiology theory:

Genetics : Mutation in Nucleotide-binding oligomerization domain-containing protein 1 (encodes a protein that binds to intracellular bacterial peptidoglycans)

NOD2 $\rightarrow$ susceptibility gene in Crohn disease $\rightarrow$ Abnormal recognition and response to intracellular pathogens.

Less effective at recognizing and luminal microbes

Abnormal intestinal epithelial tight junction barrier function

Trans Epithelial lux of luminal bacterial component activates immune responses
mucosal immune response

Immunosuppression is the mainstay of IBD therapy.

Inflammation

Clinical manifestations of IBD generally depend on the area of the intestinal tract involved.

Colon

Extraintestinal manifestation

Arthritis, Eye manifestation, Skin manifestation

> Small
> intestines

## Crohn's disease

## Definition

It is a chronic inflammatory disorder that most commonly affect the lleum and colon but has the potential to involve any part of the gastrointestinal tract from the mouth to the anus.

## Site Of Involvement

## Any Part

Any part of the GIT from the mouth to the anus.

Colon
ileum (30\%) colon
(20\%) or both.

Commonly (75\%) have perianal lesions such as abscesses,fistulas, and skin tags.
most commonly terminal ileum.

## Clinical Features

- Affects any age but has its highest incidence in young adults(11-35 years old).
- Extremely variable presentation.



## Chronic disease

remissions and relapses over a long period of time.
> In long-standing crohn's disease,
Thickening of the intestine may produce an ill-defined mass in the abdomen.

## Extraintestinal manifestations :



## Crohn's disease

## + Clinical Findings

## 01

 Recurrent right lower quadrant colicky pain (obstruction) with diarrhea and weight loss

02
Bleeding occurs only with colon or anal involvement (ulcers, fistulas, abscesses)

Aphthous ulcers in mouth


Intestinal obstruction
due to fibrosis of the gut wall after inflammation
due to extensive involvement of the small bowel

Protein-losing enteropathy
Malabsorption (steatorrhea, vitamin \& iron deficiency )
enteropatny

## loss of albumin from inflamed mucosa

between the ileum and the colon result in malabsorption

Enterovesical fistulas lead to urinary infections and passage of gas and feces with urine. (between the bowel \& bladder)

Enterovaginal fistulas produce a fecal vaginal discharge. (between the bowel \& vagina)

Peritonitis

Extraintestinal manifestations

Slight increased risk of development of carcinoma of the colon

## Crohn's disease

## Morphology

## Microscopic

1.Distortion of mucosal crypt architecture with mucosal inflammation.
2.Transmural inflammation.
3.Epithelioid granulomas (60\%) "collection of epithelioid histiocytes"
4. Fissure-ulcer and fistulas be seen microscopically.



## Gross

- Involvement is typically segmental, with skip areas of normal intestine between areas of involved bowel. Also called "regional enteritis"
- Transmural inflammation will repair by Marked fibrosis causing luminal narrowing with intestinal obstruction.
- Fissures "deep fissuring ulcers": deep and narrow ulcers that look like stabs with a knife that penetrate deeply into the wall of the affected intestine.
- fistulas: communications with other viscera (from bowel to : urinary bladder, vagina or skin ).
- Mucosa: longitudinal serpiginous ulcers separated by irregular islands of edematous mucosa. This results in the typical cobblestone effect/appearance.
- Fat: In involved ileal segments, the mesenteric fat creeps from the mesentery to surround the bowel wall (creeping fat).



Cobblestone effect

creeping fat

## Ulcerative colitis

## Definition

- Chronic relapsing ulcero-inflammatory disease of undetermined etiology.
- Most common inflammatory bowel disease.
- Ulcerations of the colon are in continuity (non-segmental) unlike

Crohn's Disease

- 20- to 30-year age group but may occur at any age.


## Etiology

- The cause is unknown
- Antibodies that cross-react with intestinal epithelial cells and certain serotypes of Escherichia coli (normal lora) have been demonstrated in the serum of some patients with ulcerative colitis.


## Site Of Involvement

Lesion is limited to the mucosa, ulcers are wide based but not deep penetrating, the normal mucosa between them appear like polyps "pseudopolyps" Ulcerative colitis is a disease of the rectum, and the colon.

rectum

Rectum is involved in almost all cases
(it starts at the rectum then extend proximally)
The disease extends proximally from the rectum in a continuous manner without skip areas, it may involve a part or the whole colon "pancolitis".

## ilium

The ilium is not involved as a rule

## What is the definition of a polyp?

The term polyp is used to describe any nodule or mass that projects above the level of surrounding mucosa; it may be hyperplastic or neoplastic.

## Why are the lesions in ulcerative colitis called pseudopolyps?

These lesions are not really the result of mucosal proliferation but rather are the result of mucosal ulceration. Focal areas that are unaffected by ulceration appear to project above the denuded mucosa surrounding them.

## Ulcerative colitis

## Clinical features

## Clinical Features

Could have general manifestations like : Signs of anemia: fatigue, pallor, dyspnea, palpitations but mainly :

## Acute phase

during relapse, the patient has :

- Fever
- leukocytosis
- lower abdominal pain
- Bloody diarrhea and mucus in the stool (dysentery)


## Chronic Course

The disease usually has a chronic course, with remissions and exacerbations.

## Complications

Acute Phase

## Complications

Chronic Ulcerative colitis

## Toxic megacolon

Severe bleeding, fever \&
abdominal pain
(dilation of the colon, with functional obstruction)

Increase risk of developing colon carcinoma.(ADEN OCARCINOMA)

The presence of high-grade dysplasia in a mucosal biopsy imposes a high risk of cancer and is an indication for colectomy

## Clinical Findings



Fever, tenesmus, weight loss

Recurrent left-sided abdominal cramping with bloody diarrhea and mucus
primary sclerosing cholangitis (UC > CD), erythema nodosum, iritis/uveitis (CD > UC), pyoderma gangrenosum, HLA-B27 positive arthritis.

Toxic megacolon (dilated colon, removed by surgery) (up to $10 \%$ of patients).
Mortality rate $50 \%$.

## Ulcerative colitis

## Morphology

443 Prof Ahmed note:
We are not sure if its dysplasia (and he deleted the word from the slides)

## Microscopic

- The inflammation is usually restricted to the mucosa.
- Active inflammation correlates well with the severity of symptoms.

| active/acute phase | chronic phase |  |
| :---: | :---: | :---: |
| neutrophils, Cryptits, crypt abscess | crypt atrophy and distortion |  |
| Microscopic Appearance <br> 57 Sisfy: | This image shows an ulcer bc inflammatory cells. Note the at the edge of the ulcer. C regenerating crypts with | se with fibrin, capillaries, and istorted regenerating crypts mpare the shape of the hat of the normal crypts |
| Gross |  |  |
| - Involves mainly the mucosa, diffuse hyperemia with numerous superficial ulcerations in the acute phase <br> - The regenerated or non ulcerated mucosa may appear polypoid (inflammatory pseudopolyps) in contrast with the atrophic areas or ulcers. | lesion |  | ulcers.

lesion

## Extraintestinal manifestations



Arthritis Peripheral arthritis, ankylosing spondylitis, or osteoporosis

Uveitis is the inflammation of the uvea, the pigmented middle layer of the eye, which comprises the iris, ciliary body, and choroid.

Skin lesions
(pyoderma gangrenosum)
rapidly progressive painful, red papules $\rightarrow$ pustules $\rightarrow$ deep ulcers with central

Sclerosing pericholangitis (fibrosis around bile ducts), leading to obstructive jaundice

## Summary

|  | Crohn's Disease | Ulcerative colitis |
| :---: | :---: | :---: |
| Site | Any part of the GIT | Colon only |
| Pattern | Skip areas of normal mucosa | Diffuse involvement of mucosa |
| Depth of the ulcer | Deep ulcers ( fissure ) | Superficial ulcers |
| Extent of inflammation | Transmural inflammation | Mucosal inflammation only |
| Fistula formation | Yes | No |
| Creeping mesenteric fat | Yes | No |
| Fibrous thickening of wall | Yes | No |
| Granulomas | Yes | No |
| Toxic megacolon | No | Yes |
| Dysplasia | Rare | Common |
| Carcinoma | Rare | more common (10\%) |
| Mucosal appearances | Cobblestone | Pseudopolyps |
| Bowel wall | Thickened wall Narrow lumen | Thin wall Dilated lumen |
| Lymphoid reaction | Marked | Moderate |
| Complications | Short gut syndrome Fistula formation Bowel perforation Stricture formation | Haemorrhage Electrolyte loss ,Toxic megacolon Systemic effects |
| Recurrence after surgery | Common | No |

## Crohn's disease Summary

- Can involve any part of GIT
- Involvement of discontinuous segments of intestine (skip areas)
- Noncaseating epithelioid cell granulomas
- Transmural (full-thickness) inflammation of the affected parts
- Fibrosis, obstruction, fistula formation and extraintestinal features


Transmural inflammation

## Keywords

- Any part of GIT : commonly terminal ileum , perianal lesions
- segmental, with skip areas
- fibrosis causing intestinal obstruction.
- fistulas
- Deep Ulceration
- cobblestone effect
- Focal inflammation

Crohn's Disease

- creeping fat
- Transmural inflammation.
- Thickening
- Epithelioid granulomas non caseating
- Malabsorption
- COULD HAVE BLOODY DIARRHEA IF IT INVOLVES THE COLON
- Less risk to develop into carcinoma
- erythema nodosum, iritis/uveitis (CD > UC)
- Crypt distortion \& abscesses (in both)
- continuity (non-segmental)
- Maybe due to cross-react with Escherichia coli
- disease of the rectum, and the colon.
- bloody diarrhea
- inflammation is restricted to the mucosa.
- superficial ulcerations


## Ulcerative

 colitis- polypoid
- Higher risk with colon carcinoma than CD
- primary sclerosing cholangitis (UC >CD)
- p-ANCA antibodies ( some times)
- HLA-B27 positive arthritis.
- Crypt shortening \& abscesses
- Crypt distortion \& atrophy
- Toxic Megacolon

IF YOU WANT A SUMMARY CLICK HERE

DR. MAHA \& DR AHMED CASES \& QUESTIONS CLICK HERE

## you

詵MCQsWhich type of inflammatory bowel disease is characterized by longitudinal serpiginous ulcers separated by islands of edematous mucosa?
A- Crohn's disease
B- Ulcerative colitis

C- Diverticulitis
D- Irritable bowel syndrome

Which extraintestinal manifestation is more commonly associated with ulcerative colitis than Crohn's disease?

A- Erythema nodosum

C- Sacroiliitis
D- sclerosing cholangitis

B- Pyoderma gangrenosum

Which complication is more common in ulcerative colitis compared to Crohn's disease?

A- Intestinal obstruction
C- Risk of carcinoma of the colon

B- Fistula formation

D- Malabsorption

Which type of inflammatory bowel disease is associated with cobblestone appearance and creeping fat?

A- Crohn's disease
B- Ulcerative colitis

> | C- Diverticulitis | D- Irritable bowel syndrome |
| :--- | :--- |

## you

 MCQsWhich type of inflammatory bowel disease primarily affects the colon and is associated with bloody diarrhea?
A- Crohn's disease
B- Ulcerative colitis
C- Diverticulitis
D- Irritable bowel syndrome

Which of the following is a common complication of Ulcerative colitis?

| A- Toxic megacolon | B- Intestinal obstruction |
| :---: | :---: |
| C- Malabsorption | D- Fistula formation |

What gene is mostly associated with Ulcerative colitis?

A- HLA-DR8
B- HLA-DR7

C- HLA-B27
D- HLA-B-37

Which type of inflammatory bowel disease is associated with a higher risk of intestinal obstruction?

A-Crohn's disease B-Ulcerative colitis

C- Diverticulitis
D- Irritable bowel syndrome

## you <br>  CASES

1. A 27-year-old woman presents with a 9-month history of bloody diarrhea and crampy abdominal pain. Three weeks ago, she noticed that her left knee was swollen, red, and painful. Her temperature is $38^{\circ} \mathrm{C}$ ( $101^{\circ} \mathrm{F}$ ), respirations are 32 per minute, and blood pressure is $130 / 90 \mathrm{~mm} \mathrm{Hg}$. Abdominal palpation reveals
 tenderness over the left lower quadrant. Laboratory studies show moderate anemia, with a hemoglobin level of $9.3 \mathrm{~g} / \mathrm{dL}$. Microscopic examination of the stool reveals numerous red and white blood cells. A diffusely red, bleeding, friable colonic mucosa is visualized by colonoscopy. The colon is subsequently removed and the surgical specimen is shown in the image. Which of the following is the most likely diagnosis?

| A.Carcinoid tumor | B.Crohn disease | C.Pseudomembra <br> nous colitis | D.Ulcerative colitis |
| :--- | :--- | :--- | :--- |

2.The patient described in Question 2 is at increased risk of developing which of the following complications?
A.Adenocarcinoma B.Fistula
C.Granulomatous lymphadenitis
D.Transmural inflammation
3.A 25 -year-old woman is brought to the emergency room with symptoms of acute intestinal obstruction. The patient has an 8-month history of blood-tinged diarrhea and cramping abdominal pain. Her temperature is $38^{\circ} \mathrm{C}\left(101^{\circ} \mathrm{F}\right)$, and respirations are 32 per minute. There is abdominal tenderness to palpation. Laboratory studies show moderate anemia, with serum hemoglobin of $9.3 \mathrm{~g} / \mathrm{dL}$. Microscopic examination of the stool reveals numerous RBCs and WBCs. A CT scan of the abdomen shows massive distention of the transverse colon. Which of the following is the most likely underlying cause of this patient's colonic disorder?

| A.Carcinoid tumor | B.Crohn disease | C.Pseudomembra <br> nous colitis | D.Ulcerative colitis |
| :--- | :--- | :--- | :--- |

## you <br>  CASES

 4. A 21-year-old man is brought to the emergency room with symptoms of acute intestinal obstruction. His temperature is $38^{\circ} \mathrm{C}\left(101^{\circ} \mathrm{F}\right)$, respirations are 25 per minute, and blood pressure is $120 / 80 \mathrm{~mm} \mathrm{Hg}$. Physical examination reveals a mass in the right lower abdominal quadrant. The patient subsequently undergoes surgery, and a segmental lesion involving the terminal ileum is resected (shown in the image). Which of the following is the most likely diagnosis?
A.Carcinoid tumor
B.Crohn disease
C.Pseudomembra nous colitis
D.Ulcerative colitis 5.A 24-year-old man is brought to the emergency room with symptoms of acute intestinal obstruction. His temperature is $38^{\circ} \mathrm{C}\left(101^{\circ} \mathrm{F}\right)$, respirations are 25 per minute, and blood pressure is $120 / 80 \mathrm{~mm} \mathrm{Hg}$. Physical examination reveals a mass in the right lower abdominal quadrant. At laparoscopy, there are numerous small bowel strictures and a fistula extending into a loop of small bowel. Which of the following is the most likely

| A.Carcinoid tumor | B.Crohn disease | C.Pseudomembra <br> nous colitis | D.Ulcerative colitis |
| :--- | :--- | :--- | :--- |

6.A 25-year-old woman presents with persistent bloody diarrhea of 4 weeks' duration. She has experienced severe abdominal cramping for the past 3 days. Her temperature is $38^{\circ} \mathrm{C}\left(101^{\circ} \mathrm{F}\right)$, respirations are 22 per minute, and blood pressure is $120 / 70 \mathrm{~mm} \mathrm{Hg}$. Physical examination reveals abdominal tenderness and mild abdominal distension. Bowel sounds are diminished. Laboratory studies show mild hypochromic, normocytic anemia. Stool cultures are negative for pathogens, and no ova or parasites are detected. A blood test for Clostridium difficile toxin is negative.
Rectosigmoidoscopy shows hemorrhagic mucosal lesions in the distal colorectal region. A biopsy of the colon reveals crypt abscesses, basal lymphoplasmacytosis and crypt distortion. Which of the following represents the most common extraintestinal manifestation of the colonic disorder in this patient?
A.Arthritis
B.Cystitis
C.Gastritis
D.Pancreatitis

EXTRA CASES MAY REQUIRE EXTRA INFO
1.A 48-year-old man comes to the office to establish routine care. He reports intermittent diarrhea and on-and-off crampy abdominal pain for the past 2 years. The diarrhea is nonbloody and is not associated with food intake. Past medical history is significant for pain in his knee joints that partially responds to ibuprofen. Temperature is $37.0^{\circ} \mathrm{C}$ ( $98.6^{\circ} \mathrm{F}$ ), pulse is $95 / \mathrm{min}$, respirations are $20 / \mathrm{min}$, and blood pressure is $115 / 70 \mathrm{mmHg}$. Physical examination shows pale conjunctiva and mild right lower quadrant tenderness. Colonoscopy later reveals focal linear ulcerations adjacent to areas of normal appearing mucosa, along with nodular mucosal changes in the descending colon and ileum. The rectal mucosa is spared. Which of the following is the most likely diagnosis?
A.Pseudomembrano us colitis
B.Diverticulitis
C.Ulcerative colitis
D.Crohn disease
2.A 35-year-old woman presents to the office because of perianal discomfort and foul-smelling discharge around the anus for the past 2 months. She also reports intermittent abdominal pain and watery diarrhea for the last few years for which she did not seek medical attention. She has no other significant past medical history and has not traveled outside of the country recently. Temperature is $37.2^{\circ} \mathrm{C}\left(99.0^{\circ} \mathrm{F}\right)$, pulse is $102 / \mathrm{min}$, respirations are $20 / \mathrm{min}$, and blood pressure is $110 / 65 \mathrm{mmHg}$. Physical examination shows canker sores on the oral mucosa. There is mild tenderness in the right lower quadrant of abdomen and an anterolateral anal fistula draining foul-smelling purulent discharge. Stool microscopy shows l-2 cell/hpf leukocytes. Colonoscopy shows skip lesions and cobblestone appearance of the descending colon with rectal sparing. Which of the following findings will be seen on light microscopy of the involved tissue sample?
A.Caseating
granulomas
B.Non-caseating granulomas
C.Distended macrophages in lamina propria
D.Infiltration of lamina propria with atypical lymphocytes
3.A 45-year-old man comes to the office with recurrent episodes of abdominal pain for the past 3 months. He states that he defecates a small volume of stools 3-4 times a day, even after which he gets a sensation of incomplete bowel emptying. The stools are semi-solid, admixed with a small amount of blood. Vitals are within normal limits. Physical examination of the abdomen shows mild distension and left-sided tenderness. Colonoscopy reveals edematous rectum, sigmoid and descending colon with loss of vascular markings and multiple pseudopolyps throughout the involved region. The mucosa is erythematous and friable, with spontaneous bleeding on contact. The remainder of the colon and small intestines are normal. Which of the following is the most likely diagnosis?
4.A 42-year-old man comes to the office because of watery diarrhea and right lower quadrant pain. The symptoms started 3 months ago and are not relieved by over-the-counter antidiarrheals. His temperature is $37.0^{\circ} \mathrm{C}\left(98.6^{\circ} \mathrm{F}\right)$, pulse is $80 / \mathrm{min}$, respirations are $20 / \mathrm{min}$, and blood pressure is $135 / 85 \mathrm{mmHg}$. Physical examination shows tenderness to deep palpation in the right lower quadrant. There is no rebound tenderness. Rovsing sign is negative. Colonoscopy reveals focal ulcerations adjacent to areas of normal appearing mucosa along with nodular mucosal changes in the colon. Which of the following cell types are the most involved in the formation of this lesion?

| A.T helper 1 (Th1) <br> cells | B.B-lymphocytes | C.T helper 2 (Th2) <br> cells | D.Eosinophils |
| :--- | :--- | :--- | :--- |

5.A 45-year-old man is brought to the office for recurrent episodes of bloody diarrhea and abdominal pain. He has had several episodes of watery diarrhea in the past 2 years. Review of systems reveals a $9-\mathrm{kg}$ (20-lbs) weight loss over this time period, fatigue, and loss of appetite. Past medical history is significant for ischemic heart disease and diabetes mellitus type II. He takes aspirin and glyburide regularly. Vitals are within normal limits. BMI is $19 \mathrm{~kg} / \mathrm{m} 2$. Physical examination shows abdominal tenderness without rebound or guarding. Colonoscopy shows erythematous and edematous bowel
 wall mucosa involving the whole colon. After appropriate workup, a colectomy is performed; findings of the involved regions are shown. Which of the following is the most likely diagnosis?

| A.Diverticulitis | B.Ischemic colitis | C.Ulcerative colitis | D.Crohn disease |
| :--- | :--- | :--- | :--- |

6.A 44-year-old woman complains of having yellow eyes, dark urine, and recurrent fever for about 3 months. She has a long history of chronic diarrhea. On physical examination, the patient is thin and jaundiced. The liver edge descends 1 cm below the right costal margin and is nontender. Laboratory studies show elevated serum bilirubin of $3.8 \mathrm{mg} / \mathrm{dL}$, normal levels of AST and ALT, and an elevated level of alkaline phosphatase ( $440 \mathrm{U} / \mathrm{dL}$ ). Endoscopic retrograde cholangiopancreatography demonstrates a beaded appearance of the extrahepatic biliary tree. Which of the following is the most likely underlying cause of diarrhea in this patient?

| A.Amebiasis | B.Amyloidosis | C.Carcinoma of <br> the ampulla of <br> Vater | D.Ulcerative colitis |
| :--- | :--- | :--- | :--- |



